

**PATHOLOGY OF THE RABBIT**  
**Pathology of Laboratory Animals Course**

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**GENERAL INFORMATION**

Rabbits are classified in the Order Lagomorpha. They differ from rodents because they possess an additional pair of incisor teeth directly behind the large incisors of the upper jaw. There are over 100 different breeds of rabbits that are descendants of the European wild rabbit, *Oryctolagus cuniculus*. The majority of rabbits used in biomedical research are New Zealand white rabbits.

The chambers of the right side of the heart are relatively thin and frequently a quantity of clotted blood will be found in the right ventricle with no evidence of contraction. The right atrioventricular valve is bicuspid instead of tricuspid.

Rabbits are hind gut fermenters with a large and complex digestive system. They practice cecotrophy, which is the ingestion of mucous-coated night feces. Cecotrophy occurs daily, and is a method of recycling nutrients such as B vitamins and proteins. It is controlled by the adrenal glands, and therefore may be altered during periods of excessive stress. Rabbits possess abundant gut associated lymphoid tissue located in the Peyer's patches, lymphoid appendix and sacculus rotundus. These structures comprise nearly 50% of the total mass of lymphoid tissue in the body. Autolysis of these tissues is rapid after death.

Rabbits have alkaline urine with dull yellow to brown calcium carbonate and triple phosphate crystals. Calcium and magnesium are excreted primarily via the urine. Urine may be pigmented dark red to orange which is an incidental finding and may indicate increased ingestion of dietary porphyrins or elevated urobilin.

Female rabbits are does; males are bucks. Bucks reach puberty at 6-10 months of age and does reach puberty at 4-9 months. The breeding lifespan of a doe is 3-4 years. The uterus has two horns and two separate cervixes and placentation is hemochorial. Does are induced ovulators. Gestation lasts 25-29 days and does give birth to 4-10 kits. Following parturition, the kits nurse 1-2 times daily. The doe's milk is high in fat and protein and kits are weaned at 4-6 weeks of age.

Ear vessels are prominent and are readily accessible for blood collection. In the rabbit, the erythrocyte measures 6.5-7.5  $\mu\text{m}$  in diameter. Polychromasia is a normal finding. Reticulocytes make up 2-5% of the red

blood cell count and the life span of the red blood cell is 50 days. Heterophils are the counterpart of the neutrophil and measure 9-15µm and have distinct acidophilic granules. Eosinophils are 12-16 µm and have large cytoplasmic granules that stain dull pink-orange with conventional hematology stains. Lymphocytes are the predominant leukocyte in circulation. Small lymphocytes measure 7-10 µm and large lymphocytes are 10-15 µm. Lymphocytes normally contain a few azurophilic cytoplasmic granules. Basophils may be numerous and represent up to 30% of the circulating leukocyte population.

## **VIRAL DISEASES**

### **1. Myxomatosis**

Myxomatosis is caused by a leporipoxvirus that is endemic in the wild rabbit population. There are two subtypes of the virus: the South American type that is found in *Sylvilagus brasiliensis* (forest rabbits) and the Californian subtype found in brush rabbits (*S. bachmani*). Myxoma virus is transmitted by direct or indirect contact and arthropod vectors such as ticks and fleas also play a role. After infection, a primary subcutaneous myxoid mass develops within 3-4 days. At 6-8 days, mucopurulent conjunctivitis, subcutaneous edema and multiple subcutaneous masses develop. In peracute cases, rabbits die suddenly with only conjunctival erythema. The high mortality rates are the result of multiorgan dysfunction with secondary bacterial infections due to immunosuppression by the virus. Clinically, there is moderate leukopenia with significant lymphopenia with a decrease in CD4+ and CD8+ lymphocytes. Histologically, there is proliferation of large, stellate mesenchymal cells, myxoma cells, interspersed in a mucinous, homogenous matrix with few inflammatory cells. There is also hypertrophy and proliferation of endothelial cells and the overlying epidermis ranges from hyperplastic to degenerative. Intracytoplasmic inclusion bodies are often present.

### **2. Shope Fibroma**

**Shope fibroma** is also caused by a leporipoxvirus that is transmitted by fleas and ticks. Like myxoma virus, the genetic sequence for this virus has also been recently determined. Shope fibroma virus is the first mammalian virus potentially capable of photoreactivating ultraviolet DNA damage due to its ability to encode a type II DNA photolyase. The Eastern cottontail rabbit is the natural host, but other species of rabbits are susceptible as well. The virus produces firm flattened subcutaneous, freely moveable, up to 7 cm diameter masses primarily on the legs and feet, and less commonly on the muzzle and in the periorbital and perineal areas. In newborn and immunocompromised adults, Shope fibroma virus can cause a fatal disseminated disease similar to myxomatosis. Histologically, there is localized

fibroblastic proliferation with infiltration by low to moderate numbers of mononuclear and polymorphonuclear cells. Fibroblasts are fusiform to polygonal and contain intracytoplasmic eosinophilic viral inclusion bodies. There is a single report of a cataract in a rabbit. The diagnosis was based on signalment, clinical signs, histologic appearance and virus isolation.

### **3. Papillomaviruses**

**Cutaneous papillomatosis** is typically a benign disease of cottontails caused by a papilloma virus that is mechanically transmitted through insect vectors. The natural host is the cottontail rabbit. Clinically, the lesions are cornified, pedunculated masses with fleshy central areas. Histologically, these lesions have the typical appearance of a typical squamous papilloma with viral inclusion bodies. In cottontails, the papillomas typically regress, but in domestic rabbits the papillomas may progress to squamous cell carcinomas. Regression is dependent on the host genetic makeup as well as the genetic variability of the virus. Papillomatosis has been studied in rabbits to learn more about the prevention of malignant progression of human papillomavirus-associated lesions in humans.

**Oral papillomatosis** is caused by a papillomavirus and usually occurs in young rabbits, 2-18 months of age. The condition is characterized by the presence of white, fleshy papillomatous masses along the ventral aspect of the tongue. The virus is spread by direct contact in areas where there has been injury to the oral mucosa. Rough or hard food, chewing on rough cage bars and or malocclusion may predispose animals to infection. The histologic appearance is a typical squamous papilloma with basophilic intranuclear inclusions in epithelial cells. A recent report documented a persistent papilloma in the conjunctiva in a Flemish Giant pet rabbit that was caused by an oral papilloma virus strain.

### **4. Rabbitpox virus**

**Rabbit pox** is caused by an orthopoxvirus that has significant homology with the vaccinia virus. The natural route of infection is by aerosol followed by viremia with viral replication in the lymphoid tissue with systemic spread. Clinically, rabbits are febrile with weight loss followed by ocular discharge and dyspnea. Papular lesions occur in the oropharynx, respiratory tract, skin, mucocutaneous sites, spleen, lymph nodes and liver and are characterized by focal necrosis with leukocyte infiltration. Rabbitpox virus is proposed as an animal model for human smallpox.

### **5. Rabbit herpesviruses**

**Leporid herpesvirus 3 (Herpesvirus sylvilagus)** is a gamma herpesvirus found in wild cottontail rabbits. Juveniles are affected to a greater degree than adults. There is prominent lymphoproliferative disease in lymph nodes, spleen, kidney and liver.

There is a recent report of a **novel alpha herpesvirus** causing an outbreak of disease in rabbits in Alaska. Affected rabbits had many lesions similar to myxomatosis including necrosis of ocular and anogenital skin and lymphoid necrosis, but with vasculitis, intranuclear viral inclusions and syncytial cells.

Rabbits are very sensitive to infection with **herpes simplex virus**. Affected rabbits exhibit typical neurologic signs and anorexia and weakness. There is a nonsuppurative, necrotizing meningoencephalitis with amphophilic intranuclear inclusion bodies in neurons and astroglial cells. This is a zoonotic disease and cases in rabbits have been traced back to a herpetic lesion in a human.

Rabbits are animal models for herpes simplex virus keratitis, malignant catarrhal fever, pseudorabies and bovine herpesvirus type 5.

## **6. Rabbit coronavirus**

Pleural effusion and cardiomyopathy due to **coronavirus** occurs in laboratory rabbits. This virus is antigenically related to human coronavirus strain 229E and it has been suggested that the rabbit virus is a human contaminant. Transmission is through direct contact and there are carrier animals. Gross lesions of pleural effusion disease include pleural effusion, pulmonary edema, right-sided cardiac dilatation, peritoneal effusion, mesenteric lymphadenopathy, necrosis of the liver, kidney and lung, iridocyclitis, and lymphoid depletion. Histologically, there is lymphoid depletion of splenic follicles, focal degenerative changes in the thymus and lymph nodes, proliferative changes in glomerular tufts, and uveitis. In the cardiomyopathy form, there is focal to diffuse myocardial degeneration and necrosis, pulmonary edema, lymphoid depletion to hyperplasia, and diaphragmatic muscular degeneration and necrosis. The differential diagnosis for myocardial necrosis in rabbits is hypovitaminosis E, salmonellosis, Tyzzer's disease, pasteurellosis, encephalitozoonosis, and detomidine-containing anesthetic agents.

**Coronavirus** can cause enteritis in young rabbits, 3-8 weeks of age. Clinically, the affected rabbits are thin and dehydrated with fecal staining in the perineal region. The cecum is distended and filled with watery, beige to tan fecal material. The histological appearance is similar to rotavirus with necrosis of villous epithelial cells and M-cell necrosis. Diagnosis is by finding typical viral particles in feces by electron microscopy.

## **7. Rabbit rotavirus**

**Rotavirus** causes mild to severe diarrhea with high morbidity in suckling and weanling rabbits. The virus is transmitted by direct contact by ingestion and is endemic in many rabbitries. It can be found in normal rabbits free of disease and antibody titers in normal rabbits may also be present.

Clinically, the rabbit is dehydrated and the cecum is distended, congested and filled with fluid contents. Histologically, in the small intestine there is villar atrophy, blunting, and fusion with vacuolation and flattening of apical enterocytes. In the cecum, there are focal areas of desquamation with basophilic debris in the cytoplasm of affected enterocytes. Diarrhea is more severe with coinfections such as those with *E. coli*.

## **8. Rabbit viral hemorrhagic disease virus**

**Rabbit viral hemorrhagic disease (RVHD)** is caused by a Lagovirus in the family *Caliciviridae* and is considered a foreign animal disease. Other viruses in the *Lagovirus* genus include European Brown Hare Syndrome Virus and Rabbit Calicivirus. This is the only reportable disease in rabbits in the U.S. To date, there have been four separate outbreaks in the U.S. and the virus sequences show similarity to genomes from China. RVHD is a peracute disease of adult rabbits that results in hepatic, enteric, and lymphoid necrosis. The virus is transmitted by direct contact and by contaminated fomites. Carrier states are present and the virus is shed in the urine for up to 4 weeks and long term fecal shedding may be possible. This virus has a predilection for hepatocytes and macrophages, where it replicates. The clinical signs vary but include sudden death, fever, depression, CNS signs, and serosanguinous discharge. Some animals will have a more subacute course of diseases, dying 1-2 weeks after infection. Necropsy findings include hepatomegaly, splenomegaly, and hemorrhage and serosal ecchymoses. Histologically, there is hepatic necrosis that begins in the periportal areas and spreads to the entire lobule. There is also heterophilic infiltration, crypt necrosis, pulmonary edema, hemorrhage, and lymphocytolysis. There are fibrin thrombi in the small caliber vessels throughout the body. In an outbreak in Illinois, clinical signs included depression, anorexia, fever, paddling, convulsions and sudden death. Diagnosis was made by hemagglutination assay and viral antigen-detection ELISA.

## **9. Rabies Virus**

Rabbits are susceptible to infection with **rabies virus**. All reports have been in states with enzootic raccoon-variant rabies virus. Affected rabbits were housed outdoors with potential or reported contact with wildlife. The clinical disease is the paralytic form and affected rabbits die within 3 to 4 days. Diagnosis is by immunofluorescent testing of brain tissue. Prevention is through double caging of outdoor housed rabbits and prohibition of free-roaming while outdoors.

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## **BACTERIAL DISEASES**

### **1. Pasteurella multocida**

Pasteurellosis is probably the most significant disease of rabbits. In conventional rabbit colonies, the incidence of infection may be high. Close to 50% and up to 70% of the animals may harbor the organism in the upper respiratory tract and tympanic bullae. *P. multocida* is a Gram negative, bipolar staining bacillus that is transmitted through direct contact from animals shedding the organism from nasal and/or vaginal secretions. Nursing rabbits can become infected within the first week of life from nursing carrier does. Aerosols do not appear to be an important means of spread and using a modified barrier system can prevent infection. Fomites may be involved in transmission; however, a large number of organisms are required for infection. Interspecies transmission has been experimentally reproduced. There seems to be a seasonal influence with infection because most problems occur in the spring and fall. Predisposing factors include increased atmospheric ammonia concentration, pregnancy, concomitant disease, environmental disturbances and experimental manipulation.

*P. multocida* causes a wide range of clinical disease in rabbits including rhinitis, pneumonia, otitis media, meningoencephalitis, abscessation, mastitis, dermatitis and septicemia. Some of the gross lesions associated with infection of the respiratory tract by *P. multocida* are catarrhal to mucopurulent rhinitis, atrophic rhinitis, chronic pneumonia

characterized by localized consolidation of the anteroventral lobes with atelectasis, acute fibrinous pneumonia with fibrinohemorrhagic lobar pneumonia and pleuritis with possible pericarditis and/or pyothorax, and pulmonary abscesses.

Histologically, the pneumonia may be characterized by chronic bronchitis with peribronchial lymphocytic infiltration to alveolitis with primarily heterophilic inflammation. In the acute necrotizing form, there is destruction of alveoli and small airways, alveolar flooding with fibrinous exudate and erythrocytes and infiltration by large numbers of heterophils. Multinucleate giant cells may be present in affected alveoli. Other bacteria that cause similar lesions in the lung of rabbits are Bordatella bronchiseptica, Staphylococcus aureus, and Klebsiella pneumoniae. The diagnosis should be confirmed with bacterial culture. For control of this important disease, infected rabbits should be culled and barrier housing with adequate ventilation should be used.

*P. multocida* infections outside of the respiratory tract are characterized by necrosis, large numbers of heterophils and bacteria.

**2. Bordatella bronchiseptica** is often present together with Pasteurella multocida. Its role as a definitive cause of disease in the respiratory tract of rabbits has not yet been firmly established. The organism can be recovered from the upper and lower respiratory tract of healthy rabbits. It is transmitted by direct contact through aerosols. Suppurative bronchopneumonia can be produced experimentally by treating rabbits with corticosteroids, then infecting them. However, B. bronchiseptica has been isolated from natural cases of localized pneumonia. Histologically, there is a chronic interstitial pneumonia, chronic bronchiolitis and perivascular and peribronchial accumulations of lymphocytes, plasma cells, and macrophages.

### **3. Staphylococcus aureus**

Strains of varying pathogenicity of this Gram positive bacterium can cause clinical disease in limited individuals, or produce colony problems. A recent study showed that colonization capacity is an important virulence determinant in rabbit staphylococcosis. The most common clinical lesions in rabbits due to *S. aureus* are subcutaneous abscesses, pododermatitis, mastitis and septicemia. The organism is transmitted by direct contact via aerosol. Like *P. multocida*, carrier animals can harbor the bacterium in the upper respiratory tract. Umbilical vessels and skin abrasions are two other possible entry sites. After inoculation, *Staphylococcus* can spread hematogenously or via local extension.

**Ulcerative pododermatitis** or "sore hock" is a common problem. Overweight males housed on wire-floor cages are predisposed to sorehock. Poor sanitation is another predisposing factor. Clinically, there are ulcerative skin lesions on the plantar surface of the metatarsal and/or metacarpal

regions. Histologically, there is epidermal hyperplasia with ulceration and/or erosion covered by a serocellular crust with a mixed inflammatory cell infiltrate in the dermis. Diagnosis is made by demonstration of Gram positive cocci in section and by positive bacterial culture.

**Bacterial mastitis** has been attributed to the following organisms: *Staphylococcus* sp., *Pasteurella multocida*, and *Streptococcus* sp. In lay terms, it is called “blue breast” and occurs most commonly in recently kindled and heavily lactating does. Orphan young can spread disease to an unaffected doe and infection can spread to multiple mammary glands. Clinically, the skin overlying the mammary glands has a red to dark blue discoloration and the gland contains serous to purulent exudate. Nursing young may develop an acute fatal septicemia. Histologically, the lesions are suppurative with necrosis and bacteria are often present.

**Pneumonia** caused by *S. aureus* is often very suppurative and is composed of large amounts of white purulent material. Histologically, there are focal suppurative necrotizing lesions with colonies of cocci. The bacteria are often present in section, but infections should always be confirmed with bacterial culture.

**Septicemia** usually occurs in the very young and sporadically in adults. There are suppurative lesions disseminated throughout the body, especially in the lung, kidney, spleen and heart.

#### 4. Treponema paraluiscuniculi

**Treponematosi**s is common in wild rabbits and is often referred to as rabbit syphilis or vent disease. The disease is transmitted venereally, although transmission through extragenital contact can occur and the organism is able to penetrate intact mucous membranes. Susceptibility is age and breed dependent and the disease is generally self-limiting. Treponema paraluiscuniculi is a 5-20 µm, Gram negative helical bacillus with tight or irregular spirals. Clinically, there is edema and erythema at the mucocutaneous junctions of the vulva, prepuce, anal region, muzzle, and periorbital area. Lesions are often crusty. Popliteal and inguinal lymph nodes may be enlarged. The histologic changes are confined to the epithelium and superficial dermis and are characterized by epidermal hyperplasia, epidermal cell necrosis, erosions, and ulcerations with infiltration by predominantly plasma cells and lymphocytes. The diagnosis can be made by making a wet preparation of skin scrapings and examining them under dark field microscopy or by serology. The organism can also be demonstrated in tissue sections with silver stains and can also be detected by serology by detection of the reagin antibody.

#### 5. Pseudomonas aeruginosa

*Pseudomonas aeruginosa* causes a moist dermatitis with a characteristic green color.

**6. Arcanobacter pyogenes**

*Arcanobacter* (Corynebacterium) *pyogenes* causes suppurative and ulcerative dermatitis in rabbits.

**7. Fusobacterium necrophorum** has been reported to cause suppurative and ulcerative dermatitis.

**8. Clostridiosis** in rabbits has been attributed to infection with **Clostridium perfringens**, **C. difficile**, and **C. spiroforme**. **C. spiroforme** produces a type E iota toxin and is the most common of the clostridial bacteria associated with enteritis complex in juvenile rabbits. Infections in rabbitries are common and at necropsy of diarrheic rabbits, it is isolated from over 50% of the cases, and in one study, 90% of these strains were toxigenic. Concurrent infections (**E. coli**, **Eimeria** sp, **Cryptosporidia**, and rotavirus) can also allow colonization and proliferation of clostridial bacteria with subsequent toxin production. There are different clinical forms of the condition. In the peracute form, there is death with little or no premonitory signs. In the chronic condition, there is anorexia, wasting and intermittent diarrhea over several days. At necropsy, the body is in good nutritional condition and there is soiling of the perineal region with watery green to tarry brown feces. There is often a straw colored peritoneal effusion, ecchymoses on the cecal serosa, with occasional involvement of the distal ileum and proximal colon. There may be epicardial and thymic ecchymoses. The cecum and adjacent areas are frequently dilated and are filled with watery to mucoid, green to dark brown material and gas. Hemorrhage and ulceration and/or fibrin may markedly thicken these areas. Histologically, there is necrotizing typhlocolitis with effacement of the mucosal architecture, loss of epithelium, ulceration, fibrinous exudation, congestion, hemorrhage, and infiltration by primarily heterophils. Thrombi may be present on the mucosal surface. The diagnosis can be confirmed by anaerobic bacterial culture and the toxins can be identified. **C. perfringens** causes an enterotoxemia-like condition in young rabbits that result in cecal hemorrhage and edema. **C. difficile** causes disease in rabbits after antibiotic administration and/or dietary change. In contrast to other species, lesions in rabbits due to *C. difficile* most commonly affect the ileum and not the colon as in other species.

**9. Clostridium piliforme** is the causative agent of Tyzzer's disease and is a Gram negative, motile, filamentous, spore forming bacillus. Predisposing factors are important in this condition and include poor sanitation, stress and sulfonamide therapy. Many other species of laboratory and domestic animals are also infected; therefore interspecies transmission must be prevented. Survivors can become chronically infected and serve as carriers. **C. piliforme** is transmitted by direct contact through ingestion and the organism can

survive in soiled bedding for up to one year. The bacterium causes an acute disease characterized by a sudden outbreak of profuse, watery diarrhea with a short course and high mortality rate. At necropsy, there is a classic triad of lesions that include segmental necrosis, edema and hemorrhage of the small and large intestine; multifocal hepatic necrosis, and myocardial necrosis. Histologically, there is necrosis, edema, and hemorrhage with intracellular bacterial present in enterocytes, hepatocytes and cardiomyocytes. The bacilli can be readily demonstrated with Giemsa, PAS, and silver stains.

The classic triad of lesions is necrotizing myocarditis, hepatitis and typhlocolitis

#### **10. E. coli**

The attaching and effacing (enteropathogenic) strains cause colibacillosis in rabbits and are a major cause of enteritis in commercial rabbitries. The organism is not normally present or is present in small numbers within the gastrointestinal tract of suckling and weanling rabbits. There is a rapid proliferation of these bacteria with a change in intestinal pH due to such things as intestinal coccidiosis and diets that require a high HCl concentration for digestion, such as high carbohydrate diets. Some strains affect only suckling rabbits and attach to the full length of the small and large intestine, while other strains affect weanlings only and attach only to the ileum and large intestine. The organism attaches to the Peyer's patch dome epithelium and then later colonizes and attaches to enterocytes. At necropsy, the body is dehydrated, there is perineal staining with watery, yellow to brown fecal material, the cecum is distended with watery yellow to gray-brown contents and there may be serosal ecchymoses, edema in the cecal and colonic walls and enlarged mesenteric lymph nodes. The small intestine is usually grossly normal. Histologically, changes are most severe and extensive in weanling rabbits. Ileal villi are blunted with edema and heterophilic infiltration of the lamina propria. The enterocytes at the villar tips are swollen with attached bacilli.

**11. Lawsonia intracellularis** is a curved, obligate intracellular Gram negative bacillus that causes proliferative enteropathy not only in rabbits, but in many other species. The organism produces diarrhea in suckling, weanling, and adult rabbits acutely and can also cause subclinical disease. The disease in rabbits is similar to that in hamsters and pigs. At necropsy, there are semi-fluid, mucinous contents in a thickened colonic and rectal mucosa. Histologically, there is variable involvement in the terminal small intestine, cecum, and colon. Lesions vary from erosive and suppurative to proliferative. In the erosive form, there is focal to segmental loss of enterocytes with heterophilic infiltration. The proliferative form is characterized by multifocal to diffuse enterocyte hyperplasia and hyperplasia of crypt and villar epithelium with infiltration by variable numbers of lymphocytes, heterophils,

macrophages and occasionally, multinucleate giant cell macrophages. Bacteria can be demonstrated within enterocytes with silver stains. By electron microscopy, curved, bacillus-like organisms are present within the cytoplasm at the luminal edge of the epithelium.

**12. Salmonella typhimurium** and **S. enteritidis** are Gram negative bacilli that can cause rare infections in rabbits that result in septicemia, diarrhea, abortions and death. These bacteria are transmitted by the fecal-oral route and cause polyserositis, focal hepatic necrosis, splenomegaly, enteritis with fibrinous exudate, necrotizing myocarditis and suppurative metritis.

**13. Yersinosis** due to **Yersinia pseudotuberculosis** occurs rarely in domestic rabbits and is an acute to chronic infection. The organism is transmitted by ingestion of contaminated food and water. Wild rodents and birds are carriers. The clinical signs are nonspecific and include poor condition and weight loss. Histologically there is necrosis in the liver, spleen, cecum, and lymph nodes and occasionally, the reproductive tract may be affected. There are large numbers of coccobacilli within necrotic areas.

**14. Francisella tularensis**, the causative agent of Tularemia or "Rabbit Fever" is a Gram negative bacillus. The bacterium is transmitted through direct contact and through insect vectors. Ticks appear to be the most important vector, but other vectors such as horseflies, mosquitoes, sucking lice and biting lice are also capable of transmitting the agent. Rabbits are usually found dead. Death usually occurs in 8-14 days after infection. There is necrosis of the spleen, liver and lymph nodes with colonies of bacilli.

**15. Listeria monocytogenes** is a Gram positive coccobacillus transmitted through ingestion of contaminated feed and/or water and transplacentally that causes hepatic necrosis and nonsuppurative meningoencephalitis in rabbits. It also causes fever, abortions and sudden death in does in late gestation. Infected newborn kits may develop systemic disease, may have stunted growth and/or develop meningoencephalitis.

**16. Cilia-associated respiratory (CAR) bacillus** is a Gram negative, 6-8  $\mu\text{m}$  motile, non-spore forming bacillus that causes generally subclinical infections in rabbits. CAR bacillus isolates that infect mice and rats are host specific and do not infect rabbits. The organism colonizes the ciliated epithelial cells lining the larynx, trachea, and bronchi. Histologically, there may be a chronic tracheitis with goblet cell hyperplasia. The organism can be demonstrated in section with silver stain.

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## **MYCOTIC DISEASES**

1. **Ringworm** caused by Trichophyton mentagrophytes, Microsporum canis and M. gypseum is the most common fungal disease in rabbits. Rabbits may serve as inapparent carriers and they can transmit infection to other animals, as well as humans. The young and immunocompromised are most susceptible. Clinically, lesions are most commonly present on the head and ears and are raised, circumscribed, and erythematous. Histologically, there is hyperkeratosis, epidermal hyperplasia, folliculitis, and arthrospores. Diagnosis is by skin scrapings cleared in 10% potassium hydroxide solution. In tissue sections, the arthrospores are stained with methenamine silver and periodic acid Schiff stains.

2. Aspergillus fumigatus and A. flavus is occasionally found at necropsy, almost exclusively in wild rabbits. It can result in disseminated lesions in the liver, kidney, brain, lung, heart, intestine and spleen. The lesions are circumscribed nodules with a central area of necrosis surrounded by neutrophils, lymphocytes, plasma cells, macrophages, and multinucleate giant cells. Fungal hyphae can be demonstrated with silver or PAS stains.

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## **PROTOZOAL/MICROSPORIDIAL DISEASES**

### **1. Encephalitozoon cuniculi**

*Encephalitozoon cuniculi* is an oval, 1 x 2 µm Gram positive, obligate intracellular microsporidian parasite that is widespread in domestic rabbits and is probably the most common spontaneous microsporidian infection in animals. Infection in rabbits is usually subclinical, but can cause nervous system disease and death in heavy infections. Dwarf rabbits are highly susceptible to infection and development of disseminated disease. Three

major types of clinical disease can occur: a neurological form, an ocular form and a renal form. Clinical signs of the neurologic form include head tilt, seizures, ataxia, paralysis and muscular weakness and usually occur approximately 30 days after infection. The ocular form is associated with cataracts and extensive damage to the lens with uveitis.

Natural transmission is by ingestion of spore-contaminated urine and transplacental transmission also occurs from pregnant does to their kits. Spores can survive in the environment for at least 4 weeks at room temperature. Spores are spread hematogenously within the cytoplasm of macrophages. The spores selectively parasitize vascular endothelium, especially in the brain and kidney, as well as renal tubular epithelium. Then the spores localize in the liver, lung, adrenal gland, spleen and other highly vascular organs. Within the cell, the spores are contained within a parasitophorous vacuole or pseudocyst and are called trophozoites or schizonts that multiply by ordinary fission or schizogony. When the trophozoites mature, they become sporonts, then sporoblasts, and then eventually spores. The organism has a polar filament that it uses to penetrate host cell membranes to inject sporoplasm into the host cell.

Antemortem diagnosis is difficult, since there is a high prevalence of seropositivity across different colonies. A recent paper described the use of cerebrospinal fluid (CSF) coupled with clinical signs to arrive at a preliminary diagnosis. Affected rabbits had a lymphomonocytic pleocytosis and elevated protein levels in the CSF. Only 20% of rabbits have detectable spores in the urine. PCR was used in one study to detect organisms in samples of liquefied lens material.

Definitive diagnosis is by histopathology. There are no gross lesions in the CNS, but histologically, there is focal, nodular, nonsuppurative to granulomatous meningoencephalitis with astrogliosis and perivascular lymphocytic cuffs. In ocular lesions, there is usually a granulomatous response with/without rupture of the lens capsule. Gross lesions of the kidney include focal, irregular, depressed pale areas, 2-4 mm diameter on the cortical surface. Histologically, there is focal to segmental, granulomatous to chronic interstitial nephritis with tubular ectasia, and spores within tubular epithelial cells, macrophages, and in areas of inflammation. Spores can be demonstrated with Gram, Giemsa, and carbol fuchsin stains. Immunohistochemistry can be used to identify the spores.

Albendazole, fenbendazole and anti-inflammatory drugs in addition to supportive care have been used to treat encephalitozoonosis.

## **2. Toxoplasma gondii**

This protozoan rarely causes clinical disease in laboratory rabbits. In a recent study, brown hares and rabbits were experimentally infected with *Toxoplasma gondii*. The hares had fatal, disseminated disease, while the rabbits had mostly subclinical disease. The typical findings included enteritis,

mesenteric lymphadenitis, splenomegaly and necrotizing hepatitis. Histologically, there is necrosis with tachyzoites and/or protozoal cysts. The principal differential diagnosis is *Encephalitozoon cuniculi*.

### 3. Coccidiosis

**Intestinal coccidiosis** is caused by numerous species in the genus **Eimeria**. The species considered to be most pathogenic in rabbits are **magna**, **intestinalis** and **flavescens**. **Irresidua**, and **piriformis** are considered to be intermediately pathogenic. Least pathogenic species include **perforans**, **neoleporis** and **media**. Coccidiosis is a common, widespread problem in commercial operations and research facilities. Coccidia may act as copathogens in other conditions and as with many of the conditions of the gastrointestinal tract in rabbits, changes in environment and management may predispose to infection. Coccidia are transmitted through fecal-oral contact and infections with more than one species is not uncommon. After passage in the feces, the oocysts require one or more days to sporulate. After the sporulated oocysts are ingested, sporozoites are released and then invade enterocytes and multiply by schizogony. One or more sexual cycles take place, then gametogony occurs and oocysts are formed and passed in the feces. Clinical disease occurs most frequently in weanlings. The sexual stage causes the most damage and results in extensive destruction of enterocytes and other cells within the lamina propria. Gross lesions include dark green to brown watery foul smelling exudate in the cecum and colon with edema and congestion of the mucosa. Where the lesion is located depends on the species involved. Histologically, there is destruction and necrosis of enterocytes, villar atrophy, marked heterophilic infiltration and presence of gametocytes and oocytes. The disease can be diagnosed by fecal flotation or by mucosal scrapings. Bacterial culture should also be performed, as there are often co-infections.

**Hepatic coccidiosis** occurs in both wild and domestic rabbits and is due to infection with **Eimeria stiedae**. Weanlings are most often affected; older rabbits develop immunity. The organism is transmitted through the ingestion of sporulated oocysts. After ingestion, the sporozoites penetrate the intestinal epithelium and are then transported to the liver, where they invade biliary epithelial cells and undergo schizogony. After, gametogony, oocysts are released into bile ducts, pass to the intestinal tract via the bile and are then passed into the feces. Clinically, infections are often inapparent. However, anorexia, debilitation, constipation or diarrhea may be present in heavy infections. Other clinical signs may include enlarged liver, pendulous abdomen, and icterus. Liver enzymes and serum bilirubin may be elevated. At necropsy, there is hepatomegaly with multifocal, raised yellow to pearl gray, circumscribed foci that contain inspissated dark green to tan material. The gallbladder mucosa is thickened and filled with viscid green bile and debris. Histologically, there is bile duct hyperplasia with ectasia and papillary

projections covered by reactive epithelial cells and gametocytes and oocysts. Periportal fibrosis and mixed inflammatory cell infiltrate may also be present. Oocysts are present in gallbladder aspirates or impression smears. Histopathology is pathognomic.

**4. Cryptosporidiosis** due to *Cryptosporidium parvum* and *C. cuniculus* is a rare primary cause of enteritis in young rabbits. It is usually identified as an incidental finding and causes villous blunting, a decrease in crypt-villous ratio, and edema.

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#### **PARASITIC DISEASES**

##### **1. Psoroptes cuniculi**

This is the ear mite of rabbits and is the most common and costliest ectoparasite infection of rabbits. Ear mites are transmitted by direct contact and spend their entire life span in the external ear. Mites can survive off the

host in the crust material for up to 21 days. Severely affected ears may contain as many as 10,000 mites. The mites are nonburrowing and chew and pierce the epidermis of the external ear. This activity incites an inflammatory response that is similar to an IgE mediated type I hypersensitivity reaction. The clinical appearance is the presence of light brown, thick, crusty, foul smelling exudate in the external ear canal and pinnae. The skin beneath the crusts is alopecic and erythematous. Self-excoriation can lead to secondary bacterial infections. Histologically there is hyperkeratosis, heterophils, macrophages, eosinophils, parasites, and eggs. The mites are easily demonstrated on swabs. A recent study documented that moxidectin, an equine dewormer, was a safe and effective treatment for psoroptic mange in rabbits. Another paper found selamectin at a dose of 6 - 18 mg/kg was shown to eliminate mites from rabbits naturally infested with *P. cuniculi*.

2. Fur mites, *Cheyletiella parasitovorax*, can cause mild alopecia without pruritis or no clinical signs. These mites are transmitted by direct contact and the entire life cycle is spent on the rabbit. Clinically, there is alopecia, scaliness and crusts, especially over the dorsal trunk and scapular areas. Histologically, there is mild hyperkeratosis with mononuclear cell infiltration. The diagnosis is confirmed by finding the mites in skin scrapings.

3. Sarcoptic mange due to *Sarcoptes scabiei* and *S. cuniculi* causes alopecia and dermatitis involving the face, nose, lips, and external genitalia. The mites burrow through and inhabit the epidermis causing irritation and producing a hypersensitivity reaction with inflammation. There is parakeratotic hyperkeratosis, acanthosis, lymphoplasmacytic and eosinophilic inflammation and cross-sections of mites, eggs and mite pigment. Selamectin, a novel ivermectin, can be used at a dose of 6-18 mg/kg to treat sarcoptic mange in the rabbit.

4. The pinworm of rabbits is *Passalurus ambiguus*. It is fairly common in rabbitries and causes occasional diarrhea. The parasite is transmitted through the fecal-oral route. Adult worms are present in the cecum and colon and larvae are present on the mucosa of the small intestine and cecum. Diagnosis is made by fecal flotation. Eggs are morulated and are slightly flattened on one side. Most cases are asymptomatic, but impaired weight gain, poor breeding and death have been reported with heavy infections.

## 5. Cestodes

Rabbits are the intermediate hosts for *Taenia serialis* and *Taenia pisiformis*. Both *T. serialis* and *T. pisiformis* can produce lesions in the subcutaneous tissues and/or mesentery as well as the liver. The Laboratory Animal Resources area at Colorado State University reported three cases

within a daily census of 250 rabbits over 10 years, a <1% incidence. There is a single report of *Taenia serialis* causing exophthalmos in a rabbit. It presented as a soft tissue swelling within the orbit of the right eye. Surgery was performed and a large cystic structure was removed. Histopathology revealed the cyst was a coenurus of *Taenia serialis*.

#### **6. Obeliscoides cuniculi**

*Obeliscoides cuniculi* is a trichostrongyle found in the stomach of rabbits that graze fresh grass or are fed fresh grass as feed. Most infections are asymptomatic, but in heavy infections anorexia, lethargy and weight loss may be seen. Treatment is ivermectin injected subcutaneously and then repeated 2 weeks later.

#### **7. Baylisascaris procyonis**

The larval stages of the raccoon roundworm produce necrotizing tracts/lesions mainly in rabbits housed outdoors that have consumed feed contaminated by raccoon feces. Clinically, there is a syndrome of progressive neurological signs including circling, torticollis, tremor and ataxia. Histologically, there are areas of malacia with perivascular cuffing and infiltration by lymphocytes, plasma cells and heterophils. Sections of larvae may be present within the areas of malacia, or in more normal-appearing areas away from the malacia. Digestion of the brain may be necessary to find the larvae. Visceral lesions may be present in the heart, liver, and kidney

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## NUTRITIONAL AND METABOLIC DISEASES

1. Nutritional problems are rare due to quality control standards in the commercial feed industry. However, problems can arise especially with the use of individually formulated diets. **Vitamin E deficiency** can result in muscular soreness and stiffness. Grossly, there are pale streaks in skeletal and cardiac muscle. Histologically, there is myofiber degeneration and necrosis with mineralization and histiocytic inflammation. **Vitamin E deficiency** can cause neonatal mortality and infertility and ocular malformations in kits.

2. Rabbits are very sensitive to levels of **Vitamin D** in the diet. In fact, toxicity can result from levels as little as five times normal. Adults are more sensitive than younger rabbits. Clinical signs are nonspecific and include anorexia, weight loss and infertility. There is increased calcium absorption from the intestine, increased renal tubular resorption and increased resorption from bone. Histologically, there is calcification of the renal tubular epithelium and glomerular and tubular basement membranes, smooth muscle, myocardium, intima and media of larger arterioles and arteries, gastric mucosa, large intestine and lung. In the skeleton, there is osteodystrophy with osteoid dysplasia and osteosclerosis. There is excess production and deposition of an abnormal osteoid that is highly cellular with many active osteoblasts.

3. **Hypo and hypervitaminosis A** produce similar clinical manifestations and include poor conception rates, congenital anomalies, fetal resorption, abortion, and birth of thin, weak kits. Ocular malformations may be present in kits. Administration of Vitamin E can lower levels of Vitamin A in cases of hypervitaminosis A.

4. The Watanabe rabbit has been used extensively as an animal model of natural endogenous **atherosclerosis**. This trait is due to a single-gene defect in the gene that codes for low density lipoprotein (LDL) receptors. These rabbits develop a fulminant hypercholesterolemia in the face of a low cholesterol diet. These rabbits have increased plasma LDL cholesterol concentrations and increased plasma concentrations of apolipoprotein E. These lesions are very similar to those in man, but in rabbits they do not progress to advanced or complicated lesions as in man. However, dietary

modifications such as the addition of fats to the diet can produce lesions more similar to those in humans. Atherosclerotic lesions can also be induced experimentally in rabbits by feeding a high cholesterol diet and/or producing arterial injury by balloon catheter. Watanabe rabbits develop subcutaneous xanthomas and there is a report documenting hyperlipidemic ocular lesions affecting the corneoscleral junction and iris.

**5. Carbohydrate overload,** low fiber, high starch diets fed to young animals results in high concentrations of starches in the cecum and colon and a change in pH. This can lead to proliferation of E. coli, Clostridium perfringens, or C. spiroforme. During the fermentation of these starches, toxins are produced that may damage the mucosal surface and cause movement of water and electrolytes into the lumen.

**6. Pregnancy toxemia** occurs in does usually during the last week of pregnancy. Primiparous, obese animals on high planes of nutrition that suddenly go off feed are most at risk. Clinical pathological abnormalities include ketosis, hypocalcemia, hyperphosphatemia and fluctuating blood glucose. At necropsy, there are excessive body fat stores with fatty infiltration of the liver, kidney, and adrenal glands.

**7.** There is a recent report of osseous proliferations of extremities and mandibles with proliferative gastroduodenopathy in a group of rabbits attributed to **chronic fluorosis** that was traced back to the feed.

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## **CONGENITAL DISEASES**

### **1. Mandibular Prognathism (Malocclusion)**

Malocclusion is the most common dental abnormality of rabbits and is inherited in an autosomal recessive pattern. It may also be caused by trauma, dietary problems and neoplasia. In this condition, the mandible is abnormally long in relation to the maxilla, which results in failure of the incisors to wear normally and causes impaired mastication. The congenital form appears at 8-10 weeks of age. Clinical signs related to malocclusion include anorexia, dysphagia, bruxism, ptyalism, weight loss, and dental disease. Depending on the primary cause, treatment is corrective burring or extraction of affected teeth with supportive care and a change to a higher fiber diet.

### **2. Congenital Glaucoma**

Congenital glaucoma or buphthalmia is an autosomal recessive condition of New Zealand white rabbits. One or both eyes may be affected. The globe is enlarged due to increased intraocular pressure as a result of the absence or underdevelopment of the aqueous humor outflow channels with incomplete cleavage of the iridocorneal angles by three months of age. Corneal edema, scarring and/or cataracts may also be present in the affected eye(s). Histologically, there may be abnormal insertion of the uveal tissue onto the cornea and a lack of pectinate fibers with poor definition of the ciliary cleft and trabecular meshwork.

### **3. Splayleg**

**Splayleg** is a descriptive term applied to a condition in which rabbits lack the ability to adduct one or all legs and come to a standing position. This condition may be due to inherited syringomelia, hypoplasia pelvis, femoral luxation and distal foreleg curvature.

### **4. Endometrial Venous Aneurysms**

**Endometrial venous aneurysms** are considered congenital defects characterized by multiple blood filled endometrial varices that are composed of dilated, thin walled veins that rupture and bleed periodically into the uterine lumen.

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## **MISCELLANEOUS CONDITIONS**

### **1. Vertebral fracture**

The skeleton composes only 6-8% of the total body weight of the New Zealand white rabbit versus 12-13% of a cat's body weight. The bones of a rabbit are relatively fragile and fractures occur readily, especially with improper handling. Vertebral fractures are caused by improper handling leading to sudden, unsupported movement of the hindlimbs that causes fracture and less commonly vertebral luxation. Most fractures occur in the lumbosacral region, cause spinal cord damage, and produce paralysis and urinary incontinence.

### **2. Trichobezar**

Trichobezar or "wool block" are masses of hair and ingesta in the stomach that result from excessive self-grooming. They are common and are usually an incidental finding. Predisposing factors may include low fiber diets, experimental manipulation and stress. Trichobezars may cause complete or partial obstruction with subsequent gastric rupture and peritonitis. Anorexia and fatty liver can also be seen. Gastrotomy to remove the blockage may be required as a life-saving measure.

### **3. Barbering**

Barbering or hair chewing is most common in young and group housed rabbits. It is characterized by alopecia without dermatitis on the face and back. Boredom and low roughage diets are considered to be predisposing factors. The differential diagnosis for hair loss includes hair pulling for nests, behavioral problems, malnutrition, ectoparasites, dermatophytosis, bacterial infections, cage rubbing and seasonal molting.

### **4. Cataracts**

Spontaneous cataracts have been observed in New Zealand white rabbits during toxicologic studies as an incidental finding. An autosomal recessive mode of inheritance is suggested.

### **5. Urine scalding**

Urine scalding can occur as a result of the following problems: primary incontinence due to neurological conditions, conditions that prevent the rabbit from adopting a correct stance for urination, conditions that prevent normal grooming, calcium carbonate deposits in the bladder sediment, anatomical defects, poor husbandry and reproductive disease resulting in perineal inflammation. Secondary bacterial infection is common. Treatment is clipping and cleaning the affected area and antibiotics if needed.

## **6. Myocardial degeneration and necrosis**

Certain drugs including catecholamines and the anthracycline antibiotics have been reported to cause myocardial degeneration and necrosis in rabbits. There is a report of suspected myocardial damage due to the **administration of ketamine/xylazine anesthesia**. The authors believe it may be due to impairment of coronary blood flow due to coronary artery constriction with ischemia.

## **7. Prolapse of the Deep Gland of the Third Eyelid**

Prolapse of the deep gland of the third eyelid has been recently reported and appears clinically as a protrusion of a large tissue mass from the medial canthus of the eye. Histologically, the mass is composed of bilobated glands arranged in an alveolar-like pattern without inflammation. The cause is proposed to be abnormal laxity of the supporting connective tissue.

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## **NEOPLASTIC/PROLIFERATIVE DISEASES**

### **1. Reproductive System:**

**Uterine adenocarcinoma** is the most common spontaneous neoplasm of the rabbit. The incidence increases with age and nearly all breeds are affected. The role of estrogens is equivocal. Grossly, there are multiple,

nodular thickenings that protrude into the uterine lumen. Histologically, these thickenings are composed of acinar and tubular structures supported by a vascular myxoid stroma. There is serosal implantation and metastasis to the lung, liver, and regional lymph nodes. A **uterine choriocarcinoma** with metastasis to the lung and mesentery has been recently reported.

**Leiomyoma/leiomyosarcoma** has been reported as incidental findings at necropsy.

**Mammary carcinoma** has been reported frequently in laboratory rabbits. Cystic hyperplasia progresses to benign neoplasia with progresses to invasive adenocarcinoma. Metastasis is to the lungs and regional lymph nodes.

In the testis, **interstitial cell tumor** is the most common neoplasm. There is a single report of **gynecomastia associated with a testicular interstitial cell tumor** in a buck. Sertoli cell tumors and seminomas have also been reported. A testicular **granular cell tumor** in a pet rabbit has been reported.

## 2. Nervous System

**Pituitary adenoma** occurs in aged New Zealand white rabbits. Some secrete prolactin that can cause mammary gland hyperplasia and dysplasia. Rabbit mammary tissue is especially responsive to prolactin. Blood prolactin levels can be measured and pituitary glands can be imaged by computed tomography. There is a recent case report of a prolactin-secreting pituitary adenoma with development of a cystic mammary adenocarcinoma in a New Zealand white rabbit.

**Neurofibromas** and **neurofibrosarcomas** have been reported. As in other species, they are locally invasive and very difficult to completely surgically excise. Recurrence is common.

## 3. Musculoskeletal System:

**Osteosarcoma** is rarely reported in the rabbit. It can occur in the mandible, ribs, long bones and extraskeletal locations. As in other animals, metastasis is common and is usually to the lungs and lymph nodes. There is a single report of an extraskeletal fibroblastic osteosarcoma in a rabbit that occurred in the lip.

An **ossifying fibroma** was reported in the right maxillary region of a miniature rex rabbit.

## 4. Respiratory System:

**Mesothelioma** has been reported in the rabbit.

## 5. Gastrointestinal System:

**Bile duct adenoma** and **bile duct adenocarcinoma** have both been reported as incidental findings at necropsy. These neoplasms have minimal clinical significance.

A solitary **biliary hamartoma with cholelithiasis** was reported from a single transgenic New Zealand white rabbit.

#### **6. Urinary System:**

**Renal cell carcinoma** and **nephroblastoma** have been reported in the rabbits. Nephroblastoma or embryonal nephroma may be single or multiple and affect one or both kidneys. They are slow growing and are unlikely to metastasize.

#### **7. Hematolymphatic System:**

**Lymphoma** is most common in juvenile and young adult rabbits. It is typically the visceral form that involves the liver, spleen, and kidney, although rare localized forms have been reported. Occasionally, leukemia is present. At necropsy, there is lymphadenopathy, splenomegaly, and hepatomegaly with multiple, white circumscribed nodules. Histologically, the neoplastic cells are lymphoblastic. Both B-cell and T-cell types have been observed. There is a single report of a B-cell lymphoma in the Harder's gland of the rabbit.

**Thymoma** occurs in rabbits at a low incidence and is usually diagnosed at necropsy as an incidental finding, however, radiographic examination often reveals an anterior mediastinal mass with enlarged cardiac silhouette with pleural effusion. It may cause coughing, tachypnea, dyspnea and exercise intolerance. Thymomas have been associated with paraneoplastic syndromes such as myasthenia gravis, autoimmune disease, and hypercalcemia of malignancy, etc. Recently, exfoliative dermatitis was reported in a case of thymoma in a rabbit. There were many similarities seen with exfoliative dermatitis in cats secondary to thymoma.

#### **8. Integumentary System/Mesenchymal:**

**Trichoblastoma**, a benign cutaneous neoplasm of hair follicle origin is not uncommon. Viral-induced tumors include  **Shope fibroma** and **papilloma** were discussed under the virus section. **Squamous cell carcinomas, other hair follicle tumors, and sebaceous gland carcinoma** have also been reported.

**Lipoma, liposarcoma, myxosarcoma, fibrosarcoma, hemangiosarcoma** and **malignant melanoma** have all been reported.

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