PATHOLOGY OF THE RABBIT

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I. GENERAL

Classification
- Order Lagomorpha: Rabbits have an additional pair of incisor teeth directly behind the large incisors on the upper jaw.
- There are over 100 breeds of rabbits, which are descendants of the European wild rabbit, *Oryctolagus cuniculus*. The majority of rabbits used in biomedical research are of the New Zealand White breed.

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

Digestive System
- Rabbits are hind gut fermenters with a large and complex digestive system. They practice cecotrophy, which is the reingestion of mucous-coated night feces, which occurs daily, and is a method of recycling cecotrophs that are rich in B vitamins and proteins. Cecotrophy 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.
- Hematopoietic System
- Ear vessels are prominent and are readily accessible for blood collection.
- The erythrocyte measures 6.5-7.5 um in diameter; polychromasia is a normal finding; reticulocytes are 2-5% and the life span of the erythrocyte is 50 days.
- Heterophils are the counterpart of the neutrophil and measure 9-15 um in diameter and possess distinct, acidophilic cytoplasmic granules.
- Eosinophils measure 12-16 um in diameter and have large cytoplasmic granules that stain dull pink-orange with conventional hematology stains.
- Lymphocytes are usually the predominant leukocyte in circulation. Small lymphocytes measure 7-10 um in diameter and larger ones measure 10-15 um. Lymphocytes may contain a few azurophilic cytoplasmic granules.
• Basophils may be numerous and represent up to 30% of the circulating leukocyte population.

**Urinary System**

• 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.

• Hematuria may be seen in the following conditions: uterine adenocarcinoma, uterine polyps, episodic bleeding from endometrial venous aneurysms, cystitis, polyps in the urinary bladder, pyelonephritis or renal infarction with hemorrhage.

• Musculoskeletal System

• The skeleton comprises only 6-8% of the total body weight of a New Zealand White rabbit versus 12-13% of a cat’s total body weight.

• The bones are relatively fragile and fractures occur readily, especially with improper handling.

**Cardiovascular System**

• 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.
**VIRAL DISEASES**

**Poxviruses**

**Myxomatosi**

**General:** endemic in wild population; occurs occasionally in laboratory rabbits.

**Etiology:** Leporipoxvirus (closely antigenically related to rabbit fibroma virus)

**Transmission:** direct or indirect contact; also by arthropod vectors

**Pathogenesis:** following inoculation, a primary subcutaneous myxoid mass is present within 3-4 days. In 6-8 days, there is a mucopurulent conjunctivitis, subcutaneous edema and multiple subcutaneous masses. In the peracute syndrome, rabbits die suddenly and the only visible lesion is reddening of the conjunctiva. Recent studies have shown that leporipoxviruses may be immunosuppressive through down regulation of MCH Class I mediated antigen presentation as well as inhibition of tumor necrosis factor production. Myxoma virus also produces a serine proteinase inhibitor.

**Histopathology:** there is a proliferation of large, stellate mesenchymal cells termed 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 may be present in epithelial cells.

**Diagnosis:** gross lesions are highly suggestive; virus isolation.

**Fibromatosis (Shope Fibroma)**

**General:** relatively widespread disease in wild rabbits; regarded as a benign, self-limiting disease.

**Etiology:** Leporipoxvirus (antigenically related to hare and squirrel fibroma virus)

**Transmission:** mechanically through arthropod vectors

**Gross lesions:** firm, flattened subcutaneous, freely moveable, up to 7 cm diameter masses located primarily on the legs and feet, but also found on the muzzle and peri orbital and perineal areas.

**Histopathology:** 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.

**Differential:** Myxomatosis
**Rabbit Pox**

**General:**
A highly fatal, extremely contagious disease with rare outbreaks in laboratory colonies in the U.S. and the Netherlands.

**Etiology:**
Orthopoxvirus (a strain of *Vaccinia* virus).

**Pathogenesis:**
Viral infection of the respiratory tract followed by viremia with replication in lymphoid tissue and skin.

**Transmission:**
Direct contact/inhalation.

**Gross lesions:**
Localized to confluent papules in the skin, also papular lesions in the oropharynx, respiratory tract, spleen and liver.

**Histo:**
Focal necrosis with leukocyte infiltration and lymphoid necrosis.

**Diagnosis:**
Virus isolation and fluorescent antibody test.

**Papillomaviruses**

**Cutaneous Papillomatosis**

**General:**
A benign disease of wild rabbits with spontaneous outbreaks in domestic rabbits.

**Etiology:**
Papillomavirus.

**Transmission:**
Mechanical spread via insect vectors.

**Gross lesions:**
Cornified, pedunculated masses with fleshy central areas.

**Histo:**
Typical squamous papilloma.

**Oral Papillomatosis**

**General:**
Usually found in young rabbits, 2-18 months of age; lesions regress within a few weeks.

**Etiology:**
Papillomavirus.

**Transmission:**
Spread by direct contact in areas of oral abrasion.

**Gross lesions:**
Typical papillomas usually located along the ventral aspect of the tongue.

**Histo:**
Basophilic intranuclear inclusions in epithelial cells.

**Adenovirus**

Has been reported in commercial rabbit operations in Hungary. Causes enteritis with profuse diarrhea and dehydration in young rabbits with low mortality. High numbers of *E. coli* have been found in the small intestine and cecum in association with this viral infection, so it is speculated that *E. coli* plays some role in the disease.
**Parvovirus**

Has been isolated from large numbers of clinically normal rabbits in Japan and serological survey of laboratory rabbits in the United States have found relatively high antibody titers in large numbers of rabbits. Oral or intravenous inoculation may result in transient depression and anorexia with no mortality. This virus may be a complicating factor in interpreting research data. Its significance in the enteritis complex is unknown.

**Herpesviruses**

**Herpesvirus sylvilagus**

**General:** found in wild rabbits; proposed model for Epstein-Barr virus infection. Attempts to infect New Zealand White rabbits have been unsuccessful.

**Etiology:** Gamma herpesvirus

**Lesions:** juveniles are affected to a greater degree than adults are. Leukocytosis, monocytosis and lymphocytosis with myocarditis, interstitial pneumonia and lymphocytic myositis. Prominent lymphoid hyperplasia of nonlymphoid organs, including kidney and lungs.

**Herpesvirus-like infections**

Systemic infections have been observed in Canada. The disease has a sudden onset and infects rabbits of all ages. At necropsy, there are multiple hemorrhages and hydropericardium. Microscopically, there are necrotic foci in the spleen, adrenal glands, dermis and lung. Intranuclear viral inclusion bodies in the lung, dermis and spleen. Syncytial giant cells in the spleen.

**Herpes simplex**

Rabbits are susceptible; causes a necrotizing meningoencephalitis. Transmitted from human to rabbit.

**Rotavirus**

**General:** results in mild to severe diarrhea with high morbidity and varying mortality usually confined to suckling and weanling rabbits. Endemic in most commercial rabbitries. Rotavirus has been isolated from the intestinal contents of clinically normal rabbits and antibodies to the virus have been demonstrated in some animals. Copathogens such as *E. coli* and intestinal coccidia frequently play a significant role in this disease.

**Etiology:** Rotavirus, most common isolate is group A serotype 3

**Transmission:** direct contact with ingestion
Gross lesions: dehydration and a distended, congested cecum filled with fluid contents.

Histo: very similar to Coronavirus. Small intestine: villous atrophy, blunting, fusion and vacuolation to flattening of apical enterocytes in the jejunum and ileum with edema in the lamina propria and submucosa. Cecum: focal areas of desquamation with basophilic debris in the cytoplasm of affected enterocytes.

Diagnosis: ELISA or find virus on electron microscopy

Differential: Coronavirus, colibacillosis, coccidiosis and clostridial enteropathies.

Coronavirus

General: Coronavirus has been associated with pleural effusion disease and cardiomyopathy in laboratory rabbits and is used as a model of cardiomyopathy. The virus is antigenically related to human coronavirus strain 229E and it has been suggested that the rabbit virus is actually a human contaminant. Coronavirus has been associated with an epizootic of enteritis in young rabbits 3-8 weeks of age.

Transmission: Direct contact; carrier animals.

Gross lesions: a. Pleural Effusion Disease: pleural effusion, pulmonary edema, right-sided heart dilatation, peritoneal effusion, mesenteric lymphadenopathy, necrosis of liver, kidney, lung; iridocyclitis; and lymphoid depletion.

b. Cardiomyopathy: right-sided heart dilatation.

c. Enteritis: thin, dehydrated, fecal staining in perineal region. Distended cecum filled with watery, off white to tan feces.

Histopathology:

- Pleural Effusion Disease: lymphoid depletion of splenic follicles, focal degenerative changes in the thymus and lymph nodes, proliferative changes in glomerular tufts, and uveitis.

- Cardiomyopathy: focal to diffuse myocardial degeneration and necrosis, pulmonary edema, lymphoid depletion to hyperplasia, diaphragmatic muscular degeneration and necrosis.

- Enteritis: changes confined to small and large intestine and include villous atrophy, vacuolation and necrosis of enterocytes, mucosal edema and mixed inflammatory cell infiltrate.

- Diagnosis: Demonstration of viral particles by electron microscopy

- Differential diagnosis for myocardial necrosis:

- Hypovitaminosis E, Salmonellosis, Pasteurellosis, encephalitozoonosis, and anesthetic agents containing detomidine.
**Paramyxovirus**
Laboratory rabbits are susceptible to experimental infection by Sendai virus, but viral replication is confined to the upper respiratory tract and rabbits are asymptomatic.

**Calciviruses**

**Rabbit Viral Hemorrhagic Disease (RVHD)**

**General:** a peracute disease of adult rabbits that results in hepatic, enteric and lymphoid necrosis and a terminal massive coagulopathy. Devastating outbreaks have occurred throughout Asia, Europe and Mexico. The disease is newly established in Australia due to an accidental release of the virus.

**Transmission:** direct contact and via contaminated fomites. Carrier states are present. Virus is shed in the urine for up to 4 weeks and long term fecal shedding is possible. In Australia, insect vectors are suspected.

**Pathogenesis:** the virus has a predilection for hepatocytes where it replicates in the cytoplasm. Hepatic necrosis begins in periportal areas, then spreads to affect the entire lobule. In experimental infections, there is up to 90% mortality.

**Clinical signs:** seen only in rabbits older than 40-50 days of age. Sudden death, fever, depression, CNS signs, serosanguineous nasal discharge.

**Gross lesions:** Hepatomegaly, splenomegaly, hemorrhage and serosal ecchymoses.

**Histo:** Hepatic necrosis with polymorphonuclear cell infiltration, cryptal necrosis, pulmonary edema and hemorrhage and lymphocytolysis. Fibrin thrombi in small vessels of multiple organs.

**Diagnosis:** Detection of viral antigen through ELISA or hemagglutination test.

**Differential Diagnosis:** Severe bacteremias with disseminated intravascular coagulation, pulmonary pasteurellosis and enterotoxemias.

**European Brown Hare Disease**

**General:** An acute, contagious, highly fatal disease of European and varying hares that closely resembles RVHD.

**Transmission:** Direct, fecal-oral.

**Pathogenesis:** predilection for hepatocytes as in RVHD.

**Gross lesions:** Pulmonary congestion and edema, hepatic congestion and hemorrhages.

**Histo:** Periportal to massive coagulative and lytic hepatic necrosis, inflammation, fatty degeneration, cholangitis and intracytoplasmic
hepatocellular basophilic material. Less inflammation than in RVHD.

**Diagnosis:** Hemagglutination and ELISA tests

**Differential diagnosis:** see RVHD

**Rabbit Calcivirus**

A recently identified nonpathogenic virus that is most closely related to RHDV. This virus preferentially multiplies in the small intestine.
BACTERIAL DISEASES

Pasteurellosis

Etiology: Pasteurella multocida, a Gram negative, bipolar staining bacillus

General: Pasteurellosis is a major disease problem in the rabbit. In conventional, non-barrier maintained rabbitries, over 50% and up to 70% of the animals may harbor the organism in the upper respiratory tract and tympanic bullae. P. multocida causes a variety of clinical syndromes including chronic rhinitis (snuffles), otitis media, pneumonia (chronic purulent bronchopneumonia to acute fibrinous pneumonia), infections of the genital tract, abscessation, conjunctivitis and septicemia. There is a seasonal influence as most problems occur in the spring and fall. Concurrent infections with Bordatella bronchiseptica may occur; however, P. multocida is considered to be the primary pathogen. Predisposing factors include increased atmospheric ammonia, pregnancy, concomitant disease, environmental disturbances and experimental manipulation.

Transmission: Direct contact with animals shedding the organism from nasal or vaginal secretions. Sucking rabbits can be infected within the first week of life from nursing carrier does. Aerosols do not appear to be an important means of spread. Using a modified barrier system, rabbits can be maintained free of the organism even when housed in the same facility housing infected rabbits in other areas. Fomites may be involved; however, a large number of organisms are required for infection. Interspecies transmission has been experimentally reproduced.

Pathogenesis: The upper respiratory tract is regarded as the primary nidus of infection. The organism then spreads to other tissues; for example, to the lower respiratory tract by aerogenous routes; to the middle ear via the eustachian tube; hematogenously; local extension; and to the external genital tract by venereal spread or nasal inoculation. Some mucoid variants (have a hyaluronic acid capsule) of serotype A resist phagocytosis. Virulent type A strains also have the ability to adhere to mucosal epithelium, which is apparently mediated by fimbriae. Other mucoid variants as well as smooth variants (serotype D) are phagocytosed but resist killing. Some isolates of serotype D have been reported to produce a heat labile, dermonecrotic toxin, but the contribution of this toxin to the strain’s virulence is not known. Experimentally, it has been shown that P. multocida increases expression of vascular cell adhesion molecule 1 by aortic endothelium.

Clinical signs: Variable depending on the type of syndrome. May include chronic snuffles, purulent conjunctivitis, localized abscesses, respiratory difficulty, infertility and sudden death.

Gross lesions: a. Catarrhal to mucopurulent rhinitis
b. Atrophic rhinitis  
c. Otitis media – dull yellow to gray viscous exudate in tympanic bullae  
d. Chronic pneumonia – localized consolidation of the anteroventral lobes and atelectasis  
e. Acute fibrinous pleuropneumonia – fibrinohemorrhagic lobar pneumonia and pleuritis; +/- pericarditis and/or pyothorax  
f. Genital tract: pyometra, suppurative orchitis, abscesses, suppurative mastitis  
g. Localized abscesses in the brain, myocardium, testes, muscle, subcutis, etc.  
h. Peracute septicemia: congestion and hemorrhage

Histopathology:

Otitis media: squamous metaplasia of the lining epithelium with primarily heterophilic inflammation in the submucosa

Pneumonia: chronic bronchitis with peribronchial lymphocytic infiltration to alveolitis with primarily heterophilic infiltration. 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. Multinucleated giant cells may be present in affected alveoli.

Genital: acute, necrotizing transmural metritis and serositis. Suppurative orchitis with abscessation.

Septicemic: hemorrhage, variable thromboses of small vessels and focal degeneration of the liver and adrenal glands

**Acute suppurative meningoencephalitis**

**Diagnosis:** Confirm by bacterial culture

**Differential diagnosis:** *Bordatellois*, *Stapylococcosis*, and infection with *Klebsiella pneumoniae*

**Control:** Cull infected animals, good ventilation, establish a SPF colony, barrier housing, prophylactic antibiotic therapy and treatment of clinically affected animals. It may be difficult to cull all carriers because of false negative cultures.

**Stapylococcosis**

**Etiology:** *Stapylococcus aureus*. Most disease causing strains in rabbits are hemolytic, coagulase-positive, mostly type C strains.

**General:** Outbreaks occur sporadically in commercial and laboratory facilities and manifestation of disease ranges from localized abscessation to acute septicemia.

**Transmission:** Direct contact, aerosol. Carrier animals can harbor the organism in the upper respiratory tract. Possible entry sites include umbilical vessels and skin abrasions.
Pathogenesis: After inoculation, the organism can spread hematogenously or via local extension resulting in pyoderma, purulent mastitis, internal abscessation, septicemia and purulent bronchopneumonia. Pododermatitis or “sore hock” may occur in association with abscesses or mastitis.

Gross lesions: Suppurative lesions composed of a thick, purulent exudate can be found in the subcutis, mammary gland, genital tract, conjunctiva and the respiratory tract. Suppurative emboli can be found in the kidney, lung, brain and heart. With mastitis, the affected glands have swollen, red areas with induration of the overlying skin due to chronic abscessation. In pododermatitis, the swelling and exudate is usually concentrated along the ventral hock area.

Histo: Focal suppurative necrotizing lesions with colonies of cocci.

Diagnosis: Demonstrate Gram positive cocci on Gram-stained sections. Confirm by bacterial culture, but must determine if the isolate is a pathogenic strain (Beta hemolytic)

Differential diagnosis: Pasteurellosis, Tyzzer’s Disease and listeriosis.

Tyzzer’s Disease

Etiology: Clostridium piliforme. Gram-negative, motile, pleomorphic, 0.5 x 8-10 um, filamentous, spore-forming bacillus

General: An acute disease characterized by a sudden outbreak of profuse, watery diarrhea, a short course and high mortality in affected animals. Predisposing factors are important and include poor sanitation, stress and sulfonamide therapy. Many other species of laboratory animals and domestic animals are also affected; therefore, interspecies transmission must be prevented. Survivors can become chronically infected and serve as carriers.

Transmission: Direct via ingestion. Transplacental transmission is suspected in rabbits, but not proven. The organism can survive in soiled bedding for up to one year.

Clinical signs: Profuse, watery diarrhea with anorexia, dehydration and rapid death.

Gross lesions: Classic triad. If chronic, ileal stenosis.
Intestine: segmental necrosis that may be transmural, edema and hemorrhage
Liver: multifocal pale gray to red, 2mm foci of necrosis
Heart: pale gray to tan streaks in the myocardium

Histo:
- Intestine: intracellular bacilli in enterocytes and affected muscular layers with necrosis, fibrin, edema and hemorrhage
- Liver: foci of coagulative necrosis clearly delineated from unaffected tissue; intracellular bacilli within hepatocytes especially in areas bordering the necrosis
Heart: focal to segmental myocardial degeneration with mononuclear cell infiltration and bacilli within adjacent myocardial fibers

Diagnosis: Gross and histology. The bacilli can be readily demonstrated with Giemsa, periodic schiff acid and silver stains. Serology is also useful.

**Listeriosis**

**Etiology:** *Listeria monocytogenes*. Gram positive, motile, non spore-forming coccobacillus

**General:** Occurs sporadically as an epizootic in rabbitries. Characterized by 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.

**Pathogenesis:** This organism has tropism for the uterus and placenta.

**Transmission:** Ingestion (contaminated feed and water are possible sources) and transplacental infection.

**Gross lesions:** Multiple necrotic foci in the liver and spleen; lymphadenopathy; ecchymoses; acute metritis; hydrothorax; ascites; and anasarca.

**Histo:** Coagulative necrosis with polymorphonuclear cell infiltration.

**Diagnosis:** Bacterial culture.

**Treponematosis**

**Etiology:** *Treponema cuniculi*. Characteristic Gram-negative, 5-20 um, helical rods with tight or irregular spirals

**General:** The disease is also referred to as rabbit syphilis and vent disease and is common in wild hares. This disease occurs occasionally in conventional facilities and asymptomatic rabbits may be serologically positive.

**Transmission:** Venereal, although transmission through extragenital contact can occur. The organism can penetrate intact mucous membranes. Susceptibility is age and breed dependent.

**Gross lesions:** 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.

**Histo:** Lesion is confined to the epithelium and superficial dermis. Epidermal hyperplasia, epidermal cell necrosis, erosions and ulceration and infiltration by predominantly plasma cells and lymphocytes with fewer heterophils.

**Diagnosis:** Scrapings with wet mount preparation and examination under dark-field microscopy or in silver-stained tissue sections. Reagin antibody and fluorescent treponemal antigen test.
Differential diagnosis: *Pasteurella* sp. infections of the external genitalia and lesions due to trauma.

**Bordatelllosis**

**Etiology:** *Bordatella bronchiseptica*

**General:** The role of this organism in respiratory disease is not firmly established. It can be recovered from the upper and lower respiratory tract of healthy rabbits. In cortisone treated rabbits, suppurative bronchopneumonia has been reproduced experimentally and the organism has been isolated from natural cases of localized pneumonic lesions.

**Transmission:** Direct transmission by aerosol. *Bordatella bronchiseptica* may impair airway clearance mechanisms and facilitate establishment of *Pasteurella multocida*.

**Lesions:** Chronic interstitial pneumonia, chronic bronchiolitis and perivascular and peribronchial infiltrations.

**Diagnosis:** Bacterial culture. Organisms often present in large numbers.

**Cilia-Associated (CAR) Bacillus**

**Etiology:** CAR bacillus, a Gram negative, 0.2 x 6-8 um, motile, non-sporeforming bacillus. The strain that infects rabbits is closely related to *Helicobacter* sp.

**General:** Infection in rabbits is nearly always subclinical and the significance in rabbits is not really known. This organism colonizes the epithelial cells that line the larynx, trachea and bronchi. Isolates that infect mice and rats are host-specific and do not infect rabbits.

**Lesions:** Usually none. Chronic tracheitis with goblet cell hyperplasia.

**Diagnosis:** Demonstrate organisms with silver stains.

**Salmonellosis**

**Etiology:** *Salmonella typhimurium* and *Salmonella enteriditis*, Gram negative, non-sporeforming bacilli.

**General:** Causes rare infections that result in septicemia, diarrhea, abortions and death.

**Transmission:** Direct by the fecal-oral route.

**Clinical signs:** Depression, fever, +/- diarrhea.

**Lesions:** Acute form: Polyserositis, focal hepatic necrosis, splenomegaly, enteritis with fibrinous exudate and suppurative metritis. Peracute form: congestion and hemorrhages.
Diagnosis: Bacterial culture.

**Yersiniosis (Pseudotuberculosis)**

**Etiology:** *Yersinia pseudotuberculosis*, Gram negative, pleomorphic, motile, coccobacillus.

**General:** Results in acute to chronic infection of wild rabbits and rodents. Occurs rarely in domestic rabbits.

**Transmission:** Direct by ingestion of contaminated food and water. Wild rodents and birds carry the organism.

**Clinical signs:** Nonspecific; poor condition and weight loss.

**Lesions:** Caseous necrosis in the liver, spleen, cecum, lymph nodes and occasionally reproductive tract.

**Diagnosis:** Large numbers of coccobacilli within necrotic areas in tissue sections; confirm with culture.

**Bacterial Mastitis**

**Etiology:** *Staphylococcus, Pasteurella multocida, Streptococcus* sp.

**General:** Another term is “blue breast”. Occurs occasionally in recently kindled and heavily lactating does.

**Transmission:** Orphan young can spread disease to an unaffected doe; infection can spread to multiple mammary glands.

**Lesions:** The skin overlying the mammary glands has a red to dark blue discoloration; the gland contains serous to purulent exudate; nursing young may develop an acute fatal septicemia.

**Diagnosis:** Clinical signs and confirm with culture.

**Other Bacterial Diseases**

*Pseudomonas aeruginosa* can produce moist dermatitis. *Streptococcus* sp. causes septicemia in young rabbits. Acute diplococcal infections have been observed rarely. *Klebsiella pneumoniae* is an occasional causative agent of acute hemorrhagic bronchopneumonia. *Arcano (Corynebacterium) pyogenes* and *Fusobacterium necrophorum* have been reported to cause suppurative and ulcerative skin lesions.

**Enteritis Complex**

**Mucoid Enteropathy (Mucoid Enteritis)**

**Etiology:** Multifactorial; one or combinations of bacteria, toxins, dietary irregularity and/or obstruction are suggested.

**General:** A major cause of disease and mortality in young rabbits. This disease can be reproduced experimentally by ligating sections of
the large intestine. It is a subacute, frequently fatal disease, characterized by the passage of copious quantities of gelatinous mucus with feces. Rabbits 7-10 weeks of age are most often affected; however, rabbits aged between 5-20 weeks may also be affected.

Pathogenesis: It is suggested that an alteration in the cecal environment results in the production of a goblet cell secretagogue by an undetermined bacterium. The secretagogue is absorbed through the cecal mucosa and is transported to the colon where it exerts its effect.

Clinical signs: Anorexia, polydypsia and subnormal temperature in addition to the abnormal feces.

Gross lesions: Gastric distention by fluid and gas; distention of the jejunum by translucent, watery fluid; cecal impaction by dry contents and gas; distention of the sacculated colon by the characteristic clear, gelatinous mucoid exudate.

Histo: Striking goblet cell hyperplasia in the jejunal, ileal and colonic mucosa with minimal or no inflammation. In the colon, the crypts and lumen are distended with mucus and mucus plugs. There are minimal to absent lesions in the cecum. Goblet cell hyperplasia of the gallbladder and mild nephrosis has been described.

Diagnosis: Characteristic histologic appearance. Demonstrate goblet cells with periodic acid schiff or alcian blue stains.

Differential diagnosis: Any infectious or management problem that results in disruption of normal microbial environment (coccidiosis, clostridiosis, trichobezars or constipation).

Carbohydrate Overload

It is theorized that low fiber, high starch diets fed to young animals results in high concentrations of starch in the cecum and colon which may result in the proliferation of *E. coli*, *Clostridium perfringens*, or *Clostridium spiroforme*. Bacterial toxins produced during the fermentation process may damage the mucosal surface and cause movement of water and electrolytes into the lumen, resulting in diarrhea and dehydration followed by death.

**Clostridiosis**

**Etiology:** The species implicated in the enteritis complex include *Clostridium perfringens*, *C. difficile*, and *C. spiroforme*. All are Gram positive, anaerobic bacilli. *C. spiroforme* produces a type E iota toxin.

**General:** *C. spiroforme* is the most common clostridial pathogen associated with the enteritis complex in juvenile rabbits. Infections occur commonly in rabbitries. At necropsy of diarrheic rabbits, it was isolated from over 50% of the cases, and of those, 90% of the strains isolated were toxigenic in one study. *C.*
**perfringens** causes an enterotoxemia-like condition in young rabbits that results in cecal hemorrhage and edema. *C. difficile* causes colitis in rabbits following prolonged therapy with penicillin and ampicillin.

**Pathogenesis:** The normal gut flora acts as a microbial barrier and any disruption of this barrier (feed changes, weaning, antibiotic therapy, and concurrent infections) allows colonization and proliferation of the organism with subsequent toxin production. It is not uncommon to find another pathogen such as *E. coli*, *Eimeria* sp., *Cryptosporidia*, or rotavirus present as a coinfection.

**Clinical signs:** Peracute form: death, with little or no signs. Chronic: anorexia, wasting and intermittent diarrhea over several days.

**Gross lesions:** Peracute: The carcass is in good body condition with perineal soiling. Subacute to chronic: thin and dehydrated carcass; staining of the ventral abdomen, perineum and rear legs with watery green to tarry brown feces; straw colored peritoneal effusion; ecchymoses in 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.

**Histo:** 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.

**Diagnosis:** History, including management practices and age may be helpful. Histology and identification of the bacteria in sections and on smears of intestinal contents. Confirm by anaerobic bacterial culture. An assay to identify the toxin in cecal contents is available.

**Differential diagnosis:** Coccidiosis, Tyzzer’s disease, and colibacillosis.

**Colibacillosis**

**Etiology:** attaching and effacing (enteropathogenic) strains of *Escherichia coli*.

**General:** *E. coli* is a major cause of enteritis in commercial rabbitries and is occasionally a problem in research facilities. The organism is not normally present or is present in small numbers within the gastrointestinal tract of suckling and weanling rabbits. When a change in intestinal pH occurs, there is a rapid proliferation of the bacteria. Factors that promote this growth are intestinal
coccidiosis and diets that require a high hydrochloric acid content for digestion. The isolated stains are enteropathogenic (cause intestinal disease, but do not produce enterotoxins). Some strains affect only suckling rabbits and attach to the full length of the small and large intestine, while other stains affect weanlings only and attach only to the ileum and large intestine.

**Pathogenesis:** The organism colonizes and attaches to the Peyer’s patch dome epithelium then later colonizes and attaches to enterocytes. Intestinal lesions are most severe at 7-14 days postinoculation.

**Gross lesions:** Dehydrated carcasses, perineal staining with watery, yellow to brown fecal material. The small intestine is usually grossly normal. The cecum and colon may be distended with watery yellow to gray-brown contents. May see serosal ecchymoses, edema in the cecal and colonic walls and enlarged mesenteric lymph nodes. In the very young, the stomach will be full of undigested milk.

**Histo:** Changes are most severe and extensive in weanlings. Villi in the ileum are blunted; there is edema in the lamina propria with heterophilic infiltration. The enterocytes at the villar tips are swollen with attached bacilli.

**Diagnosis:** History and gross and microscopic lesions are suggestive. Culture and characterization of the organism.

**Differential:** Acute coccidiosis, clostridiosis, viral enteridities, Tyzzer’s disease and mucoid enteropathy.

**Vibriosis**

*Vibrio* sp. has been associated with typhlitis with degeneration and hyperplasia of cryptal epithelial cells. Organisms can be identified within epithelial cells by silver stains. The rabbit can be successfully used as an animal model to study attenuated *Vibrio cholera* immunogenicity through development of ileal loops and intraduodenal inoculation.

**Proliferative Enteropathy**

**Etiology:** *Lawsonia intracellularis*, a 0.2 x 1.5 um, slightly curved, bacillus.

**General:** Causes a diarrhea with mortality in suckling, weanling and adult rabbits. The disease is similar to that in hamsters and pigs. The bacterium that causes disease in rabbits is antigenically and genetically similar to the bacteria that produces disease in other species.

**Gross lesions:** Semi-fluid, mucinous contents in the colon and rectum.

**Histo:** 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 polymorphonuclear cell infiltration. The proliferative form is characterized by multifocal to diffuse
enterocyte hyperplasia and hyperplasia of crypt and villar epithelium with infiltration by mononuclear inflammatory cells.

**Diagnosis:** Demonstrate organisms within enterocytes by silver stains.
PROTOZOAL DISEASES

Intestinal Coccidiosis

Etiology: *Eimeria* sp. The species considered to be the most pathogenic in the rabbit are *intestinalis* and *flavescens*. The following are considered to be moderately pathogenic: *magna*, *irresidua* and *piriformis*. The following are considered to be the least pathogenic: *perforans*, *neoleporis* and *media*.

General: Coccidiosis is a common, widespread problem in commercial operations and research facilities. It is an important economic and complicating disease. Coccidia may act as a copathogen in other infections. As with the other causes of enteritis, changes in management practices such as feeding or experimental procedures can predispose to infection and disease.

Transmission: Fecal-oral. After passage in the feces, the oocysts require one or more days to sporulate. After the sporulated oocysts are ingested, sporozoites are released which invade enterocytes and multiply via schizogony. One or more sexual cycles (depending on the species) takes place, then gametogony occurs and oocysts are formed and passed in the feces.

Pathogenesis: Clinical disease occurs most frequently in weanlings. The stage that causes the most damage is the sexual stage that results in extensive destruction of enterocytes and other cells within the lamina propria.

Clinical signs: None to acute, profuse, watery, green diarrhea.

Gross lesions: The cecum and colon contain dark green to brown, watery, foul smelling material. The mucosa is congested and edematous.

Histo: Location of the lesions is dependent on the species involved. Destruction of enterocytes, villous atrophy, marked heterophilic infiltration and presence of gametocytes and oocytes.

Diagnosis: Fecal flotation or mucosal scrapings with microscopic examination for oocysts. Bacterial culture should also be performed, as there are often coinfections.

Differential: Colibacillosis, Tyzzer’s disease, clostridiosis, viral enteridities and mucoid enteropathy.

Hepatic Coccidiosis

Etiology: *Eimeria stiedae*.

General: This disease occurs in both wild and domestic rabbits and results in poor weight gains, clinical disease and even death in affected colonies. Weanlings are most often affected; older rabbits develop immunity.
Transmission: After ingestion of sporulated oocysts, sporozoites penetrate intestinal epithelial cells then are transported to the liver where they invade epithelial cells lining bile ducts 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.

Pathogenesis: None to anorexia, debilitation, constipation or diarrhea. May also see hepatomegaly, pendulous abdomen, icterus and death. Elevated liver enzymes and serum bilirubin on clinical pathology.

Hepatomegaly with multifocal, raised, yellow to pearl grey, circumscribed, 0.5-2 um foci which contain an inspissated dark green to tan material. The gallbladder mucosa is thickened and filled with viscid green bile and debris.

Bile duct hyperplasia with ectasia, papillary projections covered by reactive epithelial cells and gametocytes and oocysts. Periportal fibrosis and mixed inflammatory cell infiltrate.

Diagnosis: Oocysts are present in gallbladder aspirates or impression smears. Histology is pathognomic.

Encephalitozoonosis (Nosematosis)

Etiology: *Encephalitozoon cuniculi*, an oval, 1 x 2 um, Gram positive, obligate intracellular microsporidian with a characteristic coiled polar filament in the mature spore stage.

General: Encephalitozoonosis is widespread in domestic rabbits and is probably the most common spontaneous microsporidian in animals. In rabbits, infection is usually subclinical and can be a complicating factor with interpretation of laboratory data. In heavy infections, nervous system disease and death may result. Dwarf rabbits are especially susceptible to infection.

Transmission: Ingestion of contaminated urine. Transplacental infection occurs, as does infection by inhalation of spores.

Pathogenesis: The polar filament is extruded and penetrates host cell membranes. The sporoplasm is injected through the tube into the host cell without contact with the external environment. The spores are spread hematogenously via macrophages. They selectively parasitize vascular endothelium, especially in the brain and kidney, as well as renal tubular epithelium. The spores localize in the liver, lungs, adrenal glands, spleen and other highly vascular organs. Intracellularly, the spores are contained within a parasitophorous vacuole or pseudocyst and are termed trophozoites or schizonts, which multiply via ordinary fission or schizogony. When the trophozoites (schizonts) mature, they become sporonts, then sporoblasts and then eventually spores. With time the pseudocyst becomes overcrowded and ruptures. Spores are released and infect adjacent cells. Spores are spread
to the urine through infected renal epithelial cells. The life cycle is complete in 3-5 days.

**Gross lesions:** Lesions are usually confined to the kidneys and consist of focal, irregular, depressed, pale areas, 2-4 mm in diameter on the renal cortical surface. In severely affected kidneys, lesions may coalesce with adjacent foci.

**Histo:** Kidney: focal to segmental, granulomatous to chronic interstitial nephritis with tubular ectasia and spores within tubular epithelial cells, macrophages, in areas of inflammation or free within collecting tubules. Central nervous system: focal nonsuppurative, granulomatous meningoencephalitis with astrogliosis and perivascular lymphocytic cuffing. In dwarf rabbits, uveitis with cataractous change has been reported.

**Diagnosis:** Characteristic lesions and demonstration of Gram positive spores. Spores stain a distinct purple color with carbol fuchsin stain and also stain well with giemsa.

**Differential:** *Toxoplasma gondii. E. cuniculi* stains poorly with hematoxylin and eosin (H&E) and is Gram positive; *T. gondii* stains well with H&E and stains poorly with a Gram stain. Spores of *E. cuniculi* are birefringent.

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**Toxoplasmosis**

*Toxoplasma gondii* rarely causes clinical disease in laboratory rabbits. Areas of multifocal necrosis, granulomatous inflammation and tachyzoites and tissue cysts are present in the lung, liver and spleen.

**Cryptosporidiosis**

*Cryptosporidium parvum* has been identified in the small intestine of rabbits and is a rare primary cause of enteritis. It is usually identified as an incidental finding and can cause villous blunting, a decrease in crypt-villous ratio and edema.
HELMINTH DISEASES

Oxyurisosis (Pinworms)

Etiology: *Passalurus ambiguus.*

General: A fairly common occurrence in rabbitries; animals are usually asymptomatic, but occasionally, diarrhea occurs.

Transmission: Direct. Adults are present in the cecum and colon and larvae are present on the mucosa of the small intestine and cecum.

Diagnosis: Fecal flotation. Eggs are morulated and are slightly flattened on one side.

Baylisascariasis

This disease is caused by infection with *Baylisascaris procyonis* and is a problem of wild rabbits and/or pet rabbits housed outdoors. Infection results from accidental contamination of feed by infective raccoon feces. This is primarily a disease of the central nervous system but lesions (migration tracts) can also be seen in visceral tissues such as heart, liver and kidney. Diagnosis is by identification of the parasite, which has prominent lateral alae, in tissue sections.

Cestodiasis

This disease is primarily a problem of wild rabbits and outdoors pet rabbits. Rabbits are the intermediate host while the definitive host may be a canid or felid. May see a cysticercus (*Taenia pisiformis*) in the liver, mesentery, etc. or a coenurus (*Taenia serialis*) in the subcutis and underlying skeletal muscle. Several species of adult tapeworms can be found in the small intestine of wild rabbits; the life cycles are not well known, but orbatid mites or ants are suspected to be intermediate hosts.

Other

*Obeliscoides cuniculi* is a trichostrongyle found in the stomach of rabbits that graze fresh grass or are fed fresh grass as a feed.
ECTOPARASITES

Aural Acariasis (Ear Mites)
Etiology: *Psoroptes cuniculi*
General: Ear mites are the most common and costliest ectoparasite infection of rabbits.
Transmission: Direct contact. The mite spends its entire life span in the external ear. Severely affected ears may have up to 10,000 mites. The mite may survive off the host in crust material for up to 21 days.
Pathogenesis: The mite is a nonburrowing parasite that chews and pierces the epidermis of the external ear. The incited inflammatory reaction is suggestive of an IgE mediated type I hypersensitivity reaction.
Gross lesions: Light brown, thick, crusty, foul smelling exudate within the external ear canal and pinnae. The skin beneath the crusts is alopecic and erythematous. Self-excoriation may lead to secondary bacterial infections.
Histo: Hyperkeratosis, inflammation and parasites and eggs.
Diagnosis: Mites are easily demonstrated on swabs of material.

Cheyletiellosis (Fur Mites)
Etiology: *Cheyletiella parasitovorax*
General: No clinical signs or mild alopecia without pruritus.
Transmission: Direct contact. The entire life cycle is spent on the rabbit.
Gross lesions: Alopecia, scaliness and crusts, especially over the dorsal trunk and scapular areas.
Histo: Mild hyperkeratosis with mononuclear cell infiltration.
Diagnosis: Skin scrapings to find the mite.

Other Mites
Sarcoptic mange due to *Sarcoptes scabei* and *S. cuniculi* as well as *Notoedres cati* occur rarely and result in alopecia and dermatitis involving the face, nose, lips and external genitalia.
MYCOTIC INFECTIONS

**Dermatophytosis (Ringworm)**

**Etiology:** *Trichophyton mentagrophytes, Microsporum canis* and *M. gypseum*.

**General:** Infections are relatively uncommon. Rabbits may serve as inapparent carriers and infection can be transmitted from human handlers to rabbits. The young and immunocompromised are most susceptible.

**Transmission:** Direct contact.

**Gross lesions:** Raised, circumscribed, erythematous areas on the head and ears that may spread to the paws.

**Histo:** Hyperkeratosis, epidermal hyperplasia, folliculitis and arthrospores.

**Diagnosis:** Skin scrapings from the periphery of lesions cleared in 10% KOH solution will reveal arthrospores. Methenamine silver and PAS stain the arthrospores well in section.

**Aspergillosis**

Pulmonary aspergillosis due to *Aspergillus fumigatus* and *A. flavus* are occasionally found at necropsy. Lesions are characterized by circumscribed nodules with a central area of necrosis surrounded by mononuclear cells and multinucleated giant cell macrophages. Fungal hyphae are best demonstrated with silver of PAS stains.
NUTRITIONAL AND METABOLIC DISEASES

**Vitamin E Deficiency**
Nutritional problems are rare due to quality control standards; however, problems may arise when diets are individually formulated. Clinically, there is muscular soreness and stiffness, neonatal mortality and infertility. Gross necropsy lesions include pale steaks in skeletal and cardiac muscle. Histologic lesions include myofiber degeneration and necrosis with mineralization and histiocytic inflammation.

**Hypervitaminosis D**
Rabbits are very sensitive to vitamin D toxicosis and toxicity can result from levels as little as five times normal. Adults are more sensitive than younger rabbits. Clinical signs are non-specific 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 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, which is highly cellular with many active osteoblasts.

**Hypo and Hypervitaminosis A**
Clinical manifestations are similar and include poor conception rates, congenital anomalies, fetal resorption, abortion and birth of thin, weak kits.

**Pregnancy Toxemia**
This disorder occurs in does usually during the last week of pregnancy. Primiparous, obese animals on high planes of nutrition that suddenly become anorexic 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.

**Atherosclerosis**
The Watanabe rabbit has been extensively used as an animal model of natural endogenous hypercholesterolemia. 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, reduced plasma high-density lipoprotein concentrations and increased plasma concentrations of apolipoprotein E. The lesion is very similar to that in people, but does not progress to advanced or complicated lesions. However, dietary modifications such as the addition of fats to the diet can produce lesions more similar to those in humans. Hypercholesterolemia can also be induced experimentally in rabbits by feeding a high cholesterol diet and/or producing arterial injury by balloon catheter.
CONGENITAL DEFECTS

**Congenital Glaucoma (Buphthalmia)**
This condition occurs occasionally in New Zealand White rabbits and is inherited in an autosomal recessive pattern. One or both eyes may be affected. Enlargement of the globe due to increased intraocular pressure as a result of the absence or underdevelopment of the outflow channels with incomplete cleavage of the iridocorneal angles characterizes buphthalmia.

**Malocclusion**
Malocclusion is very common among all breeds of rabbits and is inherited in an autosomal recessive pattern. 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.

**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.

**Endometrial Venous Aneurysms**
These are considered to be a congenital defect characterized by multiple blood filled endometrial varices that consist of dilated, thin walled veins that rupture and bleed periodically into the uterine lumen.
NEOPLASMS

Uterine Adenocarcinoma
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 in development of this neoplasm 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 most commonly to the lung and liver.

Lymphosarcoma
Lymphosarcoma is seen most commonly in juvenile and young adult rabbits and is typically the visceral form involving the liver, spleen and kidney. Occasionally, leukemia is present. At necropsy, there is lymphadenopathy, splenomegaly and hepatomegaly with multiple, white circumscribed nodules. Histologically, the cells are usually of the lymphoblastic type.

Pituitary Adenoma
Prolactin secreting pituitary adenomas in aged New Zealand White rabbits cause mammary gland dysplasia. Histologically, the glands have cystic areas lined by reactive epithelial cells with papillary projections extending into the cystic lumina. Blood prolactin levels can be measured and will be elevated.

Thymoma
Thymomas occur in rabbits at a low incidence and are usually diagnosed at necropsy. Clinically, they 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. There is a report of a successful surgical removal of a thymoma in a rabbit.

Transplantable Neoplasms
There are a few transplantable neoplasms that have been studied in rabbits and these include Vx2 carcinoma, Brown-Pearce carcinoma, Greene melanoma, Dos Santos hepatoma, Kato sarcoma, Andrewes rabbit sarcoma I and Kondrateva osteogenic sarcoma.

Other Neoplasms
Several other neoplasms occur spontaneously in the rabbit and include fibroma, squamous cell carcinoma, teratoma, renal carcinoma, nephroblastoma, leiomyoma and leiomyosarcoma, mammary gland adenoma and adenocarcinoma, osteosarcoma, hemangioma and hemangiosarcoma, fibroma and trichoblastoma. Interstitial tumors are probably the most common neoplasm of the testes in rabbits.
MISCELLANEOUS CONDITIONS

Vertebral Fracture
Vertebral fracture results from improper handling leading to sudden, unsupported movement of the hind limbs which causes fracture and less commonly vertebral luxation. Most fractures occur in the lumbosacral region, cause spinal cord damage and produce paralysis.

Trichobezars
Trichobezars 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.

Barbering
Barbering or hair chewing is most common in young; group housed rabbits and 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 problem, malnutrition, ectoparasites, dermatophytosis, bacterial infections, cage rubbing and seasonal molting.

Prolapse of the Deep Gland of the Third Eyelid
This has been recently reported and clinically appears 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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