# Syllabus

## VETERINARY PATHOLOGY DEPARTMENT, AFIP
## WEDNESDAY SLIDE CONFERENCE
## 1992-1993

129 microslides
50 lantern slides

Prepared by

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# PREFACE

The Registry of Veterinary Pathology, Armed Forces Institute of Pathology, has conducted the Annual Wednesday Slide Conference Program for more than three decades. The cases presented each Wednesday throughout the academic year are distributed to more than 100 active participants, including military and civilian veterinary pathologists throughout the United States and Canada, as well as other British Commonwealths, and Far Eastern and European nations. The diagnosis, comments, a synopsis of the discussion, and references for each case are forwarded to participants weekly. Our list of active contributors continues to grow.

This study set has been assembled in an effort to make the material presented at our weekly conferences available to a wider circle of interested pathologists and other scientists.

This set, composed of 120 cases, 129 microslides and 50 lantern slides, was assembled from the cases studied during the 1991-1993 conferences.

We wish to thank each contributor for his or her participation and for the permission to use cases in this study set. We also wish to give special thanks to the American Veterinary Medical Association, the major sponsor of the Registry of Veterinary Pathology.

## LIST OF SLIDES

| Slide # | Animal | Tissue | Diagnosis |
|---|---|---|---|
| 1 | Pig | brain | *Actinobacillus Equuli* |
| 2 | Bovine | gall bladder, liver | *Salmonella dublin* |
| 3 | Cat | Lung, spleen | *Cytauxzoon felis* |
| 4 | Rat | spinal cord | Chordoma |
| 5 | Horse | brain | Nigropallidal Encephalomalacia |
| 6 | Elk | spinal cord | Enzootic ataxia |
| 7 | Sheep | brain, cerebral cortex | Polioencephalomalacia |
| 8 | Pig | liver | Hepatosis dietetica |
| 9,L1 | Horse | small intestine | Lymphosarcoma: large granular lymphocyte |
| 10 | Horse | hoof wall | Laminitis, chronic |
| 11 | Horse | pancreas | Eosinophilic granulomatosis |
| 12 | Horse | placenta | Cystic adenomatous hyperplasia of allantois |
| 13 | Gerbil | liver | *Bacillus piliformis* |
| 14 | Dog | brain | Canine distemper |
| 15 | Rat | ear | Zymbal's gland carcinoma |
| 16,L2 | Lagomorph | small intestine | Campylobacter-like organism |
| 17 | Dog | small intestine | *Clostridium perfringens* |
| 18 | Dolphin | mammary gland | *Crassicauda grampicola* |
| 19 | Dog | cecum | Carcinoid |
| 20 | Cat | kidney | *Histoplasma capsulatum* |
| 21 | Mouse | pancreas | Pancreatic hyperplasia and fibrosis (TGF-alpha) |
| 22 | Rat | kidney | Hyalin droplet nephropathy and tubular cell dysplasia |
| 23 | Primate | colon | *Balantidium coli* |

## LIST OF SLIDES

| Slide # | Animal | Tissue | Diagnosis |
|---|---|---|---|
| 24,L3,4 | Mouse | heart | Hemangiosarcoma |
| 25 | Pig | lung | Swine infertility and respiratory syndrome (SIRS) virus |
| 26 | Bison | esophagus | Malignant catarrhal fever |
| 27 | Bovine | lung | *Haemophilus somnus* |
| 28 | Pig | kidney | Ricin toxicity with disseminated intravascular coagulation |
| 29 | Cat | subcutis | Vaccine-induced panniculitis |
| 30,L5 | Primate | brain, cerebrum | Astrocytoma |
| 31 | Dog | lung | Lymphomatoid granulomatosis |
| 32 | Dog | spinal cord | Spinal myelinopathy of hounds |
| 33,L6 | Mouse | liver, spleen | Granulocytic leukemia |
| 34,L7 | Primate | liver | Leptospirosis |
| 35,L8 | Mouse | liver | Cryptosporidium |
| 36 | Primate | pancreas | *Trichospirura leptostoma* |
| 37 | Horse | brain | Eastern equine encephalitis virus |
| 38 | Emu | liver, spleen | Eastern equine encephalitis virus |
| 39,L9, 10 | Opposum | lung, pancreas | *Mycobacterium avium* |
| 40 | Nutria | brain | Rabies |
| 41 | Rat | ear | Auricular chondritis |
| 42 | Dog | kidney, liver | Canine adenovirus Type 1 |
| 43,L11 | Dog | kidney | Renal cell carcinoma |
| 44 | Bovine | small intestine | *Yersinia pseudotuberculosis* |

## LIST OF SLIDES

| Slide # | Animal | Tissue | Diagnosis |
|---|---|---|---|
| 45,L12, 13,14 | Bovine | liver | Pyrrolizidine toxicity |
| 46 | Dog | nasal mucosa | *Rhinosporidium seeberi* |
| 47 | Dog | lung | Mesothelioma |
| 48,49 | Rat | heart, pericardium | *Streptococcus pneumoniae* |
| 50,51, L15,16 | Primate | stomach | *Helicobacter pylori* |
| 52 | Primate | lung | Retroperitoneal fibromatosis |
| 53 | Penguin | lung, liver | *Plasmodium* sp. |
| 54 | Goat | mammary gland | Caprine arthritis and encephalitis |
| 55 | Hedgehog | lung | *Cryptococcus neoformans* |
| 56 | Rat | fibroadipose tissue | Hibernoma, malignant |
| 57 | Lagomorph | brain | *Encephalitozoon cuniculi* |
| 58,L17 | Pig | uterus | Cystic endometrial hyperplasia |
| 59 | Horse | heart, myocardium | African horse sickness |
| 60 | Horse | kidney | *Halicephalobus deletrix* |
| 61 | Fish | gill | Branchitis, proliferative and histiocytic |
| 62,63 | Fish | head kidney | *Mycobacterium* sp. |
| 64 | Bovine | brainstem | *Neospora caninum* |
| 65 | Bovine | lung | *Dictyocaulus viviparus* |
| 66,L18, 19 | Bovine | skin, bone marrow | Congenital dyserythropoiesis |
| 67 | Bovine | liver | Bacillary hemoglobinuria |
| 68,L20, 21 | Primate | lung | *Coccidioides immitis* |
| 69 | Dog | uterus | Subinvolution of placental site |

## LIST OF SLIDES

| Slide # | Animal | Tissue | Diagnosis |
|---|---|---|---|
| 70 | Primate | kidney | Nephroblastoma |
| 71 | Primate | liver | *Entamoeba histolytica* |
| 72,L22, 23,24 | Dog | skin, liver | Superficial necrolytic dermatitis |
| 73,74, L25 | Primate | lung | Aspiration pneumonia: mineral oil |
| 75 | Dog | lung, kidney | Canine herpesvirus |
| 76,L26 | Horse | stomach | Cantharidin toxicity |
| 77 | Primate | lung | *Staphylococcus aureus*, *Pneumonyssus simicola* |
| 78 | Beaver | liver, lung | *Francisella tularensis*, Tularemia |
| 79 | Cat | lung | Feline herpesvirus type 1 |
| 80 | Dog | heart | *Prototheca* sp. |
| 81,82 | Chicken | heart | *Listeria monocytogenes* |
| 83,L27 | Pheasant | cecum, liver | *Heterakis isolonche*, amyloidosis |
| 84 | Parakeet | heart | *Leucocytozoon* sp. |
| 85,L28, 29 | Sarus crane | liver | Leiomyosarcoma |
| 86,L30 | Lagomorph | lung | *Pseudomonas aeruginosa*, *Klebsiella* |
| 87 | Dog | esophagus | *Spirocerca lupi* |
| 88 | Bovine | mammary gland | *Nocardia asteroides* |
| 89 | Mouse | mammary gland | Adenocarcinoma: mouse mammary tumor virus |
| 90 | Primate | tibia | Vitamin C deficiency: myelofibrosis |
| 91 | Rat | tibia | Osteosarcoma |
| 92,L31, 32 | Dog | bone | Hypertrophic osteodystrophy |

## LIST OF SLIDES

| Slide # | Animal | Tissue | Diagnosis |
|---|---|---|---|
| 93,L33, 34 | Bovine | mandible | Aneurysmal bone cyst |
| 94,L35, 36 | Dog | heart, coronary arteries | Atherosclerosis |
| 95 | Koala | eye, palpebral conjuctiva | *Chlamydia psittaci* |
| 96 | Bovine | bone marrow, spleen, red pulp | Leukocyte adhesion deficiency |
| 97,L37, 38 | Pig | ovary | Hemangioma |
| 98,99 | Cat | kidney | Amyloidisis, familial renal |
| 100 | Cat | liver | Hypereosinophilic syndrome |
| 101, L39,40 | Mouse | ovary | Teratoma |
| 102 | Cat | liver | Cholangiohepatitis lymphoplasmacytic |
| 103 | Dog | haired skin | Lymphoma, intravascular |
| 104 | Bovine | haired skin | Bovine herpesvirus-2: pseudolumpy skin disease |
| 105, 106 | Cat | haired skin, subcutis | Dermatophytic mycetoma |
| 107 | Pig | haired skin | Zinc deficiency: parakeratosis |
| 108, L41,42 | Snake | liver | Boid inclusion disease |
| 109 | Elephant | heart | Encephalomyocarditis virus |
| 110 | Shrimp | hepato-pancreas | Necrotizing hepatopancreatitis |
| 111 | Iguana | heart, great vessels | Metastatic mineralization ateriosclerosis |
| 112 | Dog | brain, cerebrum | Rocky mountain spotted fever |

## LIST OF SLIDES

| Slide # | Animal | Tissue | Diagnosis |
|---|---|---|---|
| 113, L43,44, 45 | Primate | brain, cerebrum | Morbillivirus encephalitis |
| 114, 115 | Bovine | brain, brainstem | Bovine spongiform encephalopathy |
| 116, L46,47 | Horse | Brain, cerebrum | Borna disease virus |
| 117 | Dog | kidney | Fanconi-like syndrome |
| 118 | Dog | small intestine | Lymphangiectasia |
| 119 | Horse | fibroadipose tissue | Calcinosis circumscripta |
| 120 | Dog | small intestine | Minute virus of canines, canine parvovirus-2 |
| 121 | Dog | lung | Pulmonary alveolar microlithiasis |
| 122 | Bovine | lung | Bovine respiratory syncytial virus |
| 123 | Cat | heart | Endomyocarditis |
| 124 | Dog | lung | *Pneumocystis carinii* |
| 125 | Bovine | teat | Foot and mouth disease |
| 126, 127,L48 | Killer Whale | brain, uterus | Zygomycosis |
| 128, L49,50 | Lagomorph | spleen, lung | Herpesvirus |
| 129 | Dog | stomach | Granulosa cell tumor |

# COMMENTARY ON SLIDES

Microslide 1

**History.** An approximately 8-week-old male Yorkshire pig was submitted for necropsy. The owner had recently purchased 625 pigs from a feeder pig sale and had lost 6 pigs with similar clinical signs. Affected pigs developed ataxia, tremors, and recumbency with death occurring within 24 hours after the onset of signs. The pigs were housed in a barn maintained at 60°F. and fed a 12.5% ration containing corn and soybean meal.

**Gross Pathology.** Both stifle joints, the right coxofemoral joint, the left carpal joint, the right scapulohumeral joint, and the atlanto-occipital joint contained large amounts of yellow opaque fluid with fibrin. A large yellow thrombus was adherent to the left atrioventricular valve.

**Laboratory Results.** Actinobacillus equuli was obtained from two joint swabs, cerebrospinal fluid, lung, and the valvular thrombus. Pasteurella multocida was also recovered from the lung. Virus isolation attempted on lung and spleen was negative.

**Contributor's Diagnosis and Comments.** 1. Brain, cerebrum, meningoencephalitis, suppurative, acute, disseminated, due to Actinobacillus equuli.
2. Bacteremia, due to Actinobacillus equuli.

Numerous microabscesses are dispersed throughout the brain and were evident within all levels examined at necropsy. The majority of microabscesses were found in grey matter, yet were also evident in white matter. A few sections contained vascular thrombosis and necrosis within a pia-arachnoid vessel; the thrombus contained numerous bacteria. Microgliosis and focal white matter vacuolization with macrophages were noted in a few sections. Additional changes seen in the other organs included a suppurative arthritis, multifocal suppurative nephritis, fibrinopurulent endocarditis, and a suppurative bronchopneumonia.

Actinobacillus equuli is a rare cause of septicemia in young pigs. Septicemia occurs rapidly with pigs dying within a few hours to a few days after infection. A variety of lesions can be seen and include renal petechiae, hemorrhagic lesions in the lung, polyserositis, and valvular endocarditis. Actinobacillus equuli must be distinguished from Actinobacillus suis which also causes acute septicemia in pigs. Colonies of A. equuli are nonhemolytic and become viscous as they age. A. equuli also differs from A. suis in producing acid from mannitol but not from arabinose, cellobiose, and salicin. A. equuli also does not split esculin.

**AFIP Diagnosis.** 1. Brain, cerebrum: Meningoencephalitis, acute, multifocal, moderate, with vasculitis, thrombosis, and intravascular colonies of coccobacilli, Yorkshire, porcine.

**Conference Note.** Participants reviewed the differential diagnosis of septicemic bacterial disease in pigs including Haemophilus parasuis, Streptococcus suis, Salmonella cholerasuis and Erysipelothrix rhusiopathiae. While not considered as common, Actinobacillus suis, and A. equuli have also been isolated from sporadic outbreaks of acute septicemia in swine. Pigs from herds that have had no previous exposure to the organism are thought to be more susceptible. A comparison was drawn between this case and the more commonly seen A. equuli infection in horses.

Actinobacillus equuli is a small, gram-negative, nonmotile, rod-shaped organism. It is part of the normal intestinal microflora of horses. In this species, it is considered an opportunist and a frequent cause of suppurative embolic nephritis and arthritis in young foals, as well as in animals debilitated by parasitism or stress. In contrast to earlier publications, recent reports have questioned any role that horses might play in the transmission of A. equuli to pigs.

**Contributor.** C. E. Kord Animal Disease Laboratory, P.O. Box 40627, Melrose Station, Nashville, TN 37204.

**References.**

1. Cutlip RC, Amtower WC, Zinober MR: Septic embolic Actinobacillosis of swine: A case report and laboratory reproduction of the disease. Am J Vet Res, 1972, 33:1621-1626.

2. Miniats OP, Spinato MT, Sanford SE: Actinobacillus suis septicemia in mature swine: Two outbreaks resembling erysipelas. Can Vet J, 1989, 30:943-947.

3. Taylor DJ: Miscellaneous bacterial infections. Disease of Swine, 6th ed. Leman AD, et al, Eds., 1986, Iowa State University Press, Ames, IA; pp 627-645.

4. Timmoney JF, Gillespie JH, Scott FW, Barlough JE: The genus Actinobacillus. Hagan and Brunner's Microbiology and Infectious Diseases of Domestic Animals, 8th ed., 1988, Comstock Publishing Associated, Ithaca, NY; pp 125-131.

Microslide 2

**History.** A feedlot with 7,000 Holstein calves experienced high death losses in 2-3 month old calves. There was acute onset with few clinical signs noted. Usually, the calves were found dead.

**Gross Pathology.** The livers were mottled with multifocal, 1-2 millimeter, pale foci. The gallbladder wall was

edematous and the lumen contained a large fibrin clot.

**Laboratory Results.** A pure growth of Salmonella dublin was recovered from the liver, small intestine, spleen and gallbladder.

**Contributor's Diagnosis and Comments.**
1. Cholecystitis, chronic active, diffuse, severe, gallbladder, Holstein, bovine.
2. Hepatitis, necrotizing, subacute, multifocal, mild, liver.

The feedlot receives day old Holstein calves from Oregon & California. They are held in large mixed groups at a staging area before being trucked to a feedlot in central Arizona.

Heavy winter rains this year provided wet conditions in the feedyard and contributed to the outbreak. The presence of large fibrin clots in the gallbladder, edema of the gallbladder, and multifocal white foci in the liver are gross lesions highly suggestive of Salmonella dublin infection.

**AFIP Diagnosis.**
1. Gallbladder: Cholecystitis, necrotizing, subacute, diffuse, severe.
2. Liver: Hepatitis, necrotizing and histiocytic, subacute, multifocal and random, mild.

**Conference Note.** Gram-negative coccobacilli were noted within a few of the larger hepatic vessels in some sections. Bovine salmonellosis primarily involves serotypes S. typhimurium, S. enteritidis, or S. dublin. In calves, salmonellosis is a serious and frequently fatal disease characterized by fever, diarrhea, dehydration, and neutropenia. Grossly, enteric salmonellosis can vary from a catarrhal to hemorrhagic enteritis, commonly associated with a fibrinous pseudomembrane on the mucosal surface. Typically, the ileum is the most severely affected segment of the enteron. Subsequent to the bacteria invading the mucosal surface, salmonella can become septicemic, resulting in mesenteric lymphadenopathy, fibrinous cholecystitis, and numerous small foci of necrosis within the liver and spleen. Necrotic areas eventually form histiocytic foci known as "paratyphoid nodules". More chronic infections often cause an anterior bronchopneumonia.

Salmonellae possess several virulence factors that contribute to the development of diarrhea and septicemia. Adhesion pili facilitate the organism's attachment to mucosal surfaces. The presence of flagella on salmonellae is associated with greater intracellular survival in macrophages. Cytotoxins present in the bacteria's outer cell wall are thought to chelate cations such as calcium and magnesium. This can result in permeability changes in the cell membrane and selective leakage

of molecules. The severe diarrhea often seen in salmonellosis is due to the production of enterotoxins that bind to the enteric mucosal epithelium. Lipopolysaccharide (LPS) and it's various structural components are also very important to the pathogenicity of salmonellae. LPS consists of the O-side chain, a core protein, and a lipid A portion. Most of the endotoxin-mediated effects are attributable to the lipid A portion.

Salmonellae reside in the gallbladder and intestinal tract of carrier animals. Recent studies on dairy farms in this country have shown that there is asymptomatic sporadic shedding of Salmonella sp. by dairy calves; this may pose a zoonotic risk to dairy farm employees and consumers of unpasteurized milk.

**Contributor.** University of Arizona Veterinary Diagnostic Laboratory, 2831 N. Freeway, Tucson, AZ 85705.

**References.**

1. Barker IK, Van Dreumel AA: In: Pathology of Domestic Animals, 1985. Ed: KVF, Jubb Kennedy PC and Palmer N. Academic Press, Orlando FL. Vol 2 pp 33-36.

2. Lance S.E., et al, Salmonella infections in neonatal dairy calves, JAVMA, 1992;201:864-868.

3. Murray M.J., Salmonella: Virulence factors and enteric salmonellosis, JAVMA, 1986;189:145-147

Microslide 3

**History.** 10-year-old male domestic shorthair, feline. This cat was found in a pasture in a near comatose state and was submitted to a local veterinarian. Hemorrhage was noted in the sclera of the left eye. Cat was found dead in the cage the next morning.

**Gross Pathology.** Widespread petechial and ecchymotic hemorrhages in lung, heart, and small intestine. Lymph nodes were very congested and hemorrhagic.

**Contributor's Diagnosis and Comments.** Intravascular histiocytosis with intracellular protozoa, lung, spleen, feline. Feline cytauxzoonosis.

The submitting veterinarian forwarded several tissues including heart, kidney, lymph node, and intestine in addition to the tissues included for the WSC. In virtually all tissues the vasculature contained numerous large cells with intracellular protozoa consistent with Cytauxzoon felis. A second cat was found ill and died within 24 hours. Similar gross and microscopic lesions were also observed in this second cat. In domestic cats cytauxzoonosis is a rapidly fatal disease. Based

on experimental studies, wild felidae are thought to be the natural host.

**AFIP Diagnosis.** Lung and spleen, vessels: Histiocytosis, intravascular, diffuse, severe, with intrahistiocytic protozoa, Domestic Shorthair, feline.

**Conference Note.** The unique histomorphologic appearance and pathogenesis of this organism were discussed. As in this case, the presence of prominent, large schizont-containing phagocytic cells within and often occluding the lumen of vessels in the lung and spleen was considered pathognomonic. Cytauxzoon is a genus of protozoan parasites in the family Theileriidae, which also contains Theileria and Gonderia. Theileriidae are characterized by having a schizogenous tissue phase as well as an intraerythrocytic phase. Cytauxzoon differs from other members in this family in that schizonts are found in mononuclear phagocytes rather than lymphocytes.

Cytauxzoonosis is known to occur in numerous species of domestic and wild ungulates in Africa, as well as feral felidae (bobcats) in the southern United States. The domestic cat is considered to be a dead-end host because of the rapidly fatal course of the disease. Natural transmission of the organism is thought to involve ticks. Infected cats become febrile with signs typical of an acute hemolytic anemia (depression, generalized pallor and icterus). Gross lesions include; splenomegaly, large edematous mesenteric lymph nodes, ecchymotic hemorrhages in the lung and other viscera, and distended abdominal vessels.

Feline blood smears containing the erythrocytic phase of Cytauxzoon must be differentiated from other erythroparasites with similar clinical signs (Haemobartonella felis). H, felis is characterized by multiple coccoid bodies around the periphery of the red blood cell. Cytauxzoon are generally single organisms within the erythrocyte having a signet ring-like appearance.

**Contributor.** Texas Veterinary Medical Diagnostic Laboratory, P. O. Box 3200, Amarillo, TX 79116-3200.

**Reference**

1. Cowell RL et al: Feline cytauxzoonosis. Compend Contin Educ, 1988, 6:731-734.

2. Bendele RA et al: Cytauxzoonosis-like disease in Texas cats. Southwestern Vet, 1976, 29:244-246.

3. Glenn BL et al: Cytauxzoonosis in bobcats. J Am Vet Med Assoc, 1983, 183:1155-1158.

4. Kier AB et al: Experimental transmission of Cytauxzoon felis from bobcats (Lynx rufus) to domestic cats (Felis domesticus). Am J Vet Res, 1982, 43:97-101.

5. Kier AB et al: Interspecies transmission of Cytauxzoon felis. Am J Vet Res, 1982, 43:102-105.

6. Simpson CF et al: Ultrastructure of schizonts in the liver of cats with experimentally induced cytauxzoonosis. Am J Vet Res, 1985, 46:384-390.

7. Wagner JE: A fatal cytauxzoonosis-like disease in cats. J Am Vet Med Assoc, 1976, 168:585-588.

Microslide 4

**History**. This H & E section is from a 1-year-old, male, Sprague-Dawley rat. This control animal was killed because of weight loss, posterior paresis, and abdominal distention.

**Gross Pathology**. The lumbosacral spinal column has a bilobed, white to tan, firm, 3.8 x 2.5 x 2.0 cm nodule that is invasive to the sublumbar musculature. The colon and rectum were distended.

**Contributor's Diagnosis and Comments**. Chordoma.

The incidence of chordomas in this laboratory is very low (<0.5 percent). Chordomas are locally invasive neoplasms that originate from the embryonic notochord. Microscopically, this tumor contains the characteristic large round to oval clear or vacuolated cells that are partially separated by a thin fibrous stroma. The differential diagnosis for this case included liposarcoma and chondrosarcoma.

**AFIP Diagnosis**. Mass in the lumbosacral area: Chordoma, Sprague-Dawley rat, rodent.

**Conference Note**. Comparative aspects of chordomas were discussed. Chordomas have been reported in humans, ferrets, rats, mice, dogs and mink. In humans and rats chordomas are uncommon; they occur more frequently in males (2:1 and 3:1 ratio, respectively); they arise predominately from the lumbosacral vertebral area; and they are characterized as locally destructive, slow growing neoplasms that commonly metastasize to the lungs and other organs. In ferrets, chordomas occur primarily in females (2:1 ratio); they are located on the tip of the tail; and there are no reported instances of metastasis.

Chordoma can be differentiated from chondrosarcoma by it's immunohistochemical characteristics. Chordomas express both cytokeratin and vimentin positivity, while chondrosarcomas are cytokeratin negative. Chordomas are also variably positive for neuron specific enolase and S-100 protein; the latter is related to the presence of stromal glycosaminoglycans of the chondroitin sulfate type.

**Contributor**. Merck Research Laboratories, Safety Assessment, WP 45-212, West Point, PA 19486.

**References.**

1. Dunn D.G., et al: A Histomorphologic and Immunohistochemical Study of Chordoma in Twenty Ferrets (Mustela putorius furo), Vet Pathol 28:467-473 (1991)

2. Stefanski S.A., et al: Chordomas in Fischer 3444 Rats, Vet Pathol 25:42-47 (1988)

Microslide 5

**History.** This 6-year-old Appaloosa, female equine was in a pasture with a 3-month-old colt at her side, and several other horses. The animal developed a sudden clinical onset with severe and erratic signs including erratic walking or sleepy idleness. There was an apparent difficulty with prehension, mastication and swallowing. The body temperature remained normal. Approximately 10 days with no improvement, the owner elected to have the animal euthanized.

**Gross Pathology.** Necropsy was performed by the attending veterinarian and only the brain was submitted to the diagnostic laboratory. Examination of the brain displayed discrete, sharply demarcated, roundly elongated yellowish-buff colored areas in the globus pallidus and substantia nigra. These lesions were present in both hemisections (bilateral).

**Contributor's Diagnosis and Comments.** Focal encephalomalacia. Microscopically, the areas (that were observed grossly) show necrosis and malacia with pyknosis and karyolysis of neuroglial nuclei; degeneration of neurons and scattered spheroids. There is a sharp boundary with adjacent normal tissue and macrophages are accumulating at the junction. Some sections display intralesional hemorrhage.

Etiology: These alterations are consistent with yellow star thistle (centaurea solsitialis) or Russian Knapweed (centaurea repens) toxicosis.

Inspection of the pasture where the horses were grazing revealed a large percentage of the plants to be Russian Knapweed. The toxin in Centaurea plants has not been identified, however prolonged ingestion of these plants until an apparent threshold is exceeded results in the lesions appearance. The exact mechanism is unknown.

**AFIP Diagnosis.** Brain, brainstem: Necrosis, focally extensive, severe, with hemorrhage, Appaloosa, equine.

**Conference Note.** The appearance of a well-demarcated area of necrosis within the extrapyramidal nuclei of the brainstem was considered characteristic for nigropallidal encephalomalacia. Conference participants estimated the lesion to be approximately 5 to 10 days old, based on the presence of

numerous debris-filled histiocytes (gitter cells) and the few remaining degenerating neurons within the necrotic focus. The survival of many of the capillaries within the area may represent a variation in sensitivity among different cell types to the unknown toxic principle.

Nigropallidal encephalomalacia occurs in horses following prolonged consumption of Centaurea plants. Clinically, hypertonia of the lips, tongue and facial muscles result in the animal's inability to eat or drink. Ruminants can ingest the plant without ill effect. Gross lesions can be unilateral or bilateral and are usually limited to focal areas of malacia in the substantia nigra and/or globus pallidus of the brainstem.

**Contributor**. Animal Disease Diagnostic Laboratory, Utah State University, Logan, UT 84322-5600.

**References**.

1. Cordy DR: Centaurea species and equine nigropallidal encephalomalacia. Effects of poisonous plants or livestock, edited by Keeler RK, Vankampen KR, James LF, Academic Press, pp 327-336, 1978.

2. Farrell RK, Sande RD, Lincoln SD: Nigropallidal encephalomalacia in a horse. J Am Vet Assoc, 1971, 158:1201-1204.

3. Innes JRM, Saunders LZ III: Nigropallidal malacia in horses in California associated with ingestion of Yellow Star Thistle. Comp Neuropathol, Academic Press, pp 613-614, 1962.

4. Sullivan ND: The Nervous System Chpt. 3, Pathology of Domestic Animals, 3rd Ed. Vol. 1, Edited by Jubb KVF, Kennedy PC, Palmer N. Academic Press, pp 258, 1985.

Microslide 6

**History**. This 6-year-old female Roosevelt Elk (Cervus elaphus) had been unable to stand for about two months and would fall down when she tried to move. One other animal previously demonstrating similar symptoms was subsequently killed by a bull elk. A third animal was also weak in the hind end.

**Gross Pathology**. The animal is in fair to good body condition and demonstrates no significant gross alterations.

**Laboratory Results**. Liver copper levels - 5 ppm (weight); approximates level of 20 ppm dry weight (=5-57 ppm wet wt.) recorded in cases of enzootic ataxia in wapiti in New Zealand.

**Contributor's Diagnosis and Comments**. Spinal cord: Leukomalacia, diffuse, severe, Roosevelt elk, cervid.

All sections of the spinal cord are affected by

bilateral, extensive demyelination, with naked axons and axonal spheroids which predominate in the descending fibers. Significant microscope alterations were not detected in sections of cerebrum, cerebellum, medulla or midbrain. Publications associate this condition in red deer and elk (wapiti) with marginal or deficient copper reserves, as were present in this case. Copper supplementation appears to prevent clinical evidence of enzootic ataxia in deer. Elk are born with adequate copper reserves, but when placed on a deficient diet, depletion results in clinical signs in young adults. In sheep, enzootic ataxia occurs in the newborn and young; congenital disease results in major cerebral alterations whereas spinal demyelination is a feature of delayed onset. The specific pathogenesis of enzootic ataxia in elk is not well defined.

**AFIP Diagnosis**. Spinal cord, lateral and ventral funiculi: Axonal degeneration, diffuse, severe, with dilated myelin sheaths.

**Conference Note**. Some sections also contain degenerative changes in the ventral horn nuclei. Microscopically, spongy degeneration of the spinal cord white matter is a nonspecific change that can pose difficulties in interpretation. A similar histologic lesion can result from various demyelinating conditions, congenital hypomyelinogenesis, intramyelinic edema, or a Wallerian-type degeneration from primary neuronal injury. Special stains such as luxol fast blue and Bodian's can be helpful in further evaluating the presence of myelin and the extent of axonal injury in these lesions.

As a trace element, copper is essential in the formation of numerous metalloenzymes which are involved in such diverse functions as: the uptake and transfer of iron to transferrin molecules (ceruloplasmin); hemoglobin synthesis (aminolevulinic acid); mitochondrial production of ATP (cytochrome c. oxidase); the synthesis of certain neurotransmitters (dopamine-beta-hydroxylase); normal cross-linkage of elastin and collagen fibers (lysyl oxidase); and the synthesis of melanin pigment (tyrosinase). Thus, copper deficiency can result in various abnormalities of the nervous, skeletal, hematopoietic and integumentary systems. The pathogenesis of the lesion seen in enzootic ataxia is not clear. It is thought that decreased cytochrome c. oxidase levels within oligodendrocytes may result in insufficient mitochondrial ATP production necessary for phospholipid synthesis and normal myelin maintenance.

**Contributor**. Animal Health Centre, B.C. Ministry of Agriculture, Fisheries and Foods, Box 100, Abbotsford, B.C., Canada V2S 4N8.

**References**.

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Microslide 7

**History**. A 4-month-old crossbred ewe lamb was received into the quarantine facility of the National Institutes of Health Ungulate Unit. On day five of quarantine, the animal was anorectic, unresponsive, and had a stiff legged stance. Upon physical examination, the animal was found to be blind, with decreased rumen sounds, and facial twitching. Despite supportive treatment (calcium gluconate, Vitamin B complex, dexamethasone, and sodium bicarbonate) the lamb progressed to recumbency and convulsions. Treatment consisted of sodium bicarbonate, ketamine, and ice packs (to reduce a fever of 106°F). The following day, the animal remained blind and anorectic. She also exhibited head pressing and teeth grinding. The animal was euthanized with an overdose of barbiturates and submitted for necropsy.

**Gross Pathology**. No significant findings at gross necropsy.

**Laboratory Results**. At necropsy, CSF and brain stem were collected and submitted for bacterial cultures. Listeria isolation was attempted from the brain stem. No bacteria were cultured from the CSF; cold enrichment of the brain stem failed to yield Listeria monocytogenes. Pseudomonas species and Staphylococcus species were cultured from the brain stem but are considered contaminants.

**Contributor's Diagnosis and Comments**. Cerebral cortex: Neuronal degeneration, multifocal, laminar, moderate, with associated vacuolar change of the neuropil, endothelial cell hypertrophy, and meningeal edema.
Condition: polioencephalomalacia.

Polioencephalomalacia (PEM) is a disease of unknown etiology affecting the central nervous system of ruminants. Affected ruminants usually exhibit anorexia, blindness, muscle tremors which may progress to convulsions, opisthotonos, purposeless chewing movements, and occasionally hyperthermia. Young ruminants, weanling to two years old, are most at risk; breed and sex predilections are not recognized. Polioencephalomalacia occurs most frequently in the late fall - early winter and it is more severe in feedlot animals versus

those pastured. Lesions consist of laminar cortical necrosis, predominantly affecting the middle to deep layers of the cerebral cortex and are usually bilaterally symmetric. Differential diagnoses for PEM include listeriosis, lead toxicity, the dumb form of rabies, nitrofuran toxicosis, hypomagnesemia, hypovitaminosis A, chlorinated hydrocarbon toxicosis, infectious thromboembolic meningo-encephalitis, type D enterotoxemia, and brain abscesses.

Historically, PEM has been attributed to thiamine deficiency, based on the following evidence: the occurrence of similar conditions in monogastrics caused by thiamine deficiency, the ability of thiamine injections to alleviate the neurologic signs of PEM, reports of lowered blood thiamine levels and decreased activity of thiamine co-factors in ruminants with PEM. However, recent studies indicate that a high sulfate diet may be the cause of the laminar cortical necrosis and suggest that thiamine may serve to attenuate clinical signs. In a study performed by Rousseaux et. al., sheep fed a high sulfate diet developed PEM, while those on a low sulfate diet did not. The high sulfate group was subdivided, with half receiving thiamine supplementation and half receiving a thiamine deficient diet. While both groups had typical histologic PEM lesions, only the group fed the thiamine deficient diet manifested neurologic signs. One proposed pathogenesis is that dietary sulfate is metabolized in the rumen into a toxic metabolite, which is absorbed systemically, producing its toxic effect in the brain. Several researchers have reported smelling hydrogen sulfide gas in the rumens of animals suffering from PEM. Ruminants may inhale as much as 60% of the eructated rumen gases; inhalation of hydrogen sulfide, a known cellular toxin, may cause the characteristic cerebral necrosis. Lending further support to this theory is that animals that have succumbed to pit gases, composed primarily of hydrogen sulfide, also exhibit laminar necrosis of the cerebrum. Other investigators speculate that the role of dietary sulfate is to modulate thiamine levels, either by acting as an anti-metabolite of thiamine or by altering the rumen microflora to favor the growth of thiaminase producing bacteria. The mechanism of the laminar cerebral necrosis remains unresolved.

**AFIP Diagnosis**. Brain, cerebral cortex: Necrosis, laminar, multifocal, moderate

**Conference Note**. The extent and severity of the lesions varied among different sections. In addition to the differentials listed by the contributor, cerebral anoxia and certain nerve agents can produce similar laminar necrosis.

Theories on the pathogenesis of PEM were discussed. Thiamine deficiency is a well documented cause of CNS lesions in carnivores, usually restricted to the thalamus, caudate nucleus, inferior colliculi, and central nucleus of the cerebellum. Thiamine is an essential cofactor for transketolase activity in

the pentose shunt pathway and for normal carbohydrate oxidation on which the nervous system depends for energy production. In ruminants, high-concentrate low-forage diets result in ruminal acidosis with a proliferation of thiaminase-producing bacteria and a subsequent thiamine deficiency. The laminar distribution of necrosis seen in ruminants with PEM is distinctly different from the lesions seen in thiamine deficient carnivores, although the mechanism for this is not clear.

Recent studies implicating excess dietary sulphur in the pathogenesis of PEM have shown that thiamine metabolism may be more indirectly involved. The toxic effects of high dietary sulphur appears to be unique in ruminants. Sulphate in the rumen is metabolized to toxic sulphur-derived free radicals which are absorbed systemically and postulated to cause membrane injury via lipid peroxidation. Brain tissue, with it's high lipid content, is thought to be the target organ. Free thiamine appears to have a sparing effect, possibly by acting as a scavenger of these toxic metabolites.

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Microslide 8

**History**. The owner had 3-4 finishing or near-finishing pigs from a 10-sow operation die in the past year; some with sudden death, and others that exhibited labored breathing before death. Some would recover, but would perform poorly. The deaths coincided with a change in feed one year earlier from discarded dog food from a commercial plant to food scraps from a restaurant. This pig died 12 hours after onset of respiratory distress.

**Gross Pathology**. The liver was dark red and lobules were sharply defined. There was irregularity in size of the lobules and in the surface of the liver. The lung had dark red firm areas in the cranial lung lobes. No gross lesions were seen in other organs, including heart and skeletal muscle.

**Laboratory Results**. Liver selenium levels were 470 parts per billion (deficient = 100-350 ppb, adequate = 1,400-2,800 ppb). In addition to liver lesions, there was some vacuolation and fragmentation of skeletal muscle fibers, but not of heart muscle. A Pasteurella species was isolated from the lung. The stomach mucosa was atrophied in some areas and contained numerous lymphocytes and a few neutrophils.

**Contributor's Diagnosis and Comments**. Diffuse massive hepatic necrosis and hemorrhage with moderate periportal fibrosis, nutritional.

The history and gross and microscopic lesions were consistent with hepatosis dietetica. Liver analysis showed marginal amounts of selenium were present, indicating that other factors, such as vitamin E deficiency, may have played a role in the pathogenesis.

Massive hepatic necrosis is defined by destruction of entire liver lobules. In addition to vitamin E/selenium deficiency in pigs, it has been observed in heart failure, heatstroke, administration of various drugs and endotoxemia in various species and in coxsackie B virus infection in mice and hepatitis B virus infection in humans. Fibrinoid degeneration of arterioles can be seen in some cases of hepatosis dietetica and necrosis may result from vascular injury to the liver lobule. Although massive hepatic necrosis has been observed in some cases of heart failure, hepatosis dietetica can be observed with or without myocardial or skeletal muscle lesions due to vitamin E/selenium deficiency (mulberry heart disease, nutritional myopathy).

**AFIP Diagnosis**. Liver: Necrosis, lobular, submassive, moderate to severe, with hemorrhage

**Conference Note**. In arriving at a morphologic diagnosis, the term submassive was preferred to massive (ie complete) due to a rim of viable hepatocytes remaining at the periphery of most

lobules. In addition to those listed by the contributor, differential diagnoses in this species includes iron-dextran poisoning, cresol poisoning, and plant-derived acute hepatotoxins such as gossypol, and Xanthium (cocklebur).

Vitamin E and selenium perform similar biologic functions as natural antioxidants in the body. Vitamin E scavenges free radicals formed both intra and extracellularly, reducing lipid peroxidation damage of membranes. Selenium is an important constituent of glutathione peroxidase, which is also involved in blocking the propagation of lipid peroxidation reactions. Deficiencies in one or both of these antioxidants can lead to excessive free radical production and peroxidative damage to cell membranes. This damage leads to an influx of extracellular calcium into the cytosol, and subsequent disruption of normal cellular functions. Other lesions commonly associated with Vitamin E and/or selenium deficiency in pigs include skeletal and cardiac muscle necrosis (white muscle and mulberry heart disease), steatitis (yellow fat disease), and serous effusions (edema)

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**References**.

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Microslide 9, Lantern Slide 1

**History**. This 15-year-old, Arabian gelding was euthanitized after a 7 month course of diarrhea, weight loss, depression, and weakness.

**Gross Pathology**. There was marked loss of muscle mass and mild subcuticular edema along the sternum. Bowel walls were thickened, particularly involving the small intestine. The mucosa of affected areas was thickened, raised, smooth and tan to white. GALT was raised and often ulcerated. The gross photo included illustrates a section of ileum with GALT. Multifocal linear red erosions were noted in the mucosa of the jejunum and ileum. Mesenteric, cecal and colic lymph nodes were enlarged.

Both kidneys had pale tan cortices.

**Laboratory Results**. Total protein = 3.7 g/dl; calcium = 8.8 mg/dl; fecal culture: negative for Salmonella; albumin = 1.3 g/dl; globulin = 2.4 g/dl; fecal parasitic exam: negative. Oral glucose tolerance test: markedly decreased glucose absorption.

Peritoneal fluid analysis: Smears revealed macrophages, neutrophils and a large population of large granular lymphocytes (LGL). LGL were about 15 um in diameter with a moderate amount of lightly basophilic cytoplasm. Many of these cells had a cluster of large azurophilic granules. Granules varied somewhat in size and some appeared to be located within a vacuole. Nuclei were round to indented and often eccentric. Nuclei had a coarse chromatin pattern lacking obvious nucleoli.

Special stains: Cytoplasmic granules of neoplastic cells did not stain with toluidine blue, stained variably with PAS, and stained dark blue to black with PTAH.

**Contributor's Diagnosis and Comments**. Ileum, malignant lymphoma.

Microscopic examination of the gastrointestinal tract in this case revealed infiltration of neoplastic cells throughout the small intestine, cecum, large colon and small colon. Esophagus and stomach were spared. Tumor cell infiltration was generally limited to the lamina propria of the mucosa and the submucosa in most areas of the bowel, except in areas of GALT, where tumor cell infiltration was transmural. Tumor cell infiltration was also seen in the mesenteric, cecal and colic lymph nodes and within the renal cortices.

Horses are affected with malignant lymphoma less frequently than are cattle, dogs and cats, but malignant lymphoma appears to be one of the leading causes of neoplasm-related death in the horse. Clinical diagnosis of lymphoma in the horse is often difficult because the clinical manifestations in the equine species is extremely variable. Malignant lymphoma in the horse has been classified into the following four groups based on presumptive sites of tumor development: multicentric, alimentary, thymic and cutaneous. The incidence of the alimentary type of lymphoma in the horse is generally uncommon. The clinical signs of a alimentary lymphoma are primarily referable to malabsorption and disturbances of alimentary function. Diarrhea is a variable, but not frequent, clinical presentation. A retrospective study of equine alimentary lymphoma revealed that most cases involved young adult horses.

In this case, the cytologic and histologic appearance of most of the neoplastic cells was suggestive of large granular

lymphocytes. Lymphoproliferative disorders of LGL have been reported in humans, rats, cats and there is a single case report in the horse where multiple tissues including the intestinal tract were involved.

**AFIP Diagnosis**. Small intestine: Lymphosarcoma, Arabian, equine.

**Conference Note**. This case was reviewed by the Department of Hematopathology at AFIP. The histologic appearance of diffusely infiltrating sheets of neoplastic round cells, with fusion and clubbing of villi and thickening of the intestinal wall was considered characteristic for enteric lymphosarcoma. A diagnosis of the large granular lymphocyte (LGL) variant is best made from cytologic evaluation, as was done in this case using peritoneal fluid. Immunophenotypic studies of fresh or frozen tissue specimens can be done to demonstrate CD16 cell surface markers. Diagnosis from paraffin-embedded tissue sections alone is not reliable due to alterations in cell morphology resulting from fixation and processing. A previously reported case of LGL tumor in a horse described neoplastic cells containing eosinophilic granules which stained dark blue to black with phosphotungstic acid hematoxylin (PTAH), were variably periodic acid-Schiff (PAS)-positive (diastase resistant), and were negative with Giemsa, nonspecific esterase, peroxidase, and toluidine blue stains. Differentials for neoplasms of granulated cells in the horse include myeloproliferative disease, mast cell tumor, basophilic enteritis, melanoma, granular cell tumor, and neoplasm of globule leukocytes.

Large granular lymphocytes are a unique population of lymphocytes characterized by having abundant cytoplasm containing azurophilic granules. The granules are thought to play a role in the cytolytic function of these cells; i.e. natural killer (NK) cell activity and antibody-dependent cellular cytotoxicity (ADCC). In people, large granular lymphocytes constitute approximately 15% of circulating blood lymphocytes and two distinct immunophenotypes are recognized. The majority are termed T-cell type and consist of CD3+, CD8+, CD4- cells. These cells exhibit low NK activity and variable ADCC function. The remainder are CD3-, CD8- natural killer type cells of unknown lineage. They possess strong natural killer and antibody-dependent cell-mediated cytoxicity activity. Lymphoproliferative disorders of both subtypes of large granular lymphocytes have been described.

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Microslide 10

**History**. The tissue submitted is from a 6-year-old Shire gelding presented for a 1-month history of lameness. On presentation, the horse was extremely reluctant to move. Warmth and notching were identified around the coronary band and mild to moderate digital pulses were palpated.

**Gross Pathology**. There was a deep depression along the coronary band of both forefeet. The soles of both forefeet were dropped and had a prominent convexity. There was a 5 cm. defect in the medial aspect of the right fore sole that was filled with brown exudate. On cut surface, a deep wide tract extended caudally from this defect to the bulb of the heel undermining the entire medial half of the sole and extending laterally past the midline. There was partial disruption of laminae continuous with this focus proximally to the coronary groove. P3 was markedly rotated and the wide gap between the white line and the cranial aspect of P3 was filled with marked hyperplasia of the remaining primary laminae. Multiple cavitated defects and tracts extended through these hyperplastic laminae. There was an intervening space between the laminae consistent with disruption of secondary laminae. Sectioning of the left fore foot revealed a 40 degree rotation of P3 with respect to the hoof wall. Dense white tissue identified in horizontal section as hyperplastic primary laminae filled the wide gap.

**Contributor's Diagnosis and Comments**. Chronic laminitis, resulting in hyperplasia of epidermal laminae and osteolysis of P3.

The section provided is taken from a horizontal plane section of equine hoof and includes an outer thin remnant of hoof wall (most of which was trimmed off to facilitate processing), a piece of P3, and intervening tissue filling the expanded space between the cranial aspect of the third phalanx and the hoof wall. Approximately half of the width of the thickened wedge consists of markedly hyperplastic epidermal laminae with intervening laminar corium; the superficial half consists of necrotic and keratinized laminae that are continuous with the hoof wall. The hyperplastic laminae closest to P3 have moderate disorganization with variable atrophy or irregularity of secondary laminae. There are frequent individual dyskeratotic cells and keratin pearl-like structures within the epidermal laminae. Keratin pearl-like structures sometimes occur in the dermis. The superficial laminae closest to the hoof wall consist of long cores of keratin with intervening sheets of ballooned necrotic and keratinized keratinocytes. There are linear clefts in the plane of the laminae sometimes interspersed with amorphous granular debris and bacteria. A line of epidermal laminar rupture disrupts multiple laminae. There is marked osteolysis of the cranial aspect of P3 with prominent scalloping of bony trabeculae, irregular tide lines, and filling of lytic spaces with fibrovascular tissue.

Equine laminitis is somewhat of a medical enigma. There is general agreement that ischemia of the distal digit, particularly the laminar region, is a pathologic component; however, the exact etiology of this ischemia remains a subject of opinion, conjecture, and research. Reduction of the blood supply may occur by a variety of mechanisms (for example, vasoconstriction, arteriovenous shunting, microthrombosis, perivascular edema). The consequence of this vascular compromise is acute laminar degeneration, generally referred to as laminitis.

James Moore of the University of Georgia has used microcirculatory assessment techniques to demonstrate profound increases in digital venous, capillary, and tissue pressures and in post capillary resistance to blood flow during the early stage of laminitis. It was established that vascular permeability within the foot did not change. Moore hypothesizes that the initial inciting hemodynamic "cause" of acute laminitis following carbohydrate overload is digital venoconstriction. Venoconstriction would reduce the efflux of blood from the laminar capillaries resulting in increased capillary pressure and simple hydrostatic-mediated movement of fluid into the interstitial space. Subsequently, the increased tissue pressure would (1) further impede the flow of blood through the digital microcirculation resulting in dermal laminar ischemia, (2) provide the environment necessary for development of microthromboses, and (3) result in the opening of arteriovenous shunts at the level of the coronary band.

The pathogenetic consequence of severe acute laminitis is edema of the dermis adjacent to the basal epidermal layer and necrosis and atrophy of secondary epidermal laminae. A clinical consequence of acute laminitis may be rotation of the third phalanx, attributable to necrosis of the laminae with loss of the suspensory function of these laminae. Converging biomechanical factors including loss of suspensory function of the soft laminae, weight of the horse, the leverage force placed on the toe, and the pulling force of the deep digital flexure tendon may combine to force the third phalanx from the hoof wall. The response of the epidermis to this insult when the tissue damage is not extreme is marked hyperplasia. The epidermal hyperplasia is accompanied by marked increase in keratin and the result is a wedge of epidermis (not granulation tissue as sometimes erroneously reported) between the third phalanx and the hoof wall resulting in persistence of the rotation. Some data suggest that an Epidermal Growth Factor (EGF) mediated response may be involved in the hyperproliferative response that is characteristic of chronic laminitis. Disruption of the hyperplastic laminae in the case and the presence of bacteria is a consequence of protrusion of P3 through the sole.

**AFIP Diagnosis**. Hoof wall, epidermal laminae: Hyperplasia, with hydropic degeneration, necrosis, and dyskeratosis, Shire, equine.

**Conference Note**. Although laminitis is a well recognized clinical and gross necropsy diagnosis, the microscopic lesion is rarely seen due to the difficulty in obtaining a good histologic section of the equine hoof. Conference participants noted that the changes involving the cranial surface of P3 included both osteolysis and the deposition of new osteoid. Numerous osteoclasts were observed along the surface of the bony trabeculae.

There are a wide variety of predisposing factors implicated in the development of laminitis including: carbohydrate overload, ingestion of cold water (water founder), trauma to the soles of the foot (road founder), endometritis (post-parturient laminitis), and ingestion of lush grass pasture by obese horses (grass founder). As mentioned by the contributor, the cause of the decreased laminar microcirculation that leads to ischemic necrosis of the laminae remains unproven.

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Microslide 11

**History**. Tissue from a 6-year-old thoroughbred-cross mare. This mare was emaciated despite the fact that throughout an eight-week long illness, normal appetite had apparently been maintained. It had normal vital signs, soft, poorly formed faeces, ventral oedema, areas of hair loss on the face and distal extremities, loss of chestnuts and ulceration of the coronary bands.

**Gross Pathology**. The mare had blotchy erythematous foci in the oral cavity, oedema of the soft palate and hyperkeratosis of the nonglandular part of the stomach. The pancreas was markedly enlarged, hard, white and it contained numerous yellowish gritty foci. Similar foci were apparent throughout the liver, the walls of both the small and large bowel and in the mesenteric lymph nodes.

**Laboratory Results**. This mare was hypoalbuminemic and had a significantly elevated level of serum alkaline phosphatase. A glucose tolerance test revealed an abnormally long absorption time and a prolonged persistence of the absorbed glucose in the blood due to delayed clearance.

**Contributor's Diagnosis and Comments**. The mare had eosinophilic granulomatosis, a fatal condition of unknown aetiology.

This section of pancreas shows widespread loss of acinar tissue, marked fibroplasia and granulomas containing central necrotic eosinophilic aggregates surrounded by relatively thin zones containing giant cells and macrophages. There is widespread infiltration of the organ with eosinophils and intra-acinar and periductal lymphocytic infiltration is also a feature. Much of the acinar tissue present has a disorganized appearance.

Equine eosinophilic granulomatosis is an uncommon multisystemic and generally fatal chronic wasting disease which affects Thoroughbred horses and their cross-breds. It has been reported in Europe (Lindberg, 1985), Australia (Pass and Bolton, 1982) and North America (Nimmo et al, 1985). It is probably an immune-mediated disease and much of the pathology appears to be due to eosinophil degranulation in tissues. Eosinophil

granulomas form in affected organs, particularly the skin, alimentary tract, mesenteric lymph nodes, pancreas and liver.

**AFIP Diagnosis.** Pancreas: Pancreatitis, chronic, sclerosing, eosinophilic, with eosinophilic granulomas, thoroughbred-cross, equine.

**Conference Note.** Conference participants believed that chronic eosinophilic pancreatitis secondary to parasite migration should be included in the differential diagnosis for this lesion. The larvae of Strongylus equinus commonly migrate through the pancreas during their lifecycle; migration tracts can resemble the granulomas seen here.

As in this case, horses with equine eosinophilic granulomatosis have been reported with a variety of lesions affecting multiple organs including ulcerative coronitis, loss of chestnuts, and widespread eosinophilic granulomatous inflammation that can involve the liver, pancreas, and multifocal areas of the gastrointestinal tract from the distal esophagus to the anus. Clinically, there is malabsorption, weight loss, and hypoalbuminemia. The pathogenesis of this syndrome remains unproven and controversial. Although parasitic, viral, and toxic etiologies have all been proposed, an exaggerated and ongoing hypersensitivity reaction against a yet unidentified antigen may be the best explanation of this complex disease.

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Microslide 12

**History.** This mature thoroughbred, female, equid aborted eight weeks prior to term. The mare had no history of reproductive problems and had delivered several live foals in earlier pregnancies.

**Gross Pathology.** A single discoid pale firm mass approximately 30 cm diameter bulged 2 cm from the allantoic surface of the placenta. On incision, numerous 1 to 5 mm

diameter cysts containing mucous, often white flecked fluid were present throughout the mass.

**Laboratory Results**. Placental bacteriology; (i) Heavy mixed growth of Enterobacter agglomerous and nonhaemolytic Streptococci (ii) Scanty growth of Streptococcus zooepidemicus.

**Contributor's Diagnosis and Comments**. Equine allantois, cystic adenomatous hyperplasia (dysplasia). Aetiology unknown.

Adenomatous hyperplasia of the allantois in horses is an unusual proliferative placental lesion which has been reported previously in 3 horses (1,2). In these cases and in a further 10 cases (Hartley W.J., Shiraprasad, H.L., personal comunication) abortions occurred between 7 and 11 months of gestation. The lesions were multiple in 6 placenta and single in 3. The nodules arise from allantoic epithelium but their cause and significance remain uncertain. Placentitis is present in many cases but it is not clear whether or how the proliferative response is related to inflammation elsewhere in the placenta. If an association was present it would be reasonable to expect a much higher prevalence of allantoic hyperplasia.

**AFIP Diagnosis**. Placenta, allantois: Hyperplasia, cystic adenomatous, focally extensive, moderate, with suppurative allantoitis, thoroughbred, equine.

**Conference Note**. The pathogenesis of this lesion and it's association with abortion are unknown. Although some features are suggestive of neoplasia, the multifocal distribution of the lesion on the allantoic surface and the lack of infiltration into the underlying chorionic stroma favor a diagnosis of dysplasia or hyperplasia. The lesion is usually seen in the region of the placenta where the umbilical vessels attach. The frequent association of cystic glandular hyperplasia of the allantois with chronic placentitis may indicate that this is a secondary, reactive process. Despite the marked inflammatory cell infiltrate present in the cystic glands of this animal, special stains (Gram's stain and Gomori methenamine silver) failed to reveal infectious agents. Conference participants noted certain sections contained an amorphous eosinophilic material in the chorionic epithelium resembling amyloid.

Other miscellaneous lesions have been associated with the equine placenta. Sacculation of the umbilical cord is characterized by alternating fluid filled saccules resulting in a thickened, malformed cord. These sacculations tend to be pathologic only when associated with mineralization of the placental vessels. Torsion of the umbilical cord may be found in abnormally long cords (over 100cm.). Mineralization of the amnion occurs and is considered an incidental finding.

Pedunculated yolk sac cysts or remnants are occasionally seen attached to the umbilical cord. They can undergo osseous metaplasia forming boney cystic structures with gelatinous centers.

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Microslide 13

**History.** Twenty percent of the animals in a shipment of gerbils arrived exhibiting nonspecific signs of lethargy and diarrhea. Several of the animals were anorectic and died 24 hours after arrival

**Gross Pathology.** There was fecal staining of the perineum. The intestines were edematous, contained watery contents and foci of necrosis covered by pseudomembranous exudate. The liver contained multiple pinpoint yellow-white foci.

**Laboratory Results.** Culture of the liver yielded E. coli.

**Contributor's Diagnosis and Comments.** Liver: Hepatitis, acute, necrotizing, random, multifocal to confluent, marked, with hepatocellular intracytoplasmic filamentous bacteria, etiology-- consistent with Bacillus piliformis.

Tyzzer's disease was diagnosed based on the pattern and distribution of the lesions and the presence of distinctive intrahepatocytic filamentous bacteria. In this case these are relatively easily seen on the H&E stained sections in viable hepatocytes at the edge of necrotic lesions. A Warthin-Starry silver stain demonstrated the organisms in the liver and intestinal lesions.

**AFIP Diagnosis.** Liver: Hepatitis, necrotizing, subacute, multifocal, random, moderate, with intrahepatocellular filamentous bacteria, breed unspecified, gerbil.

**Conference Note.** Bacillus piliformis affects many species causing a characteristic multifocal necrotizing hepatitis. The degree of associated inflammation varies, and may be minimal in peracutely fatal cases. Grossly, hepatic lesions are characterized by numerous small, discrete yellowish-white foci scattered throughout the liver, and must be differentiated from salmonellosis and viral causes of hepatic necrosis. Other tissues affected will vary between species, but commonly includes the intestines and the myocardium. Immunosupressed and young (weanling) animals are predisposed to more severe disease. Resistance to the organism may be B cell-related, as nude mice (T-cell deficient) have not been shown to be at increased risk of infection.

Bacillus piliformis is a pleomorphic, gram-negative, spore-forming, obligate intracellular bacterium. The vegetative form seen here is unstable outside the host cell and is difficult to culture in cell-free media. The more resistant spore form is passed in the feces and can survive as long as one year. Fecally shed spores are considered infective and may explain the severe disease seen in coprophagous species such as rabbits, gerbils, and hamsters. Extended positive antibody titers demonstrated in mice, rabbits and rats indicate that some animals develop persistent or latent infections; acting as a reservoir for further transmission.

**Contributor.** Greenlee Pathology Associates, 1331 Record Crossing, Dallas, TX 75235.

**References.**

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Microslide 14

**History.** This 2-month-old, female, German Shepherd Dog developed rapidly progressive posterior paresis and ataxia about 2 weeks after vaccination with a modified-live canine distemper vaccine. Three of four vaccinated pups were affected.

**Contributor's Diagnosis and Comments.** Brain: Moderate to severe, multifocal, acute nonsuppurative polioencephalitis

with intranuclear and intracytoplasmic inclusion bodies. Post vaccinial canine distemper encephalitis.

The lesions in this case consisted of moderate to marked nonsuppurative perivascular cuffs with prominent satellitosis, neuronal degeneration and neuronophagia with frequent intranuclear, and less often, intracytoplasmic eosinophilic inclusion bodies. There were scattered spheroids and areas of gliosis with minimal meningeal involvement. Both brain and spinal cord were involved with lesions largely restricted to gray matter. Lesions were most severe in the thalamus, pars and medulla with relative sparing of the cerebral cortex.

The history of recent vaccination along with the character and distribution of the lesions is highly suggestive of vaccine-induced canine distemper encephalomyelitis. In cases of post-vaccination distemper encephalomyelitis, neuronal necrosis and neuronophagia are usually pronounced and lesions are most severe in the pars and thalamus.

Immunohistochemical staining demonstrated abundant canine distemper antigen within affected areas. Fresh brain tissue was cultured and a cytopathic effect was found in canine kidney cells. This finding strongly supports the hypothesis of a vaccine-induced infection, as mild type virulent distemper virus causes a cytopathic effect in canine macrophages, but not in epithelial cells.

**AFIP Diagnosis**. Brain, brainstem: Encephalitis, nonsuppurative, multifocal, moderate, with eosinophilic intranuclear and intracytoplasmic inclusions, German Shepherd Dog, canine.

**Conference Note**. Conference participants noted the broad spectrum of neuronal degenerative changes and necrosis represented in this section. However, syncytia formation and demyelinization of white matter were not prominent features.

Canine distemper must be differentiated from other causes of nonsuppurative encephalitis with viral inclusions. Rabies inclusions are confined to the cytoplasm (Negri bodies) and are commonly seen in the hippocampal neurons of affected dogs. Pseudorabies is associated with clinical signs of self-mutilation; intranuclear inclusions are present in neurons of the spinal ganglia, spinal cord, medulla, and pons. Canine adenovirus type 1 can cause vasculitis and hemorrhage in the central nervous system, with intranuclear inclusions found in endothelial cells. Canine herpesvirus causes necrosis with characteristic herpes intranuclear inclusions in multiple systems including the nervous system, but typically affects young dogs less than three weeks old.

Vaccine-induced canine distemper is associated with a reversion of the attenuated vaccine-virus to a virulent state

capable of causing clinical disease. The most reliable marker to distinguish vaccine-induced disease from natural infection by field strains of canine distemper is the relative ability of the virus to infect macrophages or epithelial cells. Attenuated vaccine strains have been adapted through serial passages to replicate in both macrophages and epithelial cells. Virulent wild strains of canine distemper are easily replicated in canine alveolar macrophages, but are much less cytopathic for epithelial cells. The concurrent vaccination of dogs with canine parvovirus or other immunosuppressive agents has been postulated by some researchers to increase the risk of vaccine-induced distemper.

**Contributor.** NYSCVM - Department of Pathology, Cornell University, Ithaca, NY 14853.

**References.**

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Microslide 15

**History.** Tissue from an adult Fischer-344 male rat that was assigned to a chronic toxicologic carcinogenic study.

**Gross Pathology.** A large, 20 x 15 x 15 mm, firm, mottled mass was observed involving the area adjacent to and below the left ear.

**Contributor's Diagnosis and Comments.** Carcinoma, Zymbal's gland, left ear, Fischer-344 rat.

Specimen was placed in decal solution for a short time prior to trimming.

**AFIP Diagnosis.** Left ear (per contributor): Squamous cell carcinoma, Fischer-344 rat, rodent.

**Conference Note.** Conference participants agreed that the mass most likely originated from the Zymbal's gland, but preferred a less specific morphologic diagnosis due to the lack of clear sebaceous differentiation. Although there was some variation, most sections included the following histologic features: invasion of adjacent bone and skeletal muscle;

formation of anastomosing cords and cysts lined by keratinizing stratified squamous epithelium; proliferation of fibrous stroma; marked anisocytosis, anisokaryosis, cellular atypia, and numerous multinucleated cells; large areas of necrosis and hemorrhage, and a prominent inflammatory component.

Zymbal's gland is really a complex of three specialized sebaceous glands located near the anterior-ventral region of the external ear canal. The glands produce holocrine secretions rich in lipids (sebum) that empty into the ear canal near the tympanic membrane. The major excretory ducts are lined by stratified squamous epithelium. Microscopically, Zymbal's gland can be differentiated from the modified sebaceous cells of the clitoral and preputial glands by the presence of red cytoplasmic granules in the latter.

Neoplasms of the Zymbal's gland rarely occur spontaneously, but are easily induced by various chemical carcinogens. The morphologic classifications of hyperplasia, adenoma, and carcinoma represent a continuum of changes in the process of neoplastic transformation. Early hyperplastic and dysplastic changes may be missed, as the gland is often not examined microscopically unless a growth is visibly detected at necropsy. Grossly, Zymbal's gland tumors appear as a single, variably sized, firm subcutaneous nodule just below the ear. Ulceration is not uncommon.

Zymbal's gland carcinomas are less well circumscribed than adenomas and are invasive. They can contain both neoplastic sebaceous and squamous differentiation in varying proportions; often consisting of squamous cells exclusively. A prominent inflammatory infiltrate may be present. Metastasis to the lungs and regional lymph nodes has been reported.

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**References**.

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Microslide 16, Lantern slide 2

**History**. This is tissue from an 8-week-old New Zealand

White rabbit that was a clinically normal sentinel animal.

**Gross Pathology**. The distal segment of the ileum was thickened and corrugated in appearance.

**Contributor's Diagnosis and Comments**. 1. Enteritis, histiocytic, subacute, segmental (ileum), marked.
2. Intraepithelial protozoan consistent with Coccidia (Eimeria), multifocal, mild.
Disease: Histiocytic Enteritis. Etiology: Intraepithelial Campylobacter-like bacteria (associated).

Other variable microscopic changes included areas of villous widening and blunting, patchy regions of mild to moderate hyperplasia of intestinal crypt epithelium, multifocal areas of superficial mucosal ulceration, lacteal dilatation and occasional crypt "abscessation."

This case is similar to "Histiocytic Enteritis" reported by Umemura et. al., in which accumulations of epithelioid macrophages with occasional multinucleated cells infiltrate and distend the lamina propria of the distal small bowel. Schoeb and Fox described a series of cases of enterocolitis in young rabbits in which a variety of proliferative and histiocytic lesions were noted. Both groups demonstrated intracellular Campylobacter-like bacteria within the apical cytoplasm of mucosal epithelium.

In this case, Warthin-Starry silver stains (pH 4.0) did reveal small curved organisms (consistent with Campylobacter) within the apical cytoplasm of infrequent intestinal crypts. Acid fast stains were negative. Occasional stacks of large slender intracellular rod shaped bacterial organisms (suggestive of Bacillus piliformis) were seen within superficial epithelium on the silver stain, but were considered incidental.

**AFIP Diagnosis**. Small intestine: Enteritis, histiocytic, diffuse, moderate, with villous blunting and fusion, New Zealand white rabbit, lagomorph.
Small intestine: Intraepithelial protozoa, etiology--consistent with Eimeria sp.

**Conference Note**. The differential diagnosis for enteritis in rabbits includes Tyzzer's disease, coccidiosis, salmonellosis, clostridial enterotoxemia, mucoid enteropathy, hairballs, and colibacillosis. Conference participant's noted that normal rabbits may have a proportionally high number of histiocytes within their intestinal mucosa and stressed the need for caution in evaluating histiocytic enteritis.

Silver-positive, campylobacter-like organisms have been implicated in the pathogenesis of proliferative enteric lesions of rabbits, pigs, hamsters, ferrets, and other species. However,

efforts to demonstrate an etiologic relationship for this organism by fulfilling Koch's postulates have been unsuccessful. Most evidence indicates that these intracellular bacteria are antigenically distinct from known Campylobacter species. Campylobacter-like organisms found in affected pigs, hamsters, ferrets and rabbits are thought to have at lease one unique antigen in common.

**Contributor.** Department of Laboratory Animal Resources, A-115 Scaife Hall, University of Pittsburgh, Pittsburgh, PA 15261.

**References.**

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2. Umemura T, Tsushitani U, Totsuka M, Nakarne J, Yamashiro S: Histiocytic enteritis of rabbits. Vet Pathol, 1982, 19:326-328.

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4. Fox JG, et al: Proliferative colitis in ferrets. Vet Pathol, 1989, 26:515-517.

Microslide 17

**History.** This 2-year-old, Labrador Retriever cross, intact male dog was presented by the owners to the diagnostic laboratory within 2-3 hours of death. The owners indicated that the dog had died rapidly after a brief episode of hemorrhage from the mouth and anus.

**Gross Pathology.** There was blood staining of the hair around the mouth and perineum. The abdominal cavity contained approximately 500 ml of blood tinged fluid. The serosa of the entire small and large intestine was diffusely red to reddish-purple, granular, and dull. Serosal blood vessels of the small intestine were congested. The stomach contained approximately 500 ml of bloody fluid, and the small and large intestine contained small to moderate amounts of similar fluid. The mucosa of the small and large intestine was thickened and dark red.

**Laboratory Results.** Electron microscopic examination of intestinal contents was negative for virus particles. Aerobic culture of small intestine isolated an abundant growth of Salmonella (serotype livingstone), hemolytic Escherichia coli, and moderate growth of alpha hemolytic Streptococcus species and Pseudomonas aeruginosa. Anerobic culture isolated an abundant growth of Clostridium perfringens.

**Contributor's Diagnosis and Comments.** Enteritis,

**Contributor's Diagnosis and Comments**. Mastitis, parasitic, chronic, with granulomatous cysts, periductal plasmacytosis, squamous metaplasia of ducts and intraductal embryonated eggs; probable etiology Crassicauda grampicola.

Although a definitive identification of the nematode was not performed, parasitic mastitis in the Atlantic white-sided dolphin has been previously attributed to Crassicauda grampicola (Geraci et al, 1978). These authors suggested that parasite-induced damage to a significant portion of the gland might adversely affect calf survival and thus herd productivity. There is considerable fibrous tissue and adipose tissue within a few interlobular septa of this gland but the degree of lobular involution is difficult to assess without a nonparasitized gland for comparison.

The exact life cycle of this spirurid nematode is unknown, although it probably involves an intermediate invertebrate host. In the study by Geraci et al (1978), the youngest infected animal was 2 years old, suggesting that dolphin calves probably do not become infected by direct egg transmission from the milk. Nematodes noted in subcutis of this dolphin were likely also Crassicauda species. Members of this genus have been found in the urinary passages and vasculature of cetaceans, and have also been recovered from the mammary glands of harbor porpoises.

Most of the pathological findings in the 3 dolphins necropsied were deemed incidental and the cause of the stranding was not determined. Pulmonary edema and mild alveolitis were present in the lungs of all 3 animals and was consistent with aspiration of seawater during the stranding incident.

**AFIP Diagnosis**. Mammary gland: Galactophoritis, eosinophilic, chronic, diffuse, moderate, with granulomas, spirurid eggs, and a degenerating nematode, Atlantic white-sided dolphin (Lagenorhynchus acutus).

**Conference Note**. In arriving at a morphologic diagnosis of galactophoritis, conference participants felt that the inflammation appeared centered on mammary ducts. Histologic features of this section include hyperplasia and squamous metaplasia of duct epithelium; several cavitated granulomas containing numerous, often embryonated nematode eggs surrounded by large foamy macrophages and fewer multinucleated giant cells; interstitial fibrosis infiltrated with lymphocytes, plasma cells, and scattered eosinophils; and mineralization. Multifocally, there are degenerating fragments of an adult spirurid nematode also surrounded by eggs.

Although many are not evident on this section, histologic features used to identify spirurids include

coelomyarian polymyarian musculature, prominent lateral cords with a stalk-like base, eosinophilic material within the pseudocoelom, and a large intestine composed of many uninucleate cells having a brush border. The outer cuticle can vary from smooth to ornamented with alae or spines. As seen here, spirurid eggs are small, thick-shelled, nonoperculated, and frequently embryonated.

The probable genus of this nematode is Crassicauda. In dolphins and porpoises, this parasite has been described as causing granulomas and fibrotic nodules in the subcutaneous blubber, urinary tract, mammary gland, pterygoid sinus, and vascular system. The mode of transmission from mother to calf is not known. This case illustrates the need to learn more about the lifecycle and pathogenicity of potentially debilitating helminths found in cetaceans.

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**References**.

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Microslide 19

**History**. An 11-year-old Bichon Frise (canine) was presented with a sudden onset of profuse hemorrhagic diarrhea. At surgery, a cecal mass was discovered.

**Gross Pathology**. A large artery and vein were associated with the cecal mass, and numerous adhesions were present in the abdomen.

**Laboratory Results**. Over 48 hours the PCV dropped from normal to a PCV of 7.

**Contributor's Diagnosis and Comments**. 1. Cecum: Carcinoid, invasive, mucosa, submucosa and muscularis.

2. Cecum and colon: Acute cecocolitis, mucosa (cecum), submucosa and muscularis (colon).

3. Ileum: Serositis, focal fibrinous with smooth muscle atrophy and necrosis.

Sheets of tumor cells partially subdivided by thin fibrovascular septa showed positive immunoreactivity (staining)

for NSE (neuron specific enolase), chromogranin, and synaptophysin, with slight to equivocal staining for serotonin in only a few cells. These staining results are consistent for a carcinoid.

**AFIP Diagnosis**. Cecum: Carcinoid, Bichon Frise, canine.

**Conference Note**. The neoplasm consists of closely-packed polygonal cells with abundant, finely granular, vacuolated cytoplasm. The cells are arranged in small nests and packets supported by a thin stroma; a pattern considered typical of neuroendocrine tumors. In addition to the special stains mentioned by the contributor, the neoplasm stained positively with a Churukian-Shenk silver stain, demonstrating the argyrophilic (silver reducing) properties of the intracytoplasmic granules. Many sections contained less cellular areas with cholesterol clefts surrounded by macrophages and multinucleated giant cells. These clefts may have resulted from previous hemorrhage and subsequent release of membrane phospholipids from degenerating cells. Amyloid, which has been reported in canine rectal carcinoids, was not evident with congo red staining.

Intestinal carcinoids are rare in domestic animals. They arise from endocrine cells scattered throughout the gastrointestinal mucosa. These cells normally produce a variety of secretory products which act to modulate digestive functions via endocrine, paracrine, and neurocrine mechanisms. Similar endocrine cells are present in the tracheobronchial tree, liver, pancreas, and genitourinary system, and can also give rise to these tumors. In humans, carcinoids are infrequently associated with the systemic release of vasoactive amines like serotonin, resulting in diarrhea, erythema, hypertension, right heart failure, and other clinical signs collectively known as the "carcinoid syndrome". A similar syndrome has not been described in animals.

**Contributor**. Department of Veterinary Pathobiology, College of Veterinary Medicine, University of Minnesota, St. Paul, MN 55108.

**References**.

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2. Giles RC Jr, Hildebrandt PK, Montgomery CA Jr: Carcinoid tumor in the small intestine of a dog. Vet Pathol, 1974, 11:340-349.

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Microslide 20

**History**. A 5-year-old female oriental shorthair feline was said to be lethargic, anorexic, icteric, anemic and lame. Samples of the kidney, liver, spleen and lung were submitted for histopathologic evaluation.

**Contributor's Diagnosis and Comments**. Nephritis, very mild, focal to multifocal, histoplasmosis; diffuse membranous glomerulonephritis.

The other organs, the liver, spleen and lung also showed histoplasma infection. This disseminated infection probably induced the glomerular changes.

**AFIP Diagnosis**. 1. Kidney: Nephritis, interstitial, histiocytic, multifocal, mild, with yeast, Oriental Shorthair, feline.
2. Kidney, glomerular capillaries and arterioles: Fibrin thrombi, diffuse, severe, with intravascular yeast.

**Conference Note**. Participants discussed lesions in both the interstitium and glomeruli. Multifocally, there are interstitial aggregates of macrophages which contain clusters of 3-5 micron yeast. GMS and PAS procedures accentuated the organisms. Occasionally, narrow-based budding was seen. The morphology of the organism is consistent with that of Histoplasma capsulatum. Numerous glomerular capillaries and arterioles contain fibrin thrombi. A differential diagnosis that also included toxoplasmosis, leishmaniasis, and encephalitazoonosis was discussed.

The widespread formation of fibrin thrombi was speculated to be the result of disseminated intravascular coagulopathy (DIC). A possible pathogenesis for DIC in this case was discussed. Diagnosis of DIC depends on demonstration of concomitant thrombocytopenia and factor deficiency.

Histoplasma capsulatum is a saprophytic, mycelium-producing, soil fungus with a parasitic yeast form that occurs in tissue. Exposure is via inhalation of microconidia which are subsequently phagocytized by and replicate in pulmonary macrophages. Control of the organism at this stage results in an inapparent pulmonary infection which is thought to be common in the cat. Dissemination via the mononuclear phagocyte system can result in the much less common systemic form of histoplasmosis. Lesions containing numerous yeast organisms may be seen in the lungs, spleen, liver, lymph nodes, bone marrow, gastrointestinal tract, kidneys, adrenal glands, central nervous system, and skin. Nonspecific signs of weight loss, lethargy, and fever characterize the disseminated disease in cats. Anemia

and hypoalbunemia are also common findings. Feline leukemia virus infected cats have not been shown to be at increased risk.

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**References**.

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Microslide 21

**History**. This was a 5-month-old male mouse, line MT42 on CD-1 background, transgenic mouse (TGF-alpha). It was clinically normal at time of necropsy. TGF-alpha transgenic mice were developed by Dr. Glenn Merlino, National Cancer Institute, Bethesda MD.

**Gross Pathology**. Pancreas is firmer and rounder than normal.

**Contributor's Diagnosis and Comments**. Pancreatic lesions of TGF alpha transgenic mice.

1. Duct hyperplasia.
2. Interstitial fibrosis.
3. Islet cell hyperplasia.

The pathogenesis of the pancreatic lesion is not well described. A description of the changes seen has been published (Jhappan, et al). Tumors do not develop spontaneously in the pancreas but do occur in high incidence in liver. The overexpression of TGF-alpha is suggested to have some role in the development of both liver tumors and the pancreatic lesions.

**AFIP Diagnosis**. Pancreas, ducts: Hyperplasia and acinoductular metaplasia, multifocal, moderate, CD-1 background, MT42 transgenic mouse, rodent.
Pancreas, islets: Hyperplasia, multifocal, moderate.
Pancreas, interstitium: Fibrosis, diffuse, moderate.

**Conference Note**. The creation of transgenic strains of mice such as this one has permitted researchers to study the function of specific genes and their encoded products in the context of the whole animal. Transforming growth factor alpha

(TGF-alpha) is a member of the epidermal growth factor family of proteins. It is a known mitogen for several different cell types and its expression is well documented in a variety of tumors, primarily carcinomas. The role of TGF-alpha in the development of neoplasia is unclear, but it has been implicated as a possible tumor promoter. Elevated expression of TGF-alpha occurs in these mice and has been associated with abnormalities in the growth and differentiation of a wide variety of tissues, particularly targeting liver, mammary gland and pancreas. The livers of male, TGF-alpha transgenic mice are predisposed to develop multifocal, well-differentiated hepatocellular carcinomas. TGF-alpha also plays a role in mammary gland proliferation and morphogenesis; elevated levels have been implicated in the development of dysplastic and neoplastic changes in mammary epithelium. Pancreatic changes are as seen here; intralobular and interlobular fibrosis, striking ductal hyperplasia and acinoductular metaplasia. Lesions become increasingly more severe in older mice, but neoplastic transformation does not occur in the pancreas. Grossly, the pancreases from these mice appear abnormally round and nodular.

Tissues were fixed in Bouin's solution. The lymphatic nodules seen in this section were interpreted to be normal peripancreatic lymphoid tissue that became entrapped in the hyperplastic process. Participants noted the prominent high endothelial venules in these nodules. A focally extensive section of small intestine was fused along one margin of the pancreas. Reportedly, TGF-alpha promotes villous epithelial hyperplasia in the duodenum of these mice, resulting in larger, thicker, hypercellular villi.

**Contributor.** National Cancer Institute, NCI-FCRDC, Building 538, Frederick, MD 21702-1201.

**References.**

1. Jhappan C, Stahle C, Harkins RN, Fausto N, Smith GH, Merlino GT: TGFα Overexpression in Transgenic Mice Induces Liver Neoplasia and Abnormal Development of the Mammary Gland and Pancreas. Cell, 1990 61:1137-1146.

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Microslide 22

**History**. At 6 weeks of age this male, Fischer-344/NCr rat received a diet containing 1000 ppm of EHEN (N-ethyl-N-hydroxyethylnitrosamine) for the next two weeks. At 26 weeks of age, rats received 500 ppm of DEAI (diethylacetylurea), a hydrolysis product of barbital. At 36 weeks of age, rats were sacrificed.

**Gross Pathology**. Kidneys - granular.

**Contributor's Diagnosis and Comments**

1. Hyaline droplet nephropathy.
2. Old age rat nephropathy.
3. Foci of renal tubular cell dysplasia (atypical hyperplasia).

The hyaline droplets are found in many tubules. They are round and pale pink-greenish in color. Characteristically, crystalline and angular droplets are seen in some tubules. Tubular hyperplasia is seen in multiple areas. The dysplasia (atypical hyperplasia) is much less common and morphologically different from regenerative tubules of nephropathy.

There are other renal lesions in these kidneys, mostly due to the drug exposure.

**AFIP Diagnosis**. Kidney, tubular epithelium: intracytoplasmic hyalin droplets, multifocal, moderate, with tubular degeneration and necrosis, F344/NCr rat, rodent.

Kidney: Nephritis, lymphoplasmacytic, interstitial, multifocal, mild, with tubular regeneration and thickened tubular basement membranes.

Kidney: Tubular cell dysplasia, multifocal, mild.

**Conference Note**. Although the predominant lesions were related to the hyalin droplet nephropathy, several features of the spontaneous age-related nephropathy common in laboratory rats were also noted. These features included interstitial aggregates of lymphocytes and plasma cells, interstitial fibrosis, hypercellular tubules lined by large cells with more basophilic cytoplasm (regeneration), thickened tubular and glomerular basement membranes, protein casts, and areas of mineralization. The foci of renal tubular dysplasia were associated with the chemical exposure described in the history; lesions were not present in all sections. These were characterized by variably-sized, intratubular proliferations of epithelial cells demonstrating gradations from atypical hyperplasia to renal cell adenoma. Dysplastic foci did not metastasize, invade locally, or develop other features of malignancy.

α-2u globulin is a low molecular weight protein of

unknown function synthesized in the liver of male rats. Normally it is filtered and largely reabsorbed in the kidney, where accumulations of the protein occur within secondary lysosomes of the proximal tubular epithelial cells (hyalin droplets). Several pharmacological agents and hydrocarbons are known to markedly increase the size and number of hyalin droplets, possibly by binding to the α-2u globulin and interfering with normal lysosomal hydrolysis. Hyalin droplet nephropathy is characterized by abundant, variably-sized, intracytoplasmic globular to crystalline droplets in tubular epithelium, with subsequent degeneration, necrosis, and regeneration of affected tubules, and granular cast formation. Since α-2u globulin hyalin droplet formation is unique to male rats and is not found in other mammals or female rats receiving similar agents, the associated nephropathy is generally not considered relevant when assessing the potential toxicity of these compounds in humans.

**Contributor**. National Cancer Institute, NCI-FCRDC, Building 538, Frederick, MD 21702-1201.

**References**.

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5. Haisa Y, et al: Experimental induction of renal tumors. CRC Critical Reviews in Toxicology, 1987, 17(4):279-294.

Microslide 23

**History**. This 3-year-old, male pigtail macaque (Macaca nemestrina) developed diarrhea and died 20 months after inoculation with Simian Immunodeficiency Virus.

**Gross Pathology**. This animal was thin (3.14 kg) and dehydrated. The large bowel was distended with foul-smelling grey-brown fluid stool. Multiple 2-3 mm red-black foci were visible beneath the serosal surface of the cecum and proximal colon. Several thick, grey-white fibrinous deposits were present

on the serosal surface near the ceco-colic junction; the adjacent mucosal surface contained multiple 0.5-1.5 cm diameter crateriform ulcers with a raised hemorrhagic rim and variable amounts of yellow-grey fibrin centrally.

**Laboratory Results.** Bacteriologic culture of colonic ulcer: *E. coli*, *Bacillus* sp., enterococci.

**Microscopic Description:** Cecum and colon. Multifocally within the colon are deep necrohemorrhagic ulcers associated with numerous large (~60 x 120 um) ciliated protozoa. These trophozoites have a flocculent eosinophilic cytoplasm containing a prominent, intensely basophilic, kidney-shaped macronucleus (~20 x 20 um), numerous food vacuoles with ingested debris, and 1-2 variably-present, lucent contractile vacuoles. These organisms are within the lumen, deep in colonic glands, throughout the submucosa and extend to the outer longitudinal layer of the muscularis externa. Many protozoa are clustered at the leading edge of the ulcer, around submucosal vessels, and, in most sections, are present in submucosal, serosal or mesenteric venules and lymphatics. They have elicited diffuse transmural inflammation consisting of lymphocytes, histiocytes and neutrophils, accompanied by congestion and focal hemorrhage. The flask-shaped ulcers contain a dense accumulation of neutrophils, lymphocytes and histiocytes, with numerous bacterial colonies, occasional fungal hyphae, and necrotic debris; they extend to the muscularis externa and undermine the overlying necrotic and hemorrhagic mucosa. The corresponding serosal surface is thickened and infiltrated by lymphocytes and histiocytes.

Additionally, there are numerous aggregates of dull pink, foamy macrophages within the superficial and deep colonic lamina propria, lymphatic nodules and submucosa at the periphery of the ulcers. These macrophages contain abundant slender, 10-12 um, acid-fast bacilli in their cytoplasm.

**Contributor's Diagnosis and Comments.**

1. Severe, subacute, multifocal necrohemorrhagic ulcerative typhlocolitis and proliferative serositis with intralesional and angioinvasive ciliated protozoal trophozoites.
2. Moderate, chronic, multifocal granulomatous typhlocolitis with intracellular acid-fast mycobacteria.

Etiology:
1. *Balantidium coli*
2. *Mycobacterium avium-intracellulare* (presumptive)

Etiologic Diagnosis:
1. Cecal/colonic balantidiasis; protozoal typhlocolitis
2. Cecal/colonic mycobacteriosis

Balantidium coli (Subkingdom Protozoa, Phylum Ciliophora, Subphylum Rhabdophora, Class Litostomatea, Subclass Trichostomatia, Order Vestibuliferida, Family Balantidiidae) is the largest, and only ciliated, protozoan to infect humans. It is a relatively common inhabitant of the cecum and colon of wild and captive New World monkeys (cebus/capuchin, howler, and spider monkeys), Old World monkeys (rhesus, cynomolgus, and celebes black macaques and baboons), and the great apes (chimpanzees, gorillas, orangutans). B. coli also colonizes the cecum and colon of pigs, dogs, rats, hamsters, and guinea pigs and the gastrointestinal tract of birds (pigeons, sparrows) and insects (cockroaches). Swine are believed to be the natural reservoir, since B. coli is a commensal of their large bowel lumen, and several outbreaks of balantidiasis in humans or dogs were related to ingestion of water contaminated with pig feces. This protozoan is further spread among human and nonhuman primates by direct fecal-oral contact (including coprophagy) or ingestion of food contaminated with arthropod carriers.

B. coli has a direct life cycle and exists in either trophozoite or cyst forms, both of which can be shed in the feces and are infective. The large (30-150 x 25-120um) ovoid-to-ellipsoid trophozoite is surrounded by a pellicle from which arise multiple longitudinal rows (kineties) of cilia. At the narrow (anterior) end is a cleft (periostoma) lined by cilia, which communicates with a tubular cystoma. Food (RBCs, WBCs, bacteria, and other debris) is apparently ingested here and traverses the cytoplasm (endosarc) in numerous food vacuoles; excretion occurs at the larger (posterior) end via the cytopyge. Additional internal structures include two contractile vacuoles (one posterior and one central clear area), and a large, intensely-staining, kidney-shaped macronucleus, sheltering a small spherical micronucleus. Trophozoites reproduce by either sexual (conjugation) or asexual (binary fission) methods.

B. coli cysts are smaller (40-60 um), poorly-staining, spherical-to-ovoid structures lacking cilia but with distinct macronuclei. Within the host's rectum, trophozoites secrete a double wall and encyst prior to or after passage in the feces; the organism may remain motile within the cyst for a short period. Trophozoites are exceptionally motile in fresh fecal specimens, traveling in a rapid spiral pattern, but they quickly disintegrate.

In human and nonhuman primates, B. coli infestation may have one of several outcomes (for an excellent review, see Reference 5). First and most commonly, B. coli may be carried as an asymptomatic recurrent or chronic infestation, as in pigs, with no mucosal involvement and either no clinical symptoms or occasional mild, transient diarrhea. Second, mucosal colonization may progress to induce inflammation and superficial erosions or ulcers associated with persistent, sometimes bloody

diarrhea and fever. This syndrome frequently involves co-infection with other nematode parasites (Trichuris suis in pigs, Trichuris trichuris and Enterobius vermicularis in humans, and Trichuris spp. in nonhuman primates) or pathogenic bacteria (Shigella flexneri in macaques). The third and sometimes fatal syndrome results when B. coli trophozoites, by virtue of their ability to secrete hyaluronidase, invade beyond the muscularis mucosae and submucosa, producing deep ulcerations and abscesses (similar to Entamoeba histolytica). Histologically, trophozoites are often clustered perivascularly and readily invade mesenteric capillaries and serosal lymphatics, travelling to regional lymph nodes or, rarely, to other organs, such as liver or lung, where they may cause abscesses. The invasive nature of B. coli may result in perforation of the cecum, appendix, or colon, leading to peritonitis. It is likely that other factors, such as malnutrition, concomitant parasitism, or immunodeficiency (as seen in this SIV-infected macaque with colonic mycobacteriosis) also contribute to invasive balantidiasis.

**AFIP Diagnosis.** Colon: Colitis, necrosuppurative and ulcerative, multifocal, severe, with hemorrhage and ciliated protozoal organisms, pigtailed macaque (Macaca nemestrina), primate, etiology--consistent with Balantidium coli. Colon, lamina propria: Colitis, histiocytic, multifocal, mild.

**Conference Note.** Special stains presented at the conference revealed abundant intracellular acid-fast bacilli within the histiocytic cells of the lamina propria. Bland infiltrates of plump histiocytes in the mucosa, without the formation of giant cells and caseous centers typical of granulomas is considered characteristic of Mycobacterium avium-intracellulare in immunosuppressed primates.

The differential diagnosis for ulcerative colitis in nonhuman primates includes entamoebiasis, yersiniosis, shigellosis, campylobacteriosis, oxyuriasis, and acanthocephaliasis. Balantidium coli is a unicellular protozoan commonly found as a commensal in the cecum and large intestine of pigs. Humans and nonhuman primates are considered relatively resistant to the organism, and most infections are asymptomatic. As in this case, B. coli can act opportunistically to cause a severe, florid necro-ulcerative and hemorrhagic lesion of the colon and cecum. The conditions which favor the progression of B. coli infections are not well understood, but virulence differences among strains and host resistance factors are considered important variables.

Trophozoites of Balantidium coli are easily recognized in tissue sections as large, oval-shaped, ciliated organisms possessing an anterior grove or vestibule leading to a cytostome "mouth", a posterior cytopyge "anus", and a large macronucleus. Direct microscopic examination of fresh stool or colonic

scrapings is the most reliable method to detect B. coli trophozoites in feces as they deteriorate quickly after defecation and are not easily preserved with fixatives.

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Microslide 24, Lantern slides 3, 4

**History**. This 23-week-old C57 BL6 x 129 transgenic mouse was one of several mice with knockout (gene deletion) for the p53 tumor suppressor gene. This mouse was a homozygote.

**Gross Pathology**. A one cm diameter nodule was observed in the posterior aspect of the left rear leg. The mass was dark red in color. At tissue trimming, a dark red area of discoloration was observed at the base of the heart.

**Contributor's Diagnosis and Comments**. Hemangiosarcoma, subcutis, with local muscle invasion and metastasis to the heart, transgenic mouse. Cause: null mutation for p53 tumor suppressor gene.

Mice in this study have developed a high incidence of malignant tumors at an early age. Tumors have consisted of lymphoblastic lymphomas, osteosarcomas, rhabdomyosarcomas, hemangiosarcomas, mammary adenocarcinomas, malignant schwannomas, and several benign and malignant testicular tumors. In this study we have observed a number of hemangiosarcomas arising from the subcutis or muscles. One other case had metastasis to the liver and diaphragm. Cardiac metastasis is rare in naturally occurring and experimentally induced neoplasia in the mouse. Hemangiosarcomas have been observed in the hearts of $B_6C_3F_1$ mice given 1,3 butadiene by inhalation. (National Toxicology Program, personal communication.)

**AFIP Diagnosis**. Heart: Hemangiosarcoma, C57BL/6 x 129 transgenic mouse, rodent.

**Conference Note**. In addition to the glass microslide, 2X2 slides of both the primary tumor in skeletal muscle and the metastatic lesion in the heart were provided. The base of the heart was largely replaced by an infiltrative mass of pleomorphic, plump spindle cells that formed small blood-filled spaces. Several participants felt that the degree of cellular atypia and stromal proliferation seen in this neoplasm were unusual for hemangiosarcomas in mice. Other histologic features included multinucleated neoplastic cells, bizarre mitoses, anisokaryosis, low numbers of inflammatory cells and rare, small foci of extramedullary hematopoiesis.

An alteration usually involving a single point mutation in the highly conserved codons of the p53 tumor-suppressor gene is the most common genetic lesion found in human tumors. Mutation of the p53 gene is also associated with a familial inherited cancer susceptibility in people (Li-Fraumeni syndrome). The creation of transgenic mice which are homozygous for a null allele of the p53 gene has provided new clues as to the role of this gene. Affected mice are viable and appear normal, but are predisposed to a variety of spontaneous neoplasms, particularly lymphomas and sarcomas. Heterozygous mice with a single normal allele develop fewer tumors and they occur at a greater age. These studies have shown that an oncogenic mutation in the p53 gene is not required to predispose animals to tumor development. The mere loss of a normal p53 allele is sufficient.

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**References**.

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Microslide 25

**History**. The submissions came from a 1000 sow, farrow to finish, operation. The farm was experiencing increased death loss in baby pigs in the first two weeks of life, which was most noticeable in the first 3-5 days after birth. Affected baby pigs were weak, failed to nurse and often developed mild diarrhea. The tissues were from three moribund baby pigs.

**Gross Pathology**. The submitted pigs were thin with small amounts of green yellow feces staining the skin around the anus.

**Laboratory Results**. Twenty of the 33 sows were positive by the indirect immunofluorescent assay for the PRRS virus at the 1:20 dilution.

**Contributor's Diagnosis and Comments**. Diffuse acute interstitial pneumonia; etiology--porcine reproductive and respiratory syndrome virus.

Porcine reproductive and respiratory syndrome is referred to by several different names worldwide. In Europe and some areas of the United States it may be referred to as blue ear pig disease, or Lelystad virus, sow infertility and respiratory syndrome (SIRS), or porcine epidemic abortion and respiratory syndrome (PEARS). The disease appears to be caused by a fastidious enveloped RNA virus. Studies indicate some antigenic diversity between strains of the virus. Clinically, the disease presents as reproductive failure (abortions, stillbirths, and weak neonatal pigs), or respiratory disease which is seen in neonatal pigs, or in postweaning pigs. In enzootically infected herds the disease may present with only sporadic reproductive problems and more consistently as respiratory disease in weaned pigs. The virus is immunosuppressive, causing increased disease incidence in affected swine herds, and exacerbations of diseases which are endemic in the herd. Increased incidence of encephalomyocarditis virus, leptospirosis, pseudorabies, staphylococcal dermatitis, TGE, porcine parvovirus or

Actinobacillus pleuropneumoniae may complicate the clinical and histologic presentation of PRRS. In some herds increased incidence of these diseases are the first indication of PRRS infection in the herd. Gross lesions are usually unremarkable in affected piglets. The most common microscopic lesion is a histiocytic and lymphocytic interstitial pneumonia, with nonsuppurative encephalitis and seen less commonly.

**AFIP Diagnosis.** Lung: Pneumonia, interstitial, necrotizing, subacute, diffuse, moderate, with hemosiderosis and edema, crossbred, porcine.

**Conference Note.** In discussing the differential diagnosis, conference participants considered encephalomyocarditis virus (EMCV), swine influenza virus, porcine parvovirus, and to a lesser extent, pseudorabies and cytomegalovirus. Swine infertility and respiratory syndrome (SIRS) is a newly emerging and economically important disease affecting most swine producing countries. The syndrome is characterized by pyrexia and anorexia in nursery and breeding pigs, reproductive failures (stillborn, mummified, and weak-born pigs) in pregnant sows, and interstitial pneumonia in young pigs. As in this case, the pneumonia is characterized by diffuse thickening of alveolar septa by macrophages, lymphocytes and fibrin. Alveoli often contain small aggregates of necrotic cells. Experimentally reproduced cases in gnotobiotic piglets also result in a subacute mononuclear encephalitis, perivasculitis, and myocarditis. There were no gross or microscopic lesions seen in stillborn fetuses. Recent studies have characterized the etiologic agent as a fastidious, nonhemagglutinating, enveloped RNA virus tentatively classified as a non-arthropod-borne togavirus, possibly of the genus Arterivirus, which includes equine arteritis virus. A similar syndrome of reproductive and respiratory disease has been reported in pigs with EMCV (ref. 4).

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Microslide 26

**History**. This 7-month, 4-day-old female American Bison had a 2-week history of nasal discharge, foam around mouth, progressing to limping, dehydration, crusting at mucocutaneous junctions and coronary bands.

**Gross Pathology**. Crusting of all mucocutaneous junctions. Extensive ulceration of tongue and esophagus.

**Contributor's Diagnosis and Comments**. 1. Severe subacute multifocal to coalescing ulcerative esophagitis, with necrotizing vasculitis.

2. Malignant catarrhal fever virus infection.

There are multiple coalescing ulcers of the esophageal mucosa, each with a deep bed of inflammatory cells including many neutrophils. Most of the superficial blood vessels of the ulcerated mucosa contain thrombi. The non-ulcerated surface has a diffuse subepithelial infiltrate of macrophages and lymphocytes, with small numbers of plasma cells and neutrophils. In the deeper layers of the lamina propria, there are foci of inflammation, necrosis and fibrin deposition. A cellular inflammatory infiltrate dissects into the skeletal muscle layers and the peri-esophageal connective tissue. Inflammation of blood vessels in the mucosa, muscularis or adventitia is common, in most cases as an infiltration of the adventitia and to a lesser extent of the media. There is occasional fibrinoid necrosis of segments of the media or adventitia of blood vessels.

The disease in this bison is presumably caused by alcelaphine herpesvirus 1, a lymphotropic gammaherpesvirus affecting domestic and wild ruminants worldwide. In the US, this African form of malignant catarrhal fever has occurred in several species of ungulates in zoos and wild animal parks, and has occasionally escaped from containment into the domestic cattle population. Most of the cases of malignant catarrhal fever in domestic cattle in the US are caused by the sheep-associated virus. From clinical and pathologic standpoints the two forms of

the disease are indistinguishable. The clinical signs range from acute, with sudden death, to subacute, with oronasal discharge and possible neurologic signs, to chronic, with inanition. Gross lesions can be widespread, with inflammation and necrosis of the mucosa of the gastrointestinal, respiratory and urinary tracts, and enlargement of lymph nodes. There is lymphoproliferation, lymphoid infiltration of numerous organs, and vasculitis ranging from lymphoid infiltration of the adventitia to transmural inflammatory infiltration and fibrinoid necrosis. There are two major schools of thought on the pathogenesis of vasculitis, immune complex deposition in vessel walls, versus delayed hypersensitivity. The virologic diagnosis of African MCF is difficult. The PCR technique and in situ hybridization may improve diagnostic capabilities for AHV-1. The sheep-associated virus has historically been even more elusive, and has only recently been isolated for the first time.

**AFIP Diagnosis**. Esophagus: Esophagitis, necrotizing, erosive and ulcerative, subacute, multifocal, moderate, with lymphohistocytic vasculitis and fibrin thrombi, American Bison (Bison bison).

**Conference Note** A differential diagnosis includes malignant catarrhal fever, bovine virus diarrhea, rinderpest, bluetongue, bovine papular stomatitis, and infectious bovine rhinotracheitis. The diagnosis of malignant catarrhal fever is normally based on key histologic features: erosive-ulcerative lesions of the mucosa and skin, lymphoproliferation, and characteristic vasculitis. The typical vascular lesion is an accumulation of primarily mononuclear cells in the adventitia, and a necrotizing fibrinoid vasculitis. Gross lesions associated with MCF were reviewed including conjunctivitis; corneal opacities; small foci of infarction, hemorrhage and inflammation in the kidney and urinary bladder; lymphadenopathy; and erosions and ulcerations of the muzzle and nares, oral mucosa and gastrointestinal tract.

The pathogenesis of MCF is still poorly understood. Initial viral replication occurs in lymphocytes. There is marked T-lymphocyte proliferation with apparent viral-induced transformation of large granular lymphocytes (LGL), a subset of lymphocytes associated with T-suppressor cell and natural killer cell activity. One theory is that these cells become dysfunctional, leading to lymphoproliferation and tissue injury by abnormal natural-killer cells. The possibility of an immune complex-mediated vasculitis or "Arthus reaction" has also been proposed.

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Microslide 27

**History**. This 15-month-old Simmental steer was found dead in a feedlot.

**Gross Pathology**. Cranial-ventral suppurative bronchopneumonia with multifocal abscesses in both lungs. Severe interstitial emphysema with emphysematous bullae in dorsal region of caudal lobes.

**Laboratory Results**. Haemophilus somnus isolated from the lungs. Viral isolation was not attempted.

**Contributor's Diagnosis and Comments**. Acute fibrinopurulent bronchopneumonia with acute bronchiolar necrosis; etiology--Haemophilus somnus.

In the lung section submitted, there is a diffuse fibrinopurulent alveolitis with lesions of purulent and necrotizing bronchiolitis. Subpleural and interlobular septal lymphatics are distended with a fibrinous or fibrinopurulent exudate. A fibrinous pleuritis is also present.

In recent years, we have seen an increased incidence of H. somnus pneumonia in young beef and dairy calves as well as in feedlot cattle. The condition is usually subacute or chronic and is most commonly characterized by a fibrinopurulent bronchopneumonia and bronchiolitis. Lesions of bronchiolitis obliterans can be prominent in some cases. Lesions of diffuse necrotizing bronchiolitis being uncommon in experimentally induced H. somnus pneumonia, it is suspected that concurrent or preceding viral infections (IBR, $PI_3$, REV) might cause these lesions. Pasteurella multocida is also a common cause of suppurative bronchopneumonia in calves.

**AFIP Diagnosis**. Lung: Bronchopneumonia, fibrino-suppurative, diffuse, severe, with hemorrhage and marked

interlobular and pleural fibrinosuppurative exudate, Simmental, bovine.

**Conference Note.** This section was prepared with a hematoxylin-phloxine-saffron stain; the saffron component stains fibrous connective tissue yellow. Recent reports indicate that Haemophilus somnus may be a more important etiology of calf pneumonia than previously recognized, particularly subacute to chronic bronchopneumonias. H. somnus-induced lower respiratory tract disease appears to be much more prevalent than the septicemic infection in calves, which is associated with thromboembolic meningoencephalitis (TEME), diphtheritic laryngitis, chronic tracheitis, and synovitis.

Participants discussed the differential diagnosis for fibrinous pneumonia in cattle including Haemophilus somnus, Pasteurella multocida, Pasteurella hemolytica, Mycoplasma mycoides subsp. mycoides, atypical interstitial pneumonia, and smoke inhalation. Pneumonic infection by Hemophilus somnus results in histologic changes ranging from acute to chronic, purulent to fibrinopurulent bronchiolitis and bronchopneumonia with or without necrosis of bronchiolar walls, vasculitis, thrombosis, and congestion. Pleural and interlobular septal lymphatics are frequently distended by fibrinocellular exudates and/or large thrombi. Grossly, H. somnus pneumonia appears as a cranial-ventral, grey to red-grey, lobular consolidation, often with bronchial exudate, numerous small abscesses, and fibrinous pleuritis. The role of endotoxin in producing fibrin thrombi was discussed.

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**References.**

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Microslide 28

**History.** As part of a research protocol, this 7-month-old, female, Micro Yucatan pig (Sus scrota) received a lethal dose of ricin (6 ug/kg) intravenously and died in severe respiratory distress 22 hours later. Venous blood samples were

obtained pre-injection and 22 hours postinjection.

**Gross Pathology**. At necropsy there was a left ventricular myocardial infarct and 30 ml of straw-colored fluid in the peritoneal cavity.

**Laboratory Results**.

| Test | Preinjection | Postinjection |
|---|---|---|
| Na+ (meq/L) | 145 | 135 |
| K+ (meq/L) | 4.07 | 14 |
| Cl- (mmol/L) | 99.59 | 93.20 |
| Mg+2 (mg/dL) | 2.20 | 7.20 |
| Ca+2 (mg/dL) | 9.65 | 9.17 |
| Phosphorus (mg/dL) | 7.10 | 21.03 |
| BUN (mg/dL) | 14.04 | 41.00 |
| Creatinine (mg/dL) | 0.70 | 1.78 |
| Alk Phos (u/L) | 73.22 | 451.79 |
| AST (u/L) | 50.52 | 1864.56 |
| ALT (u/L) | 57.07 | 85.62 |
| LDH L (u/L) | 818.73 | 5060.89 |
| SDH (u/L) | 4.27 | 774.70 |
| GGT (u/L) | 54.18 | 159.13 |

**Contributor's Diagnosis and Comments**. 1. Kidney: Intravascular fibrin thrombi, diffuse, severe, glomeruli, with diffuse, marked glomerular necrosis; compatible with disseminated intravascular coagulation (DIC).

2. Kidney: Hyaline proteinosis (hyaline droplet nephrosis), multifocal, moderate, cortical tubules.

This case was submitted as an excellent example of intravascular coagulation in the kidney. Fibrin thrombi were also observed microscopically in blood vessels of the lung, spleen, bone marrow and eye. The liver had moderate diffuse centrolobular hepatocellular necrosis, compatible with ischemia.

The lesions induced by lethal intravenous ricin intoxication in laboratory swine are poorly documented. In laboratory mice, rats, rabbits and dogs parenterally intoxicated with ricin, hematological and tissue changes consistent with disseminated intravascular coagulation (DIC) have been reported. These changes included decreased platelet counts, petechial hemorrhages, fibrin thrombi and multifocal necrosis.

The pathogenesis of DIC in ricin intoxication remains speculative. It is unknown whether the ricin induces the formation of intravascular thrombi directly or indirectly. One indirect mechanism of thrombus formation may be via elevated endotoxin levels. A proposed hypothesis postulates that ricin impairs the phagocytic function of Kupffer cells so that they

cannot clear endotoxins from the portal blood. The endotoxins then may produce endothelial membrane damage with resultant platelet activation.

**AFIP Diagnosis**. 1. Kidney, glomeruli and interstitial capillaries: Fibrin thrombi, diffuse, moderate, with glomerular necrosis, micro Yucatan pig, porcine.

2. Kidney, tubular epithelium: Hyaline droplet change, multifocal, moderate.

**Conference Note**. The significance of the densely basophilic material seen in occasional tubular epithelia was not known. Conference participants reviewed the laboratory data provided by the contributor. Platelet count and coagulation profile were not available. The pathogenesis of DIC leading to the formation of glomerular capillary microthrombi was discussed. Hemostatic alterations predisposing to DIC include blood stagnation; decreased clearance of activated procoagulants; or release of tissue thromboplastin, activated procoagulants, or endotoxins into the circulation. Endotoxins' thrombogenic properties include causing widespread damage to endothelium, direct activation of both the intrinsic and extrinsic coagulation pathways, and enhanced expression of tissue thromboplastin on the surface of certain cells.

Changes in the clotting profile associated with DIC were reviewed. Abnormalities in secondary hemostasis screening tests (i.e. One-Stage Prothrombin Time, Activated Partial Thromboplastin Time, and Activated Clot Time) and thrombocytopenia are usually present in cases of fulminant DIC. Schistocytosis, hypofibrinogenemia, and decreased antithrombin III are also frequently present. The Fibrinogen Degradation Products (FDP) test is probably the most common method of confirming DIC, although increased FDPs can occur in other conditions such as severe internal hemorrhage from any cause.

Ricin is a lectin present in the seeds of Ricinus communis; its toxic effects have been well known for nearly a century (ref. 2). Lectins are plant proteins that bind to monosaccharides of glycoprotein receptors on the cell surface. Some lectins, such as ricin and abrin, are toxic by virtue of their ability to inactivate ribosomes and markedly inhibit cell protein synthesis. These lectins may also have therapeutic potential as antineoplastic agents.

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Microslide 29

**History**. This domestic shorthair feline was given rabies vaccine subcutaneously in this site approximately 2 months prior to development of lesion.

**Gross Pathology**. Subcutaneous mass, lumbar region.

**Contributor's Diagnosis and Comments**. Necrotizing pyogranulomatous cellulitis, severe, skin, associated with administration of rabies vaccine.

Lesions of this type are seen with some frequency in cats, and less frequently in dogs.

**AFIP Diagnosis**. Subcutis (per contributor): Steatitis, pyogranulomatous, focally extensive, severe, with lymphoid follicles and amphophilic foreign material, Domestic Shorthair, feline.

**Conference Note**. Although infectious and nutritional causes of steatitis must be ruled out, this lesion was considered characteristic for vaccine-induced panniculitis. The inflammation is moderately well-circumscribed with a linear necrotic tract in the center, rimmed by numerous large macrophages and a mixture of lymphocytes, plasma cells and eosinophils. An amphophilic, amorphous, globular, grey foreign material presumed to be residual vaccine is present within histiocytes and extracellularly. Several lymphoid follicles have formed around the periphery. Special stains (Gram's stain, PAS) failed to reveal infectious organisms.

The incidence of injection site reactions, particularly in cats, has apparently increased with the approval and widespread use of subcutaneous rabies vaccines. In addition to inflammation, these vaccines have been implicated in the development of various sarcomas at injection sites in cats. The majority have been fibrosarcomas, but rhabdomyosarcoma, malignant fibrous histiocytoma and osteosarcoma have also been reported. One theory is that the persistence of aluminum-based adjuvants used in some rabies vaccines results in inflammatory and immunologic reactions as seen in this case, and may eventually induce neoplastic transformation in the involved tissue. Intramuscular rabies vaccinations have also been associated with

sarcomas.

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Microslide 30, Lantern slide 5

**History.** This 4-1/2-year-old, male, pigtail macaque (Macaca nemestrina) was inoculated with the simian immunodeficiency virus and died 30 months later.

**Gross Pathology.** After fixation in 10% buffered formalin the brain was transversely sectioned for gross examination. A well circumscribed 2.0 x 1.5 x 1.5 cm, firm, yellow-white mass with a central cavitation was located within the parenchyma of the right frontal lobe. It extended from the surface of the central fissure rostral to, and extending caudally past, the right corpus callosum.

**Laboratory Results.** No recent laboratory values were available.

**Contributor's Diagnosis and Comments.** Malignant astrocytoma (astrocytoma, grade 3; microcystic astrocytoma).

There is a well circumscribed, expansile, minimally compressive, and unencapsulated neoplasm within the right frontal lobe of the cerebrum. The mass is composed of a sheet of closely packed pleomorphic cells that suggests a tight, but ill-defined, whorling or interlacing pattern. In some sections there are irregular spaces filled with necrotic eosinophilic cellular debris, pyknotic and karyorrhectic nuclei, and red blood cells. There is no lobulation to the mass but in some sections satellite masses can be seen to "bud" as small rounded tumor masses into the surrounding parenchyma. The tumor extends to but does not

infiltrate the leptomeninges.

The tumor cells are fusiform to polygonal in shape with generally indistinct boundaries. The cells have scant to moderate pale gray cytoplasm that appears somewhat longitudinally fibrillar in the spindle-shaped cells. Nuclei are generally centrally located, are polygonal to round to elongate, and where cytoplasm is scant, adjacent nuclei sometimes display nuclear molding. The chromatin is vesiculated. Occasional nuclei have one to two small basophilic to amphophilic nucleoli. The mitotic index is moderate (0-3/Hpf).

There are occasional multinucleated cells distributed throughout the tumor. Multifocally, especially perivascularly, there are small infiltrates of plasma cells and lymphocytes.

Finally, there is multifocal gliosis around the tumor periphery.

Tumors of the central nervous system are relatively rare in non-human primates. There are a few reports of astrocytomas in laboratory primates.

Because grossly the tumor was closely associated with the meninges, was generally firm, and had a well-circumscribed appearance, the primary differential diagnosis of meningioma had to be considered. However, there were central cystic and hemorrhagic spaces present on cut section and microscopically the tumor was unencapsulated, blended smoothly (though abruptly) into the parenchyma, and caused minimal compression of the surrounding parenchyma. Additionally, there was no hint of the lobulation that characterizes meningeal tumors.

Astrocytomas of grade 1 or 2 generally are composed of cells recognizable as protoplasmic, fibrillary, pilocytic, or gemistocytic. In astrocytomas of grade 3 or 4 the cells are anaplastic and by light microscopy are more difficult to identify as being of astrocytic origin.

Immunohistochemistry was performed and the tumor cells were positive for GFAP and S-100, and negative for NSE. These results support the diagnosis of astrocytoma (but are not definitive).

The high cellularity, invasiveness, frequent mitoses, moderate anaplasia, satellitosis, necrotic and hemorrhagic foci, and presence of multinucleated giant cells all argue in favor of malignancy. The lack of marked cellular anaplasia, of pseudopalisades surrounding necrotic areas, of vascular endothelial proliferation, and general lack of nuclear hyperchromatism mitigate against classifying this tumor as a type 4 astrocytoma (or "glioblastoma multiforme"). Thus

classification as type 3 seems appropriate in this case.

In humans, grades 3 and 4 astrocytomas are found predominantly in the frontal lobes, often in association with the corpus callosum. This tumor is more likely to occur in males than females by a ratio of 3 to 2.

We wish to thank Dr. Damon R. Averill, Jr. for his consultation on this case.

**AFIP Diagnosis**. Brain, cerebrum: Astrocytoma, pigtailed macaque (Macaca nemestrina), primate.

**Conference Note**. Conference participants noted that some margins of this tumor are unusually well-circumscribed for an astrocytoma. Neuroglial tumors (gliomas) are derived from glial cells of neuroectoderm origin. These include astrocytoma, oligodendroglioma, ependymoma, and medulloblastoma. Astrocytoma and its more anaplastic counterpart glioblastoma multiforme account for 80% of adult primary brain tumors in humans. Microscopically, well-differentiated astrocytic tumors have been further characterized by the predominate cell type present, fibrillary, protoplasmic, gemistocytic, or pilocytic astrocytes. Astrocytomas tend to become more anaplastic with time. They are typically infiltrative and, in less differentiated tumors, there can be significant histologic variation in appearance in different areas of the same tumor. Criteria normally used to judge malignancy of neoplasms often do not apply as well to gliomas. Metastasis outside the cranial cavity is rare. Features of malignancy include hemorrhage and necrosis, proliferation of vascular endothelium, increased mitotic figures, anisokaryosis, and multinucleated giant cells.

The incidence of spontaneously developing brain tumors in nonhuman primates is reported to be very low. Participants discussed the association of high-level radiation exposure with increased risk of developing primary brain neoplasms. Studies have reported finding brain tumors in up to 14% of monkeys surviving two years or more after exposure to doses of 200 to 1000 rads.

In domestic animals, the highest incidence of spontaneously developing glial tumors occurs in dogs, with an apparent predisposition for brachycephalic breeds. In addition to dogs, astrocytomas have been reported in cats and cattle. They can occur in the brain or spinal cord.

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Microslide 31

**History**. This 2-year-old, intact male Schnauzer was presented to the Veterinary Teaching Hospital at Texas A&M University's College of Veterinary Medicine with a 1-month-long history of labored respiration. Thoracic radiographs showed multiple masses in the chest cavity. Fine needle aspirates of the masses were suggestive of a mesenchymal tumor.

**Gross Pathology**. Approximately 50 ml of serosanguinous fluid was present in the thoracic cavity. A large, 10x8x4cm, white to tan, moderately firm, multinodular mass occupied the cranial mediastinum. Similar appearing but smaller (up to 3cm) nodules were present in the right caudal lung lobe, and the tracheobronchial lymph nodes were firm and enlarged. A 0.6 cm tan-white, moderately firm nodule was present in the left atrial wall.

**Laboratory Results**. CBC showed eosinophilia (5.2 x $10^3/mm^3$).

**Contributor's Diagnosis and Comments**. Lymphomatoid granulomatosis.

Microscopically, the tumor is composed of sheets of large atypical, pleomorphic lymphoreticular cells heavily infiltrated by eosinophils and lesser numbers of lymphocytes and plasma cells. Tumor cells are embedded in a fine meshwork of fibrovascular connective tissue and are characterized by irregular open-faced nuclei with prominent, occasionally multiple nucleoli and a moderate amount of slightly basophilic, well-demarcated cytoplasm. Mitotic figures and binucleated neoplastic cells are common.

Lymphomatoid granulomatosis is a rare neoplastic disease that involves the lungs, intrathoracic lymph nodes and occasionally the liver, hepatic lymph nodes and the spleen of young dogs. Lymphomatoid granulomatosis occurs in humans in which it has been described as an angiocentric, angiodestructive lymphoreticular proliferative and granulomatous disease that primarily involves the lungs, although the skin, kidneys and brain are frequently affected. Recent studies suggest that lymphomatoid granulomatosis is a form of peripheral or post-thymic T cell lymphoma. Persistent eosinophilia and eosinophilic infiltration of the tumor (as in the present case) has been frequently reported in dogs with lymphomatoid granulomatosis. This disease must be differentiated from malignant histiocytosis described in aging Bernese Mountain Dogs; pulmonary nodular eosinophilic granulomatosis (related to heartworm disease); and the giant cell variant of large cell anaplastic pulmonary carcinoma.

**AFIP Diagnosis**. Lung: Lymphosarcoma, with eosinophilic infiltrates, Schnauzer, canine.

**Conference Note**. Clinically and histologically this case is compatible with previously published descriptions of canine lymphomatoid granulomatosis. Conference participants favored a less specific diagnosis due to the lack of clear angioinvasion. Lymphomatoid granulomatosis (LYG) is an obscure disease of humans characterized by pulmonary infiltrates of lymphoid and plasmacytoid cells, with morphology ranging from normal to atypical, and by angioinvasion. Initially localized to the lungs, the disease may spread to the brain, kidneys, liver, and other organs, with up to 50% of patients developing malignant lymphoid tumors. The name lymphomatoid granulomatosis has been used to describe a somewhat similar condition in dogs that differs from human LYG by the presence of large numbers of eosinophils, intrathoracic lymph node involvement, and, in most cases, a lack of lesions in other organs. Binucleate cells and mitotic figures are common. Grossly, there are nodular pulmonary lesions that are indistinguishable from metastatic lung tumors or lymphosarcoma.

The cause of lymphomatoid granulomatosis is unknown; preneoplastic, allergic, and immune-mediated etiologies have all been proposed. Most evidence indicates that the large anaplastic cells in canine LYG are lymphoid in origin; they do not stain for lysozyme or express histiocytic markers, and there is no evidence of phagocytic activity. In dogs, the disease responds well to chemotherapy. Because canine LYG has a much better prognosis than lymphosarcoma, some investigators feel that it represents a pleocellular, but relatively benign variant of T-cell lymphoma. The continued development of immunohistochemical tests to detect surface CD markers on leukocytes of domestic animals should help to better define lymphoproliferative diseases such as this in the

future.

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Microslide 32

**History**. This 4-year-old male English Foxhound presented with mild swaying of the hindquarters which increased in severity with exercise. The clinical signs developed gradually over the previous six months. Muscle atrophy was not a feature and no abnormalities were seen with spinal radiography and myelography.

**Gross Pathology**. There were no significant abnormalities.

**Laboratory Results**. Routine hematologic and clinical chemistry profiles (total protein, albumen, urea, alanine aminotransferase, alkaline phosphatase) were within normal limits.

**Contributor's Diagnosis and Comments**. Spinal myelinopathy, degenerative myelopathy, hound ataxia.

Sections of spinal cord taken at different levels show vacuolar degeneration of lateral and ventral white matter columns. There is relative sparing of dorsal columns. Macrophages are present in small numbers and are located in the

vacuolated fibers. Glial scarring is prominent. Axonal swellings are present only in a small proportion of fibers.

Similar degenerative white matter lesions were seen in the medulla oblongata and mid-brain. These lesions were confined mostly to the medial lemniscus, the median longitudinal fasciculus, and the spinothalamic and spinocerebellar tracts. Isolated vacuolated fibers, some containing macrophages, were also present in otherwise normal white matter. Examination of resin-embedded sections showed vacuolated myelin sheaths around apparently intact axons and thick-thin transitions in myelin sheath thickness (photomicrographs). Mixed sensory and motor peripheral nerves and muscle histochemical fiber type profiles appeared normal.

This is a case of hound ataxia, a condition reported in English Foxhounds, Harriers and Beagles maintained mainly on a diet of paunches (ruminant stomachs) with occasional meat supplementation (1,2,3,4). Further cases cease to occur when the ruminant stomachs are replaced with raw meat in the diet. The structural changes were indicative of a primary myelinopathy and similarities were noted with changes described in subacute combined degeneration of the spinal cord in human beings, a neuropathy caused by methionine and methylation deficiency (4,5,6). Mean serum methionine levels were significantly lower ($P>0.01$) and mean liver methionine synthetase levels were significantly greater ($P>0.01$) in affected dogs restored to a balanced diet. The elevated methionine synthetase levels possibly reflected compensatory reactions to the associated dietary change.

**AFIP Diagnosis**. Spinal cord, myelin sheaths: Dilation, diffuse, mild to moderate, with axonal degeneration, English Foxhound, canine.

**Conference Note**. In a primary myelinopathy, as is suggested here, destruction or loss of myelin precedes any axonal changes. This is distinct from the secondary demyelination (Wallerian degeneration) in which myelin loss occurs subsequent to initial axonal injury, such as compressive "wobbler" myelopathies in the dog and horse. This lesion shares histomorphologic similarities to degenerative myelopathies described in Afghans, Rottweilers, Miniature Poodles, Jack Russel Terriers, German Shepherd Dogs and other breeds of dogs. Many are thought to be hereditary. It has also been compared to the demyelinating condition in people linked to a defective synthesis of methionine resulting from a vitamin $B_{12}$ (cobalamine) deficiency. Although the definitive pathogenesis has not been determined, a nutritional or toxic etiology seems likely given the common dietary history and the different breeds of dogs affected. The suspected cause of this condition in dogs is a methionine deficiency associated with a diet of predominately

ruminant stomachs (paunch). Methionine donates methyl groups needed in the synthesis of choline, a vital component of myelin, and is therefore critical for continued myelin biosynthesis.

Ultrastructural examination of these spinal cords revealed myelinated axons that varied from normal to having disproportionately thin myelin sheaths. Many axon sheaths were vacuolated and disrupted. Commonly, fibrous astroglial cell processes were located between myelinated axons and deposits of myelin debris.

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Microslide 33, Lantern slide 6

**History**. This 15-month-old CD-1 control mouse was used in a carcinogenicity study and was submitted for necropsy in moribund state.

**Gross Pathology**. Spleen, thymus and many lymph nodes markedly enlarged and green.

**Laboratory Results**. None.

**Contributor's Diagnosis and Comments**. Leukemia, granulocytic.

The diagnosis of granulocytic leukemia rather than granulopoiesis was based upon the uniformity in the development of the granulocytes (band and early segmented stage), extremely wide distribution of the granulocytes, high mitotic activity and the absence of any inciting inflammatory process. The incidence of granulocytic or myelogenous leukemia in aged CD-1 mice in this laboratory is approximately 1/1000.

**AFIP Diagnosis**. Liver, spleen, lymph node: Granulocytic leukemia, CD-1 mouse, rodent.

**Conference Note**. Conference participants discussed the importance of differentiating granulocytic leukemia from severe myeloid hyperplasia. In this case, features supporting the diagnosis of granulocytic leukemia include the following: extensive replacement of both white pulp in the spleen and follicles in the lymph node by neoplastic cells; the high mitotic rate with several atypical mitoses; the lack of a pronounced extramedullary hematopoiesis corresponding to the severe granulocytic response; the presence of immature myeloid cells in the circulation; the invasiveness of the cells in the liver; the marked enlargement of the spleen (3-4 times normal); and the lack of an associated inflammatory lesion found at necropsy. Another important criterion to consider is the presence or absence of various stages of granulocyte maturation. Typically, granulocytic leukemia consists of a more uniform population of immature myeloid cells. Although the range of maturation present in these cells was considered unusual for granulocytic leukemia, including many ring forms and more mature granule-containing segmented cells, there was a overall predominance of the immature stages. A similar range in developmental stages is described in chronic myeloid leukemia of people.

Participants noted that numerous macrophages within these tissues contained intracytoplasmic, eosinophilic, needle-shaped crystals. Similar appearing structures have been associated with a lung lesion in mice termed acidophilic macrophage pneumonia (AMP). These crystalloid inclusions are thought to be derived from the breakdown of eosinophil granules. AMP has been described as the major cause of death in motheaten mice, a mutant C57BL strain.

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Microslide 34, Lantern slide 7

**History**. This 1-year-old female white lipped tamarin (Saguinus lobictus) was found icteric and lethargic in its cage. Within 30 minutes she developed dyspnea, seizures, epistaxis, and hemorrhage from oral cavity, and subsequently died during seizures.

**Gross Pathology**. Marked jaundice of oral mucous membrane, subcutis and viscera. Lungs were congested.

**Laboratory Results**. Serum samples taken at necropsy were negative for Leptospira sp.

**Contributor's Diagnosis and Comments**. Liver, hepatocellular dissociation, multifocal, moderate, acute with cholestasis. Syndrome: Acute Leptospirosis.

Warthin-Starry stained sections reveal spirochetes within renal tubules (See photomicrograph provided). They are morphologically compatible with Leptospira sp.

Natural infection of New World primates with leptospirosis is rare. Marked jaundice and mild hepatic lesions on light microscopy have been reported in primates with acute leptospirosis. Three days prior to this animal's demise two other tamarins had acutely developed icterus and died. Food or water contamination by infected rats is the most likely mode of transmission.

**AFIP Diagnoses**. 1. Liver: Hepatocellular dissociation, diffuse, moderate, white lipped tamarin (Saguinus lobictus), primate.
2. Liver: Hepatitis, portal, subacute, multifocal, mild.
3. Kidney: Nephritis, tubulointerstitial, acute to subacute, multifocal, mild to moderate.

**Conference Note**. A Warthin-Starry procedure (pH 4.0) performed on a section of kidney revealed numerous spirochete organisms both in the inflammatory foci and within normal-appearing tubules. Most sections contained relatively few areas

of interstitial inflammation. The presence of many neutrophils in the interstitium and within scattered tubules was considered atypical for leptospirosis. Occasional foci of tubular degeneration and necrosis were present. The predominant lesion in the liver was hepatocellular dissociation, a nonspecific change also reported with blue-green algae toxicity, feline panleukopenia, and high fever.

The leptospira species pathogenic for man and animals is L. interrogans, which is composed of over 180 different serologic variants or serovars. Serovars are grouped into approximately 20 serogroups on the basis of shared antigens, each serogroup having its preferred animal host or hosts. The pathogenesis of leptospira infection was discussed. The organisms cross intact mucous membranes or abraded skin, enter the circulation and disseminate hematogenously throughout the body. In the kidney, they migrate through vascular endothelium to reach the interstitial space, eventually traversing intercellular junctions to reach the tubular lumina . Icterus is a common clinical sign in most species, resulting from toxin-induced hemolysis and hepatocellular injury. Petechial and ecchymotic hemorrhages are often seen on mucous membranes and visceral surfaces.

In humans, leptospirosis is usually an acute, mild, self-limiting, febrile illness. A less common, severe form known as Weil's disease is associated with hemolysis, jaundice, focal hemorrhages, cholestasis with mild, focal hepatocellular degeneration, interstitial nephritis, tubular degeneration and necrosis, and focal skeletal muscle necrosis. Natural leptospirosis in nonhuman primates is reportedly uncommon and the severity of infection may be species dependent. As with humans, an acute, fatal illness associated with clinical jaundice, hemorrhage and fever with only mild elevations in liver function tests is suggestive of leptospiral infection.

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Microslide 35, Lantern slide 8

**History**. Purified Cryptosporidium parvum oocysts were administered by gastric gavage to a group of BALB/C nu/nu mice.

**Gross Pathology**. Some mice had yellow tissues and extremities (icterus). Livers were diffusely swollen, had an accentuated reticular pattern, and numerous pinpoint to two mm white spots. Gallbladders and bile ducts were distended, opaque, and had thickened walls. Pancreas was severely atrophied and remaining tissue was dull gray. Soft formed feces were present in colons.

**Laboratory Results**. All mice were shedding variable numbers of Cryptosporidium oocysts. Oocysts were also detected in bile aspirated from gallbladders. Liver bacterial cultures were negative.

**Contributor's Diagnosis and Comments**.
Cholangiohepatitis and cholecystitis, granulomatous, chronic-active, multifocal to diffuse, moderate to severe, with biliary hyperplasia, focal biliary ulcerations, periportal hepatocyte coagulation necrosis, and biliary Cryptosporidium. Etiologic diagnosis - hepatobiliary cryptosporidiosis.

Cryptosporidium is a widespread pathogenic protozoan causing intestinal infections in humans and other animals. Diarrhea may be life threatening in immunocompromised hosts. Extraintestinal cryptosporidiosis is far less common. In humans with AIDS, Cryptosporidium organisms have been associated with inflammation of the extrahepatic bile ducts, intrahepatic bile ducts, and pancreatic ducts which may account for manifestations of pancreatitis, cholangitis, and obstructive cholestasis. SIV-infected Rhesus monkeys and immunodeficient Arabian foals have been reported with biliary and pancreatic cryptosporidiosis. In the athymic nude mouse model, Cryptosporidium causes cholecystitis, cholangiohepatitis, and pancreatitis due most likely to an ascending infection from the intestinal tract to bile and pancreatic ducts. Hepatobiliary cryptosporidiosis has also been reported in SCID and NIH III (bg/nu/xid) mice.

Slides submitted for this conference contain tissue sections from four mice and five different blocks; therefore, some variability is to be expected. In this nude mouse model of disseminated cryptosporidiosis, the extent and severity of bile duct inflammation is remarkable. No pathogens or disease processes other than cryptosporidiosis were detected in controls of infected mice, though the possibility of an undetected co-pathogen cannot be totally ruled out. Foci of acute hepatocyte coagulation necrosis may be due to ischemia - rare fibrin thrombi can be found in portal veins.

**AFIP Diagnoses.** 1. Liver: Cholangiohepatitis, chronic-active, multifocal, moderate, with epithelial hyperplasia and adherent coccidia, Balb/c nu/nu mouse, rodent, etiology--- consistent with Cryptosporidium spp.
2. Liver, hepatocytes: Necrosis, multifocal, random, with acute inflammation.

**Conference Note.** A 2X2 slide depicting the gross lesions in an affected mouse was provided. Hepatomegaly and a markedly distended gallbladder and common bile duct are present. Histologically, portal and periportal areas exhibit moderate fibrosis and a prominent, mixed inflammatory cell infiltrate. Bile ducts are dilated and hyperplastic and often contain cryptosporidial organisms attached to the luminal surface. Multifocal areas of coagulative necrosis with little accompanying inflammation are also present within the liver. Participants discussed a differential diagnosis for acute hepatic degeneration and necrosis in mice that included mouse hepatitis virus, ectromelia, reovirus, mouse adenovirus, endotoxin and ischemia.

Cryptosporidium is an intracellular coccidian parasite of mammals, birds, and reptiles. The parasite develops asexual (meronts) and sexual (macrogametocytes and microgametocytes) lifeforms similar to other coccidia, although the size (1-6 µm) and the location of these various stages within an extracytoplasmic parasitophorous host vacuole are unique. Cryptosporidium infections of people primarily cause a transient, infectious diarrhea in children, similar to giardiasis. In AIDS patients and other immunodeficient individuals, it can cause a severe and potentially fatal chronic malabsorptive diarrhea. Utilization of athymic (nude) mice as an animal model has demonstrated the importance of T-cell immunity in controlling cryptosporidial infections. Recent studies have suggested that both CD4+ T lymphocytes and gamma-interferon act synergistically to prevent initiation of cryptosporidium infections, but may act through independent mechanisms to limit the extent or duration of infection.

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Microslide 36

**History**. Weight loss, progressive weakness were observed in two adult (6 and 10 year old) male marmosets; both were euthanatized.

**Gross Pathology**. Pancreas: partial adhesions with stomach; all other organs without significant alterations (both animals).

**Laboratory Results**. Clinical pathology (both animals): slight anemia; parasitologic examination of feces negative. However, nematode (spirurid) eggs have occasionally been found in the feces of other marmosets of the facility.

**Contributor's Diagnosis and Comments**. Pancreatitis, chronic, with dilated ducts and ductuli containing nematodes. Etiology: Trichospirura leptostoma.

The pancreatic ducts and ductuli are dilated and contain cross sections of nematodes. In some areas there is little tissue response to the parasite, whereas in other regions inflammation and fibrosis can be observed. The inflammatory infiltrate is mainly lymphocytic. Pigment deposits are occasionally present, and show a positive reaction in special staining for lipofuscin. Additionally, acinar atrophy is found in various areas. However, the atrophy is not severe enough to cause functional insufficiency of the exocrine pancreas. A chronic enteritis is usually also present in affected animals as well as a slight to severe anemia.

According to the literature, the parasite (Trichospirura leptostoma) can be found in Callithrichs, Callicebus, Saimiri and Aotus monkeys and is very common. The worms measure up to 2 cm in length and produce typical thick-shelled, spirurid eggs. Most often, there should be little tissue response to the parasite. The life cycle of the trichospirura is dependent on arthropods as an intermediate host. Investigations in our facility have shown that cockroaches acted as intermediate hosts. According to the

literature, infection with trichospirura is usually asymptomatic. However, in our facility a heavy infestation together with chronic enteritis and anemia was considered to be the cause for the bad general condition in some marmosets.

**AFIP Diagnoses**. 1. Pancreas, interlobular ducts: Ectasia, multifocal, moderate, with periductal lymphoplasmacytic inflammation, intralobular duct proliferation, and intraluminal nematodes, marmoset (Callithrix jacchus), primate.
2. Pancreas, acini: Atrophy and loss, lobular, multifocal, mild.

**Conference Note**. The sections contain several intraductal tangential sections of coiled, adult male and female spirurid nematodes. Morphologic features noted by participants included an outer cuticle with spines, polymyarian, coelomyarian musculature, prominent lateral cords, a triradiate muscular esophagus, a large intestine lined by many uninucleate cells, sperm-filled testis, and less frequent sections of thick-shelled, embryonated eggs. Multifocal lobules contained areas interpreted as acinar atrophy and fibrosis and, less commonly, areas of ductal proliferation. The periductal inflammation is primarily mononuclear with a relatively mild eosinophilic component. This may be due in part to the intraductal location of the parasite. The inflammation is rarely associated with damage to acinar tissue.

The prevalence of Trichospirura leptostoma in captive populations of marmosets may be underestimated. The parasite burden is often low and may be localized within the gland, and infections are typically asymptomatic. It is recommended that longitudinal sections of the pancreas be collected when screening for this parasite.

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Microslide 37

**History**. This 18-month-old miniature pony was in apparent normal health Thursday evening, October 11, 1991, became

sick Friday with rapidly progressive neurologic disease resembling EEE or Rabies. Euthanasia was performed Saturday by the attending veterinarian.

**Gross Pathology**. Severe diffuse pulmonary edema; severe splenic congestion; brain and other organs were without visible lesions.

**Laboratory Results**. Part of brain was sent to Yale Arbovirus Laboratory for EEE virus isolation and mouse inoculation and EEE was confirmed by Dr. Robert Shope.

**Contributor's Diagnosis and Comments**. Severe acute diffuse meningoencephalitis caused by EEE virus.

Most of the cerebral cortex and midbrain were involved. There was edema of neuropile, severe vasculitis with endothelial hyperplasia, large perivascular cuffs in both brain and meninges with mononuclear cells. Scattering neutrophils are present among glial cells in the most severely affected parts of the brain which also showed occasional neuronal necrosis. The scarcity of neutrophile infiltration is unusual and is probably the result of the short duration of the disease (2 days).

EEE is caused by an arbovirus (Alphavirus of the family Togaviridae), transmitted from wild birds to man and horses by mosquitoes, causing severe neurologic disturbances with sleepiness, blindness, paralysis, and often death. Outbreaks, mostly in August and September, have occurred intermittently in the Northeast and Mid-Atlantic states with over 80 human fatalities since EEE was first recognized in 1938. Severe outbreaks are often seen in years with severe spring rain storms, causing flooding and formation of prime mosquito habitats.

The native wild birds of the northeast (grackles, blackbirds, blue jays, catbirds, herons, egrets, ibis, robins, and towhees) frequently show virus infection and/or antibodies without having clinical or histopathological evidence of disease. Non-native birds of North America such as pheasants and partridges, together with horses and man, are highly susceptible.

The primary biologic vector for EEE virus in birds is the cedar marsh mosquito, Culiseta melanura of the family culicidae. Its habitat is fresh water swamps of the eastern seaboard from southern Maine to the Carolinas. It feeds commonly on wild birds and is the most important biologic vector transmitting the virus from wild birds to pen-raised pheasants and chuckar partridges. It rarely bites mammals, such as man, and horses, whereas other mosquitoes, notably Aedes veans and solicitans and Culex species feed on birds and mammals.

**AFIP Diagnosis**. Brain, cerebrum: Meningoencephalitis,

subacute, diffuse, moderate, with vasculitis and neuronal necrosis, miniature horse, equine.

**Conference Note.** In arriving at a morphologic diagnosis, the modifier subacute was preferred to nonsuppurative to describe the mix of neutrophils and mononuclear cells in the cellular infiltrate. Inflammatory changes are more severe in the gray matter. In addition to the vascular lesions, scattered neuronophagia is present. Although not seen in this case, occasional intranuclear inclusions similar to those in Borna disease have been described in EEE infections. Typically, there are no gross lesions. Affected horses are initially pyrexic and depressed with eventual onset of a variety of neurologic signs including compulsive restlessness, paralysis, somnolence and blindness. A differential diagnosis includes other arboviral encephalitides (WEE, VEE), rabies, equine viral rhinopneumonitis (EHV-1), African horse sickness, Borna virus, hepatoencephalopathy and equine protozoal encephalomyelitis.

Eastern Equine encephalitis (EEE) occurs primarily, but not exclusively, along the Atlantic and Caribbean seaboards. Certain species of wild birds are relatively resistant to clinical disease and serve as the primary reservoir host of the EEE virus. In mammals, EEE infections are most important in horses and humans. Because the disease in these species is frequently fatal and the level of viremia is usually too low for transmission to arthropod vectors, they are considered dead-end hosts. Guinea pigs and white mice are also highly susceptible. A case of EEE in an adult cow was recently reported (ref.9).

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Microslide 38

**History**. This 20-month-old, female emu (Dromaius novaehollandie) was from a flock comprised of twenty-four adult breeders which was located in southern Louisiana. During the late summer of 1991, sixteen birds were affected by an acute disease characterized clinically by depression, recumbency, regurgitation and profuse, usually bloody, diarrhea. The course of illness was short and resulted in mortality in fourteen birds despite intensive supportive therapy.

**Gross Pathology**. Consistent gross findings in the ten birds necropsied included blood-stained feathers around the vent and ecchymotic hemorrhages distributed over the serosa of the intestine. The lumen of the intestinal tract was either devoid of ingesta or contained variable amounts of unclotted blood and mucus. The mucosa was deeply reddened, but in most cases was otherwise grossly normal, although fibrin was loosely adherent to it in some areas. Lesions seen in some birds included patchy subcapsular hemorrhages and a friable texture to the liver, ecchymotic hemorrhages on the epicardial and endocardial surfaces of the heart, slight enlargement and congestion of the spleen, and hemoperitoneum.

**Laboratory Results**. Microbiological culture of various tissues failed to demonstrate a consistent bacterial pathogen. Screening of liver by high performance liquid chromatography for the presence of anti-coagulant agents was negative. An inoculum prepared from a pool of jejunum, liver, and spleen was cytopathic for Vero cell monolayers. The cytopathic agent was identified as a Togavirus by electron microscopy and confirmed to be eastern equine encephalomyelitis virus by complement fixation. Positive seroconversion to the virus was confirmed in the two surviving birds.

**Contributor's Diagnosis and Comments**. 1. Hepatitis, necrotizing, widespread, piecemeal to multifocal random, severe,

acute, with hepatocellular disassociation and hemorrhage, liver, emu.

2. Splenitis, necrotizing, diffuse, severe, acute with necrotizing vasculitis of sheathed capillaries, spleen, emu.

Etiology: Eastern Equine Encephalitis virus.

Of interest in this case is the differing viscerotropism of the EEE virus in emus. Brain from all birds was examined and lesions were not found. Microscopic findings in the intestine were not dramatic and consisted of hemorrhage in the lamina propria and necrosis of villus tips in some areas. When encountered, elements of the diffuse lymphoid system were necrotic. The prominent mononuclear cells in the walls of the sheathed capillaries of the spleen are thought to be the cells to which systemic antigen is first presented and were virtually obliterated in infected emus. The hemorrhage in multiple tissues was thought to be due to a terminal coagulopathy.

It can be speculated that emus are naive hosts, being more acclimated to arid climates and unaccustomed to the mosquito inhabited swamps of Louisiana. Death may have resulted before the neurotropic effect of the virus could be realized. In most other avian species in which EEE causes overt disease, clinical signs and lesions are confined to the central nervous system; however, a disease similar to that in emus has been described in whooping cranes (Dein et al).

**AFIP Diagnoses.** 1. Liver, hepatocytes: Necrosis, diffuse, severe, emu (Dromaius novaehollandie), avian.
2. Spleen: Vasculitis, necrotizing, acute, diffuse, severe, with lymphoid necrosis.

**Conference Note:** In contrast to the neurotropic form of eastern equine encephalitis seen in the previous case, these sections depict the acute, viscerotropic form that has been infrequently described in birds such as emus and cranes. The disease is characterized by ascites, esophageal varices, and extensive necrosis of hepatocytes, periarteriolar sheath cells in the spleen, and glomerular tufts in the kidney. Renal gout is a common secondary finding in affected birds. EEE in birds is more often associated with lesions limited to the central nervous system consisting of a nonsuppurative encephalomyelitis and vasculitis without appreciable neuronal degeneration or neuronophagia.

The inherent differences among various avian species in susceptibility to the EEE virus is striking. In its sylvatic cycle, the virus is transmitted by mosquitoes between many species of native birds which develop only subclinical infection. Other species such as pheasants, chukkar partridges, cardinals, and sparrows are highly susceptible to infection and develop serious disease. Morbidity and mortality are usually very high.

Turkeys, ducks and pigeons are also susceptible with deaths primarily seen in younger birds. Infected chickens seldom develop clinical disease. In some species, cannibalism of sick or dead birds by others in the flock is an important method of transmission. As ratite (emu, ostrich, and rhea) production increases in popularity, diseases such as EEE may become increasingly important. Vaccination of susceptible flocks prior to the mosquito season is an effective method of prevention.

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Microslide 39, Lantern slides 9, 10

**History.** This 1-year-old, male opossum (Didelphis virginiana) from the Knoxville Zoo had an 8 day history of poor appetite, soft stools and lethargy; clinical signs progressed to marked depression, tachypnea, tachycardia and blindness. After a two day course of treatment with oxytetracycline the animal was euthanatized. A CBC three days prior to euthanasia was normal.

**Gross Pathology.** The pleural cavity contained 5 ml of clear yellow fluid. There were disseminated, variably discrete, 2-10 mm diameter, soft to firm, pale tan, raised foci in all lung lobes (photo). A 5 x 3 x 3 cm firm to friable yellow mass was present in the mesentery; the mesenteric lymphatics were distended by multiple to coalescing 2 mm, soft, beaded nodules (photo). The pancreas had multiple, randomly distributed, friable, 1-6 mm, white to tan foci.

**Laboratory Results.** Lung: Mycobacterium avium-intracellulare, serotype 1 was cultured and subsequently typed by the Veterinary Services Laboratory, Ames, IA.

**Contributor's Diagnosis and Comments.** 1. Lung: Moderate, multifocal, subacute, necrotizing and granulomatous pneumonia, opossum (Didelphis virginiana).

2. Pancreas: Moderate, multifocal, subacute,

necrotizing and granulomatous pancreatitis.
Etiology: Mycobacteriosis.

The pulmonary and pancreatic lesions are attributed to M. avium-intracellulare serotype 1 infection. The pancreas has necrotic inflammatory foci containing colonies of acid-fast bacilli by the Fite-Faraco stain. Occasional macrophages in the peripheral histiocytic/lymphocytic infiltrate contain acid-fast bacilli (photo). Multinucleate macrophages are rare. The lungs have poorly delineated, multifocal to coalescing areas of marked alveolar infiltrates of foamy macrophages with lesser numbers of lymphocytes and alveolar septal histiocytic/lymphocytic infiltrate, marked type II pneumocyte hyperplasia and central necrosis with a variable neutrophilic infiltrate. Necrotic debris occasionally extends into secondary bronchi. Rare, intact and fragmented, acid-fast bacilli (0.2 x 1.2 um) were demonstrable within the vacuolated cytoplasm of macrophages.

Mycobacteria are aerobic, acid-fast bacteria. The M. avium-intracellulare complex (MAI) are ubiquitous, facultative, zoonotic, Runyon group III mycobacteria. Of the at least 31 serovars of MAI, serovars 1, 2, 3, and 8 are the most common isolates in animals and man. MAI infections have been reported in numerous domestic and exotic species. Identification of the organism is based on staining properties (acid-fastness), culture requirements, conventional biochemical tests, HPLC, and nucleic acid probes.

MAI infections are often associated with infiltrative enterocolitis and mesenteric lymphadenitis with variable pulmonary, hepatic, splenic, integumentary, and CNS involvement. Mycobacterial lesions have been classically characterized as tuberculoid or lepromatous. The increased incidence of MAI infections, especially in immunocompromised human patients, has resulted in the recognition of more unusual or atypical reactions, eg. more necrosis, less cavitation (human), less granulomatous inflammation and lack of encapsulation. The pancreatic and pulmonary (as well as mesenteric lymph node, adrenal, liver, myocardial and brain) lesions in this case were unusual and similar to lesions described in non-immunosuppressed macaques and immunosuppressed humans.

**AFIP Diagnoses**. 1. Lung: Pneumonia, necrotizing, subacute to granulomatous, multifocal, severe, with type II pneumocyte hyperplasia and pleuritis, opossum (Didelphis virginiana), marsupial.
2. Pancreas: Pancreatitis, necrotizing, subacute to chronic, with acinar loss and duct proliferation.

**Conference Note**. Mycobacterium avium is primarily an avian pathogen. With a few exceptions, mammals are relatively resistant to this ubiquitous organism. Interest in understanding

the pathogenicity of the M. avium-intracellulare complex (MAI) has increased in the last decade as MAI has become one of the most common causes of disseminated infections in AIDS patients. In humans, M. avium is normally an opportunistic infection of those with depressed T-cell dependent, macrophage-mediated immune mechanisms. Both innate (genetic) and acquired factors are involved in resistance. Immunity to mycobacteria is centered on the ability of macrophages to inhibit the growth of intracellular bacilli. Intracellular killing depends primarily on oxygen-independent microbicidal mechanisms. Studies have shown that tumor necrosis factor and interleukin-2 are important in mediating this mycobactericidal activity.

The necrotizing and granulomatous lesions seen in this opossum are very different from the tuberculoid granulomas associated with M. tuberculosis and M. bovis infections or the lepromatous-type inflammation typically described with MAI infections of SRV and SIV infected macaques. Conference participants discussed the apparent increased susceptibility of marsupials for mycobacterial infections, particularly Mycobacterium avium. Numerous deaths in old world marsupials such as the tree kangaroo have been attributed to mycobacteriosis. Primary sites of infection include lung, intestine and bone suggesting that inhalation, ingestion, and inoculation from fight or bite wounds may all be important routes of infection. To limit the risk of exposure to M. avium in captivity, birds and marsupials should not be housed together.

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Microslide 40

**History**. This 2-year-old, male Nutria presented with an acute episode of marked depression, dyspnea, and ataxia. Following anesthesia for radiology, the animal was noted to be only minimally responsive to external stimuli. Radiographs revealed that the intestines were gas distended. Supportive therapy consisting of subcutaneous fluids and trimethoprim-sulfamethoxazole was initiated. This animal's condition continued to deteriorate and it died overnight.

**Gross Pathology**. Both ventricles of the heart were enlarged and the left ventricle contained pale myocardial streaks. There was mild, diffuse pulmonary edema. Several pinpoint to 1 cm diameter hemorrhagic ulcers were present in the gastric mucosa. A 5 mm diameter hematoma was located over the caudal aspect of the right cerebral hemisphere.

**Contributor's Diagnosis and Comments**. Brain, meningo-encephalitis, nonsuppurative, with neuronal intracytoplasmic inclusions.
Etiology: Rabies virus.

Occasional neurons and glial cells contained eosinophilic intracytoplasmic inclusions compatible with Negri bodies. These inclusions were most numerous in hippocampal regions of the cerebrum. Because rabies was not suspected at the time of necropsy, samples of brain were not frozen for testing with standard antirabies virus antibodies. The diagnosis of rabies was confirmed by detection of the virus in formalin-fixed sections of brain submitted to the Centers for Disease Control in Atlanta, GA.

Although rabies is primarily a disease of carnivores and bats, this case illustrates that any mammal can be infected with the virus. Prior to 1977, rabies in wildlife in the mid-Atlantic region of the United States was primarily encountered sporadically in foxes and bats. Since 1977 however, there has been an epidemic of rabies in raccoons that has spread throughout this area including Washington, DC.

This nutria was housed in an outdoor exhibit for approximately one year before it died. Although there was no history of this animal having bite wounds or other injuries indicative of an animal attack, we assume that it had been bitten by a rabid raccoon at some point during this time.

In addition to the meningoencephalitis present, foci of subacute myocardial degeneration and necrosis were present which apparently affected cardiac function and led to the pulmonary edema. The cause of the cardiac lesions was not determined. The acute hemorrhagic gastric ulcers are common findings in stressed

rodents.

**AFIP Diagnosis**. Brain: Meningoencephalitis, nonsuppurative, diffuse, mild, with neuronal degeneration and necrosis, and intracytoplasmic eosinophilic inclusion bodies, nutria (Mycocaster coypus), rodent.

**Conference Note**. Although inflammatory changes usually accompany rabies infections, they can be very mild or absent. Some species variation exists. Lesions tend to be more severe in dogs compared to the relatively mild changes observed in ruminants. The most prominent lesions are usually found from the pons to the hypothalamus and in the cervical spinal cord. Changes noted in these sections include congestion, occasional small glial nodules, minimal perivascular cuffing by mononuclear cells, mild inflammation and edema of the meninges, and neuronal degeneration and necrosis. Neuronal lesions are characterized by both swelling with central chromatolysis, eccentrically positioned nuclei, and loss of Nissl substance and, in other areas, shrunken angular neurons with hyperchromatic nuclei. Neurons throughout the section including the Purkinje cells of the cerebellum frequently contain eosinophilic intracytoplasmic inclusions, or Negri bodies. These inclusions vary in size and shape and are reported to occur most commonly in the hippocampus of carnivores and in Purkinje cells of ruminants.

Rabies infection is rare in rodents and lagomorphs, but an increased number of cases in these species was observed in the mid-Atlantic states concurrently with the raccoon rabies epizootic occurring in the 1980s. Woodchucks (Marmota monax) were affected much more frequently than other rodents. Recently, oral vaccines have been developed in an attempt to contain outbreaks of rabies in wildlife.

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Microslide 41

**History**. This adult, female, Sprague-Dawley rat presented with a bilateral diffuse thickening of the auricular pinnae. No other clinical signs were noted. There was no evidence of trauma to the ears, and no other rats in the colony were affected. The rat had not been used in research protocols.

**Gross Pathology**. Both ears were diffusely thickened throughout the pinnae to twice the normal thickness.

**Contributor's Diagnosis and Comments**. Chondritis, granulomatous, diffuse, moderate, pinna.

Auricular chondritis, also known as auricular chondropathy, is a spontaneous disease of auricular cartilage. This disorder is characterized grossly as a thickening of the auricular pinnae. The lesions are typically bilateral and diffuse to nodular. Chondrolysis and mineralization are often a part of the lesion. Microscopically, the lesion consists of a proliferation of cartilage with an accompanying granulomatous inflammation. This condition has been reported in the Sprague-Dawley, Wistar, and Fawn-hooded rats. Similar lesions can be produced experimentally in rats immunized with type II collagen. Auricular chondritis has been proposed as a model for relapsing polychondritis, a human disease in which several cartilage-containing tissues, including the ear are affected.

**AFIP Diagnosis**. Ear, pinna: Chondritis, granulomatous and proliferative, chronic, diffuse, moderate with mineralization, Sprague-Dawley rat, rodent.

**Conference Note**. The majority of the auricular cartilage in these sections has been replaced by granulomatous inflammation that surrounds nodules of proliferating immature cartilage and fragmented, mineralized remains of necrotic cartilage. Participants felt that the inflammation was much less prominent around preexistent cartilage. Two distinct early processes have been described histologically to explain the development of this lesion, chondrolysis and granulomatous inflammation.

The primary cause of spontaneous auricular chondritis in rats is unknown. It is a progressive, bilateral, degenerative change that differs from relapsing polychondritis of people by the lack of acute inflammation and by confinement of lesions to the ear. Circulating antibodies to type II collagen have been reported in people with relapsing polychondritis. The disease typically involves cartilage at multiple sites including the ear, nose, trachea, and ribs.

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Microslide 42

**History**. This 3-month-old, male, mixed breed dog was presented comatose with a history of anorexia, diarrhea and vomition.

**Laboratory Results**. Canine adenovirus 1 isolated from liver.

**Contributor's Diagnoses and Comments**. 1. Moderate multifocal necrosis, liver, with Cowdria type A inclusions in hepatocytes, endothelium and Kupffer cells.
2. Cowdria type A inclusions in glomerular endothelial cells, kidney.
Lesions were consistent with canine adenovirus 1.

Vaccination has decreased the incidence of disease caused by canine adenovirus 1 (CAV-1) to a rarity. CAV-1 causes clinical disease in dogs, foxes, and other Canidae. Parenchymal cells of the liver and vascular endothelial cells of multiple tissues are targets of viral localization and injury.

**AFIP Diagnoses**. 1. Kidney, glomerular and interstitial vasculature: Basophilic intranuclear inclusion bodies, multifocal, mild, mixed breed, canine.
2. Kidney, glomeruli: Synechia, multifocal, mild.
3. Liver: Necrosis, centrilobular, multifocal, moderate with basophilic intranuclear inclusions.

**Conference Note**. Inclusions in the liver were noted in endothelial cells, hepatocytes and Kupffer cells. Participants discussed the gross lesions associated with canine adenovirus 1 (CAV-1). Ecchymotic and paintbrush hemorrhages on serosal surfaces, congestion and edema of superficial lymph nodes, fibrin on the surface of the liver and marked edema of the gallbladder are common findings. Hemorrhages can also occur in the lung, kidney and brain. In a minority of cases, local deposition of circulating immune complexes in the kidney and eye results in

glomerulonephritis and uveitis from a type III hypersensitivity reaction. Icterus is not usually a prominent feature.

CAV-1 is the cause of infectious canine hepatitis. The virus is antigenically distinct from canine adenovirus 2, which produces respiratory disease in dogs. Coyotes, wolves, foxes, raccoons and bears are also susceptible to CAV-1. The development of widespread hemorrhage is due to direct damage to vascular endothelium and subsequent initiation of the clotting cascade, accelerated consumption and exhaustion of clotting factors (DIC), and failure of the injured liver to replace these factors. The prognosis for regeneration of the liver is good in animals surviving the acute stages of the disease.

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Microslide 43, Lantern slide 11

**History**. This eight year old, female, mixed breed dog presented with weight loss and occasional vomiting. An anterior abdominal mass was evident on abdominal radiographs. Exploratory laparotomy revealed the mass to be an enlarged left kidney. A nephrectomy was performed. There was no evidence of metastatic spread.

**Gross Pathology**. The 2X2 slide depicts an enlarged kidney (321g) that has been incised along its length. One pole is expanded by a large, well-circumscribed nodule (85mm diameter). The overlying capsule is stretched and bears conspicuous blood vessels. Cut surfaces reveal an ovoid mass of firm, pale tissue with a central cystic cavity that contains blood. Renal tissue adjacent to the tumor edge is markedly compressed; elsewhere it is unremarkable.

**Contributor's Comments**. Normal and compressed renal parenchyma is sharply demarcated from a mass of solid and tubular carcinoma. Constituent cells have abundant eosinophilic cytoplasm and variably round to oval nuclei. There is some bizarre karyomegaly, hyperchromasia and a few mitoses. At the edge of the lesion there is occasional penetration of adjacent

connective tissue. Reticulin staining shows the packeted appearance common to epithelial tumors.

The histological appearance is of renal tubular carcinoma. These are uncommon tumors that may metastasize via renal veins. There is no overt evidence of metastatic spread in these sections. Experience with a small series of these tumors indicates that they may be associated with quite long survival (Lucke and Kelly, 1976; Bastin and De Paoli, 1977; Goldschmidt, 1984).

**AFIP Diagnosis**. Kidney: Renal cell carcinoma, mixed breed, canine.

**Conference Note**. Primary renal neoplasms are uncommon in the dog, accounting for 0.3 to 1.7% of all tumors in this species. Renal carcinoma is more common than renal adenoma or nephroblastoma. They occur primarily in mature animals (average age 8 years). Although no breed predisposition exists, males are affected twice as often as females. As in this case, the gross appearance is usually of a well demarcated mass arising in one pole of the kidney, compressing the adjacent parenchyma. Frequent metastasis to lung and lymph node occurs, although metastasis to the liver, bone, peritoneum, brain, spleen, muscle, adrenal glands, eye, and intestine is also possible. Anorexia, fever, hematuria, weight loss and a palpable abdominal mass are common presenting signs. Paraneoplastic disorders that have been reported with renal carcinoma include polycythemia, secondary pulmonary hypertrophic osteoarthropathy, and leukemoid reaction. An inherited syndrome of bilateral renal cystadenocarcinomas and generalized nodular dermatofibrosis has been described in middle-aged and older German Shepherd Dogs, with bitches also often developing multiple uterine leiomyomas.

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Microslide 44

**History**. This 3-year-old Mexican Corriente mixed breed steer was one of a group of twenty steers purchased in northern Mexico approximately four months earlier for use as roping calves. Three others had died within several days. Two of these were found dead with no premonitory signs. This steer was presented *in extremis*. Antemortem signs observed by the referring veterinarian included hypothermia, a clear nasal discharge, a small amount of hemorrhage from the anus, and petechiae in mucosal membranes.

**Gross Pathology**. Multiple reddened foci were scattered throughout the ileum. Occasional small ulcers were present in the oral cavity and the esophagus. Body fat reserves were undergoing gelatinous atrophy. The liver was small.

**Laboratory Results**. *Yersinia pseudotuberculosis* was isolated from the small intestine. No *Salmonella* sp. were isolated from tissues collected at necropsy. Assays for arsenic, nitrate, nitrite, and lead in body tissues were negative. No bacilli were observed in a blood smear.

**Contributor's Diagnosis and Comments**. Severe, acute, multifocal, purulent, necrotizing enteritis with intralesional gram-negative bacterial colonies (enteric yersiniosis).

There are four reports implicating *Yersinia pseudotuberculosis* as a cause of enteritis in domestic cattle. Two of these reports are from Australia, the others are from Louisiana and India. The first three describe acute enteric histologic lesions resembling those seen in this case: scattered microabscesses in the lamina propria, often surrounding bacterial colonies. In one of the Australian reports, the authors found similar lesions in the colonic mucosa of many animals. In the American report, multifocal hepatic necrosis was found. We found no inflammatory or necrotic foci in either of these tissues. The Indian report described lesions in multiple viscera and a primarily histiocytic enteric mucosal infiltrate.

*Y. pseudotuberculosis* has been recovered from the feces of normal cattle. Stress has been incriminated in some disease outbreaks in other animals. Rodents and wild birds are known sources of the bacteria. We did not determine if these cattle had harbored *Y. pseudotuberculosis* since their immigration from Mexico or if they had acquired the infection in the U.S.

**AFIP Diagnoses**. 1. Small intestine: Enteritis, suppurative, multifocal, mild to moderate with edema and colonies of coccobacilli, Mexican Corriente, bovine.
2. Small intestine, mucosal villi: Coccidiosis, multifocal, minimal.

**Conference Note.** Coccidia were not present in all sections. Yersinia pseudotuberculosis is a common inhabitant of the intestines of domestic animals and a frequent cause of epizootic disease in birds, rodents, deer, and exotic ungulates. In Australia and New Zealand it is an infrequent cause of acute to chronic enterocolitis and occasional fulminate systemic infections in sheep, cattle, goats, and pigs. It has also been reported sporadically in cases of abortion, mastitis, and epididymitis in sheep and cattle. The histologic appearance of enteric yersiniosis is similar in most species. Microabcesses and pyogranulomas containing prominent colonies of Gram-negative coccobacilli typically form in the lamina propria of villi and in Peyer's patches. Similar infiltrates may be seen in the mesenteric lymph nodes. Severe systemic infections are associated with fibrinohemorrhagic enterocolitis, caseous necrosis of Peyer's patches and lymph nodes, fibrinous peritonitis and pleuritis, and multiple abscessation of the liver, spleen, lungs, and occasionally other organs. The characteristic microcolonies of coccobacilli are usually present. Diagnosis of yersiniosis from fecal cultures alone should be viewed with skepticism. Y. pseudotuberculosis, especially serotype III, has been isolated from the feces of up to 26% of healthy cattle in New Zealand.

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**References.**

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Microslide 45, Lantern slides 12, 13, 14

**History**. There were over 100 deaths of cattle within a one-year period on this property. The animals had been treated for gastrointestinal worms. Clinical signs consisted of tenesmus with occasional rectal prolapse, intermittent diarrhea, aggressive behavior, recumbency and death. Frequent growth of Senecio brasiliensis and S. oxyphyllus was observed in the pasture where the affected animals had been grazing for the last two years. No other pyrrolizidine alkaloid containing plants were observed in the pasture.

**Gross Pathology**. Emaciation, subcutaneous gelatinous edema in the sternal region and slight (500 ml) hydropericardium. The prescapular, mesenteric and hepatic lymph nodes were enlarged and moist. The liver was hard and tan-grayish; on cut surface, the hepatic parenchyma was crisscrossed by a fine meshwork of tan-white fibrous tissue. The gallbladder was distended by inspissated bile with an edematous wall and a polypoid mucosal surface (photo). Marked gelatinous edema was evident in the submucosa of the abomasal folds (photo) and mesentery (photo).

**Contributor's Diagnosis and Comments**. Liver: Fibrosis and bile ductular hyperplasia, diffuse, moderate to severe with hepatomegalocytosis and hepatocyte loss. Pyrrolizidine alkaloids (Senecio spp.) poisoning.

In Brazil there are approximately 128 species of Senecio of which S. brasiliensis, S. oxyphyllus, S. selloi, S. cysplatinus, S. heterotrichius and S. tweediei have been proved toxic for cattle both experimentally and naturally. Poisoning by Senecio spp. is an important cause of cattle losses in Southern Brazil. The natural disease is always chronic due to grazing of small amounts of the plant over prolonged periods. In the field the plant is usually consumed during its sprouting period (winter) when the pastures are poor. In the present outbreak S. brasiliensis and S. oxyphyllus were the only species of the plant present in the pasture. The clinical signs, necropsy and histopathological findings seen in this case are typical of pyrrolizidine alkaloid poisoning in cattle. In addition to the above described lesions, status spongiosus was observed on microscopic examination of the brain of this animal. It is usually accepted that this brain lesion is secondary to hepatic failure and due to hyperammonemia and/or other toxic substances not adequately metabolized by the injured liver. The lesion is the basis for the nervous signs present in many cases of bovine seneciosis. Microscopically, the polypoid lesion of the gallbladder consisted of cystic adenomatous hyperplasia and edema of the mucous membrane. This lesion is reported in association with Senecio poisoning in cattle (5) and is observed in approximately one third of the Brazilian cases of bovine seneciosis.

**AFIP Diagnosis**. Liver: Fibrosis, diffuse, moderate,

with biliary hyperplasia, megalocytosis, and nodular hyperplasia, mixed breed, bovine.

**Conference Note.** Diffusely, there is disorganization of the normal hepatic architecture and disruption of the hepatic cords by extensive fibroplasia and marked bile duct proliferation. Most sections also contain multifocal nodules of hepatocellular regeneration. This lesion was compared to the changes seen with other plant-derived chronic hepatotoxins such as lantana and phomopsin. Pyrrolizidine alkaloids are present in a wide variety of plants distributed throughout the world including Senecio, Crotalaria, and Heliotropium species. The pathogenesis of this toxin was discussed. Alkaloid compounds must be metabolized by the liver to highly reactive pyrroles to reach their full toxic potential. The characteristic hepatocellular megalocytosis is due to the toxin's antimitotic effect which is believed to involve disruption of microtubule function. Megalocytosis with pyrrolizidine alkaloids is usually more dramatic than that seen with other alkylating agents such as nitrosamines and aflatoxins. Species susceptibility to pyrrolizidine alkaloids differs significantly. Pigs are considered very susceptible, cattle and horses are moderately susceptible, and sheep are relative resistant by comparison. In addition to the liver, damage to other organs may be seen with consumption of pyrrolizidine alkaloids, especially those derived from Crotalaria sp. Renal damage, pulmonary fibrosis, emphysema and alveolar edema have been reported. Photosensitization is an inconsistent finding.

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Microslide 46

**History**. Sneezing, epistaxis, and a "vegetative tumor" in nose were described clinically.

**Contributor's Diagnosis and Comments**. Chronic polypoid hyperplasia with multifocal pyogranulomatous rhinitis and fungal organisms (Rhinosporidium seeberi).

Numerous immature forms are present with fewer of the larger intermediate and mature sporangia. Inflammation is generally confined to areas where organisms have ruptured.

**AFIP Diagnosis**. Nasal mucosa: Rhinitis, polypoid, chronic-active, with multifocal hemorrhage, thrombosis and fungal organisms, Labrador retriever, canine, etiology -- consistent with Rhinosporidium seeberi.

**Conference Note**. Sections contain a hyperplastic, polypoid and inflamed nasal mucosa containing numerous variably sized, round fungal elements representing two distinct life stages of Rhinosporidium. The more juvenile forms, called trophocytes, range in size from 20 to 80 and have a thick 3-5 micron outer eosinophilic wall and a single central nucleus. The mature sporangia are up to 400 microns in diameter and contain numerous endospores. The rupture of sporangia and release of the endospores into the stroma results in the accompanying inflammation. Diffusely, the submucosa is edematous and congested. A few vessels contain fibrin thrombi.

Rhinosporidiosis is a chronic mycotic infection occurring in the mucosa of the nose and nasopharynx, reported in man, horses, cattle, dogs, goats and waterfowl. A more disseminated infection involving the eyes, skin and genitalia may occur in humans. The exact mode of transmission and infection is unknown. The fungus reproduces in tissue by endosporulation, similar to Coccidioides, Prototheca, and Chorella. Clinical signs include sneezing, a unilateral purulent nasal exudate and epistaxis. Grossly, the lesion appears as a sessile to pedunculated, unilateral, polypoid growth. The larger sporangia may be visible as multiple small white foci beneath the mucosal surface.

**Contributor**. Experimental Pathology Laboratories, Inc., P.O. Box 12766, Research Triangle Park, NC 27709.

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Microslide 47

**History**. This 7-year-old Brittany Spaniel had a 2-week history of coughing and losing weight.

**Gross Pathology**. Numerous white miliary foci covered the parietal and visceral surfaces of the thoracic cavity. Several foci were up to 1 cm in diameter. No abnormalities were seen in abdominal viscera.

**Contributor's Diagnosis and Comments**. Mesothelioma.

The gross description of the involved surfaces and the histologic appearance of arborescent proliferations of this mesothelioma along the pleural surface are characteristic of this type of tumor. However, the extensive metastases in the form of small nests throughout the pulmonary parenchyma seems remarkable. No primary tumor was found in other tissues: this is important to note for those mesotheliomas which resemble adenocarcinoma, as does this one.

**AFIP Diagnosis**. Lung: Mesothelioma, with pulmonary metastasis, Brittany Spaniel, canine.

**Conference Note**. Numerous vessels within the pulmonary parenchyma contain emboli of spindled to polygonal neoplastic cells. Mesotheliomas are rare tumors of domestic animals that arise from the serosal lining of the pleural, pericardial or peritoneal cavities or the tunica vaginalis of the testes. In cattle, mesotheliomas usually occur as congenital peritoneal neoplasms of calves, while in humans, they frequently form in the pleura and are associated with previous exposure to asbestos. Mesotheliomas are usually malignant, but tend to spread by implantation rather than vascular metastasis. They must be differentiated from primary and metastatic adenocarcinomas of the lung. Histologically, mesotheliomas can vary from a papillary or polypoid epithelial growth reminiscent of adenocarcinoma to a more fibrous appearing proliferation of spindle cells. The epithelial pattern is more common in pleural mesotheliomas of dogs. Blood-tinged pleural or pericardial effusion is a frequently associated gross lesion in affected dogs. Ultrastructural analysis and immunohistochemical staining can assist in the diagnosis of mesothelioma. Ultrastructural features include numerous long, slender, branching microvilli, well developed desmosomes and prominent intercellular spaces. Immunohistochemical staining is usually positive for both cytokeratin and vimentin intermediate filaments.

**Contributor**. The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49007.

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Microslides 48,49

**History**. This young adult, CD male rat Rattus norvegicus is a member of a group of seventeen male and female rats, ranging from 21 to 91 days-of-age, submitted from a commercial breeder for routine health assessment. There had been a recurring problem with respiratory disease in the colony and the pathologist had specifically requested that an effort be made to submit clinically ill animals for evaluation.

**Gross Pathology**. The lungs were slightly atelectatic. The heart was completely enclosed by a thick sac.

**Laboratory Results**. This animal was seropositive for Sendai virus, pneumonia virus of mice, sialodacryoadenitis virus, Kilham rat virus, and IgG ELISA positive for Mycoplasma pulmonis. Streptococcus pneumoniae (type 16) was cultured from nasopharynx, liver, and pleural cavity.

In this group of animals submitted for health assessment Streptococcus pneumoniae (type 16) was cultured from the nasopharynx of 12/17. All 17 were seropositive for Sendai virus, 16 for sialodacryoadenitis virus, 11 for Kilham rat virus, 10 for pneumonia virus of mice, and 9 for Toolan H-1 virus. In addition, 11 of 17 were positive by IgG ELISA for Mycoplasma pulmonis.

**Contributor's Diagnosis and Comments**. Circulatory system, pericardium, pericarditis, fibrinopurulent, chronic, severe, Streptococcus pneumoniae (type 16), CD, murine.

The rats in this group had acute fibrinopurulent to chronic fibrosing pneumonia that varied from multifocal to lobar to diffuse. Most also had upper respiratory tract disease, pleuritis, mediastinitis, pericarditis, or combinations of the above. It is rare to see these classic lesions of Streptococcus

pneumoniae disease in contemporary rat stocks. While the role of Streptococcus pneumoniae infection in the respiratory problem in this colony is clear, the contributory roles of the many viral infections and of the Mycoplasma pulmonis infection are not.

It is also of interest that within 30 days two additional groups of weanling and young adult animals from the same room were submitted for health assessment. These rats were selected at random rather than for clinical signs of illness and respiratory disease was less severe and of decreased incidence in these groups. Streptococcus pneumoniae was cultured from only 3 of 30 of these animals and its role might easily have been submerged in the morass of other viral and bacterial agents present in this colony.

**AFIP Diagnosis.** Heart, pericardium; mediastinum: Pericarditis and mediastinitis, fibrinosuppurative, chronic, diffuse, severe, with gram-positive cocci, CD rat, rodent.

**Conference Note.** In addition to the lesion in the heart, most sections contained similar inflammation in the mediastinum surrounding both the thymus and mediastinal lymph node. Participants noted that Gram staining of the bacteria was variable. Streptococcus pneumoniae is a common cause of respiratory disease in nonhuman primates, rats and guinea pigs. Infection in rats can occur as a primary disease, or it may be found in association with Mycoplasma and other common respiratory pathogens. The organism initially infects the upper respiratory tract, but it readily extends into the lungs where it can spread to the pleural cavity, pericardium and blood stream. Common gross findings include rhinitis and sinusitis with a suppurative nasal discharge, conjunctivitis, otitis media, dyspnea, weight loss, and hunched posture. Virulence factors of Streptococcus include capsular polysaccharides with hydrophilic properties that discourage phagocytosis, various somatic antigens or M-proteins, and enzymes known as streptolysins which can cause intracellular degranulation of lysosomes, effectively killing phagocytic cells.

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Microslides 50, 51, Lantern slides 15, 16

**History**. This rhesus macaque (#86582) was challenged with 10 MID of $SIV_{Mac\ 251}$ on 10 Sep 91. The animal first became viremic on 17 Sep 91. Serum P27 was detectable between 24 Sep 91 and 21 Oct 91, and again on 17 Aug 92 (9 days prior to death).

The animal was last reported in good health on 20 Jul 92 (38 days prior to death [DPD]). She subsequently demonstrated progressive depression and anorexia. On the final clinical examination she appeared depressed and was reluctant to move. She was euthanatized and necropsied on 26 Aug 92.

**Gross Pathology**. Examination of the cadaver revealed severe loss of fat stores and muscle mass. The body weight at necropsy was 4.7 Kg representing a 19% reduction from the maximum body weight of 5.8 Kg recorded on 18 May 92. Organ mass indices (1.0X is normal) are as follows: Axillary lymph nodes - 1.9 X; inguinal lymph nodes - 3.2X; ileocecal lymph node - 2.4X; spleen - 0.5X; heart - 1.1X; liver - 1.2X; and brain - 0.8X. A 3 cm retroperitoneal abscess was present along the medial left ilium in the approximate location of a sublumbar or sacral lymph node. Multifocal 2 to 5 cm hyperemic, consolidated foci were present throughout all lung lobes. The color and texture of the pancreas was within normal limits, although individual lobules were prominent apparently due to interlobular edema. The fundic mucosa of the stomach was mildly congested and noticeably darker than the cardia. Minimal serous atrophy of fat was present diffusely throughout the cadaver. A complete necropsy was performed; all other organs were within normal limits.

**Laboratory Results**.

Microbiology: Campylobacter upsaliensis was isolated from the peripheral blood.

| | Normal | 17 Aug 92 | 26 Aug 92 |
|---|---|---|---|
| WBC | (7-15 K/μL) | 30.4 K/μL | 17.8 K/μL |
| BANDS | (0-4%) | 0% | 0% |
| POLYS | (30-55%) | 97% | 97% |
| LYMPHS | (35-70%) | 2% | 2% |
| CD-4 T CELLS | (15-25%) | 0.8% | nd |
| MONOS | (1-5%) | 1% | 1% |
| TOT PROT | (6.7-8.7 g/dL) | 5.6 g/dL | 4.4 g/dL |
| ALBUMIN | (3.8-4.8 g/dL) | 2.0 g/dL | 1.4 g/dL |
| GLUCOSE | (60-85 mg/dL) | 3.6 mg/dL | 66 mg/dL |
| SODIUM | (148-152 mEQ/L) | 141 mEQ/L | 141 mEQ/L |
| POTASSIUM | (3.0-3.8 mEQ/L) | 3.5 mEQ/L | 2.5 mE/L |
| CHLORIDE | (108-115 mEQ/L) | 100 mEQ/L | 102 mEQ/L |
| BUN | (22-28 mg/dL) | 32 mg/dL | 38 mg/dL |
| CREATININE | (0.4-1.4 mg/dL) | 1.1 mg/dL | 1.0 mg/dL |
| LIPASE | (25-200 IU/L) | 1055 IU/L | 1637 IU/L |
| AMYLASE | (200-1200 IU/L) | 346 IU/L | 282 IU/L |
| INSULIN | (5-35 microIU/L) | ND | 22.7 microIU/L |
| GASTRIN | (0-100 pg/mL) | ND | 278.4 pg/mL |

**Contributor's Diagnosis and Comments.** 1. Gastritis, lymphocytic, subacute, diffuse, mild, with diffuse parietal cell atrophy, fundus and antrum, stomach, etiology: Helicobacter pylori.

2. Abscess, focal, moderate, submucosa, with multifocal cytomegalic cells, fundus, stomach, etiology (secondary) Cytomegalovirus. (This lesion was not present in all sections.)

This macaque died with multiple medical problems as evident from gross pathologic findings and was immunodeficient as indicated by severe CD-4 lymphopenia. Upon noting an elevated lipase and severely reduced glucose level on 17 Aug 92 with normal renal parameters, we evaluated pancreatic function. As anticipated, the glucose value was spurious because serum separation from the blood was delayed. The reason for the elevated lipase values remained uncertain since there was no histologic evidence of pancreatitis. One possible explanation is that this increase is related serous atrophy of fat. The gastrin level and blood culture results were unexpected. Warthin-Starry silver stains of the gastrointestinal tract and abscess were performed in an attempt to locate the source of the Campylobacter organisms. Significant numbers of silver positive gram-negative bacilli consistent with Campylobacter morphology were identified in the glandular lumina and along the surface of the gastric fundus and antrum but not in the cardia or the duodenum. A mild diffuse infiltrate of lymphocytes, plasma cells, and histiocytes was present in the lamina propria. Parietal cells lacked their typical eosinophilic cytoplasm indicating either storage granule depletion or replacement with less differentiated cells. Parietal cell (or chief cell) necrosis was not observed although fundic glands were irregular in length and foci of crypt atrophy were present. Ultrastructural examination of the stomach was

performed. The bacteria were blunt-ended and flagellated although they lacked a spiral shape. They were noted in close association with epithelial cells and many were attached by narrow pedestals to the plasma membrane. These morphologic features are consistent with Helicobacter sp. Subsequent serologic assays demonstrated significant levels of H. pylori IgG present even prior to viral inoculation. Interestingly, in this monkey these levels gradually dropped in association with the onset of immunodeficiency and were not significant by the time of euthanasia.

Helicobacter pylori has been described previously in association with gastritis in nonhuman primates.[1] Although C. upsaliensis was a differential diagnosis in this case it could be ruled out by at least two criteria in addition to serologic results: Campylobacter sp. are not isolated in the stomach and do not tolerate the gastric environment; and the ultrastructural morphology of Campylobacter is different from Helicobacter. The former has a ruffled surface, tapered ends with a depression at the end and a single polar flagellum, while the latter is slightly larger with rounded ends, a smooth surface, and multiple sheathed flagella.[2] There are currently three described species of Helicobacter: H. pylori (primates including man), H. mustelae (ferrets), and H. felis (dogs and cats).[2,3,4] The ultrastructural morphology of H. felis, however, is different from the other two species by virtue of having a distinctly spiral appearance.[4] This is initially confusing because of its morphologic similarity to a nonpathogenic spirochete found in canine and occasionally human stomachs, Gastrospirillum hominis.[4,5] The appearance of the latter, however, is quite distinctive from H. pylori and H. mustelae.

Helicobacter pylori is an important pathogen in man and has been associated with gastritis, hypochlorhydria, nonulcer dyspepsia, and peptic ulcers.[2] As observed in this case, elevated gastrin levels have been described in humans.[6] Several hypotheses on the pathogenesis of H. pylori-induced inflammation and clinical syndrome have been suggested.[7]

**AFIP Diagnosis**. 1. Stomach, fundus: Gastritis, lymphoplasmacytic, diffuse, mild, with glandular atrophy and parietal cell loss, and numerous luminal silver-positive bacteria, rhesus monkey (Macaca mulatta), primate.
2. Stomach, fundus, submucosa: Gastritis, necrosuppurative, focally extensive, moderate.
3. Stomach, fundus, submucosa: Cytomegalic/karyomegalic cells, multifocal, with eosinophilic intranuclear inclusion bodies, etiology -- consistent with cytomegalovirus.

**Conference Note**. Helicobacter spp. are implicated as a cause of chronic gastritis in humans, monkeys, dogs, cats and

ferrets. In Macaques, spontaneous colonization of the gastric mucosa by H. pylori, formerly named Campylobacter pylori, has been associated with subclinical gastritis characterized by hypochlorhydria and a variable mononuclear cell infiltrate in the lamina propria. This condition is somewhat similar to chronic diffuse superficial (type B) gastritis in humans. The antrum is most often affected, but the fundus and pylorus may also be involved. As in this case, the organism is found in the superficial mucus layer and adhered to the surface epithelium, but does not actually invade through the mucosa. In contrast to human infections, H. pylori infection in macaques is not associated with ulcerations of the gastric or duodenal mucosa (peptic ulcer disease).

The pathogenesis of H. pylori-induced inflammation is not well understood. Since mucosal invasion does not occur, one theory is that pro-inflammatory substances produced by the organisms and released into the crypt lumen are transported across the mucosa resulting in inflammation. Possible bacterial products include lipopolysaccharides, a platelet-activating factor, and urease which is not only directly inflammatory but is also known to generate ammonia, a cellular toxin. Ammonia may also provide an alkaline microenvironment to protect the bacteria from gastric acid. The elevated gastrin level in this case is intriguing. In man, H. pylori infection is associated with chronic hypergastrinemia. The mechanism by which the bacteria disrupt normal gastrin-hydrochloric acid homeostasis is not clear. The inflammatory focus in the submucosa present in some sections may have been caused by an ulcer that is out of the plane of section, or it may be asociated with cytomegalovirus infection.

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Microslide 52

**History**. This adult female cynomolgus monkey (Macaca fascicularis) had a 3 day history of progressive anorexia, depression and abdominal distension. The animal was humanely killed and presented for postmortem examination.

**Gross Pathology**. At necropsy, multiple firm dense white nodules were present throughout the abdomen on serosal surfaces as well as the body wall. These nodules frequently coalesced into extensive confluent masses which encircled and entrapped the mesenteric root and bowel creating large blocks of adherent intestines. This dense sclerotic tissue was also present on the diaphragm, extending through full-thickness in some areas, and invading into the thoracic cavity where it encased focally extensive areas of the pleura and pericardium.

**Laboratory Results**. Serology: Type D Simian Retrovirus - II (SRV II) > 500u (Antibody levels over 500u are considered high and an unequivocal indication of infection).

**Contributor's Diagnosis and Comments**. Fibroblastic tissue proliferation (Fibromatosis), pleura*, diffuse, severe.
Disease: Retroperitoneal Fibromatosis
Etiology: Type D Simian Retrovirus II (SRV II) associated

* Small focal areas of fibromatous tissue extend into the superficial subpleural pulmonary parenchyma (some sections).

In this retrovirus-associated fibroproliferative disorder, there is an aggressive proliferation and infiltration of highly vascular fibrous tissue. In the localized syndrome a solitary nodule of fibromatous tissue forms beneath the peritoneum at the mesenteric attachment of the ileocecal junction. The progressive form expands throughout the abdominal cavity encircling intestines and adjacent lymph nodes, covering dorsal and ventral body walls, and can extend out into the inguinal canal or invade through the diaphragm into the pleural cavity.

Microscopically, two morphological patterns are described: proliferative and sclerotic, varying in degree of cellularity, cytomorphological appearance, vascularity, and extent of collagen deposition. Patchy inflammatory infiltrates (primarily

lymphocytes and plasma cells) are present in both forms, being more prominent in the proliferative type.

Although the aggressive, infiltrative behavior of fibroblasts in the progressive form of retroperitoneal fibromatosis can be quite striking, cellular density, degree of anaplasia, lack of true metastatic potential and inability to invade parenchymal organs all distinguish this condition from true fibrosarcomas. Retroperitoneal fibromatosis has been reported in a variety of macaque species (M. mulatta, M. fascicularis, M. nemestrina and M. fuscata) and represents a variant clinicopathologic expression associated with simian acquired immunodeficiency syndrome (SAIDS).

**AFIP Diagnosis.** 1. Lung, pleura and interstitium: Fibromatosis, focally extensive, severe, Cynomolgus monkey (Macaca fascicularis), primate.
2. Lung: Congestion, diffuse, mild, with intra-alveolar edema.

**Conference Note.** Conference participants reviewed the different classifications of oncoviruses. Most oncoviruses of veterinary importance are type-C retroviruses, the main exceptions being the type-B virus of mice (mouse mammary tumor virus) and the type-D viruses found in primates (simian type-D retrovirus) and sheep (ovine pulmonary carcinomatosis or "jaagsiekte"). There are at least 5 different serogroups of simian type-D retrovirus (SRV). Both SRV and the primate lentivirus SIV are important causes of immune deficiency syndromes in macaques. Only SRV-2 is associated with retroperitoneal and subcutaneous fibromatosis (RF/SF). RF/SF has some similarity to Kaposi's sarcoma seen in AIDS patients. Both neoplasms are retrovirus-associated vascular fibroproliferative conditions that originate from mesenchymal cells, although Kaposi's sarcoma is more vascular and hemorrhagic than RF/SF. The cytokine interleukin-6 is suspected to have an autocrine/paracrine stimulatory role in the growth of both conditions. The proliferating cells in RF/SF differentiate towards fibroblasts, endothelial cells and pericytes. In the proliferative form of the disease, many cells are positive for factor VIII-related antigen.

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Microslide 53

**History**. This adult male black-footed penguin (Spheniscus demersus) originating from a German zoo, died in summer 1991. No precedent clinical signs were observed.

**Gross Pathology**. The carcass was emaciated and severe atrophy of the pectoral musculature was observed. Furthermore, hepatosplenomegaly, hydropericardium and pulmonary hyperemia were noted.

**Contributor's Diagnosis and Comments**. Lungs: Pneumonia, interstitial, mild to moderate with intracellular hemozoin pigment deposition; numerous exoerythrocytic macro- and microschizonts in alveolar macrophages, endothelial cells and intracellular parasitemia.
Liver: Hepatitis, multifocal, lymphohistiocytic, moderate with single cell necrosis of hepatocytes and macrophages, Kupffer cell hyperplasia and intracellular hemozoin deposition; numerous exoerythrocytic macro- and microschizonts in macrophages, Kupffer, endothelial cells and intracellular parasitemia.
Spleen: Severe hyperplasia of reticuloendothelial cells with single cell necrosis; numerous macro- and microschizonts in reticuloendothelial cells.
Kidneys: Fibrinoid thrombi in glomerular capillaries; macro- and microschizonts in glomerular and stromal cells.

Avian malaria is the most important cause of death in penguins kept in open air exhibits in North American and European zoos. The causative agents, Plasmodium relictum (syn. P. praecox) and P. elongatum, virulent for penguins, are common parasites in sparrows.

The complex life cycle of the parasite in adapted animals consists of a sexual and an asexual stage of reproduction and requires a vertebrate host. Briefly, a female mosquito penetrates the skin of the bird and releases sporozoites, which form cryptozoites at the point of entry. Merozoites from this

form cryptozoites at the point of entry. Merozoites from this generation develop to metacryptozoites and can infect erythrocytes and other cells such as endothelial cells (P. relictum) as well as cells of the hematopoietic system (P. elongatum). In the erythrocyte, merozoites round up, form trophozoites, undergo schizogony and produce different numbers of merozoites. During schizogony, the parasites incompletely catabolize hemoglobin, leaving a brown pigment, hemozoin, within food vacuoles. Some erythrocytic merozoites differentiate into gametocytes (micro- and macrogametocyte). The remaining erythrocytic merozoites infect other erythrocytes. In P. elongatum infection, merozoites derived from erythrocytic schizonts are, in contrast to other Plasmodium spp., able to infect cells of the hematopoietic system. The blood-sucking arthropod ingests the gametocytic stages and in the stomach of the mosquito, macrogametes and microgametes fuse and form the ookinete. The ookinete enters the gastric mucosa and develops to the oocyst. After maturation, the oocyst liberates sporozoites, which reach the salivary glands of the insect via the hemolymph.

Superinfection observed in non-adapted hosts such as penguins is caused by two divergences from the normal life cycle of Plasmodium. Exoerythrocytic schizogony is more prominent and, more important, merozoites originating from erythrocytic schizonts are able to infect cells of the RES. Additionally, the fatal outcome of the disease in penguins is attributed to the striking involvement of the lung.

**AFIP Diagnoses**. 1. Lung: Pneumonia, interstitial, subacute, diffuse, severe, with intracellular schizonts and hemozoin pigment, black-footed penguin (Spheniscus demersus), avian.
2. Liver: Hepatitis, centrilobular and periportal, subacute, diffuse, moderate, with Kupffer cell hyperplasia, intracellular schizonts, and hemozoin pigment.
3. Kidney, glomeruli: Fibrin thrombi, diffuse, moderate, with intracellular schizonts and multifocal hemorrhage.
4. Spleen: Splenitis, histiocytic, diffuse, severe, with lymphoid depletion, intracellular schizonts, and hemozoin pigment.

**Conference Note**. Conference participants discussed a differential diagnosis for avian blood parasites including Plasmodium, Haemoproteus and Leucocytozoon. All three parasites have a lifecycle characterized by a schizogenous tissue phase and a gametogenous sexual phase in host RBCs. Plasmodium differs in having an additional asexual replicative phase in erythrocytes where invading merozoites develop into trophozoites and then undergo schizogeny. Leukocytozoon forms large (100 to 200 micron diameter) megaloschizonts within phagocytic cells. Hemoproteus forms characteristic elongated and twisted schizonts measuring approximately 8 X 35 microns; they are found in the vascular endothelium of lung, liver, kidney and spleen.

Malarial disease is the most common cause of mortality in penguins house in outdoor exhibits. It is characterized by acute onset and rapid death, often with few premonitory signs of illness. Gross lesions include hepatomegaly, splenomegaly, and subcutaneous, pulmonary and epicardial edema. Icterus and anemia are often not evident. The most striking histologic feature is the exoerythrocytic schizogony seen in the lungs, spleen, liver and other organs. An acute interstitial pneumonia is commonly found. Reticuloendothelial hyperplasia is often marked, but hemozoin pigment formation is variable. Lesions are unusually prominent in this case. Early diagnosis is extremely important. Evaluating thin blood smears for parasitemia and monitoring differential and total white blood cell counts for a lymphocytic leukocytosis (≥19,000/$mm^3$ with 50% or more lymphocytes) are considered among the more reliable methods of antemortem diagnosis of malaria in penguins.

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Microslide 54

**History**. Tissue is from a 3-year-old, female, Saanen goat that was experimentally infected orally at birth with 1.0 X 10 TCID of caprine arthritis encephalitis virus. The mammary gland was diffusely swollen and firm.

**Contributor's Diagnosis and Comments**. Mastitis, diffuse, lymphocytic, mammary gland.

The section contains mammary tissue and adipose tissue. The mammary tissue is fibrotic, hypervascular, and hypercellular. It contains a coalescing infiltrate that disrupts glandular architecture. The infiltrate is composed of both small and blastic lymphocytes. In several foci the lymphocytes are present in distinct follicular structures. Mammary glands are decreased in number. The acini are lined by severely vacuolated, cuboidal to columnar epithelial cells. The epithelial cells are often piled, and epithelial cell nuclei are large. Some acini are dilated and contain eosinophilic secretory material. Mammary ducts are dilated and are lined by piled, cuboidal epithelial cells. Aggregates of small lymphocytes are present in the acinar and ductular epithelium.

Histopathologic results are typical of the mastitis associated with caprine arthritis-encephalitis infection.

**AFIP Diagnosis**. Mammary gland: Mastitis, lymphofollicular, diffuse, moderate, Saanen goat, caprine.

**Conference Note**. Caprine arthritis-encephalitis (CAE) is a , chronic disease syndrome of goats widely disseminated throughout North America and Western Europe. The etiologic agent is a lentivirus closely related to maedi/visna virus, the cause of ovine progressive pneumonia (OPP) and encephalomyelitis in sheep. Two major forms of CAE have been described. The disease in young goats (less than 1-year-old) presents as an acute necrotizing leukoencephalomyelitis which may be accompanied by a diffuse interstitial pneumonia. Older animals generally develop a chronic proliferative lymphoplasmacytic arthritis/synovitis and interstitial mastitis. Transmission is known to occur vertically through virus infected colostrum and milk. Conference participants discussed the pathogenesis of CAE. Lifelong viral persistence following infection is a common feature of lentiviruses, in part due to their ability to infect cells of the immune system. The CAE virus replicates in specific macrophage/monocyte populations allowing it to escape from many normal host defense mechanisms. Infected macrophages present viral antigens to CD4 lymphocytes which orchestrate a lymphoproliferative immune response and an accumulation of mainly CD8 lymphocytes in affected tissues. This immune response differs markedly from other more immunosuppressive lentiviruses such as HIV and SIV, primarily because CD4 cells are not targeted and killed by the CAE virus and are therefore able to respond normally to viral antigens.

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Microslide 55

**History**. This 3-year-old, male Western European hedgehog (Erinaceus europaeus eruopaeus), presented to the hospital for weight loss, tachypnea, and a palpable mass in the caudal abdomen.

**Gross Pathology**. A round, raised, cream white mass 1.5-2 cm diameter was present in the left diaphragmatic lobe of the lung. The mass was viscid on cut section. There was also an enlarged right seminal vesicle.

**Contributor's Diagnosis and Comments**. Granulomatous and histiocytic pneumonia due to Cryptococcus spp.

Seminal vesicle was set aside for a gross presentation and subsequently misplaced, precluding any histopathologic evaluation. It grossly appeared to also be infected by Cryptococcus.

**AFIP Diagnosis**. Lung: Bronchopneumonia, granulomatous and necrotizing, focally extensive, severe, with bronchiectasis, and numerous yeasts, Western European hedgehog (Erinaceus europaeus eruopaeus), insectivore.

**Conference Note**. Sections contain a well demarcated expansile mass replacing a large portion of the lung lobe. The affected area contains high numbers of histiocytes, fewer multinucleated giant cells, lymphocytes and plasma cells and abundant 5 to 15 micron diameter, round yeast which infrequently display narrow-based budding. Larger airways are often markedly ectatic and filled with similar organisms. The less involved adjacent parenchyma is atelectatic. A mucicarmine stain viewed in conference helped demonstrated the typical thick outer capsule characteristic of C. neoformans. The capsule is composed of mucopolysaccharides which are thought to inhibit macrophage phagocytosis and antigen-antibody interactions, and may explain why inflammation is often not a prominent feature of cryptococcal infections. There are rare strains of C. neoformans, known as dry variants, that produce little capsular material and do not stain with mucicarmine.

The pathogenesis of cryptococcosis was discussed. Birds, especially pigeons, excrete infective organisms into the soil which can then be acquired by susceptible hosts through inhalation. The nasal cavity and lungs are the usual sites of primary infection. From there, the organism can spread hematogenously to the CNS, eyes, lymph nodes, bone, skin and other organs, or directly extend from the nasal cavity into the meninges and brain. C. neoformans has a predilection for both the respiratory system and the central nervous system. Grossly, pulmonary cryptococcosis usually appears as one or more circumscribed masses of a whitish, gelatinous or mucinous material. More chronic lesions can become solid and firm with increased granulomatous inflammation and fibrosis. In these lesions yeast cells may be low in number and primarily intracellular, making diagnosis more difficult.

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Microslide 56

**History.** This 2-year-old, female Sprague-Dawley rat was found dead in her cage. Salivation had been noted as a clinical sign.

**Gross Pathology.** A 3 x 2.5 x 2 cm, soft, tan, multilobulated mass was found in the thoracic cavity.

**Contributor's Diagnosis and Comments.** Brown fat: Malignant hibernoma.

This is a well encapsulated, multilobular mass which partially surrounds the thoracic aorta and is subdivided by thin bands of fibrous connective tissue.

The mass is composed of confluent sheets of cells with moderate to abundant amounts of eosinophilic, granular to vacuolated cytoplasm and a central, round nucleus with a stippled chromatin pattern and one or more prominent nucleoli. There is moderate anisokaryosis and scattered cells contain greatly

enlarged nuclei or multiple nuclei. The cytoplasm of many cells contains a single, clear, smooth walled vacuole that marginates the nucleus; these cells resemble lipocytes. The mitotic rate averages 1 to 2 per 40X field. Variably sized areas of hemorrhage are scattered throughout the mass. Some sections contain multiple areas of necrosis and/or accumulations of pigment laden macrophages which tend to be most abundant along fibrous connective tissue septa.

Hibernoma is an uncommon tumor in the rat. Most reported cases in the Sprague-Dawley rat have occurred in the mediastinum. The particular neoplasm in this case is unusual in that the proportion of cells with densely staining, granular, eosinophilic cytoplasm is much higher than that which is usually observed. Because of this feature, the variability of nuclear size, prominence of nucleoli, and the presence of mitotic figures, this neoplasm was diagnosed as a malignant hibernoma.

**AFIP Diagnosis**. Fibroadipose tissue: Malignant hibernoma, Sprague-Dawley rat, rodent.

**Conference Note**. Hibernomas are rare tumors in animals. Their behavior is usually locally invasive, but metastasis to the lung has been reported. Grossly, they appear as tan to reddish brown, greasy, lobulated masses usually arising in the thoracic or abdominal cavities or interscapular areas. As in this case, entrapment of the descending aorta is common. Microscopically, they consist of sheets and lobules of cells with prominent granular to microvacuolated eosinophilic cytoplasm. Occasional cells contain lipochrome pigments. Neoplastic cells stain strongly positive for fat.

Conference participants discussed the physiology of brown fat, an important source of heat production in neonatal and hibernating animals. The cells contain a lower lipid content and a higher phospholipid, glycogen and lipochrome content than other adipocytes. Rich in mitochondria and well innervated with sympathetic nerves, the oxidative metabolism of brown fat provides a mechanism of thermogenesis independent of the shivering stimulus. The presence of abundant and pleomorphic mitochondria with characteristic elongated transverse cristae can help to differentiate hibernomas from liposarcomas on ultrastructural evaluation.

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Microslide 57

**History**. Two groups of 40 (8 to 10 month old) and 60 (12 to 23 month old) rabbits were purchased from a laboratory supplier for use in toxicity studies. No particular clinical signs were noted. The animals were killed on schedule at the end of the studies.

**Gross Pathology**. No gross lesions were evident.

**Laboratory Results**. Clinical pathology: mild, mostly transient increase in immunoglobulin G. Serology: IFAT positive for Encephalitozoon cuniculi (indirect fluorescent antibody technique).

**Contributor's Diagnosis and Comments**. Encephalitis, granulomatous. Etiology: Encephalitozoon cuniculi.

Encephalitozoonosis is a fairly common and usually latent disease in rabbit colonies. The characteristic lesion consists of multiple granulomas of microscopic size disseminated throughout the central nervous system, including the choroid plexus, spinal cord and meninges. Typical granulomas consist of macrophages containing cellular debris and surrounded by lymphocytes and microglia. Older lesions show a necrotic center and contain epithelioid and giant cells in addition. Perivascular cuffing with lymphocytes and plasma cells is usually seen in the vicinity of the granulomas. Silver stains (Gomori's) reveal silver-positive, round to oval organisms within recent granulomas. Alterations in other organs include lymphocytic/plasmacytic infiltrates in the kidneys, myocardium, liver, small intestine, lymph nodes, male accessory genital glands, urinary bladder, eyes (iris), thyroid and adrenal glands. Granulomas are occasionally present in kidney, liver and lymph nodes. Renal and myocardial fibrosis are seen in chronic infections.

The lesions in the brain and other organs are generally more pronounced in young animals than in older rabbits.

There was no indication of an infection evident during the in-life phase of the studies, although 40% of the younger and 60% of the older rabbits were diagnosed postmortem to be infected with E. cuniculi. Similarly, the infection was not detected in

the supplier's facility despite the regular examination of randomly selected animals. Subsequent examinations showed that more than 10% of the does were seropositive and had to be eliminated from breeding.

**AFIP Diagnosis**. Brain: Meningoencephalitis, nonsuppurative, multifocal, mild, with multifocal microgranulomas and hemorrhage, Himalayan rabbit, lagomorph.

**Conference Note**. Most sections contained one or more granulomas randomly distributed within the gray and white matter. A Goodpasture's carbol fuchsin method stain was presented in conference demonstrating gram-positive organisms in the necrotic centers of these granulomas. Participants noted that polarized light was also helpful in identifying the birefringent spores of E. cuniculi. In addition to the characteristic histologic changes described by the contributor, there was multifocal perivascular edema and a mild meningitis.

Encephalitozoon cuniculi is an obligate intracellular microsporidian parasite that commonly infects rabbits, but is also found in many laboratory rodents, carnivores, birds, nonhuman primates and man. Infections in rodents and lagomorphs are usually chronic with little or no clinical signs, but the lesions, which are most prominent in the brain and kidney, can be a significant complication in experimental settings. In the brain, the organism parasitizes vascular endothelium, multiplying within an intracytoplasmic parasitophorous vacuole. Ultrastructural characteristics of mature E. cuniculi spores include a single eccentric nucleus, a large posterior vacuole, a coiled polar filament and the lack of any mitochondria.

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Microslide 58, Lantern slide 17

**History**. When slaughtered, the uterus of this sow was noted to have an unusual appearance. The entire female reproductive tract was brought to the Lab for evaluation. Gross photographs were taken, and sections were fixed for histopathology.

**Gross Pathology**. The uterus contained variably-sized cystic structures within the endometrium which extended into the myometrium. The ovaries appeared cystic, but the oviducts were grossly normal in appearance. Gross diagnosis: Multiple endometrial/uterine cysts (severe cystic endometrial hyperplasia).

**Contributor's Diagnosis and Comments**. Diffuse, cystic endometrial hyperplasia; etiology: cystic ovaries.

The uterus contained variably-sized cystic endometrial glands, lined by single or multiple layers of epithelium ranging from squamous to cuboidal to columnar to pseudostratified and hyperplastic. The epithelium lining the uterine mucosa was hyperplastic. The cysts contained a pale seroproteinaceous material. The hyperplastic and non-vesiculated endometrial luminal epithelium was suggestive of long term estrogenic influence. There was no significant inflammation. The ovary (not presented) had numerous cystic follicles with no progression toward maturity. It was felt that the uterine changes had most likely been induced by increased levels of estrogenic hormones derived from the cystic follicles. The possibility that these changes may have been induced by exposure to estrogenic mycotoxins, such as zearalenone was also entertained. Endometrial hyperplasia is common in the canine species, but is rare in swine.

**AFIP Diagnosis**. Uterus, endometrium: Hyperplasia, cystic, diffuse, severe, crossbred, porcine.

**Conference Note**. Endometrial glands are not present at birth; therefore, all instances of cystic glands can be considered acquired conditions. Possible causes of cystic endometrial glands include infection, accumulations of mucus, postpartum involution of the glands and, as is most likely in this case, hormonally induced cystic hyperplasia. Cystic endometrial hyperplasia is rare in the sow and mare but is known to occur in the bitch, cow, and ewe in association with hyperestrogenism. Sources of excessive estrogen in domestic animals include follicular cysts, granulosa cell tumors, certain mycotoxins and clover pastures. Zearalenone is an estrogenic product of the mold Fusarium roseum. Uterine edema, anestrus, and nymphomania are common findings in mature sows that have eaten zearalenone-contaminated feed. More chronic exposure to the toxin can induce endometrial gland hyperplasia and long

periods of pseudopregnancy.

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Microslide 59

**History**. An adult pony was experimentally inoculated with African horse sickness virus. Ten days subsequent to inoculation, the animal was febrile, depressed and dyspneic. Bilateral fluctuant swellings were noted in the supraorbital fossae. The following day the animal was found dead.

**Gross Pathology**. Lungs were wet and heavy, with interlobular septa markedly widened by edema fluid. There was excess fluid in the pericardial cavity. Subtle mottling was evident in the papillary muscle of left ventricle. There was edema of the intermuscular fasciae in the dorsal neck region.

**Contributor's Diagnosis and Comments**. Necrosis, multifocal, with hemorrhage and acute inflammatory cells, moderate, acute, myocardium. Etiology: African horse sickness virus (Genus Orbivirus, Family Reoviridae).

African horse sickness is an acute to subacute systemic illness of horses and other equidae. Horses are the most susceptible, with mortality rates approaching 100%. Mules and donkeys are less susceptible, and zebras are the most resistant, usually experiencing only a subclinical form of infection.

African horse sickness is transmitted by biting flies of the Culicoides genus and is endemic throughout the range of those insects in Africa, which is most of the continent south of the

Sahara. Historically, African horse sickness has made periodic incursions into other parts of the world and has proven to be extremely difficult to control and eradicate.

Gross lesions of African horse sickness consist of edema in a variety of places, but most consistently and notably the lungs and intermuscular fasciae around the ligamentum nuchae. Hydrothorax and hydropericardium are also seen with some regularity. As the disease becomes more protracted, myocardial necrosis may be grossly evident.

Histologically, there is widespread vascular change characterized by adventitial serocellular accumulations, endothelial cell swelling, and, occasionally, necrosis of vascular walls. In the lung these changes are accompanied by a generalized edema and in the heart they are characterized by microfoci of hemorrhage and, if prolonged enough, early myocardial necrosis.

**AFIP Diagnosis**. Heart, myocardium: Necrosis, multifocal, moderate, with hemorrhage, pony, equine.

**Conference Note**. The severity of the lesion varied in different sections. Participants discussed a differential diagnosis for myocardial necrosis and hemorrhage in horses including infectious myopathies (African horse sickness, equine viral arteritis, purpura hemorrhagica), nutritional myopathies (vitamin E/selenium deficiency), and various toxic myopathies (monensin, Cassia sp., Eupatorium rugosum, heavy metals, and cantharidin). African horse sickness (AHS) is described as causing four clinical syndromes in affected horses, the two most important being the pulmonary and cardiac forms of the disease. In the pulmonary form, the infection is peracute to acute and is characterized by severe pulmonary edema and hydrothorax. The cardiac form of the disease is more subacute. Clinical signs may include colic, fever, and edema of the supraorbital fossae. Grossly, edema may be seen around the trachea, ventral midline and the fascia near the ligamentum nuchae. Petechiae and ecchymoses of serosal surfaces are common findings. Two additional syndromes of AHS described in the horse are the mixed pulmonary and cardiac form and the milder "fever" form.

Other orbiviruses of veterinary importance include bluetongue, epizootic hemorrhagic disease, and Ibaraki disease. In addition to infecting various solipeds, dogs become infected with African horse sickness virus by eating meat from horses that have died of the disease. It is not known if natural infection in dogs plays any role in the epidemiology of the disease.

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Microslide 60

**History.** This 18-year-old male, castrated Quarter Horse was found ataxic in the rear limbs. Initial hindleg ataxia was followed by front leg ataxia and hypometria. Economics prevented a major diagnostic work up. The horse became recumbent and unable to get up. Euthanasia was performed. A differential diagnosis included extradural tumor, equine protozoal myelopathy, migrating parasites and fractured cervical vertebrae.

**Gross Pathology.**

1. Renal neoplasia, bilateral, severe, kidneys.
2. Edema, moderate, subcutis, head, lumbosacral area.

Both kidneys had many white solid nodules ranging from 3 cm and up to 10 cm in diameter. Nodules were seen in cortex and medulla.

**Laboratory Results.** Microbiological culture results from kidney yielded alpha-hemolytic Streptococcus spp. and Corynebacterium spp.

**Contributor's Diagnosis and Comments.** Verminous granulomatous nephritis, marked, bilateral, kidney. Etiology: Halicephalobus (Micronema) deletrix.

This horse was misdiagnosed at the gross level. What was thought to represent a renal neoplasm, was found to be a granulomatous nephritis caused by an unusual nematode. The horse had a granulomatous encephalitis at the level of the cerebellum plus intralesional nematodes explaining the signs of ataxia. Halicephalobus deletrix is a rhabditoid nematode with unique features of patchy geographic distribution, organ preference, life cycle and diagnostic difficulties. It parasitizes horses and humans. Several cases have been reported from Florida. It is one cause of equine ataxia.

**AFIP Diagnoses.** 1. Kidney: Nephritis, granulomatous, multifocal to coalescing, severe, with rhabditiform nematodes, quarter horse, equine.
2. Kidney: Nephritis, interstitial, chronic, diffuse, mild.

**Conference Note.** Halicephalobus deletrix, formerly known as

Micronema deletrix, is a facultative rhabditiform parasite of horses and humans. Lesions are similar in both species and are located primarily in the brain and less frequently in the kidney, lungs, adrenal gland and other organs. Affected tissues contain adult females, larvae and eggs, but not adult male worms. The ability of the nematode to reproduce parthenogenetically is suspected. The granulomatous inflammatory response in these sections is considered typical for Halicephalobus. It is characterized by fibrosis and infiltration with macrophages, multinucleated giant cells, plasma cells, lymphocytes, and eosinophils. Numerous nematodes are noted within the inflamed interstitium and occasionally within ectatic tubules. Lesions in the brain tend to have a perivascular orientation with milder inflammation and fewer parasites. Areas of malacia are commonly found in the neuropil. Microscopic morphologic features used to identify rhabditiform nematodes include a thin, smooth cuticle, platymyarian musculature, a typical rhabditiform esophagus with corpus, isthmus and terminal bulb, uninucleate cuboidal intestinal cells, and a single ovary containing one egg which may be embryonated.

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Microslide 61

**History.** Increased mortality was observed for 2-3 days among farm-reared channel catfish (Ictalurus punctatus) by the producer. Fish were frequently seen in shallow water or at the pond surface at night.

**Gross Pathology.** Branchial arches were thickened, moderately to severely attenuated, and occasionally hemorrhagic.

**Contributor's Diagnosis and Comments.** Focally extensive to diffuse lymphohistiocytic branchitis with epithelial hypertrophy and hyperplasia and irregular chondrodystrophy. Aurantiactinomyxon sp.

These slides represent proliferative gill ("hamburger gill") disease. Several etiologic agents have been described for this condition (see references). However, the most recent indications

are that the lesions are induced by Aurantiactinomyxon sp. Please note that there are various other superficial branchial parasites in several sections (e.g. Ambiphyra, Trichondina, Henneguya, Gyrodactylus, etc.). The clinical signs are typical of conditions causing hypoxia in fish.

**AFIP Diagnosis.** Gill: Branchitis, histiocytic and proliferative, diffuse, moderate, with multifocal chondroid degeneration and regeneration and interlamellar myxosporidian parasites, channel catfish (Ictalurus punctatus), piscine.

**Conference Note.** Diffusely, gill lamellae are thickened and clubbed and interlamellar spaces are occluded by epithelial hyperplasia, numerous infiltrating histiocytes and lymphocytes, and scattered intraepithelial myxosporidian cysts. Both degenerative and regenerative changes are present in the gill cartilage. Proliferative or "hamburger" gill disease is a serious parasitic infection of channel catfish. The disease must be differentiated from the more necrotizing gill lesions caused by Flexibacter columnaris and the non-inflammatory hyperplasia of gill epithelium associated with poor water quality and overcrowding. The etiologic organism of proliferative gill disease has not yet been proven, but it is thought to be a myxosporidian. Henneguya, Sphaerospora and, more recently, Aurantiactinomyxon have all been implicated in different outbreaks. The disease is most often associated with new or recently refilled ponds. Myxozoa are frequent obligate parasites of fish that normally cause serious disease only in instances of heavy infections. Their life cycle and method of transmission remain largely unknown. Another important myxosporidian parasite of fish is Myxosoma cerebralis, the cause of "whirling disease" in trout.

**Contributor.** Mississippi State University, College of Veterinary Medicine, P.O. Drawer V, Mississippi State, MS 39762.

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Microslides 62, 63

**History.** This 1-1/2-year-old hybrid striped bass (Morone saxatilis X Morone chrysops), was one of 24 submitted by a commercial hybrid striped bass producer. The farm manager reported that fish were doing poorly and dying in three tanks for approximately one year. Losses were approximately 10% of the tank population per month. Tanks were constructed of concrete and contained 16,000 gallons of water with a water exchange rate of 100 gallons/min. There were approximately 7,000 to 8,000 fish per tank.

**Gross Pathology.** The submitted fish was thin, pale and smaller than normal age-matched fish on the farm. Pale, round to linear foci were present in the gills. The spleen, liver, head kidney and trunk kidney were moderately enlarged and contained numerous pale to red foci (1 to 2 mm).

**Laboratory Results.** Large numbers of acid-fast bacteria were seen in impression smears from gill lesions. A mycobacterium was cultured from the spleen, head kidney and liver. Cultures were submitted to the National Animal Disease Center in Ames, Iowa for determination of species.

**Contributor's Diagnosis and Comments.** Granulomas (head kidney), multifocal to coalescing, severe, with intralesional acid-fast bacteria.

Mycobacteriosis is a relatively common bacterial disease in fish raised in intensive aquaculture facilities with recirculating water systems and in aquaria. The infection is rare in feral fish. A variety of mycobacterial species have been isolated from fish, but only two mycobacteria, Mycobacterium marinum and Mycobacterium fortuitum, are given full status in the ninth edition of Bergey's Manual of Determinative Bacteriology. Mycobacteria were cultured from this fish and others submitted from this farm, but the species of mycobacteria is not known at this time. Cultures were sent to the National Animal Disease Center in Ames, Iowa.

Histologically, much of the parenchyma of the head kidney, spleen and trunk kidney is replaced by multifocal to coalescing granulomas of various ages. Small numbers of similar granulomas are present in the liver, heart, mesenteric fat and intestine. The older granulomas have caseous centers surrounded by collars of fibrous tissue. Less chronic lesions are composed of aggregates of macrophages and necrotic cellular debris. Small to moderate numbers of acid-fast bacteria are present within granulomas.

The tissue submitted is head kidney. In teleost fish, the anterior or head kidney is composed of hematopoietic cells, lymphoid cells and adrenal tissue and for this reason is also referred to as the hematopoietic kidney. Bacterial and viral agents commonly affect the organ. Even though little to no true renal tissue exists in the organ, inflammatory conditions are referred to as nephritis.

**AFIP Diagnosis.** Head kidney (per contributor): Granulomas, multifocal and coalescing, severe, with acid-fast bacilli, hybrid striped bass (Morone saxatilis X Morone chrysops), piscine.

**Conference Note.** Piscine mycobacteriosis is a chronic progressive disease characterized by lethargy, anorexia, cachexia, exophthalmia, dermal ulceration, edema, peritonitis, and white nodules in the muscle and other organs. A differential diagnosis for the gross lesions of mycobacteriosis in fish includes other bacterial diseases caused by Flavobacterium, Nocardia, Corynebacterium and Renibacterium and the parasitic granulomas associated with certain helminth infections. These conditions can usually be differentiated without difficulty histologically. An immunostained section viewed in conference demonstrated cytokeratin positivity of the epithelioid cells forming the walls of these granulomas. This unusual feature, in addition to the ultrastructural finding of well-formed desmosomes with tonofilaments, distinguish the epithelioid cells of teleost fishes from the typical epithelioid cells associated with mammalian and avian granulomas.

Transmission of piscine mycobacteriosis has been associated with the feeding of uncooked fish parts in aquaculture operations such as hatcheries and commercial aquariums. The aquatic environment is considered a reservoir for these bacteria. M. marinum is also a significant cause of granulomatous skin disease in people. Infection can result from swimming in infected water or exposure to infected tropical fish tanks.

**Contributor.** Department of Veterinary Pathology, School of Veterinary Medicine, Louisiana State University, Baton Rough, LA 70803.

**References.**

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Microslide 64

**History**. This female Holstein fetus was aborted at 6 months gestation. Over a two month period, twelve cows in this herd of 65 cows aborted at 5 to 7 months gestation.

**Gross Pathology**. Blood-tinged subcutaneous edema, hydrothorax and ascites.

**Laboratory Results**. Bovine pestivirus (BVD virus) detected in brain and spleen by tissue culture/AGID. No pathogenic bacteria isolated from various tissues.

**Contributor's Diagnosis and Comments**. Encephalitis, multifocal, nonsuppurative, subacute, caused by Neospora caninum (or N. caninum-like protozoan).

There are many small foci of gliosis and necrosis, with mineralization of some necrotic cells. Many adjacent capillaries have hyperplastic endothelium and perivascular infiltration by mononuclear cells. There is degeneration of axons in some white matter tracts.

Sections contain cysts and/or clusters of zoites which reacted with anti-N. caninum serum in an immunoperoxidase stain. However, Barr et al (1991) found ultrastructural differences (viz tubulovesicular structures in ground substance) between such cysts and those of N. caninum in dogs. The present case was not examined ultrastructurally.

This fetus also had nonsuppurative epicarditis and myocarditis, and nonsuppurative portal hepatitis. This pattern of lesions has been recognized with increasing frequency in aborted bovine fetuses in parts of the USA (Barr et al, 1990) and Australia (McCausland et al, 1984). Barr et al, 1991, found Neospora-like protozoa in 83%, and Sarcocystis sp. in 4% of such cases.

The pestivirus was probably of no pathological significance.

**AFIP Diagnosis**. Brainstem: Encephalitis, necrotizing, multifocal, mild, with gliosis, Holstein, bovine.

**Conference Note**. Neosporosis was first described as a cause of encephalomyelitis in dogs and has since been reported in

cattle, sheep, goats and horses. The pathogenesis and life cycle of Neospora are not completely understood, but share many similarities with that of Toxoplasma gondii. The definitive host is unknown. The Neospora organism isolated from natural bovine infections is similar to N. caninum in dogs, but it has not been proven to be the same species. The protozoan has only two known life stages: tissue cysts and tachyzoites. Cysts are uncommon in the tissues of aborted bovine fetuses, but they are more numerous in neonatal deaths. As in this case, zoites are often difficult to find in H&E sections from aborted calves, but can usually be readily identified in slides stained with anti-N. caninum serum. Transplacental transmission of Neospora has been experimentally demonstrated in dogs, cats, sheep and, most recently, cattle.

The lesions in these sections are considered nearly pathognomonic for Neospora infection in aborted calves. The brain and spinal cord typically have multiple foci of necrosis rimmed by proliferating glia or mononuclear cells. Hemorrhage and mineralization can occur. Additional lesions may be found in the lung and placenta. Mummification is also reported in abortions associated with N. caninum-like organisms. In contrast to Toxoplasma infections in people and sheep, repeated transplacental infections have been reported in both cattle and dogs exposed to Neospora organisms. Apparently, prior exposure to Neospora does not elicit a maternal immune response that provides fetal protection during subsequent pregnancies. We thank Dr. J.P. Dubey of the USDA Zoonotic Diseases Laboratory, Livestock and Poultry Sciences Institute, for his consultation and assistance with this case.

**Contributor**. Regional Veterinary Laboratory, Wollongar NSW 2477, Australia.

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Microslide 65

**History**. This experimental 8-month-old castrated male crossbred Friesian bovine developed an increased respiratory rate and coughing 6 days after access to known Dictyocaulus viviparus-infected pasture. The respiratory signs became more severe and the animal became dyspneic and was euthanatized 15 days after access to this pasture.

**Gross Pathology**. At necropsy the lungs failed to collapse. Many lobules in the dorsocaudal region were consolidated and well demarcated by septal emphysema. Copious frothy fluid and many young adult Dictyocaulus viviparus nematodes were present in the trachea and bronchi.

**Laboratory Results**. Parasitological examination using the Baermann indicated approximately 5500 Dictyocaulus viviparus in the lungs. 30% of these nematodes were L4 stage, 35% were late L4 stage and 30% were immature adults.

**Contributor's Diagnoses and Comments**. Bronchus and bronchioles: Bronchitis and bronchiolitis, subacute to chronic, moderate, with epithelial hyperplasia.
Lung: Pneumonia, interstitial, subacute, moderate to severe, associated with parasitic larvae.

Lung changes in this animal are consistent with D. viviparus infection. There is bronchial and bronchiolar epithelial hyperplasia. The mucosa and submucosa of these airways are infiltrated by a mixed leukocyte population in which eosinophils predominate. There is hyperplasia of bronchus-associated lymphoid tissue and of bronchiolar smooth muscle. Bronchiolitis obliterans is evident in some airways.

There are infiltrates of eosinophils, neutrophils and macrophages in alveolar lumina and many alveoli are filled with edema fluid and fibrinous exudate. Disruption of alveolar architecture with inflammatory cell infiltration of the alveolar septa is apparent. Type 2 pneumocyte hyperplasia is a prominent feature of the lesions. There is marked interlobular and subpleural emphysema. Although the lungs had a high nematode count, only small numbers of larvae were seen in lung sections.

Dictyocaulus viviparus infection is common in western regions of Britain and Ireland. It primarily affects calves in their first year at grass. The life cycle is direct. The adult nematodes live in the bronchi. Eggs laid by females hatch quickly and first stage larvae (L1) are coughed up, swallowed and

appear in the faeces. These larvae develop to the infective third stage (L3) and migrate onto the grass. This development requires conditions of high moisture and moderate to low temperatures which explains the high prevalence of this disease in wet temperate climates. Following ingestion by a susceptible host animal, the L3 larvae penetrate the intestinal wall and pass to the mesenteric lymph nodes where they moult. The fourth stage larvae (L4) then travel via the lymph and bloodstream to the lungs where they emerge from capillaries and enter alveolar lumina approximately 7 days post-infection. The final moult to the L5 stage occurs in bronchioles a few days later. Young adults subsequently move up the bronchi and achieve sexual maturity approximately 22 days post-infection.

**AFIP Diagnosis**. Lung: Pneumonia, interstitial, eosinophilic, subacute, multifocal to coalescing, moderate, with bronchiolitis, edema and interstitial emphysema, crossbred Friesian, bovine.

**Conference Note**. Nematode parasites are rarely seen in these sections. Participants discussed a differential diagnosis for this lesion including atypical interstitial pneumonia, bovine respiratory syncytial virus, chemical toxins, and lungworms. Dictyocaulus spp. are members of the trichostrongyle family. Adult worms are characterized by platymyarian meromyarian musculature, prominent lateral chords, and a typical strongylid intestine lined by few multinucleate cells with short microvilli. Dictyocaulus are important respiratory tract parasites of domestic animals. D. filaria is the most pathogenic lungworm of sheep and goats. D. arnfeldi is a common and usually asymptomatic parasite of its natural host, the donkey, but can cause clinical disease in young horses or ponies that become infected. D. viviparous is a cause of parasitic bronchitis and pneumonia in cattle, and can also infect deer, reindeer, buffalo and camel. Clinical disease is most severe in animals less than 1 year of age. As seen in these sections, early features of infection by D. viviparous include pulmonary edema and fibrin, interstitial emphysema and a mixed infiltrate of numerous eosinophils, neutrophils, macrophages and scattered giant cells, type II pneumocyte hyperplasia, and eosinophilic bronchitis and bronchiolitis with epithelial hyperplasia. In more chronic cases there is often pronounced BALT hyperplasia, peribronchiolar fibrosis and smooth muscle hyperplasia, and bronchiolitis obliterans. Grossly, these lesions appear as large wedge-shaped red to grey consolidated areas at the posterior border of the caudal lung lobe. Other nematodes commonly found in the lungs of ruminants include Protostrongylus rufescens, Muellerius capillaris and migrating larvae of Ascaris suum.

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Microslide 66, Lantern slides 18, 19

**History.** This 4-month-old, female, Polled Hereford calf had progressive seborrhea since 1 month of age. Samples include skin and diaphyseal bone marrow.

**Gross Pathology.** Gross findings include hyperkeratotic dermatitis, alopecia, yellow discoloration of white hair, dilated heart, 4 gall stones (1-2 cm in diameter), and osteopenic bone with abundant red marrow.

**Laboratory Results.**

| | | | |
|---|---|---|---|
| RBC | $2.89 \times 10^6$ | Hct. 14.1% | Reticulocytes 0.8% |
| WBC | $8.50 \times 10^3$ | MCV 49.3 fl | 7 nucleated RBC's/100 WBC |
| Hgb | 5.0 gm/dl | MCH 17.4 pg | No Polychromasia |

**Contributor's Diagnoses and Comments.** Bone marrow, erythroid hyperplasia, ineffective erythropoiesis.
Skin, superficial perivascular dermatitis, histiocytic.
Skin, orthokeratotic hyperkeratosis with dyskeratosis.

The clinical, gross and pathologic findings are compatible with diagnosis of congenital dyserythropoiesis and progressive alopecia of Polled Hereford calves. Current data suggest this to be inherited as a simple autosomal recessive trait. Hair coat abnormalities are noticeable at birth and epidermal pathology appears to become progressively more severe. Profound anemia with dyserythropoiesis is a constant feature of the disease and is seen in all cases. The association of cutaneous and bone marrow pathology on a molecular basis remains unknown. Calves often die prior to 1 year of age. A few calves surviving longer than one year have developed fractures secondary to osteopenia. Secondary dermatophytosis is not uncommon and may be seen in some slides. The anemia is nonprogressive.

**AFIP Diagnoses.** 1. Skin: Dermatitis, chronic, diffuse, moderate, with marked epidermal and follicular orthokeratotic hyperkeratosis and dyskeratosis, Polled Hereford, bovine.

2. Bone marrow: Erythroid hyperplasia, marked, with erythroid maturation arrest.

**Conference Note.** Conference participants reviewed the laboratory results provided. Significant findings include decreased hemoglobin and an anemia classified as macrocytic, normochromic and nonregenerative based on a minimal reticulocyte response. Congenital dyserythropoiesis and progressive alopecia is a recently described hereditary syndrome of Polled Hereford calves. Cutaneous changes include multifocal to progressively generalized alopecia and hyperkeratotic dermatitis. Dyskeratosis within the epidermis and in Huxley's layer of the hair follicle in addition to a mild to moderate mononuclear cell infiltrate in the dermis are consistent findings. Grossly, the skin lesions must be differentiated from congenital hypotrichiosis, ichthyosis congenita (not reported in Herefords) and other congenital causes of alopecia. The erythropoietic changes seen in this condition share many similarites with type 1 congenital dyserythropoietic anemia of people. Bone marrow features include markedly decreased myeloid:erythroid ratios, maturation arrest of most erythroid cells at the late rubricyte and metarubricyte stages, bi- and multinucleate rubricytes, megalocytosis and varied morphologic abnormalities of nuclear chromatin. Granulocytic, lymphocytic and megakaryocytic cell lines usually appear normal, although conference participants thought that megakaryocytes may be increased in these sections. Capsular and subcapsular fibrosis of the liver has also been described in affected calves.

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Microslide 67

**History.** There had been a sudden outbreak of lethargy, mild bloat and dehydration in four animals, with mucous membranes a yellowish color. Elevated heart rate and respiratory rate, with increased lacrimation was also observed. Body temperatures were recorded as high as 105°F. The heifer from which samples were

taken was very thirsty, and exhibited hemoglobinuria before she died. Hemoglobinuria was also noted in some of the other animals. Response to antibiotic treatment was very poor. Of nine animals affected, all died.

**Gross Pathology**. Gross necropsy was done by the veterinary practitioner.

The practitioner noted the heifer to be in good body condition. There were numerous ecchymotic hemorrhages on visceral serosal surfaces. The liver had a large focal area of necrosis. Kidneys had areas of parenchymal hemorrhage or congestion. Spleen was very enlarged, appeared congested and/or hemorrhagic.

The liver specimen submitted to the laboratory was in fresh condition. A large pale focus of parenchymal necrosis was present, contrasting with the more normal adjacent tissue.

**Laboratory Results**. Bacteriology: Lung yielded scant coliforms and Proteus sp.

Liver was negative on anaerobic culture, though the direct fluorescent antibody test yielded a 3+ positive for Cl. novyi on both liver and spleen. Aerobic culture on liver was negative (the animal had received antibiotics). Splenic samples were negative for B. anthracis on direct smears and on culture. All tissues cultured were negative for Salmonella sp.

Toxicology: Liver and kidney trace mineral analysis indicated this animal to be copper deficient at 16 ppm (less than 25 ppm wet weight is considered marginal to deficient).

Trace mineral analysis on sera from five clinically affected animals indicated that selenium, copper, zinc, iodine, phosphorous levels were generally low. A skewing effect induced by the severely acute illness on the various trace mineral analyses might be anticipated. Nitrate spot test (a crude indicator for elevated serum nitrite) on sera was negative.

Clinical pathology: EDTA blood samples from four of the affected animals indicated markedly elevated white cell counts varying from 18000 to 25000/cmm of blood. Band cells were elevated in all specimens to 5-7%. All cases had a neutrophilia. Hemoglobin levels varied from 9 to 12 gm%.

Histopathology: Sections taken from liver vary. There is extensive hepatocellular necrosis and degeneration. There are patchy foci of hemorrhage, and intravascular thrombosis is seen. Sinusoids are filled with many degenerate neutrophils, as are portal areas. Numerous bacilliform bacteria are noted. On Gram stain, these are gram-positive with rounded ends, usually as

single organisms though a few short chains are seen. Subterminal spores are present which swell the lateral sides of the organisms. At times these bacilli stain poorly.

**Contributor's Diagnosis and Comments**. Hepatitis, acute, diffuse, severe, necrotizing and focally hemorrhagic, Holstein heifer, Bos taurus.

Etiology: Clostridium hemolyticum (Cl. novyi type D).

The pathologic findings are consistent with a diagnosis of necrotizing hepatitis due to Cl. hemolyticum.

The liver lesions are severe and give credence to the positive Cl. novyi FA results in the absence of other organisms. Cl. hemolyticum is fastidious, and is not always readily grown from submitted diagnostic material.

None of the affected animals survived. The animals had been turned onto the pasture a few weeks earlier. A communications cable had been recently placed across the poorly-drained pasture and buried to a depth of about ten feet. This resulted in quantities of excavated soil remaining on the surface, which became sodden with spring runoff.

The organism Cl. hemolyticum (also referred to as Cl. novyi type D) may have originated from the overturned soil and found its way into the surface water. There was no direct evidence of prior infection with Fasciola hepatica in the submitted samples.

Cl. hemolyticum is associated with wet pastures in which the pH remains at 8.0 or higher. Carrier animals may introduce the organism. The site of beta toxin production is the liver. Tissue destruction caused by liver fluke migration is thought to provide a suitable microenvironment for germination of spores of Cl. hemolyticum; a high nitrate level in the diet has also been noted as a potential predisposing cause. In this case, liver flukes are known to occur in the area.

Beta toxin (phospholipase C) released in the liver causes massive intravascular hemolysis and capillary damage. The organism also produces the eta and theta toxins of Cl. novyi. The liver lesion is considered primarily a focus of toxic rather than ischemic necrosis.

Surviving animals were immediately removed from the pasture and vaccinated with a multiple-strain clostridial vaccine that included Cl. hemolyticum.

**AFIP Diagnosis**. Liver: Necrosis, focally extensive, severe, with acute inflammation, hemorrhage, and numerous bacilli, Holstein, bovine.

**Conference Note.** The presence of numerous degenerate and necrotic neutrophils bordering the large areas of coagulative necrosis helped to differentiate this lesion from autolysis with overgrowth by postmortem bacilli. Bacillary hemoglobinuria is a acute and highly fatal disease of cattle and sheep caused by the toxins of Clostridium hemolyticum. The disease often occurs in regions endemic to Fasciola hepatica, but it may be seen sporadically in other areas. Clinical signs and gross lesions include intravascular hemolysis, hemoglobinuria, anemia, fever, jaundice, hemoglobin-stained kidneys and large necrotic foci in the liver. The pathogenesis of Clostridium hemolyticum infection in cattle is very similar to that of infectious necrotic hepatitis (Black disease) caused by Clostridium novyi type B. Both organisms are widely distributed in soil and, once ingested, can survive in the liver and other tissues of infected animals as latent spores for months. In the liver they may reside in Kupffer cells. Under anaerobic conditions, the bacteria produce beta toxin, a necrotizing and hemolytic lecithinase, which is primarily responsible for the hepatic necrosis and hemolysis. A differential diagnosis for hemoglobinuria in cattle includes bacillary hemoglobinuria, leptospirosis, postparturient hemoglobinuria, babesiosis, and hemolytic anemias associated with ingestion of rape or kale.

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Microslide 68, Lantern slides 20, 21

**History.** This adult cynomolgus monkey (Macaca fasicularis) was a control animal on a subchronic study. The animal was clinically normal during the study.

**Gross Pathology.** Left anterior and middle lobes of lung were consolidated, and tracheobronchial lymph nodes were enlarged. No other alterations were observed at necropsy.

**Contributor's Diagnosis and Comments.** Pyogranulomatous pneumonia caused by Coccidioides immitis.

Prior to coming to Syntex, the monkey was housed in a Texas facility for many months. Texas is endemic for coccidioidomycosis. No other monkeys on study were affected.

Photos are submitted of spherules containing endospores and multinucleated giant cells.

**AFIP Diagnosis.** Lung: Pneumonia, pyogranulomatous, diffuse, severe, with multifocal granulomas and fungal spherules, cynomolgus monkey (Macaca fasicularis), nonhuman primate, etiology -- consistent with Coccidioides immitis.

**Conference Note.** Fatal coccidioidomycosis has been reported in several species of nonhuman primates. Participants discussed the dimorphic lifecycle of Coccidiodes immitis. In its tissue phase the fungus occurs as distinct 10-80 micron endosporulating spherules or sporangia. The mycelial form grows in alkaline soil, such as that found in the southwestern United States, but rarely occurs in animal tissue. Infection is acquired by inhalation of fungal arthrospores which develop into mature sporangia in the lungs. Rupture of sporangia and release of endospores evokes an inflammatory response that is initially suppurative but progresses into a more pyogranulomatous reaction with granuloma formation. Spherules are most likely to be found in the center of the granulomas, often within the cytoplasm of giant cells. Dissemination of the fungus to other tissues occurs most frequently in dogs. The most common sites of extrapulmonary infection are visceral organs, bone, heart, eye, lymph node, and the central nervous system. The sporangia of C. immitus must be differentiated from the adioconidia of Chrysosporium parvum, the cause of adiospiromycosis, which are similar in size but do not endosporulate.

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**References.**

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Microslide 69

**History**. This 6-year-old female Cocker Spaniel had persistent bloody vaginal discharge. Whelped nine weeks ago. Mass found in left uterine horn near ovary.

**Gross Pathology**. Not available.

**Contributor's Diagnosis and Comments**. Subinvolution of placental site, Cocker Spaniel, canine.

Normal postpartum involution is usually complete by 9-10 weeks, with placental attachment sites having been shed into the uterine lumen by the 7th or 8th week. The cause for their retention beyond that point is unknown.

In some of the slides, syncytial or multinucleate trophoblastic cells are present near the base of the mass which extends into the myometrium almost to the serosal surface, illustrating the potential danger of uterine rupture and peritonitis due to this condition.

**AFIP Diagnosis**. Uterus: Subinvolution of placental site, Cocker Spaniel, canine.

**Conference Note**. In the diagnosis of subinvolution of placental sites, the histologic lesion must be interpreted in the context of time since parturition. Many of the same changes may occur with normal involution of the early postpartum uterus. Placentation of dogs is categorized as zonary labyrinthine, endotheliochorial, and deciduate. During the implantation process, trophoblasts lining the fetal chorionic membrane proliferate and invade the maternal tissue as two distinct cell types: cytotrophoblasts and syncytiotrophoblasts. The pathogenesis of subinvolution of placental sites in the postpartum uterus is thought to involve the failure of these syncytial cells, which are sometimes interpreted as decidual cells, to regress normally. There is also a failure to slough accumulated collagen masses within the endometrium. Key histologic features include the presence of lobulated collagen masses and remaining trophoblast-like cells at varying locations

within the uterine wall, associated with marked necrosis, hemorrhage, and inflammation. Subinvolution of placental sites should be considered in any bitch experiencing a mild persistent hemorrhagic to serohemorrhagic vaginal discharge 6- to 12-weeks postpartum. It is most common in the young bitch following the first or second gestation. Although spontaneous recovery is the most common outcome in untreated affected bitches, other more serious sequelae may occur including metritis or peritonitis as mentioned by the contributor.

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**References**.

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Microslide 70

**History**. A firm abdominal mass was palpated on the right side in a pedigreed 6-month-old male baboon (Papio cynocephalus anubis) with respiratory distress and distended abdomen. At surgery a well defined oval mass approximately 10 cm in diameter and 2 cm thick was found in the area of the right kidney.

**Gross Pathology**. The cut surface of the mass had an irregular cortical wall and a central pus-filled cavity which replaced the medulla and inner cortex of the kidney.

**Laboratory Results**. Elevated alkaline phosphatase--all other chemical laboratory parameters within normal limits.

**Contributor's Diagnosis and Comments**. Embryonal nephroma, congenital. Pyelonephritis.

Nephroblastomas are the second most common visceral tumor in children under 10 years of age. The majority are sporadic in occurrence but 1/3 of all cases may be hereditary with the defect localized to a gene on chromosome 2.

Histologically, the neoplasm had an outer fibrovascular wall, an inner margin of inflammatory cells, and a parenchyma of proliferating anaplastic epithelial cells which formed papillary projections into cystic tubules (glomerular-like structures). A karyotype analysis of the baboon's lymphocytes did not detect a

chromosomal defect. This is the third report of a nephroblastoma in a nonhuman primate and the first report in a baboon.

**AFIP Diagnosis**. Kidney: Nephroblastoma, baboon (Papio cynocephalus anubis), nonhuman primate.

**Conference Note**. Nephroblastomas are the most common primary renal neoplasm in swine, rats, chickens and rabbits. In nonhuman primates, they occur less frequently than renal cell carcinomas. Nephroblastomas are usually seen in animals under one year of age. They are typically unilateral, arising from one pole of the kidney and expanding into the medulla and pelvis. Grossly, they are firm masses varying in color and size, often with central areas of necrosis and hemorrhage. The mass is frequently surrounded by a fibrous capsule. The diagnosis is based on the characteristic histologic appearance of the tumor which shares many morphologic similarities to the developmental stages of the embryonic kidney. Nephroblastomas are characterized by varying combinations of neoplastic epithelial cells forming primitive glomeruli and tubules surrounded by a loose stroma of spindle-shaped mesenchymal cells and undifferentiated blastema. In some cases, the mesenchymal component may show areas of differentiation into fibrous, adipose, muscular or osseous/cartilaginous tissue. It is suspected that the tumors originate from neoplastic transformation occurring during normal nephrogenesis or from transformation of rests of undifferentiated blastema that persist in the postnatal kidney.

**Contributor**. AL-OEVP, Brooks Air Force Base, Brooks AFB, TX 78235.

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Microslide 71

**History**. This adult female Hanuman langur monkey (Presbytis entellus) was one of eight Hanumans housed in concrete and wire zoo exhibits. The animal was euthanatized following an acute onset of inappetence, weakness, and ataxia that progressed to lethargy over a four day period, despite antibiotic treatment.

Three other langurs, including the 4-month-old daughter of this female, died over a 6-week period with similar or no previous clinical signs.

**Gross Pathology**. The diaphragmatic lobe of the liver contains a single, discrete, round, yellow to cream colored focus, 4 cm by 6 cm in diameter, extending into the parenchyma. The cut surface of the lesion is multilocular containing white to yellow creamy material.

The duodenum contains a single dark red ovoid mucosal ulcer.

**Laboratory Results**. Antemortem blood work performed included a CBC and chemistry panel which showed leukocytosis, low albumen, and an increased serum alkaline phosphatase.

**Contributor's Diagnosis and Comments**. Hepatitis, necrotizing, multifocal, severe, with abscess formation and intralesional amoeboid trophozoites, monkey. Etiology: Entamoeba histolytica.

Four langurs (three Hanumans and one separately housed purple-faced langur), died during this outbreak. Multifocal necrotizing hepatitis was a consistent finding. Gastrointestinal lesions were only found in two monkeys. One adult had multiple ulcers in the saccular portion of the stomach. Colonic lesions were not observed in any of the cases. Although trophozoites were plentiful in this case, no amoeba could be identified in the liver lesions of one monkey. The diagnosis of Entamoeba histolytica infection was based upon the characteristic morphology of trophozoites in both the liver lesions and fresh fecal smears obtained from surviving monkeys. Characteristic features of E. histolytica trophozoites are their large size (often greater than 20 um in diameter), foamy pale cytoplasm, centrally positioned nucleolus (more readily visualized on fresh direct fecal smears) and a thin, smooth, peripherally marginated rim of chromatin within the eosinophilic karyosome.

Langur monkeys are leaf fermenters (like colobus and howler monkeys), having a tripartite stomach. The saccular portion of the stomach functions similar to that of a rumen. The higher pH of this portion allows amoeba trophozoites to excyst and invade the mucosa resulting in proximal gastrointestinal ulcerations. In simple-stomached primates (including humans), colonic ulcerations are the most common entamoeba-associated lesion, which manifests clinically as dysentery. Due to the proximal location of the alimentary lesions, diarrhea is not usually a feature of entamoebiasis in leaf-fermenting monkeys.

**AFIP Diagnosis**. Liver: Hepatitis, necrotizing, subacute, multifocal and coalescing, severe, with amoebic trophozoites, Hanuman langur monkey (Presbytis entellus), nonhuman primate.

**Conference Note**. A section treated with the PAS procedure was viewed in conference and helped to demonstrate scattered Entamoeba trophozoites in the necrotic areas. Participants discussed other causes of hepatic necrosis in old world primates including herpesviruses (simiae and varicella), hepatitis A, yersiniosis, Tyzzer's disease, salmonellosis, toxoplasmosis, and melioidosis. Entamoeba histolytica is a common cause of amoebiasis in humans and nonhuman primates, and has been rarely reported in dogs and cattle. Entamoeba invadens is the cause of amoebic dysentery in reptiles. The lifecycle of E. histolytica was reviewed. Infection is acquired from ingestion of water or food contaminated with amoebic cysts. Trophozoites normally excyst in the neutral pH of the small intestine and pass to the colon where they may reside in asymptomatic hosts or, less frequently, may colonize and invade the mucosa causing severe colitis with characteristic flask-shaped ulcers. Trophozoites reproduce by binary fission on the mucosal surface and within ulcers. Extraintestinal infection can occur via direct extension or by hematogenous spread; hepatic necrosis is the most common sequela. Trophozoites and cysts are passed from affected animals, completing the cycle. As mentioned by the contributor, langurs and colobus monkeys differ by their predisposition to develop gastric amoebiasis. Pathogenicity is related to the virulence factors of the organism and the local and systemic immune response by the host. The ability of E. histolytica to cause an irreversible influx of calcium into target cells, such as host inflammatory cells, is thought to be an important mechanism of cytotoxicity.

**Contributor**. Louisiana State University, School of Veterinary Pathology, Baton Rouge, LA 70803.

**References**.

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Microslide 72, Lantern slides 22, 23, 24

**History**. This 8-year-old, female spayed, terrier cross had a 2-week history of a progressive, ulcerative, and crusting dermatitis involving the mucocutaneous junctions, perineum, hocks, and stifles. The pads of all feet were hyperkeratotic and fissured. The dermatitis was not responsive to treatment with a variety of antibiotics. Initial CBC and serum chemistry profile

results revealed no abnormalities. Pre- and postprandial bile acids were normal at that time. Bacterial culture of a pad lesion grew Pseudomonas sp. and Streptococcus sp. Biopsy of the lesions resulted in a diagnosis of dermatitis compatible with lesions seen in hepatocutaneous syndrome. The owner refused exploratory laparotomy to look for a possible pancreatic endocrine neoplasm, but instead requested immunosuppressive therapy with prednisone. The cutaneous lesions improved transiently with resolution of most old lesions and without the development of new lesions. Within 7 weeks however, ulcerative skin lesions recurred. CBC and serum chemistry profile results indicated the development of anemia and diabetes mellitus without ketoacidosis. The dog lost weight and had sporadic vomiting. At the owners request the dog was euthanatized and necropsied.

**Gross Pathology**. The dog was very thin with regions of erosive, exudative, and crusty dermatitis adjacent to the left stifle and hock, over the right popliteal region and forearm, and at the mucocutaneous regions of the mouth and anus. The largest area over the left stifle measured 10.0 X 5.0 cm. The pads of all feet were thickened with hyperkeratotic crust and fissures. The distal aspect of the left limb of the pancreas contained a 2.0 X 1.5 X 1.0 cm. slightly lobulated, white-tan, firm, and finely encapsulated neoplasm. Peripancreatic lymph nodes were enlarged, diffusely white-tan, and firm. The liver contained widely disseminated, white-tan, firm nodules in all lobes, ranging up to 1.5 cm in diameter. Similar nodules were also seen in the lungs, kidneys, spleen, and heart. Bilateral, diffuse, and multinodular adrenocortical hyperplasia was also noted.

**Laboratory Results**.

| | | | | |
|---|---|---|---|---|
| Glucose | 246 | mg/dl | Phos | 3.1 mg/dl |
| ALT | 114 | U/L | BUN | 7.8 mg/dl |
| AST | 48 | U/L | Crt | 0.4 mg/dl |
| Alk Phos | 731 | U/L | Na | 142.0 meqv/L |
| T. Bili | 0.34 | mg/dl | K | 5.1 meqv/L |
| T. Prot | 4.3 | g/dl | Cl | 107.0 meqv/L |
| Alb | 2.4 | g/dl | Chol | 97.0 mg/dl |
| Calcium | 7.3 | mg/dl | | |

Bile Acids:

| | |
|---|---|
| Preprandial | 1.0 umol/L |
| Postprandial (2 hr) | 6.0 umol/L |

CBC:

| | | | |
|---|---|---|---|
| RBC | 3.79 X $10^6$ | WBC | 12.8 X $10^3$ |
| PCV | 23.2 % | Segs | 12,672/ul |
| Hgb | 7.7 gm/dl | Lymphs | 128/ul |

URINALYSIS:

| | | | |
|---|---|---|---|
| Color | clear | Protein | neg |
| S.G. | 1.046 | Sugar | 5+ |
| pH | 8.0 | Ketones | neg |

**Contributor's Diagnoses and Comments.**

1. Metastatic, glucagon-secreting, pancreatic endocrine carcinoma to the liver.
2. Diffuse pododermatitis characterized by marked parakeratosis, mid-epidermal intracellular edema, and marked psoriasiform acanthosis consistent with hepatocutaneous syndrome.
3. Multifocal, superficial neutrophilic epidermitis with purulent crusts and intralesional cocci.

Hematoxylin and eosin stained section of the digital pad contained severe parakeratotic hyperkeratosis with regions of purulent crusts, serum exudate, hemorrhage, and frequent colonies of cocci. The underlying epithelium is irregularly acanthotic with frequent, narrow psoriasiform rete pegs. There is a laminar zone of pallor affecting the stratum spinosum and superficial epidermal layers. The severity varies from moderate intracellular edema contributing to the characteristic "red, white, and blue" pattern of the hepatocutaneous syndrome, to more severely affected regions where the intracellular edema progresses to keratinocyte ballooning degeneration, necrosis, vesicle formation, and in some sections degenerate pustules with scattered cocci. The superficial dermis has edema, pronounced vascularity, melanosis, and infiltrates of varying numbers of lymphocytes, plasma cells, histiocytes, and neutrophils. Follicles are frequently plugged by orthokeratotic debris and occasionally have colonies of cocci.

The liver contains multifocal, metastatic, pancreatic endocrine neoplasia characterized by foci of non-encapsulated, infiltrative ribbons of neoplastic epithelial cells separated by a narrow but dense fibrovascular stroma. In some foci, the ribbon pattern is replaced by packets or thick trabeculae of neoplastic cells. The nuclei are consistently oval to elongate with stippled euchromatic nuclei and a single nucleolus. Mitotic figures are rare. There is moderate, vacuolated eosinophilic cytoplasm with indistinct cell borders. Adjacent hepatocytes are in varying degrees of degeneration and necrosis with marked fatty change. Hepatocellular and occasional canalicular cholestasis is noted. Abundant hemosiderin laden Kupffer cells and lesser numbers of lymphocytes and plasma cells are scattered throughout the parenchyma.

These characteristic skin lesions were first described in 1942 by Becker in a middle-aged woman and termed necrolytic migratory erythema (NME). Other terms used in both veterinary and human medicine to describe this condition include, diabetic dermatopathy, hepatocutaneous syndrome, and superficial

necrolytic dermatitis. They all have in common the characteristic: a) vacuolated and necrotic superficial epidermis b) angioplasia or vascular dilatation of the papillary dermis c) psoriasiform hyperplasia with confluent parakeratosis d) +/- subcorneal pustules which may or may not contain acantholytic cells. In man, these cutaneous lesions are most often associated with glucagon-secreting pancreatic tumors. These tumors have been associated with what is referred to as the glucagonoma syndrome which is seen most frequently in middle aged female patients. The glucagonoma syndrome is characterized by the presence of a glucagon secreting pancreatic tumor, NME, and the development of diabetes mellitus without ketoacidosis. In contrast to reports in man, the characteristic skin lesions of the dog have been more frequently associated with cirrhosis or other chronic liver disease. A recent report associated the development of the skin lesion with long term primadone therapy in a dog. For this reason the condition is most often referred to as hepatocutaneous syndrome. The presence of glucagon-secreting cells was confirmed in this case in the primary and in metastatic sites by peroxidase-anti-peroxidase method. We were unable to test serum for glucagon levels. Gross et al, report on 2 other confirmed cases of glucagon-secreting pancreatic tumors and associated cutaneous lesions. Although not well understood, 2 main theories exist on the pathogenesis of the hepatocutaneous syndrome. One theory concerns the development of hypo-aminoacidemia secondary to the high demand for amino acids in the synthesis of glucagon. This hypothesis was supported by the resolution of the lesions in man after amino acid supplementation. The second theory concerns the local accumulations of high levels of arachidonic acid metabolites in the skin secondary to the high levels of circulating glucagon. This hypothesis was supported by in vitro studies where excess glucagon, or serum from a patient with NME, resulted in a 200-300X increase in keratinocyte arachidonic acid production. This may also help explain the predilection for sites of friction or trauma and the transient response to membrane stabilizing glucocorticoids. Differential diagnosis should include the immune mediated dermatopathies pemphigus foliaceous and SLE. Peroxidase-anti-peroxidase staining for intercellular and basement membrane IgG deposition was negative in this case. Zinc-responsive dermatopathy, essential fatty acid deficiency, and toxic epidermal necrolysis should also be considered.

**AFIP Diagnoses**. 1. Skin: Epidermitis and dermatitis, vesiculopustular, diffuse, severe, with parakeratotic hyperkeratosis, laminar intracellular edema, epidermal hyperplasia and serocellular crust, terrier cross, canine.
2. Liver: Islet cell carcinoma, metastatic.
3. Liver: Congestion, diffuse, mild with mild centrilobular fibrosis, and cholestasis.

**Conference Note**. The clinical, biochemical, and histologic

skin changes occurring in dogs with superficial necrolytic dermatitis (SND) are very similar to those seen in people with necrolytic migratory erythema. The characteristic microscopic skin lesion consists of a band of pale-staining keratinocytes in the upper half of an acanthotic stratum spinosum sandwiched between a parakeratotic and crusted stratum corneum and a hyperplastic basophilic basal cell layer. These features are nearly pathognomonic for SND, but they are not present in all cases due to histologic variation. A differential diagnosis includes zinc-responsive dermatoses, generic dog food dermatosis, acrodermatitis enteropathica, thallium toxicity, autoimmune skin diseases, drug eruption, idiopathic erythema multiforme and cutaneous bacterial and fungal infections. Grossly, affected skin is erythematous, erosive, ulcerative, and crusted. The foot pads are the most commonly affected site, followed by mucocutaneous junctions (muzzle, lips, periocular skin, external genitalia), edges of the pinnae, and points of friction such as the hocks and elbows. Stomatitis is occasionally reported. Elevation of serum alkaline phosphatase is reported to be a consistent clinical finding in these dogs.

Although most cases of canine SND are associated with some type of chronic liver disease, the pathogenesis of the skin lesion is not clearly understood. A recent review of superficial necrolytic dermatitis in dogs (ref.5) documented markedly depressed plasma amino acid levels in all dogs tested (eight cases), and marked clinical improvement was noted following dietary supplementation with high-protein foods. Hypoaminoacidemia is also described in people with necrolytic migratory erythema and is associated with increased glucagon secretion and accelerated gluconeogenesis. However, the role of glucagon hypersecretion in canine SND is not as clear. This same study found normal plasma glucagon concentrations in five dogs tested. Possible explanations offered by the authors include the unreliability of plasma glucagon levels in measuring true pancreatic glucagon secretion, or alternatively, increased secretion of a nonimmunoreactive form of glucagon from a nonpancreatic source, i.e. glucagon of enteric origin.

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Microslides 73, 74, Lantern slide 25

**History**. This 29-year-old female rhesus monkey (Macaca mulatta) was wild caught as an adult in India and acquired from that country in 1961. Other than a long history of extended, irregular menstrual cycles, she had no other significant medical problems until 1988 when she experienced slow, progressive weight loss.

Hepatomegaly and harsh dry rales were detected on physical examination on 08-15-89. A mid-central abdominal mass was palpated on 11-15-89. By 05-90, she was cachectic, weak, and anemic; she was humanely sacrificed on 05-31-90.

**Gross Pathology**. Numerous lesions were seen in this emaciated animal. The liver was waxy and enlarged 2x normal. The small and large intestines were adhered into a fibrotic ball. The right accessory lung lobe was uniformly pale-yellow with a smooth surface. It was diffusely firm, dry, and rubbery and had a cornified texture when incised (see gross photo). Similar patchy, raised, discrete, yellowish, foci were noted primarily in hilar regions of the right lung lobes. There was a 2 cm diameter, round, sessile, fungated mass firmly attached to and arising from the endometrium. The left ovary and uterine tube were encased against the uterine serosa by well-vascularized fibrous tissue. There was a well-defined, hard, 1.5 cm nodule in the left breast. Advanced degenerative joint disease involved both stifle joints. Several atheromatous plaques were noted in the thoracic and abdominal aortic intima.

**Laboratory Results**.

1. Hypoalbuminemia (total protein 5.3, albumin 2.3).
2. Intrahepatic cholestasis (SAP 722, GGT 199).
3. Mild anemia (PCV 30.8, Hb 9.5).
4. Retrovirus antibody and cell culture negative.

**Contributor's Diagnoses and Comments**.

1. Pneumonia, interstitial, granulomatous and fibrosing, diffuse, chronic, moderate to marked, with intra-alveolar lipid foreign body, lung.

2. Fibrosis, peribronchiolar, chronic, moderate, bronchioles.

Etiologic diagnosis: Lipid pneumonia.

Cecal adenocarcinoma, endometrial adenocarcinoma, mammary carcinoma, and an ovarian granulosa cell tumor were all diagnosed microscopically. The cecal and endometrial carcinomas were histologically dissimilar. Secondary systemic amyloidosis involved the liver, spleen and gastric mucosa. Lipid aspiration pneumonia was an incidental finding. A review of the patient's medical history revealed that Agoral, a mineral oil-based laxative, was administered orally to alleviate constipation on 09-26-88.

Aspirated mineral oil acts as an inert foreign body provoking a milder inflammatory reaction than oils of animal origin which liberate free fatty acids when catalyzed by lipases.[1,2] In humans, the more direct drainage into the right bronchus leads to predominantly right-sided pulmonary lesions.[3,4] Similar right-sided pulmonary involvement in this case is not unexpected since rhesus monkeys spend nearly all their time in a vertical position. Though a presumptive diagnosis of lipid pneumonia can be made from the gross lesions and H&E stained microslide, oil red O-stained frozen section confirms lipid in the globoid, cleared, intra-alveolar spaces. Oil red O staining of alveolar lavage sediments or transtracheal lung biopsies from suspected clinical cases can also aid in the antemortem diagnosis of aspiration lipid pneumonia.[3]

**AFIP Diagnosis**. Lung: Pneumonia, granulomatous and fibrosing, diffuse, severe, with intracellular and extracellular lipid, rhesus monkey (Macaca mulatta), primate.

**Conference Note**. The term lipid pneumonia is used to describe alveolar accumulations of lipid, usually occurring within large foamy macrophages. The source of the lipid substance can be either endogenous or exogenous. Endogenous lipid pneumonia usually refers to an advanced and severe variant of alveolar histiocytosis associated with mixed inflammation, cholesterol crystals, interstitial fibrosis and giant cells. The lipid is believed to be derived from degenerating cells. Exogenous lipid pneumonia refers to an inflammatory response stimulated by a foreign lipid material, such as mineral oil, that is aspirated or inhaled. This can often be differentiated from the endogenous type by the presence of both intracellular and extracellular lipid. Large globules of extracellular lipid are usually present in addition to foamy macrophages, giant cells, fibrosis and type II pneumocyte hyperplasia. The degree and type of inflammation is primarily determined by the nature of the aspirated material. Hydrolysis of unsaturated lipids, such as those of animal origin, stimulates a more severe inflammatory response and fibrosis than occurs with oils of vegetable origin, which are removed by emulsification and expectoration. Chemically inert oils, such as mineral oil, are neither hydrolyzed nor removed efficiently by expectoration. The residual material typically causes a chronic, granulomatous

reaction. Mineral oil stains positively with oil red O but does not stain with osmium tetroxide, a stain used for lipids of animal origin.

Conference participants considered that the amorphous amphophilic material in the pulmonary interstitium might represent amyloid. Results of congo red staining were equivocal.

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Microslide 75

**History**. This 3-week-old cocker spaniel pup is from a litter in which 6 of 7 pups died within 3 weeks of age. Two pups were submitted for necropsy. Clinical signs included hypothermia, dyspnea, painful crying, tympany and opisthotonos. The pups were removed from the bitch at 2 weeks of age because of a severe mastitis in the mother.

**Gross Pathology**. Disseminated focal necroses and hemorrhages were seen in kidney and liver. The lung was congested and had a mottled appearance. There was marked hyperplasia of the mediastinal lymph nodes. There was moderate to marked alveolar edema with serosanguinous fluid in trachea and bronchi. Additionally a marked endoparasitosis (cestodes) and a mild ectoparasitosis (fleas) were demonstrable.

**Laboratory Results**.
Parasitology: Endoparasites - Dipylidium caninum. Ectoparasites - Ctenocephalus canis.
Microbiology: Liver, lung, spleen, kidney: Staphylococcus intermedius.
Milk: Staphylococcus intermedius.

Virology: Canine herpesvirus isolated from both pups out of several organs on tissue cultures inoculated with organ homogenate.

**Contributor's Diagnoses and Comments.**
1. Kidney: Nephritis, necrotizing, multifocal to coalescing, acute, severe.
2. Lung: Pneumonia, necrotizing, multifocal, acute, marked with few intranuclear inclusion bodies in bronchiolar epithelial cells.
Etiological diagnosis: Lesions compatible with canine herpes virus infection.

Clinical signs and the age of the puppies at death are typical for an infection with canine herpesvirus. Fatal infections with disseminated necroses in several parenchymal tissues are usually seen in dogs under 4 weeks of age. It has recently been found that the early infection in puppies may be due to the temperature-optimum of the canine herpesvirus. This temperature-optimum is below the normal canine body temperature. By experimental investigations it has been shown that infected puppies whose body temperatures were elevated by heating the environment had a longer survival period. Canine herpesvirus transmission in puppies occurs either during birth (within the birth canal of the bitch), or via infected littermates.

The macroscopic and microscopic alterations as described in these cases are typical for the fatal infection with canine herpesvirus. Grossly, kidneys are known to develop characteristic alterations with multifocal hemorrhages associated with pale background of necrotic tissue. Multifocal necrosis may be present in most parenchymal tissues. Histomorphologically, disseminated coalescing areas of necrosis and hemorrhage with mild mononuclear infiltrations and inclusion bodies, which may be either eosinophilic or basophilic, are reported to be typical. In these submitted sections it is easy to detect the typical necrotic areas, but inclusion bodies are not present in all sections. They are more easily detected in lung tissue than in kidney. In addition to the submitted sections, multifocal necrosis was present in liver, spleen and thymus. In brain tissues a marked leptomeningeal hyperemia with mild infiltration of mononuclear cells in the thalamus associated with multifocal necrosis and mononuclear infiltration was present. This alteration of brain tissue may have caused the clinically observed opisthotonos. The parasites detected appeared to be an incidental finding. There may have been poor management in this kennel. Staphylococcus intermedius re-isolated out of tissues upon bacterial investigations may have been the cause of mastitis, but was not investigated more closely.

**AFIP Diagnoses.** 1. Lung: Pneumonia, interstitial, necrotizing, subacute, diffuse, moderate to severe, with fibrin

and edema, Cocker Spaniel, canine.
2. Kidney: Hemorrhage and necrosis, multifocal to coalescing, moderate, with subacute interstitial nephritis, and infrequent intranuclear inclusion bodies.

**Conference Note.** The scarcity of intranuclear inclusions in these sections was not considered uncommon for canine herpesvirus disease. Canine herpesvirus infection in neonates typically causes necrotizing and hemorrhagic lesions in many organs including kidney, lungs, liver, brain, intestine, thymus, and spleen. In addition, puppies surviving the initial disease may develop segmental cerebellar dysplasia, renal dysplasia, and retinal dysplasia. In older dogs the virus is usually associated with disease of the reproductive and upper respiratory tract. Infected pregnant bitches may experience abortion, stillbirths and infertility. Genital lesions described in affected mature males include hyperemia, petechial hemorrhages, and nodular lymphoid aggregates over the base of the penis.

Three herpesviruses have been reported to cause disease in dogs. Canine herpesvirus is discussed above. Porcine herpesvirus is the cause pseudorabies in dogs and cattle. A distinctly different herpesvirus that is antigenically and biochemically similar to feline herpesvirus (FHV-1) has been isolated from diarrheic dogs. The ability of canine FHV-1 to directly produce clinical disease in dogs in the absence of other infectious agents or genetic factors has not yet been determined.

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Microslide 76, Lantern slide 26

**History**. A 10-year-old Tennessee Walking horse mare and her colt were submitted for necropsy. The mare and her colt had received a bale of alfalfa hay from a new source 2 days prior to presentation. Clinical signs included abdominal pain, dehydration, ataxia, and increased heart and respiratory rates with decreased gastrointestinal sounds. Blood was collected for analysis and the alfalfa hay was examined.

**Gross Pathology**. The mare had undergone moderate autolysis. Much of the non-glandular gastric mucosa and distal esophageal mucosa had sloughed into the lumens; the anterior 2/3 of esophageal mucosa was intact.

**Laboratory Results**. Clinical pathological data included hyperglycemia (169 mg/dl), hyponatremia (134 meq/1), hypochloremia (93 meq/1), BUN (38 mg/dl), increased creatinine (2.2 mg/dl), hypocalcemia (6.5 mg/dl), hypophosphatemia (1.5 mg/dl), increased alkaline phosphatase (161 u/1), elevated SGOT (348 u/1), and increased LDH (449 u/1).

Bacterial culture of liver and lung yielded no growth. E. coli was obtained from intestine.

**Contributor's Diagnosis and Comments**. Stomach, non-glandular, acantholysis, with microvesicle formation, acute, multifocal, due to cantharidin toxicity.

Examination of the alfalfa hay revealed numerous beetles which were identified as the striped blister beetle (Epicauta vittata sp.). Blister beetles contain the toxic substance cantharidin, which is present in the hemolymph, genitalia, and possibly other tissues of the beetles. Cantharidin is highly irritating and causes acantholysis and vesicle formation when in contact with skin and mucous membranes. Cantharidin is absorbed from the gastrointestinal tract and excreted by the kidney.

Blister beetles often live in clusters and frequently have an uneven distribution within fields of standing alfalfa. Recent changes in the harvesting of alfalfa hay, which includes simultaneous cutting and crimping, may result in dead beetles becoming entrapped within baled hay. Toxicity occurs when horses are fed contaminated hay. Clinical signs include shock, gastro-

intestinal and urinary tract irritation, renal insufficiency, frequent attempts at urination with or without voiding of urine and submerging of the muzzle in water, or frequent drinking of small amounts of water. Hypocalcemia, hypomagnesemia, and hyperglycemia are frequent clinical pathologic findings in cases of toxicity. In some cases of blister beetle poisoning, the beetles can be difficult to locate within suspected bales. An assay for cantharidin is available and can be performed on stomach contents or urine.

Similar findings were evident within the colt, which was also submitted for necropsy. Autolysis, which was recognized grossly, precluded assessment of renal, hepatic, pulmonary, and myocardial changes. Myocardial necrosis can be seen in conjunction with blister beetle poisoning. Prognosis in cases of blister beetle poisoning in horses is poor. Prevention is centered upon inspection of hay for the presence of the beetles. Beetles generally do not occur in significant numbers until June or later. Thus, hay harvested prior to June should be free of beetles.

**AFIP Diagnosis**. Stomach, nonglandular (per contributor), mucosa: Necrosis, multifocal, moderate, multifocal, moderate, with vesicle formation, and acantholysis, Tennessee walking horse, equine.

**Conference Note**. Historically, the use of cantharidin as both a therapeutic agent and as an aphrodisiac in the ground preparation "Spanish fly" dates back to the Greek and Roman civilizations. Accidental or experimental cantharidin toxicity has been reported in several species including humans, horses, sheep, rabbits, rats, mice, dogs, cats, goats, and cattle. The mechanism of action of the toxic principle is not clear. Cutaneous exposure can result in severe blistering of the skin. In addition to lesions seen in the gastrointestinal tract, systemic exposure may cause mucosal necrosis and acantholysis in the urinary bladder, and varying degrees of renal tubular damage and myocardial necrosis. Conference participants reviewed the laboratory data provided. Previous studies have indicated that finding a marked and prolonged hypocalcemia and hypomagnesemia (value not provided) is helpful in differentiating blister beetle toxicity from other causes of acute abdominal pain in the horse. Rising creatinine kinase levels may be an important indicator of continued deterioration and a poor prognosis. Elevation of plasma creatinine kinase in the horse has also been associated with muscular fatigue, pneumonia, colic, myodegeneration, tying-up syndrome, and experimentally-induced volvulus of the small intestine.

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Microslide 77

**History.** This 9-year-old male rhesus macaque (Macaca mulatta) was one of a number of monkeys being used in an experimental vaccine study. The animal exhibited fever, anorexia, lethargy, and prostration beginning 30 days after the last vaccination. The only experimental manipulations following the last vaccination were routine phlebotomy for CBC and serology.

**Gross Pathology.** The following lesions were noted at necropsy: fibrinous pleuritis/pericarditis; splenomegaly; generalized lymphadenopathy and hyperemia; cardiomegaly with supravalvular (tricuspid) subendocardial myocarditis of the right heart. The right kidney was confined within a 9 cm abscess (containing 30 ml pus) that incorporated adrenal gland, ileal loop, and omentum. The right ureter was twice the size of the left one. The lungs did not collapse upon removal.

**Laboratory Results.** Staphylococcus aureus was cultured from the large perirenal abscess, pericardial sac and endocardial lesions.

**Contributor's Diagnoses and Comments.** 1. Lung: Pneumonia, suppurative and fibrinohemorrhagic, subacute, multifocal, severe, with gram-positive cocci, consistent with embolic abscesses.
2. Lung: Pleuritis, fibrinous, chronic, diffuse, severe, with intralesional gram-positive cocci.
3. Lung: Bronchiectasis and chronic peribronchitis, multifocal with intraluminal acarid parasite, compatible with simian lung mite.

The immediate cause of death was likely acute cardiac failure, either from restrictive pericarditis or arrhythmia

secondary to conduction pathway blockade by an abscess. Staphylococcus aureus was isolated from blood and various tissues. The original source of the staphylococcal septicemia/embolic shower could not be determined.

Several cells in the lung section and in pancreatic duct epithelium exhibited large basophilic, smudgy nuclei suggestive of an adenoviral inclusion. We are in the process of performing immunostaining for adenoviral antigen, and will report results to the conference.

The overwhelming staphylococcal septicemia, massive lung mite infestation and possible adenovirus infection, are suggestive of an underlying immunodeficient state. The animal had been found negative for SRV 18 months earlier and had never been tested for SIV. The species of lung mite found in both cynomolgus and rhesus monkeys is Pneumonyssus simicola.

**AFIP Diagnoses.** 1. Lung: Pleuropneumonia, fibrinosuppurative, necrotizing, diffuse, severe, with colonies of cocci, rhesus monkey (Macaca mulatta), nonhuman primate. 2. Lung: Bronchitis and bronchiolitis, granulomatous, multifocal, moderate, with bronchiectasis, chronic pleuritis, and acarid parasites.

**Conference Note.** This rhesus monkey was later found to be infected with the immunosuppressive retrovirus SRV-2. The suspected intranuclear inclusions seen occasionally in these sections were negative on immunohistochemical staining for cytomegalovirus, adenovirus, and herpes simplex. Electron microscopic evaluation failed to identify viral particles.

Participants believed that two distinct inflammatory processes were represented in the lung sections: an acute response to the bacterial infection and a more chronic reaction to the lung mites. A primary differential diagnosis for fibrinopurulent pneumonia and serositis in nonhuman primates includes Streptococcus pneumoniae, Klebsiella pneumoniae and Escherichia coli. Staphylococcus aureus is a less common cause of septicemia in monkeys. Histologic lesions can vary from fibrinopurulent inflammation to multifocal nodular abscesses of many organs including heart, lung, kidney and lymph nodes. Other lesions associated with S. aureus bacteremia include cellulitis, vegetative valvulitis, immune complex glomerulonephritis, and septic shock. Virulence factors attributed to S. aureus include the production of coagulase, hemolysin, and protein A which may act to block host immunoglobulins by binding to the Fc fragment.

Pneumonyssus simicola is a very common pulmonary parasite of rhesus monkeys. Clinical signs are minimal except in heavy infections. Grossly, the mites cause multifocal discrete yellowish nodules, occasionally cystic, which are most apparent

in the subpleural parenchyma. Histologically, adult mites, mite eggs, and/or mite pigment are usually found within or near bronchioles affected with a granulomatous bronchiolitis and peribronchiolitis. Microscopic features of acarid parasites include a chitinized exoskeleton, a hemocoelom containing hemolymph, a gastrointestinal tract, striated muscle, and jointed appendages.

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Microslide 78

**History**. This adult male beaver (Castor canadensis) was found dead. No other history available.

**Gross Pathology**. There were innumerable, small, pale foci throughout the liver and lungs.

**Laboratory Results**. Slide agglutination positive for Francisella tularensis from a primary isolate obtained from the liver.

**Contributor's Diagnoses and Comments**. Pneumonia, acute, multifocal, necrotizing, severe. Hepatitis, acute, multifocal, necrotizing, severe.

No additional losses were recorded.

**AFIP Diagnoses.** Liver: Hepatitis, necrotizing, acute, multifocal and random, moderate, with fibrinosuppurative capsulitis, beaver (Castor canadensis).
2. Lung: Pneumonia, necrosuppurative, multifocal, moderate, with diffuse subacute interstitial pneumonia and fibrin thrombi.

**Conference Note.** The etiologic agent of tularemia is Francisella tularensis; a poorly staining, gram-negative, bipolar rod-shaped bacterium. The organism is a facultative intracellular parasite that can persist in some hosts as a latent infection. Modes of transmission include ingestion, inhalation, inoculation by biting arthropod vectors and direct penetration of intact skin or mucous membranes. Tularemia affects a wide variety of species including most domestic animals, many wild mammals, birds and humans. Rodents and rabbits are very susceptible and are thought to be the primary reservoir hosts in the United States. Fatal infections in foals and sheep have been associated with stress and heavy tick infestations. Although cattle, dogs and cats are considered relatively resistant, infections in these species do occur. Cats have been reported to have a severe systemic form of tularemia resembling "typhoidal" tularemia of people. Participants discussed a differential diagnosis including salmonellosis, listeriosis, Tyzzer's disease, yersiniosis and other gram-negative bacterial infections. Infections by F. tularensis have several similar features to those of Yersinia: they are commonly found in wildlife, potentially transmitted by insect vectors, and can cause marked lymphadenopathy, pneumonia, and septicemia. Lesions are characterized by multifocal discrete areas of caseous necrosis up to several millimeters in diameter, most commonly found in the liver, spleen and lymph nodes.

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Microslide 79

**History**. This 7-month-old Tonkinese female feline had a history of an upper respiratory tract infection of approximately two weeks duration. Antibiotic therapy initiated by the owner had little effect on clinical signs. Administration of an antibiotic tablet led to an episode of dyspnea and cyanosis. The cat was taken to the veterinarian, and after stabilization of respiratory signs, a bronchoscopy was performed. Shortly after the procedure, the animal was euthanized. Necropsy was performed by the veterinarian, and sections of lung, spleen, kidney and liver were submitted for histopathologic examination.

**Gross Pathology**. Caseous, grey-white mucous plugs were observed in the bronchi and bronchioles, filling several mainstem bronchi. Similar exudate was observed within the trachea. The lungs were diffusely firm and mottled red-purple.

**Contributor's Diagnosis and Comments**. Acute, severe, diffuse, necrotizing, and purulent bronchopneumonia with acidophilic intranuclear viral inclusions. Feline herpesvirus, type 1 (FHA-1).

Microscopically, there is severe, regionally extensive transmural necrosis of bronchi and bronchioles, with lumina frequently occluded by aggregates of degenerate neutrophils, necrotic epithelial cells and debris. The adjacent alveoli are filled with degenerate neutrophils, alveolar macrophages, fibrin, RBC's and necrotic debris. Acidophilic intranuclear viral inclusions, Cowdry type A and B, are present in remaining bronchiolar epithelium and alveolar pneumocytes. Eosinophilic material fills many bronchiolar glands. There is multifocal edema, acute passive congestion, and peribronchial aggregates of lymphocytes and plasma cells. No microorganisms were seen.

Members of the family Herpesviridae are important causes of respiratory disease in many species. Feline and canine herpesvirus, infectious bovine rhinotracheitis, equine herpesvirus (rhinopneumonitis virus), and inclusion body rhinitis in swine are frequent causes of upper and/or lower respiratory tract infections.

Feline herpesvirus, type 1 (FHA-1), originally called feline rhinotracheitis virus, is the most prevalent and most severe viral respiratory infection in cats. The virus infects only domestic and closely related wild Felidae. Naturally occurring syndromes attributed to FHA-1 infection include classic rhinotracheitis, conjunctivitis and keratitis, chronic sinusitis, neonatal disease (systemic disease with encephalitis and necrosis of visceral organs) and abortion. The virus is infectious on mucous membrane surfaces, but not by intramuscular injection, suggesting the virus is unable to replicate at higher core body

temperature.

Infection with FHA-1 most commonly causes an upper respiratory tract disease, with pneumonia a rare sequela. Virus recovered from pulmonary tissue usually reflects viral replication in bronchioles; however, both alveolar pneumocytes and macrophages are susceptible to infection. Mortality is generally low, with death usually resulting from associated dehydration, secondary bacterial infection, or immune suppression due to concurrent viral infection (such as feline leukemia virus).

**AFIP Diagnosis**. Lung: Pneumonia, bronchointerstitial, necrosuppurative, diffuse, severe, with type II pneumocyte hyperplasia and eosinophilic intranuclear inclusions, Tonkinese, feline, etiology -- consistent with feline herpesvirus type 1.

**Conference Note**. Conference participants considered the changes seen in these sections to be pathognomonic for feline herpesvirus 1 infection (FHV-1). Typical of other alpha herpesvirus, FHV-1 is a rapidly proliferating, cytolytic virus with a predilection for the epithelium of the nasal cavity, pharynx, conjunctivae, tonsils and soft palate. Clinical disease normally lasts 7 to 14 days and is characterized by fever, sneezing, coughing, mucopurulent ocular and nasal discharge, salivation, and anorexia. Pneumonia is an infrequent finding and is more commonly seen in younger cats. Other causes of upper respiratory disease in cats must be ruled out including feline calicivirus and Chlamydia psittaci. Damage to nasal epithelium by FHV-1 can predispose to chronic bacterial sinusitis in cats. Infection of pregnant queens may cause abortion or intrauterine death of the fetuses as a result of virus-induced vasculitis, thrombosis and infarction of placental vessels. Osteolytic lesions have been demonstrated in kittens inoculated intravenously with FHV-1. Up to 80% of recovered cats develop latent or persistent non-replicative infections and may serve as an important source of the infection to other cats. Reactivation of the virus is associated with stress-producing factors such as boarding, pregnancy, lactation and glucocorticoid administration.

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Microslide 80

**History**. This 5-year-old Collie had a 6-month history of intermittent bloody diarrhea, which originally developed in Florida. The dog was presented in a collapsed, coma-like state to a veterinarian. In previous months, other veterinarians had attempted to treat the diarrhea with metronidazole or a prescription diet of eggs, chicken, liver and corn.

On presentation the dog had a hematocrit of 29.5%, a platelet count of 342,000/ul and a white blood cell count of 14,400/ul. Fluid therapy with steroid and antibiotic administration (amoxicillin, neomycin) affected moderate improvement in the dog's condition. A barium contrast series was suggestive of diffuse enteritis. The veterinarian attempted colonic biopsy but the dog died immediately after anesthetic induction.

**Gross Pathology**. There was marked diffuse thickening of cecal, colonic and rectal mucosa. Disseminated 1-3 mm white foci were present in heart, kidneys, liver and lung.

**Contributor's Diagnosis and Comments**. Myocarditis, moderate, multifocal, necrotizing, granulomatous, associated with numerous algal organisms. Etiology--Protothecosis.

Other lesions in this dog were multifocal granulomatous typhlocolitis and proctitis, nephritis, hepatitis, pneumonia and lymphadenitis, all associated with numerous Prototheca-like organisms. The 10 X 12 um nonbudding oval organism (exceptionally 25 um diameter) was uninucleate, avidly PAS positive, and had an argyrophilic capsule. Daughter cells formed within the parent organism (endosporulation). No fresh tissue was submitted by the veterinarian so the organism was not cultured. Diagnosis can be confirmed in formalin-fixed tissue using immunofluorescence.

Characteristic features of disseminated protothecosis, usually due to P. zopfii, were present in this dog. There was a history of chronic bloody diarrhea which was unresponsive to antibiotics, the portal of entry was presumably enteric, and inflammatory cell infiltrates, often plasmacytic, were scanty adjacent to the many organisms. The dog's breed may also be significant since Collies are over-represented in case reports of disseminated protothecosis.

**AFIP Diagnosis**. Heart, myocardium: Myocarditis, lymphoplasmacytic, multifocal, mild, with numerous algal

organisms, Collie, canine.

**Conference Note.** Prototheca spp. are ubiquitous saprophytic algae. They are thought to be an achloric mutant of the chlorophyll-containing green algae Chlorella. Two species, P. zopfii and P. wickerhamii, are known to infect animals. The organism is not highly pathogenic, and human infections are usually associated with an accompanying immunosuppressive condition. In the dog, infection is acquired by ingestion of the algae followed by invasion of the gastrointestinal tract resulting in chronic hemorrhagic colitis. Dogs usually develop a disseminated form of protothecosis. It is characterized by a severe and typically fatal systemic disease affecting the eyes, kidneys, heart, liver, brain, spinal cord, and other organs. Collies may be a predisposed breed. Frequently, there is only a mild inflammatory response to the organism, but lesions vary from lymphoplasmacytic to granulomatous. Protothecosis usually occurs as a cutaneous lesion in the cat, forming large, firm cutaneous nodules. Prototheca also causes cystic granulomatous mastitis in cattle and granulomatous disease in salmon. Prototheca are morphologically indistinguishable from Chlorella spp. on H&E stained tissue sections. However, Chlorella contain large cytoplasmic starch granules which are intensely PAS-positive. Starch granules are smaller and much less common in Prototheca.

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Microslide 81, 82

**History.** Heart from a 4-month-old, female, silkie chicken.

**Gross Pathology.** Gross lesions included hydropericardium, pericarditis, necrotizing myocarditis.

**Laboratory Results.** Bacterial cultures: Listeria monocytogenes was cultured from the heart. fecal parasite examination: mild coccidiosis. virus cultures: negative (no

viruses were isolated).

**Contributor's Diagnoses and Comments.**

1. Heart: Caseonecrotic myocarditis, subacute, disseminated, moderate to severe. Etiology: gram-positive bacilli.
2. Heart: Granulomatous epicarditis, subacute, multifocal to disseminated, mild.
3. Heart: Vasculitis and perivasculitis, reactive, acute and subacute, disseminated, mild to moderate.
4. Heart: Epicardial steatitis, multifocal to disseminated, mild.

Etiology: Listeria monocytogenes
Etiological diagnosis: Avian myocardial listeriosis.

The histological lesions in the myocardium of this chicken are classical for listeriosis. Key features are the extensive mixed inflammatory cell infiltrate, about 40% of which are heterophils, the caseous necrosis in the center of the foci, myocardial edema, and vasculitis and perivasculitis. Some sections also showed normal mitral and aortic valves, granulomatous epicarditis, and epicardial steatitis. In the Brown & Hopps Gram stain, single black bacilli were common at the periphery of the caseous foci; the bacilli were intra- and extracellular, occasionally in clusters of 2 to 4 bacilli, occasionally in short end-to-end chains of 2 to 3 bacilli, and phagocytosed bacilli were often gram-variable. Bacilli were very difficult to find except under oil immersion magnification.

The differential diagnosis includes erysipelas and Corynebacterium infection. If a Gram stain had not been available to demonstrate the gram-positive bacilli, then many other bacteria would have to be included in the differential, including Salmonella, Pasteurella, E. coli, staphylococci and streptococci. Based solely on the gross lesions, mycotic infections and leukosis could also be included in the differential list.

This case was submitted because it represents one of the oldest recognized infectious diseases of poultry (Seastone, 1935). The vast majority of cases of Listeria infection in poultry are septicemic and tend to produce gross lesions in the liver, spleen and heart. Caseous myocardial necrosis with pericarditis can be observed with many septicemic bacterial infections of poultry, but are most often associated with salmonellosis (typhoid, paratyphoid, pullorum) and listeriosis. Myocardial salmonellosis is nearly always an infiltrative granulomatous lesion with very few heterophils and inconsistent caseous necrosis. Avian myocardial listeriosis often presents as a massive necrotizing myocarditis without the bulging inflammatory nodules so often found in avian myocardial salmonellosis. Although "monocytes" are numerous in avian

myocardial listeriosis, as the scientific name of the organism would imply, heterophils and caseous necrosis are also key features histologically.

Listeriosis of poultry is usually a septicemic infection which produces gross lesions of miliary hepatic necrosis, massive myocardial necrosis, pericarditis and occasionally meningoencephalitis. Curiously, arthritis and iridocyclitis, so common in many bacterial septicemias, have not been reported in poultry with septicemic listeriosis. Recently, an encephalitic form of avian listeriosis has been described (Cooper, 1989) in broiler chickens in California. This encephalitis form of listeriosis closely resembled macroscopically, microscopically and by tissue distribution, the same form of disease commonly seen in cattle, sheep and other ruminants. As with mammals, it is suspected that the septicemic form of avian listeriosis results from the ingestion of the bacillus and vascular invasion from the gut, while the encephalitic form of listeriosis is probably caused by direct invasion of tissues then nerves of the oro-pharynx. Septicemic listeriosis can result in meningo-encephalitis in birds and mammals, but such septicemic lesions are not confined to the brainstem.

Melanin pigmentation on the serosa of visceral organs and around the great vessels is typical and normal for this breed of chicken.

**AFIP Diagnosis**. Heart: Myocarditis, heterophilic and granulomatous, focally extensive, severe, with caseous necrosis and bacilli, silkie chicken, avian.

**Conference Note**. Listeria monocytogenes is a widely distributed organism, commonly isolated from soil, water, animal feces, silage, and the tissues of normal animals. It is a facultative intracellular bacterium that is capable of surviving a wide range of environmental conditions. It has been reported to cause disease in a variety of animals including many species of mammals, birds, fish, and even poikilotherms. The organism is typically associated with one of three disease syndromes in domestic animals and people: metritis with abortion, septicemia with disseminated microabscesses in multiple organs, and encephalitis. It can also cause mastitis in ruminants. The epidemiology and pathogenesis of Listeria infections remain poorly understood. Listeria outbreaks in poultry occur sporadically. Septicemic and less common encephalitic forms of the disease in chickens are well documented. Septicemic infections are characterized by splenomegaly, necrosis of the liver and heart, and pericarditis. In the encephalitic form, birds display nonspecific signs of nervous system disease including depression, ataxia, torticollis, opisthotonos, tremors and circling. Histologically, affected birds have microabscesses in the brainstem, lymphocytic perivascular cuffing and gliosis,

similar to lesions seen with listerial encephalitis in ruminants and occasionally horses.

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Microslide 83, Lantern slide 27

**History.** An adult female Chinese golden pheasant (Crysolophus pictus) was found dead without any observed clinical signs. Another golden pheasant in the same zoo exhibit was found dead two months earlier with similar findings.

**Gross Pathology.** The carcass was emaciated. The ceca contained numerous small white nematodes. Most of the ceca had greatly thickened walls due to contiguous nodules; the raised nodules were more isolated at the base of the ceca and in the adjacent colon (see photo).

**Laboratory Results.** Cecal nematodes were identified as adult and juvenile Heterakis isolonche.

**Contributor's Diagnoses and Comments.**

1. Granulomatous typhlitis, ceca, golden pheasant (Crysolophus pictus) due to Heterakis isolonche.
2. Amyloidosis, liver.

The cecal mucosa is poorly preserved. Contiguous focal

aggregates of epithelioid macrophages are present in the greatly expanded submucosa and involving the muscularis in some slides. Numerous cross sections of nematodes are present in many granulomas. Occasional degenerate nematodes are immediately surrounded by multinucleated giant cells. Heterophilic and lymphocytic infiltrates occur between and within granulomatous infiltrates.

This is a well documented response to this species of Heterakis in gallinaceous birds. Griner et al (1977) demonstrated some of the fusiform epithelioid reactive cells were separated by (forming) collagen by TEM.

The liver section is from the first bird; perisinusoidal amyloid deposition is associated with marked hepatocyte atrophy. Hepatic amyloidosis, not seen in the second bird, has not been reported with Heterakis isolonche infection.

**AFIP Diagnoses.** 1. Cecum, submucosa and tunica muscularis: Typhlitis, granulomatous, multinodular, diffuse, severe, with nematode parasites, Chinese golden pheasant (Crysolophus pictus), avian, etiology -- consistent with Heterakis isolonche.
2. Liver: Amyloidosis, diffuse, severe.

**Conference Note.** Heterakis spp. are frequently encountered nematode parasites in the intestine of gallinaceous birds. Hetarakis eggs are an important vector in the transmission of the protozoan parasite Histomonas meleagridis, the cause of blackhead. Heterakis have a direct lifecycle. Infective eggs are ingested by the host, hatch in the crop, gizzard or duodenum, and migrate to the cecum where they may cause varying degrees of inflammation and nodular thickening in the cecal wall. In the cecum, the second stage larvae mature into adults, which are characterized by a thin outer cuticle with cuticular alae, large lateral chords, thick polymyarian, coelomyarian musculature, a pseudocoelom, and a large intestine composed of many uninucleate cells. H. gallinarum is the most common species of Heterakis in poultry. It is thought to be only mildly pathogenic to the host bird. In contrast, H. isolonche in pheasants often causes a severe debilitating or fatal disease characterized by the formation of prominent granulomatous or fibrous nodules in the submucosa of the cecum. As seen in these sections, the nodules surrounding the parasites consist of polygonal to spindle-shaped cells arranged in whorls and interlacing bundles, sometimes having a "sarcomatous" appearance. In discussing the possible origin of these cells, most conference participants considered the histomorphology of the cells and the paucity of collagen in the stroma to be most consistent with epithelioid macrophages. Previous attempts by others to definitively identify these cells have been inconclusive. Some authors have interpreted the proliferative nodules to consist primarily of hyperplastic fibroblasts, and even neoplastic smooth muscle. The chronicity

of the lesion may be a factor in determining the cellular composition of the nodules and the degree of fibrous proliferation. As in this case, the nodules are usually associated with varying numbers of macrophages, lymphocytes, plasma cells, and multinucleated giant cells. Cecal fibrosarcomas and leiomyomas have been reported to occur in conjunction with heterakidosis. Hepatic amyloid deposition is a common finding in chronic inflammatory diseases of birds.

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**References.**

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Microslide 84

**History.** This 4-week-old red-fronted parakeet (Cyanoramphus novaezelandiae) was presented with a history of sudden death. Both parent birds were healthy, but two of the remaining four birds in the brood subsequently died suddenly.

**Gross Pathology.** There was hemopericardium as a result of rupture of the right atrium. The myocardium had multifocal grey nodular lesions (0.5-1.0 mm) some of which protruded from the surface. No other gross lesions were seen.

**Laboratory Results.** Bacteriological cultures of heart, liver and spleen were negative. The brain and trachea were negative for PMV1, avian influenza and psittacosis (by indirect immunofluorescence).

**Contributor's Diagnosis and Comments.** Myocardium: Myocarditis, mild, multifocal with hemorrhage and necrosis associated with Leukocytozoon-like megaloschizonts, parakeet, avian.

Leukocytozoonosis is a protozoal disease of ducks, geese, domestic poultry and other birds occuring in parts of North America and Northern Europe. The genus Leukocytozoon has an indirect life cycle, using Simulium spp. (black flies) as vectors. As the name suggests the gametocyte in the final host species occurs in circulating lymphocytes, or occasionally in erythrocytes. Small schizonts occur in the liver, while schizogony in heart, kidney, brain and other organs involves

larger megaloschizonts. Sporogony is thought to be confined to the vector.

Disease associated with Leukocytozoon infection has been reported in psittacines, including antipodean parakeets bred in the U.K. Megaloschizonts in psittacine cardiac, gizzard and skeletal muscle have been associated with acute illness and sudden death, and have also been implicated in chronic vomiting and wasting in budgerigars. Since many authorities believe that disease in these species involves Culicoides midges as vectors, the parasite should more correctly be classified as a member of the closely related Akiba genus of the hemoprotozoa. Definitive classification of the parasite will however depend on identification of gametocytes, which has not yet been done in psittacines.

**AFIP Diagnosis**. Heart, myocardium, endocardium, and epicardium: Megaloschizonts, multifocal, numerous, red-fronted parakeet (Cyanoramphus novaezelandiae), avian.

**Conference Note**. Participants considered the inflammation elicited by the megaloschizonts to be minimal to nonexistant in most sections. In Europe, reports of aberrant infections by a Leucocytozoon-like parasite in antipodean parakeets are not uncommon. A few cases have involved budgerigars. Based on published reports, the disease differs from the classic description of Leucocytozoon simondii infection in ducks and geese in several respects: there is a marked predilection for all types of muscle with numerous megaloschizonts found in the heart, gizzard and, less frequently, the pectoral muscles; schizogony in the liver is uncommon; and no gametocytic stages have been observed in erythrocytes. These differences may represent variation in tissue tropism and lifecycle when infecting psittacine birds or a different species of Leucocytozoon, Akiba or similar protozoa may be the cause. Grossly, the cardiac muscle and the wall of the gizzard are studded with small greyish nodules. The disease is often fatal with sudden death attributed to myocardial conduction disturbances resulting from the parasitic cysts. Three stages of megaloschizonts have been described in the muscle: an immature cyst with numerous sharply pointed clefts; a more solid, but still immature cyst with undifferentiated cytoplasm; and a mature megaloschizont containing numerous identifiable merozoites. The majority of the megaloschizonts seen in these sections were interpreted as immature.

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budgerigars and a common buzzard. Vet Rec 129:30-32, 1991.
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Microslide 85, Lantern slides 28, 29

**History**. A 12-year-old female Sarus crane (Grus antigone) had a recurrent proliferative lesion in the subcutis of the tarsometatarsal joint.

**Gross Pathology**. Chronic fibrosis and ankylosis of left foot. A gelatinous mass was noted originating from the digital flexor tendon.

**Laboratory Results**.

| Immunoperoxidase staining | |
|---|---|
| Factor VIII | - |
| Smooth Muscle myosin | + |
| Actin | + |
| S-100 | - |
| AD 1/3 | - |
| Desmin | - |

Compatible with myxoid leiomyosarcoma.

**Contributor's Diagnosis and Comments**. Tumor, left tarsometatarsus, myxoid leiomyosarcoma with renal and hepatic metastasis.

Although there are numerous accounts of metastatic, nonhemopoietic, avian neoplasms in the literature, the vast majority of these have been either carcinomas, melanomas or tumors associated with the avian leukosis/sarcoma complex (Hubbard, et al., 1983; Sasipreeyan, et al., 1988; Dillberger, et al., 1987). Aside from the leiomyosarcomas in budgerigars, reports of metastatic sarcomas in nondomestic or exotic birds are extremely rare. One review of avian necropsies placed the incidence of sarcomas at 9.9% of all avian neoplasms (Effron, et al., 1977). However, this and other reviews of exotic animal necropsies have reported no metastasis of these sarcomas in birds (Hubbard, et al., 1983; Kaneene, et al., 1985). It is well established that sarcomas preferentially metastasize through the blood, even though they are also sometimes found in lymph nodes.

Invasive fibrosarcomas in domestic poultry frequently metastasize to the liver, kidneys, heart, lungs, pancreas and intestine (Campbell, 19690. Many of these have been associated with oncogenic viral infection. Interestingly, fibrosarcomas are often myxomatous in chickens, including the classic description of the Rous sarcoma. However, it is extremely unlikely that the subcutaneous leiomyosarcoma in this case is associated with retroviral infection, since this is a case from an old bird in a closed flock with no previous history or clinical signs attributable to retroviral disease. In addition there have been no other reports of avian leukosis/ sarcoma from this zoo. Finally, although retroviral sarcoma-like disease has been reported in a few rare cases in exotic avian species, this disease has never been reported in the order gruiformes.

This case is unique in several respects. It is the first report of leiomyosarcoma in the order gruiformes, and is one of the few published cases of spontaneous metastatic sarcomas in avian species. It is especially interesting because it is the first case to document metastasis through the portal systems. This information is important for clinicians who are treating sarcomas of the hindlimbs in birds, as it suggests the need for diagnostic procedures to determine the presence of hepatic and/or renal metastasis. It is also important for pathologists to realize that multiple sections of the liver and kidney may be indicated when doing a postmortem on a bird with sarcoma of the caudal extremities. Finally, it should be noted that the diagnosis in this case required the use of immunoperoxidase stains. Without immunohistochemistry, an imprecise diagnosis of myxosarcoma, fibrosarcoma, hemangiosarcoma, or synovial cell sarcoma could have been ascribed to this case. Immunohistochemical techniques will continue to play an important role in tumor diagnosis in both domestic and exotic animal species.

**AFIP Diagnosis**. Liver: Spindle-cell sarcoma, Sarus crane (Grus antigone), avian.

**Conference Note**. A 2X2 photo of the immunostain for smooth muscle myosin was provided. This case was reviewed by the Department of Soft Tissue Pathology at AFIP. A differential diagnosis includes myxosarcoma, fibrosarcoma, myxoid leimyosarcoma, and synovial sarcoma. Participants preferred a less specific diagnosis in this case based solely on the histomorphology of the H&E sections used in conference. This tumor has several histologic features consistent with leiomyosarcoma including frequent blunt-ended nuclei, perpendicular orientation of fascicles in many areas, and the presence of PAS-positive intracytoplasmic glycogen granules. A myxoid background is occasionally seen in human leiomyosarcomas. Although positive staining for smooth muscle myosin and actin further support the diagnosis of leiomyosarcoma, conference

participants were not confident of the specificity of these immunostains when used in avian species.

Leiomyosarcomas are rare tumors in domestic animals, having been reported in the uterus, bladder, subcutaneous tissues, intestines, ovaries, and other sites. In birds, smooth muscle tumors have previously been reported in the spleen, reproductive tract and intestinal tract. This tumor was reported to have originated from the subcutaneous tissue of the tarsometatarsus. Previous cases of subcutaneous leiomyosarcomas have been suspected to arise from smooth muscle cells within vessel walls.

**Contributor.** University of Miami School of Medicine, Department of Pathology.

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Microslide 86, Lantern slide 30

**History.** This 0.5 kg, 3-week-old male, New Zealand white rabbit had anorexia, depression, and mild diarrhea of 4 days duration.

**Gross Pathology.** Mucopurulent nasal discharge; marked bilateral anteroventral consolidation and hyperemia of lungs.

**Laboratory Results.** Cultures of lung were positive for Klebsiella pneumoniae and Pseudomonas aeruginosa.

**Contributor's Diagnosis and Comments.** Lung: Bronchopneumonia, fibrinohemorrhagic, acute, multifocal and coalescing, marked, with gram-negative coccobacilli.

The histologic lesions within the lung are consistent with the organisms cultured. Exposure to Pseudomonas aeruginosa is generally via contamination of automatic water systems. Syndromes associated with Pseudomonas in rabbits include suppurative dermatitis, diarrhea, septicemia, meningitis, and suppurative bronchopneumonia. Pseudomonas causes suppurative pneumonia and septicemia in mink and guinea pigs, and along with Mycoplasma pulmonis, is a primary differential for suppurative otitis media/interna in mice. Klebsiella pneumoniae is an opportunistic pathogen most often associated with pneumonia and septicemia in primates and dogs. Sporadic epizootics occur in guinea pigs. While mice, hamsters, and rabbits are susceptible to experimental infection, spontaneous disease in rodents and rabbits is uncommon. Pseudomonas is the most frequently isolated pathogen from cases of pneumonia in rabbits at this institute. The differential diagnosis includes Pasteurella multocida and Bordetella bronchiseptica.

**AFIP Diagnosis.** Lung: Bronchopneumonia, suppurative, acute, diffuse, severe, New Zealand white rabbit, lagomorph.

**Conference Note.** The severity of the lesion varied widely among sections. Multifocally, less affected areas of the lung have mild alveolar emphysema. Pseudomonas aeruginosa is a gram-negative, non-spore forming, non-capsule producing bacillus that is associated with a variety of diseases in many species. Although infection in healthy animals is uncommon due to the organism's susceptibility to natural host defenses, once infection is established, the organism is highly pathogenic owing to the production of several toxins. Exotoxin A, a protein synthesis inhibitor, and several alkaline proteases are thought to contribute to the edema, hemorrhage, and necrosis commonly seen. Elastase is involved in the destruction of elastin in the pulmonary parenchyma. P. aeruginosa often acts opportunistically invading traumatized tissues or those predisposed by chronic moisture: severe burns in people, corneal abrasions in horses, the oral cavity of snakes (necrotic stomatitis), moist skin in sheep (fleece-rot or "green wool"), and the external ear canal of dogs (otitis externa). The organism also causes necrotic pneumonia, enteritis, and rhinitis in swine and mastitis in cattle. As mentioned by the contributor, sporadic outbreaks of P. aeruginosa infections occur in several laboratory animal species such as rabbits, mice and guinea pigs. The organism is better known for causing severe and often fatal pneumonia in young mink and chinchillas. Two types of pneumonia have been described in these animals. The first is a peracute lesion characterized by diffuse hemorrhage, hyperemia, and necrosis with few infiltrating leukocytes. Frothy

hemorrhagic fluid may be found in the trachea and nares. A second type more closely resembles the lesion seen in these sections and is characterized by bronchopneumonia with a prominent suppurative exudate within alveoli and bronchioles.

**Contributor**. Walter Reed Army Institute of Research, Washington, DC 20307-5100.

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Microslide 87

**History**. This 4-year-old Springer Spaniel began regurgitating in September. Endoscopy revealed cystic granuloma-like lesions, and subsequently, surgery was performed. The affected regions of the esophagus were resected and submitted for evaluation.

**Gross Pathology**. The esophagus was markedly thickened and fibrotic with occasional papilloma-like lesions projecting from the mucosa. Cystic and tract-like lesions were present within the wall which occasionally contained solitary and multiple nematode parasites.

**Contributor's Diagnosis and Comments**. Intramural parasitic fistulas and granulomas with intralesional adult parasites (in most sections), parasite ova and cellular atypia; possible early fibrosarcoma.

Etiologic diagnosis: Esophageal spirocercosis; verminous esophagitis

Etiology: Spirocerca lupi.

The esophagus contained irregular villonodular fistulous tracts lined by stratified squamous epithelium, adlimited by granulation tissue, which contained large numbers of mixed lymphoplasmacytic inflammatory cells, with scattered foci of neutrophilic to pyogranulomatous inflammation. Peripheral to the granulation tissue, the reaction became more fibrotic and had replaced mural skeletal muscle fibers, but also became haphazardly arranged, suggesting a neoplastic transformation into

a fibrosarcoma. Most sections contained cross sections of adult parasites which contained characteristic eggs. Also admixed within the regions adjacent to the fistulous tracts and occasionally in deeper sites were embryonated parasite eggs which measured 30-37 um in length by 11-15 um in width with parallel sides. The eggs and the adult parasites were morphologically compatible with Spirocerca lupi.

**AFIP Diagnoses**. 1. Esophagus, submucosa: Esophagitis, granulomatous, nodular, severe, with marked atypical fibroplasia and adult spirurid nematodes, Springer Spaniel, canine, etiology -- consistent with Spirocerca lupi.
2. Esophagus: Esophagitis, pyogranulomatous, focally extensive, severe, with spirurid eggs.

**Conference Note**. Spirocerca-induced granulomas are most commonly found in the aorta, esophagus and stomach of affected carnivores, but may be located in the urinary bladder, kidney, mediastinum and other tissues throughout the body. Conference participants differed in their interpretation of the proliferating spindle cells surrounding the adult nematodes. Although some considered the nodule to be neoplastic, most participants favored the diagnosis of atypical fibroplasia based on the lack of clearly invasive growth into the adjacent tissue and the mild degree of atypia. In addition to the development of esophageal sarcomas, Spirocerca lupi infection has been associated with hypertrophic osteoarthropathy, ankylosing spondylitis of thoracic vertebrae and scarring, thrombosis and aneurysm formation of the aorta. Aneurysmal rupture may occur resulting in sudden death. The adult parasites in these sections are well preserved and demonstrate features common to spirurid nematodes, including a thick outer cuticle with ornamentation, polymyarian-coelomyarian musculature, large lateral cords, an amorphous eosinophilic material within the pseudocoelom, a large digestive tract lined by many uninucleate columnar epithelial cells with surface microvilli, and reproductive organs. Many thick-shelled embryonated eggs are present admixed with pyogranulomatous inflammation in the adjacent submucosa. Neoplastic transformation of parasitized tissues has been linked with other helminthic infections including hepatic sarcomas in rats associated with Cysticercus fasciolaris, biliary carcinomas in cats and people associated with opisthorchid flukes and urinary bladder carcinoma in people associated with Schistosoma haemotobium.

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Microslide 88

**History.** This 7-year-old female Holstein calved 10 days before presentation for mastitis.

**Gross Pathology.** The left front quarter of the udder was firm and slightly enlarged. On cut section, the quarter contained thick, blood-tinged fluid and caseous material. The supramammary lymph nodes were enlarged twice normal size and contained areas of hemorrhage.

**Laboratory Results.** Mammary gland: Aerobic bacterial culture--Nocardia asteroides.

**Contributor's Diagnosis and Comments.** Mastitis, subacute to chronic, diffuse, severe, left anterior quarter, Holstein.

The mammary gland contained large coalescing areas of liquefactive necrosis. Colonies of bacteria are present in some areas surrounded by a granulomatous inflammatory response including macrophages and Langhans type giant cells, lymphocytes and plasma cells. Aerobic bacterial cultures resulted in the recovery of Nocardia asteroides in pure culture from mammary gland and milk secretion.

**AFIP Diagnosis.** Mammary gland: Mastitis, pyogranulomatous, necrotizing, multifocal to coalescing, severe, with filamentous bacilli, Holstein, bovine.

**Conference Note.** Some sections contained variably-sized, irregularly round, basophilic globular material interpreted by some participants as fungal organisms. Special stains (PAS and GMS) did not support a fungal etiology. The GMS procedure accentuated myriads of filamentous bacilli throughout the section. Nocardia are gram-positive, aerobic, branching, filamentous bacteria that can either form mycelial masses or break into bacillary forms. Some species are partially acid-fast. Nocardia, and Actinomyces are opportunistic pathogens well known for causing pyogranulomatous pleuritis, mediastinitis and peritonitis in dogs and, less frequently, cats. A thick, bloody

"tomato soup" exudate is characteristic. Infection in dogs is frequently caused by migrating plant foreign bodies such as grass awns.

Nocardia asteroides is a sporadic cause of mastitis in cattle and occasionally goats. The organism is a soil saprophyte that gains access to the mammary gland through the teat canal. Although subclinical nocardial mastitis has been reported, infection typically causes a chronic pyogranulomatous to granulomatous mastitis with fibrosis and draining sinus tracts. The infection is usually lobular in distribution. Most cases occur soon after calving. The differential diagnosis includes Mycobacterium tuberculosis, M. paratuberculosis, Candida spp., Cryptococcus neoformans, and other less common mycotic causes of mastitis. Less frequently, N. asteroides causes a severe acute suppurative mastitis in cattle which can be fatal.

**Contributor**. Department of Pathobiology, Auburn University, AL 36830.

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Microslide 89

**History**. This 6-month-old female C3H mouse was part of a pathogenesis study on mouse mammary tumor virus and was exposed to the virus naturally via milk from the infected mother. A single mass developed in the inguinal region approximately 3 weeks prior to sacrifice.

**Gross Pathology**. A single, nonencapsulated, firm, multilobulated mass was present in the inguinal subcutis.

**Laboratory Results**. Mouse mammary tumor virus was detected by immunoassay in the milk of the mother as well as within tumor tissue.

**Contributor's Diagnosis and Comments.** Mammary adenocarcinoma, mixed type A and B (Dunn Classification).
Etiology: mouse mammary tumor virus

In the Dunn histologic classification of mouse mammary tumors, mouse mammary tumor virus (MMTV) most often results in the development of either type A or B adenocarcinomas. Type A tumors are more uniform with well-differentiated acinus-like structures and cuboidal epithelium. Type B tumors are pleomorphic with mixtures of diverse patterns including tubular, papillary, cystic, solid, and comedo forms. Both type A and B patterns often occur together in single tumors, and both types have high rates of metastasis. In the type A pattern of tissue submitted, key microscopic features are the replacement of lobular architecture by expansile sheets of closely spaced, well-differentiated acini or occasional clusters and folded cords. Cells are cuboidal with homogenous cytoplasm often with bright granular eosinophilic material. Nuclear:cytoplasmic ratio is increased, and mitotic figures are numerous. Small areas of necrosis are present. The type B pattern is also evident within the same mass and is characterized by irregularly sized lobules and enlarged ducts with luminal papillary infoldings or solid centers. Cystic areas containing amorphous eosinophilic material and cell debris are evident within some lobules. Cells are pleomorphic with loss of architectural orientation. Multinucleate cells and large areas of necrosis are present.

MMTV is a retrovirus causing mammary growth disorders in C3H, GR, BR6, and R111 mice. Virus is transmitted via milk in all susceptible strains and genetically as the endogenous proviruses Mtv-1 and Mtv-2 in C3H and GR mice respectively. Both endogenous Mtv-1 and Mtv-2 proviruses are subsequently expressed as mature particles in milk of offspring. Milk-borne virus is adsorbed and carried by T lymphocytes to the mammary gland. Virus infects mammary epithelium and results in both preneoplastic (hyperplastic alveolar nodules and plaques) and neoplastic (adenocarcinomas type A and B) lesions. Transformation arises by insertional mutagenesis and activation of one or more cellular genes (int-1, int-2, and hst/K-fgf) not normally expressed in the mammary gland. Int-1 is normally expressed only during embryogenesis and is required for development of the midbrain. Int-2 and hst/K-fgf are members of the fibroblast growth factor family. Intracytoplasmic type A and extracellular type B retroviral particles are expressed in most tumors and can be identified by electron microscopy. Metastasis to lung is common and appears to be inversely related to tumor latency. Host genetic background, hormones (glucocorticoids, progestins, thyroid hormone), pregnancy, and caloric intake all can significantly affect tumor induction by MMTV with different strains of the virus varying in degree of responsiveness to these factors.

A new finding in MMTV is the presence of a superantigen in the open reading frame. A superantigen is an antigen that binds major histocompatibility class II molecules and specific beta T cell receptor families resulting in stimulation of a large proportion of T cells. Both exogenous and endogenous MMTV can exhibit a superantigen effect and cause expansion and subsequent deletion of specific CD4+ T cell families. Additionally, different strains of MMTV have been shown to reliably affect different families of CD4+ T cells resulting in altered T cell repertoires. The pathogenic significance of these findings is uncertain.

**AFIP Diagnosis.** Mammary gland: Adenocarcinoma, type B (Dunn classification).

**Conference Note.** Proliferative changes in the mammary gland of mice include simple physiologic hyperplasia associated with pregnancy and lactation; preneoplastic lesions (hyperplastic alveolar nodule and plaques); and mammary tumors which have been classified previously (Dunn, 1959) as adenocarcinoma type A, B and C, adenoacanthoma and carcinosarcoma. Other types of mammary tumors have been rarely reported. Hyperplastic alveolar nodules (HAN) consist of one or multiple foci of lobuloalveolar epithelial proliferation surrounded by a normal fatty stroma. These are well differentiated lesions that resemble normal hormone-stimulated mammary gland. Plaques are less differentiated and more closely resemble adenocarcinomas. Plaques are hormone dependent, arising during pregnancy and regressing following parturition. Both HANs and plaques are associated with the presence of clonally integrated exogenous mouse mammary tumor virus (MMTV) proviruses, and they are considered potential precursors of mammary adenocarcinoma type A (tubular pattern) and B (pleomorphic pattern) as discussed by the contributor. In these sections, conference participants considered the presence of both well differentiated lobules and more pleomorphic papillary and solid lobules within the same mass to be consistent with the type B tumor classification. Mammary adenocarcinoma type C, adenoacanthoma and carcinosarcoma all occur in older mice and are not associated with MMTV. Type C tumor morphology consists of proliferating glandular structures lined by a single layer of cuboidal epithelium surrounded by a loose myxomatous stroma resembling myoepithelial cells. Adenoacanthomas have keratinizing squamous cell areas in 25% or more of the tumor and must be differentiated from squamous cell carcinoma and trichoepithelioma. Carcinosarcomas are composed of two morphologically different malignant cell populations, a glandular epithelial component and a spindle cell mesenchymal component.

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Microslide 90

**History**. Nine of 27 cotton-topped tamarins (Saguinus oedipus) on a spontaneous colitis/colon cancer study died within 5 months of discontinuation of vitamin C supplementation to the feed. Although vitamin C was added weekly to the water in the form of a liquid multivitamin, subsequent determination of amount consumed in the water and from supplemented fruit (apples and raisins) indicated inadequate vitamin C intake. Postmortems were done on the last four which died over a two day period.

**Gross Pathology**. Necropsy was performed by the laboratory animal veterinarian who reported gingival hemorrhage, loss of teeth, and loss of integrity of cranial sutures. Colonic lesions were noted but not described. Portions of calvarium and long bones were submitted for histopathology. They had no gross lesions.

**Contributor's Diagnosis and Comments**. Marrow fibrosis and proliferation of woven bone compatible with resolving scorbutic osteodystrophy.

The clinical history, gross postmortem findings, and cessation of deaths by supplementing the diet with vitamin C support a diagnosis of vitamin C deficiency. The specimens were from adults and growth plates were closed. Proliferation of collagen-poor connective tissue (gerustmark) occurs in marrow in vitamin C deficiency. The formation of woven bone in this fibrous stroma and on trabecular surfaces in these monkeys is similar to that reported in healing stages of vitamin C

deficiency in guinea pigs. The exposure to weekly addition of low levels of vitamin C in the water may have contributed to this appearance of healing scurvy.

**AFIP Diagnosis**. Tibia, metaphysis: Myelofibrosis, with woven bone formation, cotton-topped tamarin (Saguinus oedipus), primate.

**Conference Note**. Vitamin C (ascorbic acid) is synthesized from glucose in the liver of most mammals and in the kidney of reptiles and amphibians. Guinea pigs, bats, people, nonhuman primates and many species of fish and birds have a requirement for dietary vitamin C due to a lack of the enzymes needed to synthesize the vitamin. Vitamin C is an essential cofactor in the formation of collagen. A deficiency results in failure of normal hydroxylation of proline and lysine needed to form mature collagen from procollagen. Clinical signs of acute vitamin C deficiency include anorexia, weight loss, reluctance to move, and tender joints. More chronic cases are characterized by hair loss, gingival bleeding and necrosis, loosening of teeth, hemorrhages in muscles, joints and nailbeds and epiphyseal separations. Cephalhematomas may occur in squirrel monkeys. Anemia is a common finding due to vitamin C's effect on iron absorption, folic acid metabolism and capillary integrity. Bone changes are most severe in young growing animals and result from the inability of osteoblasts to form normal bone matrix, which is rich in type-1 collagen. Failure of normal modeling by metaphyseal osteoblasts combined with continued production and vascular invasion of growth cartilage of the physis results in the formation of a submetaphyseal growth retardation lattice composed of retained cartilage. As seen in these sections, vitamin C deficiency in adult animals results in histologic changes characterized by osteopenia and myelofibrosis. There is a paucity of osteoblasts lining trabecular surfaces which are often scalloped and eroded, suggesting that there is an imbalance in normal remodeling of trabeculae in these animals.

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Microslide 91

**History**. This 15-month-old Sprague-Dawley, male rat was used in a two-year toxicity/carcinogenicity study. This rat was from a treated group.

**Gross Pathology**. Osseous mass involving right proximal tibia.

**Contributor's Diagnosis and Comments**. Osteosarcoma, right proximal tibia.

The histologic hallmark of an osteosarcoma is the production of osteoid by malignant stromal cells. Osteoid must be differentiated from ordinary collagen, fibrin, and chondroid matrix. Osteosarcomas in rats are not known to produce mature (lamellar) bone. In addition, organized looping or "networking" of the tumor bone trabeculae is not seen in conventional osteosarcomas. Osteoblast "rimming" of osteoid/bone spicules (where bone surfaces are lined with a uniform layer of osteoblasts that maintain normal polarity along the trabecular margin) is also absent. Osteosarcomas tend to infiltrate between host bone trabeculae forming what is called a "permeative" pattern at the lesion host-bone interface, sometimes with "trapping" of normal trabecular bone. Osteosarcomas often exhibit a zonation phenomenon where "older" (more productive) cells are central and "younger" (less productive) cells are peripherally located.

**AFIP Diagnosis**. Tibia; fibula: Osteosarcoma, Sprague-Dawley rat, rodent.

**Conference Note**. The tumor surrounds and infiltrates the tibia, extending into and replacing adjacent skeletal muscle. Vascular invasion by neoplastic cells is present in some sections. Spontaneous osteosarcoma is a rare tumor in rats; it has been reported in several strains with no age or sex predilection. Metastasis to the lung is not uncommon.

Osteosarcoma is the most common primary bone tumor of dogs and cats but is rare in other domestic species. Large breed dogs are at increased risk. Classification of osteosarcoma can be by site of origin or by histomorphology. Most osteosarcomas originate from the metaphyseal region of long bones (central), but two behaviorly different types may arise from the periosteum. One type behaves similarly to central osteosarcoma with early metastasis likely. The second type, known as parosteal, is a more differentiated, slower growing tumor with a better prognosis.

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Microslide 92, Lantern slides 31, 32

**History**. This 14-week-old Great Dane had a 2-week history of fever (105.8°F), depression and lameness with severe pain upon manipulation of metaphyseal area of long bones and pain when opening the mouth. This progressed to lateral recumbency. Cardiac arrest occurred soon after referral.

**Gross Pathology**. Major long bones and metacarpal bones had irregular growth plates with prominent subphyseal linear pale zones and adjacent metaphyseal hemorrhage, often with flaring and instability (See gross kodachrome). Costochondral radiographs (see kodachrome) revealed distinct subphyseal linear sclerotic zones with parallel radiolucency and scattered metaphyseal sclerosis. Junctions were enlarged and had similar changes.

**Contributor's Diagnosis and Comments**. Severe, subacute, subphyseal necrosis and hemorrhage with periostitis and irregular cartilage retention (hypertrophic osteodystrophy).

The signalment, history, radiographic changes and pathologic findings are characteristic of the earlier stages of canine hypertrophic osteodystrophy. Histologic sections of distal radius and distal femur had parallel subphyseal zones of necrosis associated with hemorrhage, osteoclasia, neutrophil accumulation and mild fibrosis. There was flaring of the physeal areas with irregular thickening due to cartilage retention associated with a lack of normal ossification. Multifocal transverse trabeculae indicated intermittent cessation of growth and proximal limiting plates were irregular with multifocal cartilage retention in the epiphysis. There was periosteal thickening with subperiosteal woven bone and moderate neutrophil accumulation.

Hypertrophic osteodystrophy is usually reported in large

breed, fast growing male dogs between 3 and 8 months of age. The etiology is unknown; however, excess calcium, "overnutrition" and hypovitaminosis C (skeletal scurvy) have been considered as possible causes. The majority of cases are self-limiting, but the disease may result in permanent bony deformation and, occasionally, death. The necrosis seen in this case is typical of the earlier stage of the disease. More chronic cases develop increased periosteal new bone, presumably to stabilize the weakened metaphyseal area.

**AFIP Diagnosis**. Long bone: Osteomyelitis, suppurative, multifocal, moderate, with necrosis of primary spongiosa and infractions, Great Dane, canine.

**Conference Note**. Inflammation is present in both the primary and secondary ossification centers. A differential diagnosis includes hypertrophic osteodystrophy and osteomyelitis from bacterial infection. Some sections contain fibrin thrombi in the metaphyseal vessels. Although there is obvious hypercellularity in the intertrabecular spaces of the primary spongiosa due to the suppurative inflammation and hemorrhage, the normal population of osteoblasts and osteoclasts is markedly decreased indicating failure of modeling of the cartilagenous trabeculae. Because cartilage production continues in the physis, a subphyseal area of unmineralized cartilage is retained in the metaphyseal region and is seen on the radiograph as a radiolucent line adjacent to the open growth plate. Osteoclasis is more intense in areas of infraction.

The clinical history of high fever, lameness, pain and swelling of multiple long bone metaphyses is typical of hypertrophic osteodystrophy. Mineralization of soft tissues and arteries in various organs has also been described in some cases. Affected dogs frequently have a neutrophilic leukocytosis, and elevated serum phosphorus levels have been reported. Attempts to identify an infectious, nutritional or hereditary cause for hypertrophic osteodystrophy have been unsuccessful. It is possible that more than one etiology exists. The Weimaraner breed may be predisposed. In a recently reported case, Escherichia coli bacteremia was discovered in an affected Great Dane puppy, but was interpreted by the authors as having developed secondary to the stress of the disease.

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Microslide 93, Lantern slides 33, 34

**History**. This 3-year-old Holstein bull was admitted to the Colorado State University Veterinary Teaching Hospital for evaluation of a firm, painful mandibular swelling of two weeks duration. The bull was reported to have been anorexic, losing weight over the previous 45 days and had been treated with antibiotics.

**Gross Pathology**. A 20 cm expansile mass was located between the bodies of the mandibles beneath the tongue. Incisors were freely movable. The mass was deep to the normal, intact oral mucosa and was encapsulated by a thick band of white gritty tissue. The subcapsular portion of the mass consisted of numerous blood-filled cavities and resembled a blood-soaked sponge. There was no gross evidence of hematoma or thrombosis.

**Laboratory Results**. Radiology: Radiographs of the mandible showed lytic and proliferative changes in both bodies of the rostral mandibles. Diffuse lysis surrounding all the incisors was observed. On the right body, cortical bone surrounding the lytic area appeared displaced, leaving a thin rim of bone at its margin. Irregular periosteal reaction extended in spiculated form into the soft tissues at the periphery of the lesion. Culture from an aspirate of the mass yielded a light growth of nonhemolytic Streptococcus and Bacillus species.

**Contributor's Diagnosis and Comments**. Aneurysmal bone cyst; rostral mandible. The etiology is unknown. Several theories have been postulated and are discussed in the references cited.

To our knowledge this is the first case of an aneurysmal bone cyst reported in the bovine. Differential diagnosis for swellings on the bovine mandible include osteomyelitis (Actinomyces bovis), fracture, abscess, hemangioma, hemangiosarcoma, and osteogenic sarcoma. Recognition of this condition is necessary in order to formulate a prognosis. In summary, the hallmarks that support the diagnosis of aneurysmal bone cyst include radiographic evidence of osteolytic expansive lesions that erode cortical bone and produce a saccular defect

that is often surrounded by a shell of periosteal new bone and is shaped like an aortic aneurysm. The gross appearance resembles that of a blood-soaked sponge and is frequently encapsulated by a thick and gritty fibrous capsule. Histologically, there are numerous blood-filled spaces separated by fibrous or osseous trabeculae of variable thickness.

**AFIP Diagnosis.** Mandible (per contributor): Aneurysmal bone cyst, Holstein, bovine.

**Conference Note.** This case was reviewed by the Department of Orthopedic Pathology at the AFIP. A differential diagnosis was discussed in conference that included aneurysmal bone cyst, enchondroma, and giant cell granuloma of bone. Telangiectatic osteosarcoma was also considered, but several features such as the lack of cellular anaplasia and the organized linkage of trabeculae in many areas, are inconsistent with osteosarcoma. The lesion was considered unusually reactive for anuerysmal bone cysts. There is a florid proliferation of pale-staining polygonal cells interpreted as osteoblast progenitors. Areas of chondroid differentiation are present in some sections.

The etiology and pathogenesis of aneurysmal bone cyst is controversial. Most authors have speculated that these cysts, also known as multilocular hematic bone cysts, arise from disruption of the marrow vasculature by trauma, neoplasia, fibrous dysplasia, arteriovenous fistulae or other causes. They are characterized by expansive osteolysis and hemorrhage. Like many hemorrhagic bone lesions, aneurysmal bone cysts often contain numerous multinucleated giant cells and must be differentiated from giant cell tumors of bone. The mechanism for the loss of bone in these vascular cysts is not known, but may be due to the relationship between vascular and piezoelectric properties of bone and their influence on bone growth. Slowed blood flow through large sinusoids, as occurs in the development of aneurysmal cysts, creates an electropositive environment which favors bone resorption. In contrast, rapid blood flow is associated with electronegativity and bone proliferation, as is suspected to occur in hypertrophic osteopathy of people and animals. Other types of cysts in bone include subchondral cysts (commonly seen in pigs and horses with osteochondosis), unicameral cysts, and osteitis fibrosa cystica (a cystic lesion associated with hyperparathyroidism, rarely seen in animals).

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Microslide 94, Lantern slides 35, 36

**History**. This 10-year-old male beagle presented with skin changes (seborrhea, hyperpigmentation), obesity, dyspnea, weakness and bradycardia. Euthanasia was performed.

**Gross Pathology**. The heart weighed 20.5 g. The coronary arteries were yellow-white and tortuous. On cut sections they had thick walls and narrow lumens. The thyroid glands were not found.

**Laboratory Results**.

| | |
|---|---|
| Thyroxin (T4) - baseline | <0.3 mcg/dl (normal 1.2-4.0). |
| Thyroxin (T4) - post stimulation | <0.3 mcg/dl (normal 1-3 X increase over baseline T4 value). |
| Triiodothyronine - | 29 ng/dl (normal 40-180). |
| Cholesterol - | 694 mg/dl (normal 120-300). |

Results are consistent with hypothyroidism.

**Contributor's Diagnosis and Comments**. Syndrome, hypothyroidism. Blood vessels, arteries, atherosclerosis, severe, systemic.

Atherosclerosis is a common cause of morbidity and mortality in humans. However, naturally occurring atherosclerosis is uncommon in animals. In dogs, it is often associated with hypothyroidism. This was a case of severe systemic atherosclerosis in an aged hypothyroid dog.

**AFIP Diagnoses**. 1. Heart, coronary arteries: Atherosclerosis, multifocal, moderate, Beagle, canine.
2. Heart, valve: Fibromyxomatous degeneration (endocardiosis), mild.

**Conference Note.** The increased amount of epicardial fat and fat cell infiltration in the myocardium were considered indicative of this animal's obesity. Affected vessels are asymmetrically thickened and disrupted by accumulations of lipid-laden foam cells within the tunica media and intima. Low numbers of lymphocytes and plasma cells and multifocal areas of mineralization are also present. Cholesterol deposition was not considered a prominent feature in these sections. Participants contrasted the vascular changes described in atherosclerosis with those seen in arteriosclerosis. The term arteriosclerosis primarily refers to vascular damage associated with hypertension, a common finding in dogs and cats with chronic renal disease or diabetes mellitus. Lesions of systemic hypertension are often prominent in the small arteries and arterioles of the kidney and the retinal and choroidal arteries of the eye. In arteriosclerosis, endothelial damage leads to thickening (medial hypertrophy) and/or hyalin degeneration of the arteriolar wall. Atherosclerosis typically affects larger elastic and muscular arteries and is characterized by intimal fatty streaks and larger fibrofatty plaques which narrow and obstruct vessels, weakening the wall and predisposing to aneurysmal dilation. Recent work using antibodies as markers of smooth muscle cells and macrophages have determined that the great majority of foam cells found in fatty streaks are macrophages and the remainder are of smooth muscle origin. Fibrofatty plaques display more histologic variability with mixtures of both macrophage and smooth muscle foam cells, extracellular lipid, cholesterol crystals, inflammatory cells, necrotic cellular debris, fibrosis and calcium deposits.

Atherosclerosis and related problems (stroke, myocardial infarction and peripheral vascular disease) remain major causes of morbidity and death in humans. In domestic animals atherosclerosis is a much less significant disease. It is most commonly seen in pigs on high lipid diets, chickens (sometimes associated with Marek's disease infection), White Carneau Pigeons, rabbits (especially the hereditary hyperlipidemia of Watanabe rabbits) and in dogs associated with hypothyroidism or diabetes mellitus.

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Microslide 95

**History**. This free-living koala was found moribund with dyspnea; euthanatized.

**Gross Pathology**. Both eyes: Swollen red conjunctivae, slight corneal opacity, scant mucopurulent exudate. Cranioventral pneumonia. Purulent cystitis and prostatitis.

**Laboratory Results**. Conjunctival exudate, urinary bladder-chlamydia AGID (Clearview,[R] Unipath, Bedford England): Positive.
Conjunctiva-routine and Haemophilus selective cultures: Scant mixed floras, mainly Micrococcus sp.
Lung-routine culture: Mixed flora, mainly Enterobacter cloacae.

**Contributor's Diagnosis and Comments**. Conjunctivitis, subacute, diffuse, lymphocytic/plasmacytic, caused by Chlamydia psittaci.

There is hyperplasia of conjunctival epithelium, hyperemia and edema of the propria, and infiltration by lymphocytes, plasmacytes and, to a lesser extent, neutrophils. The lesion is etiologically nonspecific but, in koalas, chlamydiosis is the only well-established cause. Although organisms are not obvious in the H&E sections, the AGID was strongly positive for chlamydia antigen.

The koala is an arboreal folivorous marsupial unique to eastern Australia. Zoos in other countries have captive colonies. It is considered endangered in its natural habitat and chlamydiosis may be contributing to the population decline (Brown et al, 1987).

In koalas, other lesions associated with infection by C. psittaci include rhinitis, cystitis, urethritis, prostatitis, vaginitis, metritis, salpingitis, ovarian bursitis and various acquired cysts of the female genital tract (Obendorf, 1981, Canfield, 1987).

**AFIP Diagnosis**. Eye, palpebral conjunctiva: Conjunctivitis, proliferative, lymphoplasmacytic, chronic, diffuse, moderate, koala, marsupial.

**Conference Note**. Chlamydia psittaci is an important pathogen of koalas. Infection most commonly causes conjunctivitis, rhinitis, cystitis ("dirty tail" or "wet bottom")

and reproductive disease in females. Chlamydial keratoconjunctivitis is usually bilateral, with affected animals displaying a serous to purulent discharge, blepharitis, chemosis and corneal changes that vary from corneal edema to pannus in more chronic cases. The disease is usually of long duration with clinical signs most commonly seen in adult animals. The pathogenesis is not known. Hormones such as estradiol have been shown to increase susceptibility of some animals to chlamydial infection, and some authors have speculated that the level of phyto-estrogens in the eucalyptus diet of koalas may be a predisposing factor in this species. Several epidemiologic studies have indicated that a majority of free-ranging koalas may harbor C. psittaci asymptomatically, with the organism causing opportunistic infections in stressed or debilitated animals. If this is true, attempts to eradicate Chlamydia from koala populations may be impractical.

Conference participants reviewed the diseases caused by Chlamydia psittaci in other species including psittacosis in people; psittacosis/ornithosis in birds; abortion and infertility in ewes, cows and other species; encephalomyelitis in cattle; conjunctivitis in guinea pigs and hamsters; enteritis in calves; pneumonitis in cats and polyarthritis in sheep. The mature, infectious form of Chlamydia, known as elementary bodies, can be stained with Giemsa or Macchiavello stains.

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Microslide 96

**History**. This 5-week-old Holstein calf was homozygous for the defective BLAD allele by PCR analysis. It was born with a leukocyte count of 17,400/ul (65% PMN). By the second day of age

the WBC was 23,200/ul (78% PMN) and the count progressively increased to 36,600/ul (87% PMN) by 14 days of age and 54,200/ul (93%) PMN by 22 days of age. At 25 days of age the calf had a fever of 106°F (41.1°C), a leukocyte count of 65,200/ul and was unresponsive to antipyretic therapy. At this point 2.227 $X10^9$ washed leukocytes (from a cow with a homozygous normal genotype for CD18) were administered intravenously along with additional antipyretics (banamine, aspirin) and antibiotics. The fever subsided within a day and stayed within normal limits before progressively increasing over the next week. The CBC stabilized between 69,000 and 81,000 for the next 4 days before proceeding to a zenith of 96,000/ul (91% PMN) at 30 days of age. Over the next five days the CBC wavered between 66,000 and 91,000/ul. The calf died during the night at 35 days of age and was necropsied the next morning.

At 4 weeks of age, ulcers were present on the labia, nares, tongue, and muzzle. The calf also developed a rhinitis with accumulation of exudate around the nares.

**Gross Pathology.** The nasal turbinates and sinuses were blue-black due to congestion and were covered by moderate amounts of seromucous exudate. Several ulcers (1 x 1.5 cm), covered by green-grey crusts, were present on the dorsal and ventral gingiva, the rostral hard palate, and the tongue. A small ulcer was present in the abomasum. Numerous ulcers (up to 5 x 9 cm) covered by fibrinonecrotic debris admixed with hair were in the distal jejunum and ileum. There was multifocal adherence of ileal and jejunal serosa to adjacent intestinal serosa by fibrous and fibrinous material. The spleen was enlarged (roughly 2X normal size). Red-grey, oozing, suppurative material exuded from the spleen upon sectioning.

**Laboratory Results.** Laboratory tests for infection by BVD and IBR were negative.

**Contributor's Diagnoses and Comments.**

1. Splenic red pulp, neutrophilic leukocytosis, diffuse, marked with fibrin deposition and hemorrhage (some sections).
2. Bone marrow (humerus), myeloid hyperplasia, diffuse, moderate.

Bovine leukocyte adhesion deficiency (BLAD).

Bovine Leukocyte Adhesion Deficiency (BLAD) is a newly recognized, autosomal recessive disorder described in Holstein calves. Affected animals can be identified by DNA-polymerase chain reaction (PCR) analysis of whole blood or formalin-fixed, paraffin-embedded tissues. A similar disease, Leukocyte Adhesion Deficiency (LAD) is a rare disease of human beings and has also been reported in the Irish Setter dog.

Calves homozygous for the defect have impaired neutrophil

function and are susceptible to mucosal infections. Typical lesions seen in BLAD cattle include: cutaneous papillomas, dermatophytosis, oral ulcers, enteric ulcers, and pneumonia. The cattle are often stunted in growth and have severe tooth loss due to chronic gingivitis.

The accumulation of neutrophils in the splenic red pulp of this case is seen with some consistency in BLAD cattle. It may have been exacerbated by the infusion of leukocytes several days before the death of the calf. Myeloid hyperplasia can also be seen in BLAD cattle. The mechanism for both of these lesions is uncertain and invokes much speculation.

The $B_2$ integrins (p 150,95, LFA-1, and Mac-1) are expressed on leukocytes and are essential for adherence to endothelial cells. Cattle homozygous for the defect have impaired expression of all three molecules on leukocytes. The most striking result of the impaired expression is seen in the neutrophil since expression of Mac-1 by activated neutrophils is essential for adherence to activated endothelial cells expressing ICAM-1. Macrophages and lymphocytes express other adhesion molecules that afford reasonable movement of these cells into tissues.

Virtually all active sires used for artificial insemination by the dairy industry have already been tested for BLAD status. Only a few elite bulls identified as heterozygotes have semen still being sold. The use of these elite carrier bulls on carrier or untested cows is not recommended. Testing of 87 of the top 100 TPI bulls (January 1991) for BLAD status found 15 (17.2%) were carriers. By January 1992 (after culling of carrier bulls had occurred), only 8 out of 99 of the top 100 TPI bulls were found to be carriers. Currently, no additional BLAD carrier bulls are being admitted by the major bull studs into young sire proving programs. With the use of herd bulls and previously purchased semen in farm tanks, it is still possible that homozygotically affected BLAD animals can be born on dairy farms since not all cows will be tested. Producers can virtually avoid any economic losses associated with BLAD calves by using only TL-designated sire's semen. This is the status assigned to bulls tested free of the D128G allele for CD18 that causes BLAD in the homozygous condition.

**AFIP Diagnoses**. 1. Bone marrow: Myeloid hyperplasia, diffuse, moderate, with multifocal hemorrhage and necrosis, Holstein, bovine.
2. Spleen, red pulp: Neutrophilia, diffuse, severe, with multifocal necrosis, hemorrhage and fibrin.

**Conference Note**. Leukocyte adhesion deficiency is an autosomal recessive disorder described in people, dogs and cattle. The primary defect has been identified as a decreased expression or absence of $B_2$ integrins, also known as the

CD11/CD18 family of glycoproteins. Included in this family is CD11b/CD18 (or Mac-1), which is normally found on the surface of monocytes/macrophages, neutrophils and NK cells, and is necessary for tight adherence of these leukocytes to activated endothelium expressing CD54 (ICAM-1). CD11b/CD18 also binds to complement fragment iC3b, which is important in the opsonization and phagocytosis of microorganisms. Animals with leukocyte adhesion deficiency demonstrate abnormalities in most adhesion-dependent functions including attachment to endothelium, neutrophil aggregation and chemotaxis, phagocytosis and cytotoxicity. Neutrophil function is most severely affected. Persistant leukocytosis with profound neutrophilia, recurrent bacterial infections and severe prepubertal periodontitis are common clinical findings in both calves and children with leukocyte adhesion deficiency. BLAD has been suggested as a good animal model for studying leukocyte adhesion deficiency in people.

Histologically, vessels throughout the body contain high numbers of neutrophils, but with relatively few neutrophils in the surrounding tissue due to their inability to extravasate into infected areas. Lymph nodes in affected animals range from hyperplastic to hypocellular with follicular necrosis. The tissues represented in these sections were considered characteristic of leukocyte adhesion deficiency with marked myeloid hyperplasia of bone marrow and neutrophil accumulations in the splenic red pulp. Some participants believed that there was depletion of lymphoid tissue in the splenic white pulp.

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Microslide 97, Lantern slides 37, 38

**History**. A total of 460 sows and 42 gilts with reproductive

failures including small litter size, fertilization failure, fetal death, silent estrus, anestrus, abortion and still birth, and/or old age were examined. Of the 460 sows from 2 to 8 years of age examined, 18 (3.9%) had ovarian hemangioma; however, no such disease was observed in gilts under 2 years.

**Gross Pathology**. The right ovary was enlarged, 9.5 x 6.5 x 4 cm, but the left ovary was normal in size (4 x 3.5 x 2 cm.). The outer surface of the tumor was knobby. The ovarian and uterine vessels were hypertrophied. The cut surfaces of the tumor were mottled with dark red hemorrhages and white connective tissue stroma.

**Contributor's Diagnosis and Comments**. Ovary: Hemangioma. Etiology: not known.

Ovarian hemangiomas are rare in people and animals. The gross and histological features of the case indicate clearly that it is hemangioma, and the morphological changes of ovarian hemangioma observed in the 18 sows (reference 2) were similar to those reported in women.

The histogenesis of ovarian hemangioma remains obscure. The contributor considers that hemangioma in the ovary arises from the blood vessels of the corpus luteum. Morphologically, the corpus luteum is vascularized markedly from days 6 to 18 of diestrus, but they rapidly undergo regression at the onset of estrus. When the growth of blood vessels in the corpus luteum becomes uncoordinated and excessive, it results in the formation of hemangioma.

**AFIP Diagnosis**. Ovary: Hemangioma, breed not specified, porcine.

**Conference Note**. Primary ovarian neoplasms are uncommon in domestic animals. In mature sows, hemangioma, teratoma, cystadenoma, granulosa cell tumor and various sarcomas have been reported. Hemangiomas are the most commonly occurring of these tumors, and they are usually diagnosed in the five to eight year age range. They may be unilateral or bilateral and are often associated with reproductive disorders such as small litter size, agalactia, infertility, fetal death, abortion and stillbirth. As seen in the photos provided, the tumors consist of one or multiple irregular spherical masses of red-brown spongy tissue. The histologic pattern of ovarian hemangioma may vary, but is typically biphasic with numerous cavernous vascular spaces lined by a single layer of endothelium separated by varying amounts of connective tissue stroma. Vessels may occasionally contain thrombi. The possible role of vessels within regressing corpora lutea in the histogenesis of porcine hemangiomas was discussed.

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Microslides 98, 99

**History.** This 4-year-old Abyssinian castrated male feline was presented for weight loss and ulcers on the tongue.

**Gross Pathology.** The capsular surface of both kidneys is irregularly pitted, and the tips of the papillae are necrotic. (Only the kidneys were submitted by the practitioner.)

**Laboratory Results.**

| | April 2 | April 13 | Reference range |
|---|---|---|---|
| Urea (mmol/l) | 35.6 | 69.9 | 5-10 |
| Creatinine (umol/l) | 629 | 939 | 60-165 |

**Contributor's Diagnosis and Comments.** Renal papillary necrosis, renal medullary amyloidosis, chronic tubulointerstitial nephritis with radial cortical scarring.

Many cortical tubules are dilated, probably as a result of medullary fibrosis and amyloidosis plus necrosis of loops of Henle that extended into the papilla. Occasional tubules contain calcium oxalate crystals, likely as a result of chronic renal failure rather than of ethylene glycol poisoning. A few glomeruli are amyloidotic (focal, segmental). This case is typical of familial renal amyloidosis in Abyssinian cats.

**AFIP Diagnoses.** 1. Kidney: Amyloidosis, medullary and glomerular, multifocal to coalescing, severe, with papillary necrosis, Abyssinian, feline.
2. Kidney: Nephritis, interstitial, lymphoplasmacytic, chronic,

multifocal, moderate, with intratubular oxalate crystals.

**Conference Note.** Familial renal amyloidosis in Abyssinian cats is characterized by papillary necrosis, chronic secondary interstitial disease and amyloid deposition that is predominately medullary with variable glomerular involvement. Affected cats often have clinical signs of renal failure including elevated BUN and creatinine, nonregenerative anemia, isothenuric urine specific gravity, hyperphosphatemia and proteinuria. Intratubular calcium oxalate crystal formation is considered a nonspecific finding in cats and may be associated with severe renal disease from many causes. Grossly, the kidneys appear pale and shrunken with an irregular, pitted capsular surface. Amyloid deposition in tissues may be widespread, involving the thyroid, stomach, colon, spleen, heart, adrenals, pancreas, liver, lymph nodes, and urinary bladder. Verification of the amino acid sequence of the amyloid protein AA combined with the loss of congophilic staining after permanganate oxidation demonstrates that the amyloid found in Abyssinian cats is secondary or reactive amyloid.

Canine renal amyloidosis is typically a severe, diffuse glomerular disease with a more pronounced proteinuria than is observed in affected cats. One exception is the recently described familial renal amyloidosis in the Chinese Shar-Pei breed in which medullary amyloid deposition is the most consistent finding. Pulmonary thromboembolism is a reported complication of canine renal amyloidosis due to hypercoagulable states associated with decreased plasma antithrombin III levels and increased fibrinogen. Medullary amyloidosis has also been described in the Dorcas gazelle and occasionally in cattle.

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**References.**

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Microslide 100

**History**. This 3-year-old, male (neutered) cat was treated for hypereosinophilic syndrome with prednisone (1 mg/kg BID) for five weeks and oral hydroxyurea was added during the fourth and fifth weeks. The cat was returned to the clinic during the final 8 days of his life and was fed a semiliquid diet through a gastric tube surgically placed 3 and a half weeks post-diagnosis. He died five weeks post-diagnosis.

**Laboratory Results**.

CBC results

| | |
|---|---|
| Hct (%) | 25.6% |
| retic (%) | 0.1% |
| platelets | adequate |
| WBC (/ul) | 42,000 |
| differential | |
| segs (/ul) | 11,760 |
| bands (/ul) | 420 |
| lymphs (/ul) | 6,300 |
| monos (/ul) | 1,260 |
| eos (ul) | 22,260 |

clinical chemistry analysis

| | |
|---|---|
| T. prot (g/dl) | 9 |
| globulin (g/dl) | 5.4 |

all other analyte values were within their reference ranges

protein electrophoresis

moderate increase in alpha 2 globulins
slight broad-based increase in gamma globulins

thoracentesis

| | |
|---|---|
| protein (g/dl) | 5.1 |
| specific gravity | 1.032 |
| RBC (/ul) | 50,000 |
| WBC (/ul) | 62,500 |
| differential | |
| | 98% eosinophils |
| | 2% macrophages |

fecal examination for parasite ova (three separate samples)
negative

| | |
|---|---|
| FeLV | neg |
| FIV | neg |
| FIP | neg |
| TOXO titer | 1:16 (insignificant) |
| ANA | neg |

modified Knotts test for D. immitis microfilaria neg

CITE test for D. immitis antigen neg

intradermal allergen testing
negative, except slightly positive reactions for cow's milk, beef, and lamb

bone marrow aspirate
M:E ratio 2.0 (500 cell count)
normal proliferation and maturation of all cell series
eosinophilic hyperplasia

serum iron studies

| | |
|---|---|
| serum iron (ug/dl) | 46 |
| TIBC (ug/dl) | 421 |
| UBIC (uG/dl) | 375 |
| % saturation | 10.9 |

All eosinophils in the peripheral blood, bone marrow, and thoracic effusion had normal light microscopic and transmission electron microscopic morphology.

**Gross and Histologic Pathology.** The small and large intestinal lamina propria has mildly increased numbers of eosinophils. There is mild to moderate fibrosis of the lamina propria throughout the length of the intestine. There is marked thickening of the intestinal wall owing to hypertrophy of the inner circular muscular layer. The anterior mediastinal mass is a lymph node with extensive effacement of the normal architecture owing to accumulation of massive numbers of eosinophils. The intra-abdominal lymph nodes have subcapsular and medullary sinuses filled with eosinophils. The spleen has scattered accumulations of massive numbers of eosinophils with fewer plasma cells and macrophages. The alveolar septa are diffusely thickened by eosinophils and macrophages. Multiple areas within skeletal muscle have increased acidophilic staining and loss of striations with accumulations of eosinophils, macrophages, lymphocytes, and plasma cells. There are subendocardial accumulations of eosinophils in the heart. The kidneys have multifocal, interstitial accumulations of moderate numbers of eosinophils and fewer lymphocytes and plasma cells.

**Contributor's Diagnosis and Comments.** Tissue submitted (liver): Moderate to marked hepatic periportal and multifocal coalescing eosinophil infiltration.

Also this lesion can be described as: eosinophilic periportal and multifocal coalescing hepatitis.

Pathophysiologic association: Hypereosinophilic syndrome.

Eosinophilic infiltration of various organs is well

documented in human medicine and described by varied names and subtypes depending on the organ or organs involved. The pathogenesis of these conditions is usually unknown. One hypothesis is that eosinophils process or respond to an allergen which initiates an inflammatory process, and then the inflammation becomes systemic. Normal eosinophil production is dependent on T-lymphocytes and the production of specific colony stimulating factors, IL-3 and IL-5. Recent data from human patients with hypereosinophilic syndrome have described good response to corticosteroid treatment if IgE concentrations are increased, while in others with increased concentrations of IL-5, an antibody against IL-5 has kept the disease process in control. This latter finding suggests that excessive production, for whatever reason, of IL-5 may be a basis of development of hypereosinophilic syndrome.

Eosinophils from human patients with hypereosinophilic syndromes are often described as hypodense as determined by differential gradient centrifugation. This hypodensity is thought to be caused by partial or complete degranulation of these activated eosinophils or because of malformation of the electron dense crystalline cores of the eosinophil granules. Results from electron microscopic and morphometric studies support these theories. No source of concentrated normal eosinophils was available for comparison, therefore differential gradient centrifugation was not done with eosinophils from this cat. Transmission electron microscopic study results showed normal granule morphology in the peripheral blood, bone marrow, and pleural effusion eosinophils.

Hypereosinophilic syndrome has been recognized in cats with numerous clinical, pathological and histopathological findings similar to those described in people. There is controversy over whether the condition is a variant of myeloproliferative disease such as eosinophilic leukemia. Historically, response to treatment has been dismal in cats diagnosed with hyper-eosinophilic syndrome and all have died or been euthanatized because of failing health.

The diagnostic workup in this cat ruled out most known causes of eosinophilia, such as parasitic infection or infestation, environmental allergies (the slight positive responses to cow's milk, beef, and lamb were thought too insignificant since there was no history or physical findings consistent with food allergies), infectious diseases, and eosinophilic leukemia (normal eosinophil morphology and normal proliferation and maturation progression in the bone marrow).

**AFIP Diagnoses**. 1. Liver: Hepatitis, portal, eosinophilic, diffuse, moderate to severe, Himalayan, feline.
2. Liver: Congestion, centrilobular, diffuse, moderate, with mild hepatocellular necrosis.

**Conference Note.** The diagnosis of hypereosinophilic syndrome should be considered in adult cats with significant eosinophilia, vomiting, diarrhea, weight loss, anorexia, and evidence of multisystemic disease. Physical findings may include lymphadenopathy, splenomegaly, hepatomegaly, thickened segments of bowel, and pruritic erythroderma. Although it is apparently an uncommon disease in cats, it is reported to be more common than eosinophilic leukemia. A similar hypereosinophilic syndrome has been described in people. Diagnosis in humans is based on the following criteria: at least 1500 eos/ul, a duration of six months or more, organ system dysfunction, and no other identifiable cause. Patients have an increased incidence of thrombosis which may be due to endothelial damage by eosinophil-derived major basic protein and enhanced clotting, which has been associated with eosinophilic cationic protein in vitro. The prognosis for hypereosinophilic syndrome in people or cats is considered poor.

A differential diagnosis for hypereosinophilia in cats was discussed including eosinophilic leukemia, eosinophilic enteritis/hypereosinophilic syndrome, the plaque form of eosinophilic granuloma complex, feline asthma, endo- and ectoparasitism, allergic dermatitis and eosinophilia associated with several types of neoplasia. Tumor-associated eosinophilia is uncommon in domestic animals and has been recently reported in a cat with transitional cell carcinoma of the urinary bladder (ref. 6). Cytokines associated with in vitro eosinophilopoiesis include interleukins 2, 3, and 5, and granulocyte/macrophage colony-stimulating factor. The role of these substances in the pathogenesis of eosinophilia associated with tumors or idiopathic conditions such as feline hypereosinophilic syndrome is not known.

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Microslide 101, Lantern slides 39, 40

**History.** Control animal on 14-week study. Killed at terminal sacrifice (14 weeks).

**Gross Pathology.** Swollen abdomen corresponding to mass involving entire right ovary; irregular, semi-firm, partially cystic, red, tan, 3.0 x 2.7 x 1.7 cm, cut surface - rough, mottled.

**Contributor's Diagnosis and Comments.** Right ovary: Teratoma, benign.

While ovarian teratomas are rare in most strains of mice, they develop spontaneously in about 50% of the inbred LT/Sv strain of female mice beginning as early as one month of age. An 8% incidence of ovarian benign teratomas has been reported in the B6 mice from the archives of the NCI/NTP Carcinogenesis Testing Programs.

**AFIP Diagnosis.** Ovary: Teratoma, CD1 mouse, rodent.

**Conference Note.** The compression of normal ovarian stroma and follicles at the periphery of the tumor was observed in some sections. The incidence of spontaneous ovarian neoplasms varies in different strains of mice. Granulosa cell tumors are seen in older mice of several strains with a high incidence in BALB/c mice. Teratomas develop in up to 50% of inbred LT/Sv female mice. Teratomas are usually unilateral, arising most frequently in the right ovary. The tumors are believed to originate from oocytes that develop parthenogenetically after completion of the first meiotic division. Histologically, they consist of neoplastic cells differentiating into a wide range of mature tissues representing two or more germ cell layers. Neural tissue is most commonly represented. The section viewed in conference contained skeletal and smooth muscle, adipocytes, cartilage, melanocytic cells, neurons and glial cells, and many cystic structures lined by varying types of epithelium (respiratory, stratified squamous, apocrine). Among domestic animals, teratomas occur most commonly in the horse.

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Microslide 102

**History**. The cat belonged to a husbandry of cats kept in groups of 20 animals for behavioral studies, fed with conventional industrial food and vaccinated every year against rabies, panleukopenia and feline respiratory disease complex.

A serological examination for FeLV and FIV infections was negative on April 1, 1992.

The cat was found dead on May 19, 1992, without any clinical sign, except weight loss. We received formalin-fixed samples of liver and kidneys.

**Gross Pathology**. At necropsy, the only gross lesion reported was a renal congestion.

**Laboratory Results**.
10 weeks before death:

| | |
|---|---|
| Urea: | 0.49 g/l |
| Creatinine: | 10.60 mg/l |
| Glucose: | 0.79 g/l |
| Total prot: | 83.1 g/l |
| Albumin: | 37.8 g/l |
| Ca: | 88.0 mg/l |
| P: | 37.9 mg/l |
| Alk. phos. | 38.9 Ul/l |
| SGOT: | 9.4 Ul/l |
| SGPT: | 68.9 Ul/l |

Tot Bili: 2.97 mg/l

**Contributor's Diagnosis and Comments.**

The general architecture of the liver is markedly altered:

- the portal triads are severely infiltrated by inflammatory cells: mainly lymphocytes, but also plasma cells, macrophages, neutrophils, mast cells and rare megakaryocytes are seen; sometimes, the lymphocytes are grouped in aggregates looking like follicles; the lymphatics are dilated

- the inflammatory infiltrate extends in the lobules, disrupting and destroying the limiting plate of hepatocytes

- fibrocytes and collagen form concentric rings around interlobular bile ducts; lymphocytes are adjacent to the epithelium in some ducts; a disappearance of some interlobular bile ducts is difficult to assess

- hypertrophy and hyperplasia of the bile ductules is one of the most conspicuous features of the lesion; the proliferating ductules project beyond the limiting plates, into the lobules

- the sinusoids and spaces of Disse are rich in inflammatory cells, mainly neutrophils

- the hepatocytes show different lesions: piecemeal necrosis and foci of vacuolation in perilobular areas lead to disruption of the limiting plate; necrosis of individual hepatocytes is sometimes present more centrally in the lobule.

According to the data available in the literature about hepatic lesions in cat, this lesion can be regarded as a chronic lymphocytic cholangiohepatitis. The intense lymphocytic infiltration suggests an autoimmune etiology.

A diagnosis of lymphosarcoma can be excluded, despite the extension of the cellular infiltrates, because of the polymorphism of the infiltrate, the concentric layers of cells and collagen around the bile ducts and the intensity of the ductule hyperplasia, giving evidence of an attempt to regenerate the parenchyma destroyed by necrosis.

In the cat, lymphocytic cholangitis or cholangio-hepatitis is morphologically similar to primary biliary cirrhosis (PBC) in man. This case is very similar to PBC, stage II (Robbins) because of the intense ductular proliferation.

Some aspects of this case (destruction of the limiting plate, necrosis of hepatocytes) are also very suggestive of the chronic active hepatitis (CAH) described in man and dog. This case asks the question of the existence of a true chronic active hepatitis in cats.

**AFIP Diagnosis.** Liver: Cholangiohepatitis, lymphoplasmacytic, diffuse, severe, with cholestasis and biliary hyperplasia, breed not specified, feline.

**Conference Note.** Some sections contained areas of nodular hepatocellular regeneration. The term cholangitis-cholangiohepatitis has been used with various modifiers to refer to a group of poorly defined inflammatory conditions of the feline hepatobiliary system. Chronic lymphocytic cholangiohepatitis is reportedly the most common form. There is no breed or sex predilection and the condition usually occurs in cats under 5 years of age. Clinical findings are indicative of nonspecific liver disease and include hepatomegaly, ascites, icterus and sporadic vomiting. Mild to severe elevations in SAP and SGPT, hypergammaglobulinemia, and hypoalbuminemia are characteristic of this disease. The white blood cell count may be normal or show a mild neutrophilic leukocytosis. Grossly, affected livers are enlarged and display exaggerated lobular markings and nodularity of the capsular surface. Lobular fibrosis and biliary cirrhosis can occur in more advanced cases.

A suppurative form of cholangiohepatitis occurs less frequently and is typically seen in older cats. Clinical signs are usually more severe. The etiology is unknown, but ascending infection by enteric bacteria through the bile duct has been suspected. *E. coli* is most commonly isolated. The presence of primarily neutrophils in the intrahepatic bile ducts helps to distinguish this from chronic lymphocytic cholangiohepatitis.

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**Contributor's Diagnosis and Comments**. Superficial necrotizing dermatitis, diffuse, localized and severe, with epithelial syncytial cells containing intranuclear inclusion bodies.

The submitting veterinarian was requested to send further biopsies of unfixed tissue in transport medium for virus isolation. Subsequent inoculation of EBYR cell cultures resulted in the isolation of a virus that ultrastructurally was typical of a Herpesvirus. This virus was identified as BHV-2 by neutralization tests with a polyclonal BHV-2 antiserum.

The BHV-2 virus causes two clinical forms of disease, namely (i) the more common localized infection that is restricted to the teats and udder - Bovine Herpes Mammallitis (BHV); and (ii) the uncommon, generalized dermal infection seen in cows in this herd. This latter condition is known as pseudolumpy skin disease. Reasons for the differences in development and presentation of these two forms are incompletely understood.

**AFIP Diagnosis**. Haired skin: Dermatitis, necrotizing, subacute, focally extensive, moderate, with vasculitis, vesicles, epidermal syncytia and intranuclear inclusion bodies, blonde Aquitaine, bovine.

**Conference Note**. The clinical signs observed with bovine herpesvirus-2 (BHV-2) infection differ from those seen with other bovine herpesviruses in that the primary lesions are cutaneous. Other herpesviruses, such as malignant catarrhal fever and infectious bovine rhinotracheitis, may cause skin lesions as part of a systemic disease. Pseudolumpy skin disease occurs in both dairy and beef cattle and is characterized by generalized cutaneous nodules or raised plaques which have a centralized area of depression. In contrast to lumpy skin disease (a foreign animal disease caused by a capripoxvirus) BHV-2 lesions are generally more superficial and heal without scar formation. The surface of older lesions is covered by a dry, hard, necrotic epidermis. Hair regrowth is usually complete in several weeks. Histologically, there is superficial epidermal necrosis with syncytia formation by keratinocytes and intranuclear inclusion bodies primarily in the epithelium of the stratum corneum.

BHV-2 bovine mammillitis is usually a problem of lactating dairy cows. Although the disease occurs sporadically and is generally self-limiting, it can result in a significant decrease of milk production in first calf heifers due to painful teat lesions. Gross vesicle formation is uncommon. Typical Cowdry type A intranuclear inclusions are commonly seen early in the disease, but may be difficult to find later. An intraepidermal pustular dermatitis of the udder without teat lesions has been associated with DN599 strain of herpesvirus (bovine herpesvirus-4).

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Microslides 105, 106

**History**. This adult female Persian cat was acquired in Hawaii as a stray six months prior to presentation. It had two skin masses at that time. At the time of presentation, the cat had multiple cutaneous nodules over the caudal half of its body, ranging from 1.0 x 0.5 cm to 6.0 x 7.0 cm. Several masses oozed greyish-brown necrotic material. Draining sinuses were present.

**Gross Pathology**. Seven skin specimens were submitted in formalin.

**Laboratory Results**.

FeLV - Negative
FIV - Negative
FIP - Negative

**Contributor's Diagnosis and Comments**. Skin and subcutaneous tissue: Dermatitis and cellulitis, pyogranulomatous, multinodular, severe with fungal organisms.

The dermis and subcutis contain a multinodular to diffuse inflammatory cell infiltrate of macrophages, multinucleated giant cells, neutrophils and scattered lymphocytes. Inflammatory nodules have irregularly shaped fungal aggregates at their centers. Fungal aggregates are nonpigmented and consist of tangled masses of branching, septate hyphae, 5-7 um in diameter. Large bulbous structures measuring approximately 10-30 um in diameter are present in most of the fungal aggregates. Individual fungal elements are observed in areas between fungal aggregates.

There are several reports of deep granulomatous pseudomycetomas in Persian cats in which Microsporum canis was identified as the etiologic agent. This lesion is also very similar histologically to eumycotic mycetoma which is caused by a

variety of opportunistic fungi. Clusters of individual fungal elements and scattered free hyphae are characteristic of pseudomycetomas. Definitive diagnosis depends on culture of the etiologic agent. Fungal culture was not possible in this case, since only formalin-fixed specimens were received.

**AFIP Diagnosis**. Haired skin, deep dermis and subcutis: Pyogranulomas, multifocal, coalescing, severe, with acanthosis and fungal hyphae, Persian, feline.

**Conference Note**. Grossly, the differential diagnosis includes cryptococcosis, sporotrichosis, staphylococcal folliculitis, other systemic mycosis, and neoplasia. Histologically, the lesion must be differentiated from mycetomas caused by fungi (eumycotic mycetoma) such as Pseudallescheria boydii and Curvularia spp., and mycetomas caused by actinomycetes (actinomycotic mycetoma). Mycetomas are characterized by localized, chronic tumefaction of the skin or deeper tissues, draining sinuses, and the presence of macroscopic granules (grains) in the exudate. The grains are composed of compacted clusters of fungal mycelia or bacterial filaments, often admixed with a cement-like substance. The granules of feline dermatophytic mycetoma frequently contain abundant Splendore-Hoeppli material surrounding the fungal hyphae.

Dermatophytic mycetoma, also known as pseudomycetoma, is an uncommon deep cutaneous infection of cats, with most cases having been reported in Persians. The lesion shares many features with mycetomas described in people and animals, except that the causative agent, Microsporum canis, is a dermatophyte normally limited to growth in the dead superficial keratin layers of skin. The pathogenesis of dermatophytic mycetoma is not known. Several cats have had lesions localized to the dorsal thorax suggesting that deep subcutaneous inoculation of the fungus may have occurred during cat fights. The predisposition of Persian cats for this infection remains a mystery. An underlying hereditary immune defect, such as Chediak-Higashi syndrome (reported in Persian cats), has been postulated.

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Microslide 107

**History**. This pig had been on an experimental zinc deficient diet since weaning.

**Gross Pathology**. The skin had thick crusts over the limbs, perineum and periorbital regions.

**Contributor's Diagnosis and Comments**. Parakeratotic hyperkeratosis, diffuse, severe with superficial and deep perivascular dermatitis and focal folliculitis.

The predominant change in these sections is the marked parakeratotic hyperkeratosis. There is also orthokeratotic hyperkeratosis. A superficial and deep perivascular inflammation is present consisting of lymphocytes, macrophages and a few plasma cells and eosinophils. Occasional neutrophil aggregates are present in the cornified layer and hair follicles.

The marked parakeratotic hyperkeratosis is consistent with zinc responsive dermatosis. Diffuse parakeratosis is not specific for zinc deficiency. Other causes in animals include ectoparasites and thallium toxicosis (unlikely). In the dog, vitamin A responsive dermatosis, generic dog food dermatosis, and hepatocutaneous syndrome (superficial necrolytic dermatitis) are other possible causes. A parakeratosis has been reported in pigs that is not responsive to zinc.

**AFIP Diagnoses**. 1. Haired skin: Hyperplasia, epidermal and follicular, focally extensive, moderate, with parakeratotic hyperkeratosis, mixed breed, porcine.
2. Haired skin: Folliculitis and epidermitis, suppurative, multifocal, moderate, with colonies of cocci.
3. Haired skin: Dermatitis, subacute, diffuse, mild.

**Conference Note**. Zinc is an essential component of enzymes involved in the regulation of RNA and DNA metabolism as well as certain metalloenzymes. Its importance to metabolic functions associated with growth, maturation and repair of tissues is well documented. Although zinc deficiency can occur in any domestic species, it is best known for causing parakeratotic dermatosis in pigs and dogs. Parakeratosis occurs in growing pigs, 2 to 4 months of age and is usually not pruritic. The condition must be differentiated from sarcoptic mange, exudative epidermitis due to Staphylococcus hyicus, and pityriasis rosea. Symmetrical areas of thickened, crusty skin with deep fissures develop around the eyes, ears, snout, scrotum, and lower limbs, as well as on the dorsal surface of the tongue.

In dogs, two types of zinc-responsive syndromes are described. Syndrome 1 occurs primarily in Siberian Huskies and

Alaskan Malamutes and is thought to result from an inherited defect in zinc absorption or metabolism. Both puppies and adults are affected and develop crusting, scaling and alopecia in the periorbital skin, ears, scrotum, vulva and perianal area. Secondary pyoderma is fairly common. Syndrome 2 is seen in rapidly growing, large breed puppies that are consuming diets deficient in zinc or over-supplemented with other minerals. These dogs have skin changes similar to those described in generic dog food dermatosis, characterized by crusted plaques with erosions and ulcers on the mucocutaneous junctions, footpads, pressure points and planum nasale. In addition to the keratinization defects seen in this case, zinc deficiency may be associated with anorexia, growth retardation, reproductive disorders, delayed wound healing, and immune system dysfunction. Recently, low dietary zinc levels have been implicated as a cause of chronic retinal damage in swine.

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Microslide 108, Lantern slides 41, 42

**History**. This boa recovered from severe pneumonia 2 years ago. Recently, it had increasing periods of anorexia, one episode of vomiting, and unusual posturing for 2 months. The snake was euthanized.

**Gross Pathology**. The carcass had minimal body fat. The pericardial sac contained a small amount of clear fluid.

**Laboratory Results**. No pathogenic bacteria were isolated from samples of intestine, lung, liver, kidney or spleen.

**Contributor's Diagnoses and Comments.**
1. Mild, multifocal, lymphocytic hepatitis with acidophilic intracytoplasmic viral inclusions (hepatic and biliary epithelium).
2. Moderate, diffuse hepatic hemosiderosis.

The clinical signs and lesions are consistent with boid inclusion disease. The classification of this virus is uncertain, but it may be a retrovirus. A feature of this disease is the presence of numerous viral inclusions in neurons, glial cells, and epithelium with little or no inflammation or necrosis in the affected tissues. Adult animals usually have a protracted illness, whereas young animals die acutely. Pneumonia has been associated with boid inclusion disease, but it is uncertain if the previous pneumonia in this snake was related to the viral infection. Inclusions were observed in sections of brain, kidney, intestine, and stomach in addition to those in the liver. The brown pigment within macrophages and hepatocytes stained intensely blue in a Prussian blue stained section.

**AFIP Diagnoses.** 1. Liver, hepatocytes and biliary epithelial cells: Inclusion bodies, eosinophilic, intracytoplasmic, multifocal, numerous, boa constrictor (Boa constrictor), reptile.
2. Liver: Hepatitis, lymphocytic, chronic, multifocal, random, mild.
3. Liver: Hemosiderosis, multifocal, moderate.

**Conference Note.** This lesion was considered somewhat atypical for boid inclusion disease, and many conference attendees were skeptical that the virus was the sole cause of the chronic hepatitis in this snake. Intracytoplasmic viral inclusions are numerous throughout epithelial cells. Sections also contain areas of nodular regeneration, fibrosis, biliary hyperplasia, hepatocellular vacuolar change and abundant intracellular brown pigment that participants believed could represent hemosiderin or melanomacrophage centers. Positive staining for iron supported the diagnosis of hemosiderosis. Lipid hepatocellular vacuolation is a common finding in snakes. The submitted electron micrographs were of poorly preserved tissue, but demonstrated viral particles.

Many different viruses have been isolated from reptiles, but not all have been clearly shown to produce disease. Examples of viral-induced disease in reptiles include herpesvirus-associated ulcerative dermatitis in turtles, termed "grey patch disease", and inclusion body disease of boid snakes. Boid inclusion disease affects boas and pythons and is associated with high mortality, especially in younger snakes. It has occasionally been found in boas without clinical signs. The virus may cause systemic disease with numerous inclusions in epithelial tissues throughout the body, particularly prominent in the pancreas and

kidney. A nonsuppurative encephalitis with neuronal degeneration, gliosis and loss of myelin in the white matter of the spinal cord has also been reported, primarily in pythons. Intracytoplasmic inclusions are present in neurons and glial cells.

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Microslide 109

**History.** This 14-year-old, female, African elephant was reported to have decreased food intake and was eating a large amount of gravel. Water intake remained normal. During this time her attitude was good and she passed normal stool. These signs persisted for three days then respiratory distress developed and she died shortly thereafter.

**Gross Pathology.** On postmortem examination, marked pulmonary edema and excessive pericardial fluid were noted. The heart was mottled.

**Laboratory Results.** Encephalomyocarditis virus was isolated from the heart.

**Contributor's Diagnosis and Comments.** Myocarditis, subacute, multifocal, severe, with necrosis, multifocal, moderate caused by encephalomyocarditis virus.

Encephalomyocarditis virus (EMCV), a cardiovirus in the family Picornaviridae, is infective for a wide variety of avian, mammalian and arthropod species. The host species, age, route of infection, and strain of virus are all factors that determine whether infection, disease, or a carrier state develops. Death is usually acute or peracute and pulmonary edema or congestion and cardiomyopathy are the most consistent postmortem lesions. Histologic findings include myofiber necrosis, edema and

mononuclear cell infiltration within the myocardium.

**AFIP Diagnosis**. Heart: Myocarditis, necrotizing, subacute, multifocal and coalescing, moderate, African elephant (Loxodonta africana).

**Conference Note**. The differential diagnosis includes encephalomyocarditis virus, vitamin E/selenium deficiency, foot and mouth disease, and toxic cardiomyopathy. Infection with encephalomyocarditis virus is well documented in swine, primates, raccoons, elephants and rodents. Rats and mice are considered to be the primary reservoir host and may contaminate food or water supplies via fecal shedding. The virus also causes encephalitis in some species, but this occurs less commonly than does myocarditis. The typical histologic lesion in the heart is characterized by necrosis with a variable mononuclear cell infiltrate, and in some instances, mineralization. Peracute cases may have necrosis with minimal associated inflammation. Elephants appear to be highly susceptible to EMCV virus. Other viral infections reported in elephants include rabies, foot and mouth disease, elephantpox, and herpesvirus. An epizootic of encephalomyocarditis virus was recently reported in a baboon colony (ref. 1). Affected baboons experienced acute congestive heart failure with pulmonary congestion and edema, hydropericardium, hydrothorax, ascites, and sudden death.

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Microslide 110

**History and Gross Pathology**.. The specimen has been obtained from a growout pond in late July. The farm manager noticed a decrease in feed consumption. Shrimp exhibited the following signs: atrophy of the tail musculature, a softened cuticular exoskeleton, weakness (moribund animals congregate at the outlet drain), and anorexia as indicated by an absence of

ingesta in the gastrointestinal tract.

**Contributor's Diagnosis and Comments**. Severe, chronic, multifocal hemocytic and necrotizing hepatopancreatitis with intralesional, gram-negative, intracytoplasmic bacteria.

Necrotizing hepatopancreatitis (NHP) is a severe, chronic disease of Texas cultured Penaeus vannamei that was first recognized in 1985. Mortality rates attributed to NHP range from 20-95% and the inability to control NHP was, in part, responsible for the abandonment of several shrimp farming operations in Texas. In the chronic stages of NHP, the hepatopancreatic interstitium contains dense infiltrates of hemocytes that often circumferentially surround necrotic tubules. Affected tubules lack an intact epithelium and the lumen is often obscured by eosinophilic hyalinized debris admixed with bacteria, desquamated epithelial cells and hemocytes. Intact epithelial cells are often hypertrophied and exhibit a granular, basophilic cytoplasm due to the presence of massive numbers of intracytoplasmic bacteria.

The proposed etiology of NHP and the predominant organism identified during ultrastructural examination of diseased shrimp is a Gram-negative, pleomorphic, intracellular, rickettsia-like bacterium. A second, less common, unclassified, helical, intracellular bacterial organism has been identified in NHP-diseased shrimp. It is presently unknown if the two intracellular bacteria represent different morphologic forms of the same organism or distinct, separate organisms. Due to the lack of established shrimp cell culture lines neither organism has been cultured. However, NHP has been reproduced in P. vannamei injected with a Percoll-purified, rickettsia-like bacteria, indicating the rickettsia-like bacterium is the etiologic agent of NHP. Some shrimp in the slide set may also have gill or cuticular fouling with epicommensal protozoa while intranuclear inclusions in the nerve cord, antenna gland or heart are indicative of infectious hypodermal and hematopoietic necrosis virus (IHHN) infection.

**AFIP Diagnosis**. Hepatopancreas: Hepatopancreatitis, hemocytic and necrotizing, multifocal, coalescing, moderate, Pacific white shrimp, (Penaeus vannamei), invertebrate.

**Conference Note**. According to a recent article (ref. 4), the two distinct forms of bacteria (rod-shaped and helical) seen in necrotizing hepatopancreatitis of Pacific white shrimp most likely represent two morphologic stages of the same species of bacterium. Although not yet classified, the organism shares several important morphologic characteristics with bacteria in the genus Seliberia, for which no known pathogenic species has yet been identified. The bacteria in necrotizing hepatopancreatitis are reportedly best visualized microscopically

by using Steiner and Steiner's method, which stains the pleomorphic rods brown.

Necrotizing hepatopancreatitis has been characterized by three major developmental stages which represent a continuum of disease progression. In stage I, the pleomorphic rod-shaped bacteria are present within tubular epithelial cells, primarily in the apical cytoplasm, without significant numbers of hemocytes infiltrating the interstitium of the organ. Tubular epithelial cell hypertrophy or attenuation with tubular dilation was seen in stage II. Epithelial cells were often filled with bacteria, but tubular necrosis was minimal. Stage III was characterized by more extensive tubular necrosis with prominent intraluminal and interstitial hemocytic inflammation, melanization and peritubular interstitial fibrosis. Participants believed that the section viewed in conference most closely resembled stage III disease. Other causes of necrosis in the hepatopancreas of shrimp include aflatoxicosis and "red disease", which is thought to be due to an unidentified toxin.

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Microslide 111

**History**. This 2-year, 9-month-old male, green iguana (Iguana iguana) was captive born in Costa Rica and had been at the National Zoo for the last 2.5 years. No previous health problems were noted until it was found dead.

**Gross Pathology**. The walls of the aortas and other large arteries were rigid, pale white, and mineralized. The kidneys were enlarged, firm, and pale. An acute ileocolic intussusception was also present.

**Contributor's Diagnoses and Comments.** Heart, myocardial mineralization and degeneration, multifocal. Aorta, medial mineralization and degeneration, multifocal. Etiology, metastatic mineralization.

This iguana also had marked mineralization of most small arteries, smooth muscle in the stomach and lungs, and basement membranes in hepatic sinusoids, pulmonary capillaries, renal tubules and glomeruli. In addition, this animal had mild fibrous osteodystrophy of the maxilla.

Metastatic mineralization of large arteries and other organs commonly occurs in captive green iguanas. The pathogenesis of this condition is not currently understood. Proposed etiologies include vitamin D toxicity and nutritional hyperparathyroidism. Results of preliminary studies at the National Zoo suggest that the regulation of calcium and vitamin D metabolism in iguanas differs from that in mammals and birds.

Green iguanas are primarily herbivorous, basking lizards native to the American tropics. Their vitamin D requirements are presumably met through cutaneous synthesis of cholecalciferol ($D_3$) and ingestion of ergocalciferol ($D_2$). Metabolic bone disease commonly affects this species in captivity and can usually be attributed to dietary imbalances of calcium, phosphorus and vitamin D, although lack of exposure to the proper wave lengths of UV light also appears to play an important role. Metastatic mineralization may be seen in animals with or without bone disease.

The cause of death in this animal was attributed to a combination of the cardiac lesions and the intestinal intussusception which developed shortly before death.

**AFIP Diagnoses.** 1. Heart, myocardium and great vessels: Mineralization, multifocal, moderate, with granulomatous inflammation, green iguana (Iguana iguana), reptile.
2. Great vessels: Arteriosclerosis, with osseous metaplasia.

**Conference Note.** In addition to metastatic mineralization of soft tissues, imbalances of calcium, phosphorus and vitamin D in captive iguanas may result in hypocalcemia, rickets, or fibrous osteodystrophy. Some attendees believed that myocardial regeneration was present in the sections. Arteriosclerosis associated with medial mineralization is a common problem of captive herbivorous reptiles, especially iguanas. The lesion is often most striking in the muscular tunic of the large elastic arteries with diffuse to laminar degeneration and necrosis, and massive amorphous calcium deposition resulting in thickened brittle vessels and narrowing of the lumen. The pathogenesis of this disease in iguanas is not clearly understood. Historically, it has been attributed to dietary hypervitaminosis D, but similar

and fibrinolytic systems, alterations in vascular permeability, thrombosis, infarction and hemorrhage. Endotoxin is not thought to play a significant role in the pathogenesis of this disease. Participants noted that abnormalities in this animal's hemostatic profile were consistent with previously reported cases of canine RMSF, including thrombocytopenia, prolonged PTT, and increased fibrin degradation products. Although coagulation defects are clearly an important part of RMSF, the incidence of DIC in affected dogs is thought to be low.

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Microslide 113, Lantern slides 43, 44, 45

**History**. This female rhesus macaque was captive-born and group-housed until 5 years 241 days of age when the animal was found to be infected with type D simian retrovirus. With the exception of a single episode of transient self-resolving diarrhea and transient peripheral lymphadenopathy, the animal remained healthy until 8 years 130 days of age when it exhibited exaggerated movement and blindness. Ophthalmologic exam revealed absence of a menace reflex, absence of direct and indirect pupillary responses, and normal fundus. The clinical status remained unchanged over the next 4 days and the animal was euthanatized.

**Gross Pathology**. Major organs and the central nervous system were unremarkable.

**Laboratory Results**. Type D simian retrovirus serotype 2 was isolated on 30 occasions between the time of initial isolation and euthanasia when virus was recovered from peripheral blood mononuclear cells, axillary lymph node and bone marrow, but not from cerebrospinal fluid. Serum antibody to the type D simian

retrovirus major envelope glycoprotein (gp 70) was present on a similar number of occasions.

Cerebrospinal fluid analysis (at euthanasia): Clear, colorless, WBC = 0, total protein 17 mg/dl.

**Contributor's Diagnosis and Comments.** (Note: 2 u glycolmethacrylate section, H & Lee stain) Encephalitis, nonsuppurative, with neuronal loss, gliosis, demyelination, and intranuclear acidophilic inclusion bodies, focally severe, subacute, paramyxovirus.

Microscopic abnormalities were confined to the central nervous system (CNS). There were focally severe lesions in the lateral geniculate as depicted in the slide submitted, the latero-dorsal thalamic nucleus, and to a lesser extent in the anterior thalamic nucleus consisting of neuronal loss and a wide spectrum of neuronal degenerative changes attended by perivascular and parenchymal lymphoid infiltration, astrocytosis, microgliosis, and satellitosis. Cowdry type A acidophilic intranuclear inclusions were prevalent in neurons and glial cells in these areas and infrequent elsewhere. Spongiform change was prominent in the internal capsule, corpus callosum, and corona radiata and was attended by occasional swollen axons and glial cells containing intranuclear inclusions. Severe lesions in the lateral geniculate were likely the cause of the central blindness.

By electron microscopy, the intranuclear inclusions observed in the lateral geniculate consisted of tangled arrays of relatively smooth-surfaced tubules 18-20 nm in diameter consistent with paramyxovirus nucleocapsids. Nucleocapsids were not seen in the cytoplasm or axons. Both lymphocytes and plasma cells were present in the perivascular cuffs and parenchyma with the latter cell type predominating. The spongiform change in the white matter was characterized by delaminating myelin sheaths and swollen axons in absence of conspicuous macrophage stripping of myelin and was likely secondary to neuronal loss.
This case has some similarities to reported cases of spontaneous paramyxovirus panencephalitis in macaques (1). Measles virus was believed to be the most likely etiology in these cases; however, simian virus 5, simian virus 41 and mumps could not be excluded. The present case differs in the focal and subacute nature of the lesions, lack of cytoplasmic inclusion bodies, presence of demyelination, and absence of lesions suggestive of virus infection in other organ systems. Two of the three previously reported cases also had a history of type D simian retrovirus infection. Type D simian retrovirus infection is an important cause of spontaneous acquired immune deficiency syndrome in macaques and is frequently accompanied by opportunistic virus infections (2). A persistent, rather than acute, paramyxovirus infection is suspected in this case and immunosuppression may be

a predisposing factor similar to measles inclusion body encephalitis (MIBE) in man (3). Although central nervous system infection and increased levels of the neuroreactive kyurenine pathway metabolites, quinolinic acid, and kynurenic acid have been documented in type D simian retrovirus infected macaques, the animals were asymptomatic and lesions were not observed in the nervous system (4,5). It is unlikely that type D simian retrovirus contributed directly to the CNS lesions in this case.

Virtually all paramyxoviruses can cause persistent infections. Lifelong immunity following infection with measles virus has been postulated to be due to lifelong persistence of virus (6). Subacute sclerosing panencephalitis (SSPE) and MIBE are morphologically and virologically similar fatal neurological diseases characterized by persistence of defective measles virus in the brain (3,7). Mutational events in the measles virus genome are thought to be important in the genesis of persistent CNS infection following acute measles virus infection (8,9).

**AFIP Diagnosis.** Cerebrum: Encephalitis, nonsuppurative, diffuse, moderate, with demyelination, neuronal degeneration and necrosis, and numerous intranuclear inclusions, rhesus monkey (Macaca mulatta), primate.

**Conference Note.** Viruses in the genus Morbillivirus of the family Paramyxoviridae cause several diseases of veterinary importance, including measles, canine distemper, rinderpest, phocine distemper and dolphin distemper. Acute measles infection in the CNS of nonhuman primates has been described as causing a nonsuppurative meningoencephalitis resembling measles encephalitis in people. Measles and distemper viruses are capable of causing persistent infections in tissue cell cultures and in vivo. Persistent measles virus infection in people (subacute sclerosing panencephalitis) involves both the gray and white matter and causes progressive, insidious degeneration of the brain that evolves into fatal disease. As in this case, there is often a lymphoplasmacytic perivascular infiltrate. Inclusions are prominent in neurons and glial cells. Severely involved areas are characterized by neuronophagia, neuronal loss, and dense fibrillary gliosis with numerous gemistocytic astrocytes. In people, persistent infection results from mutations in the measles virus, specifically in the virus matrix (M) gene, leading to failure of or defective matrix protein synthesis and incomplete maturation of the virus. Extracellular virus particles are not produced. Participants speculated that immunodeficiency resulting from the type D retrovirus infection may have been a factor in the pathogenesis of this case. Although type D retrovirus has been found in the brain of infected macaques, the virus in not considered directly pathogenic to the CNS.

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Microslides 114, 115

**History**. First signs of a neurologic disorder in this 5 and 1/2-year-old Simmental cow were observed about one month before euthanasia, and included anxiety, falling over, and difficulty rising from a recumbent position. The animal deteriorated and showed reduced general condition, mildly reduced milk yield and loss of weight. The veterinarian was consulted 2 weeks later. Clinical examination revealed tremor of the head, tooth grinding, hyperesthesia to sound and touch on the head, and hypermetric movements of the forelimbs.

**Gross Pathology**. Only the head was obtained for examination and there were no gross lesions detected.

**Contributor's Diagnosis and Comments**. Bovine spongiform encephalopathy.

Numerous vacuoles are present in the neuropil of various nuclei of the brainstem, especially the nucleus tractus solitarii (on most of the slides labelled S91-1697.2). Numerous neurons contain vacuoles in the perikaryon, especially in the vestibular nuclei (S91-1697.5). Gliosis is present in these areas.

Bovine spongiform encephalopathy (BSE) was first diagnosed in the United Kingdom in 1986. The number of affected cattle increased rapidly over the following years and 17,997 cases were diagnosed in 1991.[1] In Switzerland the first cow with BSE was detected in Fall 1990. Up to date (July 1992) a total of 17 cases were diagnosed, but in contrast to the developments in the United Kingdom, there is no increase in the frequency of cases detectable in our country.

BSE is caused by a scrapie-like agent, which was transmitted from sheep to cattle via feedstuffs containing ruminant derived protein in the form of meat and bone meal. Meat and bone meal is a by-product of the rendering of animal carcasses and waste animal material and has been incorporated into cattle feedstuffs as a source of animal protein for several decades. Based on epidemiological studies, the onset of exposure to the scrapie-like agent, however, was dated to 1981/82 and related to the cessation of the hydrocarbon solvent extraction of fat from meat and bone meal.[2] Since the feeding of ruminant derived protein was banned in 1988 in the United Kingdom, the number of cattle affected by BSE is expected to decline rapidly over the next few years.

The source of infection of Swiss cattle has not been identified yet. Since Switzerland was free of scrapie before 1991, our cattle most likely became infected by imported meat and bone meal.

The light microscopic changes in BSE parallel those of natural sheep scrapie in general. However, vacuoles in the neuronal processes are typically more prominent and extensive than is vacuolation of the cell bodies. Furthermore, the distribution and relative densities of the vacuolar changes in the brain are remarkably constant which contrasts with the variability of the distribution patterns described in sheep scrapie. The topography, including bilateral symmetry, of the changes are crucial to the histopathological interpretation of the lesions. The main localizations for vacuolar changes are the solitary tract nucleus, spinal tract nucleus of the trigeminal nerve, vestibular nuclei and the reticular formation in the medulla oblongata; central grey matter in the midbrain; paraventricular area in the hypothalamus and thalamus and the septal area.[3] However, vacuoles in neuronal perikarya are an incidental pathological feature in the red nucleus of cattle[4] and must therefore be distinguished from spongiform encephalopathy.

**AFIP Diagnosis**. Brainstem, multiple nuclei: Vacuolation, neuronal, mild to moderate, with gliosis, Simmental, bovine.

**Conference Note**. Prion diseases are unique neurodegenerative disorders of people and animals characterized by both inherited familial (autosomal dominant) and transmissible forms. Although scrapie in sheep and goats has long been the prototypical prion disease, the list of other species known to harbor scrapie-like disease has grown and includes cats (feline spongiform encephalopathy), cattle (bovine spongiform encephalopathy), mink (mink transmissible encephalopathy), mule deer and elk (chronic wasting disease), nyala and greater kudu (exotic ungulate encephalopathy) and people (kuru, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, and fatal familial insomnia). Bovine spongiform encephalopathy has been experimentally transferred to several other species including mice, pigs, sheep and goats. Most recently, experimental inoculation (intracerebral and intraperitoneal) of marmosets with brain homogenates from BSE infected cattle was shown capable of producing a spongiform encephalopathy in primates. It appears that the transmissible prion particle is composed largely, if not entirely, of an abnormal (protease-resistant) isoform prion protein (designated $PrP^{sc}$) derived from the normal isoform prion protein $PrP^{c}$. Current theory states that $PrP^{sc}$ is converted from $PrP^{c}$ through a posttranslational process that results in a conformational change in $PrP^{c}$. $PrP^{sc}$ is the major component of scrapie-associated fibrils (SAF), which may accumulate as plaques in the neuropil and be detected histochemically as amyloid deposits. Several features distinguish prions from viruses: prions can exist in multiple molecular forms; they are nonimmunogenic; they contain no known nucleic acid, foreign or host derived; and the only known protein component of the prion is $PrP^{sc}$, which is encoded by a chromosomal gene, not a viral genome.

Spongiform diseases in the central nervous system must be differentiated from artifactual vacuolation as might occur during histologic processing of tissue. In most cases, the presence of associated changes, such as increased numbers of glial cells reactive astrocytes help to distinguish disease from artifact. Although the histologic lesion of scrapie is typically associated with vacuoles in neuronal processes and soma, in some cases the predominant finding may be shrunken, dark, degenerating neurons with associated astrocytosis.

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Microslide 116, Lantern slides 46, 47

**History**. This 5-month-old female horse had a 7-day history of apathy and neurologic disturbances, including photophobia, missing pupillary reaction, ataxia, turning right in a circle and falling down.

**Gross Pathology**. At necropsy no obvious lesions were detected.

**Laboratory Results**. No equine herpesvirus was isolated. Borna disease virus specific antibodies were detected in the cerebrospinal fluid.

**Contributor's Diagnosis and Comments**. Severe nonpurulent encephalitis of Borna disease (BD).

In this case inflammatory lesions were found mainly in the hippocampus, laterobasal cortical areas, mesencephalon and hypothalamus.

All hippocampal areas are affected. There are massive perivascular mononuclear infiltrations characterized predominantly by lymphocytes and less frequently by macrophages and plasma cells. Infiltrates also extend into the adjacent parenchyma in which edematous changes and swollen axons (spheroids) are seen. Neuronophagia occurs only occasionally. In neurons, particularly of the hilar portion of the hippocampus, small eosinophilic intranuclear inclusion bodies are found which are compatible with Borna disease specific Joest-Degen inclusion bodies. Immunohistologically intranuclear and cytoplasmic Borna virus specific antigen was found mainly in neurons and neuronal cell processes of the hilar portion. Neurons of the dentate gyrus and of the Ca 1/Ca 2 area contained less antigen. Inclusion bodies were also positive for BDV-antigen.

BD is a progressive encephalopathy of horses and sheep, that is characterized clinically by sensory disturbances and incoordination, followed by paralysis and death. So far the disease has been reported only from Germany and Switzerland.

The infectious agent is only partially characterized. Results of recent molecular biological studies indicate that it is probably a RNA virus.

Animals probably become infected intranasally, followed by an intra-axonal spread of the strictly neurotropic virus into the brain via olfactory nerve fibers.

As indicated by studies in the rat model, clinical disease and histopathological lesions are not caused by the virus itself but by a virus-specific, CD4+ cell-mediated immunopathological mechanism.

Infected animals develop non-neutralizing serum and CSF antibodies, which have also been detected in human patients with certain psychiatric disorders. The importance of the latter findings need to be elucidated. Surprisingly, serum antibodies were also detected in patients in the USA where BD in horses and sheep is still unknown.

Enclosed microphotos:

1. BDV-specific antigen in neurons and neuronal processes in the hilar portion of the hippocampus. (Mab against 38 kd Borna virus specific antigen, PAP-technique)
2. Intranuclear eosinophilic inclusion compatible with Joest-Degen inclusion bodies. (H&E)

**AFIP Diagnosis**. Cerebrum: Meningoencephalitis, nonsuppurative, diffuse, moderate, with neuronal necrosis and gliosis, breed not specified, equine.

**Conference Note**. In addition to natural disease in horses and sheep, Borna disease virus (BDV) is capable of experimentally infecting in a wide variety of laboratory species, including macaques. The initial infection can cause a progressive fatal nonsuppurative meningoencephalomyelitis, primarily affecting the gray matter of the brain. Persistent infection is associated with minimal inflammation and, in some species, behavioral changes. Some researchers believe that Borna disease-induced behavioral changes in animals may have applications in the study of certain human psychological disorders. The etiologic agent of Borna disease is a negative-strand RNA virus that remains to be classified. It shares several pathogenic characteristics with rabies virus including a broad host range, association with behavioral abnormalities in infected animals, centripetal dissemination to the CNS via axons, and a strict neurotropism with formation of inclusions within infected cells. However, rabies replicates almost exclusively in neurons while Borna disease virus also replicates in glial cells. Another difference between the two diseases is that Borna disease viral particles have not been found in tissue sections at any stage of the disease. Attendees were unable to conclusively identify

inclusion bodies in the examined sections.

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Microslide 117

**History**. A dog with polyuria, polydipsia and glycosuria for two years was euthanized by a veterinarian. A littermate with a similar history of chronic polyuria, polydipsia and glycosuria was euthanized one week previously. Both dogs had normal blood

glucose levels. No other history was forthcoming.

**Gross Pathology**. Gross changes were absent in submitted renal tissue.

**Contributor's Diagnoses and Comments**. 1. Karyomegaly of nephric epithelium, predominantly loops of Henle.
2. Moderate acute multifocal medullary necrosis with mild multifocal interstitial fibrosis.
Etiology: Fanconi Syndrome in the Basenji.

Fanconi syndrome in the Basenji dog involves a constellation of defects of renal tubular reabsorption, as in man. There is reduced tubular reabsorption of glucose, phosphate, sodium, potassium and uric acid. Detailed information about serum chemistry and urinalysis was lacking in this dog, but the presence of glycosuria with normal blood glucose levels (paradoxical glycosuria) was characteristic for the syndrome.

There are few detailed descriptions of the histopathology of canine Fanconi syndrome. Enlarged nuclei in tubular epithelial cells, a striking feature in the present case, are recognized in some dogs. Some affected dogs are purported to have histologically normal kidneys. Medullary necrosis occurs in a proportion of dogs which develop renal failure, although this is usually described in reports as acute papillary necrosis. Other features in this case were mild interstitial fibrosis, karyomegalic cells in some glomeruli, cytoplasmic vacuolation of some renal tubules, intranuclear eosinophilic inclusions, and scattered plasmacytic infiltrates in cortex.

A recent survey of North American breeders and owners of Basenjis indicated that 10% of dogs have the condition. It is presumed to be transmitted as a recessive late-acting lethal gene. Affected females outnumber affected males (3:1). Death is associated with severe metabolic acidosis and urinary tract infection with bacterial colonization. Other canine breeds have been reported with Fanconi Syndrome.

**AFIP Diagnoses**. 1. Kidney: Necrosis, medullary, coagulative, focally extensive, with tubular epithelial karyomegaly, Basenji, canine.
2. Kidney: Nephritis, interstitial, chronic-active, multifocal, moderate.

**Conference Note**. Breed-related renal tubular transport defects in dogs include familial cystinuria reported in Irish Terriers, primary renal glucosuria in Norwegian Elkhounds, Fanconi-like syndrome in Basenjis, and possibly hyperuricosuria in Dalmatians. Tubular transport defects can also occur secondary to metabolic disease (diabetes mellitus) or toxin-related tubular degeneration (heavy metal toxicity). Fanconi-

like syndrome in Basenjis is characterized clinically by polyuria, polydipsia, hyposthenuria, aminoaciduria, hyperphosphaturia, proteinuria, and glucosuria with normoglycemia. The disease is progressive and fatal with advanced cases developing severe acidosis and dehydration leading to medullary necrosis. Blood urea nitrogen and serum creatinine levels are usually normal until renal failure develops late in the disease. Although the condition shares many similarities with idiopathic Fanconi syndrome in people, including tubular dysfunction and prominent karyomegalic epithelial cells, it differs in that bone growth retardation and stunting are not observed in dogs. Conference participants noted that pyrrolizidine alkaloid containing plants, particularly Crotalaria, can also cause karyomegaly and megalocytosis of renal tubular epithelium in domestic animals.

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Microslide 118

**History.** This 6-year-old male Viszla was examined because of chronic vomiting, diarrhea and weight loss. Serum chemistry and GI absorption tests were done. An exploratory celiotomy and intestinal resection were performed.

**Gross Pathology.** The distal jejunum, ileum, cecum and proximal colon are infiltrated with multiple, white, firm nodules. The intestinal walls are markedly thickened and the lumen is narrowed.

**Laboratory Results.** Cobalamin levels were decreased and folate levels were elevated.

**Contributor's Diagnosis and Comments.** Lymphangiectasia, diffuse, moderate, with transmural granulomatous inflammation, multifocal, moderate, small intestine, canine.

The clinical signs, laboratory, gross and microscopic findings are consistent with those described for intestinal lymphangiectasia. Lipogranulomatous lymphangitis has been associated with some cases of intestinal lymphangiectasia. The pathogenesis of lipogranuloma formation and its relationship to lymphangiectasia are not known. It is thought that granulomatous lymphangiectasia may occur due to deposition of phlogistic fatty acids in the walls of lymph vessels resulting in inflammation, granuloma formation and subsequent obstruction. Another thought is that the granuloma formation could be a foreign body reaction to saponified material leaking from ruptured lymphatics due to chronic lymph hypertension. A few dogs and humans with intestinal lymphangiectasia have recovered with dietary and corticosteroid therapy. Clinical remission has occurred in this dog on similar therapy.

**AFIP Diagnosis.** Small intestine: Lymphangitis, granulomatous, multifocal to coalescing, transmural, severe, with lymphangiectasia, Viszla, canine.

**Conference Note.** Intestinal lymphangiectasia is a common cause of protein-losing enteropathy in the dog. The resulting hypoproteinemia and hypogammaglobulinemia are often accompanied by chronic diarrhea, weight loss, lymphopenia, hypocalcemia, hypocholesterolemia, peripheral edema, and peritoneal and pleural transudates. Chylous effusion, which is common in people with lymphangiectasia, is infrequently reported in canine cases. The affected small intestine is thickened by edema and white chyle-filled villi which may be visible in the mucosa on gross examination. The histologic lesion is characterized by blunting of villi and dilation of lacteals and lymphatics throughout the full thickness of the intestinal wall and in the attached mesentery. It is not clear why some dogs, and rarely people, form lipogranulomas in association with lymphangiectasia. Similar lipogranulomas may be found in the subcapsular spaces of mesenteric lymph nodes in these dogs. The pathogenesis of lymphangiectasia may involve lymph flow obstruction secondary to inflammation of the lymphatic system or neoplasia (acquired), or it may be due to a primary malformation or insufficiency of lymphatic vessels (congenital). Additional factors may be involved since experimental blockage of mesenteric lymphatics alone does not produce diarrhea and weight loss and has not been associated with lipogranuloma development.

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Microslide 119

**History**. Summer of 1991: This 1-year-old Arab male had a fracture of left hind proximal/lateral P1 which healed uneventfully. In December 1991 the horse fell on asphalt, scraping the right stifle. Several weeks later, a nonpainful lump appeared on the right stifle. Initial radiographs were not remarkable. It was re-radiographed during March 1992, showing calcified lesions surrounding the lateral stifle. Diagnosis: Calcinosis circumscripta. The horse was euthanatized in April 1992 for reasons unrelated to this diagnosis.

**Histopathology**. Skin: Epidermis is absent from most specimens. These sections of dermis contain large, multiple, irregular islands of variably mineralized amorphous to granular, amphophilic to basophilic material with occasional hemorrhage. Variable numbers of macrophages surround the periphery of these mineralized areas, with occasional multinucleate giant cell formation. Small numbers of lymphocytes and plasma cells are interspersed throughout the connective tissue stroma separating mineralized foci.

**Contributor's Diagnosis and Comments**. Moderately severe, multifocal, mineralized granulomata. Calcinosis circumscripta.

This disease entity has been recognized in large breed dogs and occasionally in horses. Similar lesions have been observed in humans. Young dogs, less than 2 years of age are primarily affected. Greater than 50% of these dogs are German Shepherds, while Great Danes and Viszlas may also be affected. There is some evidence of familial incidence and congenital lesions have been seen in these breeds. Affected horses are generally 2 to 4

years old, with lesions primarily on the lateral aspect of the stifle.

All species affected show similar lesions. Single or multiple, firm, bulging masses, approximately 1-10 cm in diameter are visible grossly, causing dermal thickening and elevation of the epidermis. In dogs, predilection sites include limbs, footpads and bony prominences, often attached to tendons, joint capsules or periosteum. On cut surface, single to multiple foci containing chalky, gritty to thick paste-like material, consisting primarily of calcium salts are separated by thin, connective tissue stroma. Macroscopically, lesions may resemble hair follicle tumors.

Histologically, multiple well-circumscribed spherical loculi contain an amorphous, granular basophilic material which is PAS positive, occasionally metachromatic, and stains strongly with Alcian blue. These loculi are separated by connective tissue stroma and are surrounded by a peripheral zone of epithelioid and multinucleate giant cells, with some degeneration and mineralization, as well as lesser numbers of lymphocytes and plasma cells.

A cystic apocrine sweat gland origin has been proposed for the lesion ("apocrine cystic calcinosis"), although similar lesions are also found in the tongue. Occasional lesions may contain metaplastic bone or cartilage. Trauma has been implicated as an etiologic mechanism, followed by reactive hyperplasia of apocrine glands with dystrophic mineralization of excessive, and probably abnormal apocrine secretions. "Putty brisket" is a similar lesion in cattle in which there is no glandular contribution. The exact pathogenesis of this lesion is, as yet, unknown.

**AFIP Diagnosis**. Perisynovial fibroadipose tissue: Granulomas, multifocal to coalescing, with mineralized contents, Arabian, equine.

**Conference Note**. Conference participants interpreted some tissue sections to be partially lined by synovium. Calcinosis circumscripta in the horse has also been referred to as tumoral calcinosis. The condition typically involves periarticular mineral deposition with tumor-like swelling over the carpus, tarsus, or most frequently, lateral to the stifle. In dogs, lesions are usually solitary and most commonly occur in the subcutis of the limbs (especially footpads and over bony prominences), the tongue, and the paravertebral soft tissue. The mineralization is considered dystrophic since it is not associated with a systemic calcium/phosphorus imbalance. Dystrophic mineralization can follow trauma, injections, parasitic injury, collagen vascular diseases, or local metabolic disorders. There is a strong association with previous sites of

trauma in at least some cases of canine and equine calcinosis circumscripta. One theory in the pathogenesis of dystrophic mineralization is that injured cells experience a rise in cytoplasmic and mitochondrial $Ca^{2+}$ concentrations resulting in the deposition of amorphous calcium phosphate in the mitochondria. This leads to diminished mitochondrial respiration and eventually to cell death. The mitochondrial calcium phosphate is then converted into insoluble hydroxyapatite crystals, and these can act similarly to matrix vesicles as nucleators of further precipitation of extracellular calcium and phosphorus.

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Microslide 120

**History**. This 10-day-old Pomeranian puppy was from the premises of a Pomeranian breeder who had found it dead in the kennel and had noticed no previous signs.

**Gross Pathology**. No gross lesions were noted by the practitioner who performed the necropsy.

**Contributor's Diagnosis and Comments**. Small intestine, inclusion body enteropathy, due to minute virus of canines.

The mucosa of the small intestine retains its normal morphology and the villous architecture is largely intact. The villous epithelium on the sides and especially of the tips of the villi contain large amphophilic to eosinophilic intranuclear inclusions. The epithelium in the crypts of Lieberkuhn tends to have a crowded appearance and the mitotic index is high. Electron microscopic examination of the tissues shows the intranuclear inclusions in the villous epithelium to be composed of densely

packed virions of approximately 20 nm. Negative stains of the intestinal contents show the viral particles to have hexagonal profiles compatible with parvovirus.

Minute virus of canines (MVC) is a parvovirus affecting primarily puppies less than 3 weeks old, whose natural pathogenicity is not fully characterized at this time. In contrast to canine parvovirus-2 (CPV-2) whose histopathological lesions include villus necrosis and collapse and fusion of villi with dilated crypts containing regenerative epithelial cells, the intestinal lesions noted in association with minute virus of canines are minimal and are typified by the section seen here. This virus, whose only known host is dogs, was first isolated from normal adult animals in 1967. It is widespread in the population, and most reports put the seroprevalence at about 70%. MVC and CPV-2 are antigenically distinct from each other; however, they are indistinguishable by electron microscopy in negative stained intestinal contents. The cell culture range is quite restricted and at present only one cell line, the Walter Reed canine cell line (WRCC), is reported to support growth of MVC.

**AFIP Diagnosis**. Small intestine, epithelium at tips of villi: Inclusion bodies, eosinophilic, intranuclear, numerous, with mild acute enteritis, Pomeranian, canine.

**Conference Note**. Some conference attendees believed that crypt epithelial hyperplasia was present, while others thought the crypts were normal. Minute virus of canines (CPV-1) and canine parvovirus-2 (CPV-2) differ in host cell range, genomic and antigenic properties. As with other parvoviruses, CPV-1 has a predilection for actively dividing cells. The virus replicates in lymphoid tissue and is reportedly found in largest quantities in the thymus and lymph nodes. Clinical signs in young puppies vary from transient diarrhea to fatal disease. Histologically, the intestinal lesion is characterized by prominent epithelial intranuclear inclusions and villus and crypt epithelial hyperplasia that is typically generalized and uniform from villus to villus. Other lesions include transient thymic atrophy and edema and lymphocytolysis in multiple lymphoid tissues. Transplacental infections prior to gestation day 30 may result in fetal death and resorption. Anasarca or myocarditis is infrequently reported in pups born to dams experimentally infected during the last trimester of pregnancy with CPV-1.

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Microslide 121

**History**. This 9-year-old English Setter, male/castrated canine was referred to the teaching hospital with a history that included shortness of breath and a positive titer to blastomycosis. He was previously diagnosed as hypothyroid and was receiving thyroid supplementation and prednisolone. His vaccination status was current and he was on preventative heartworm medication. Radiographs revealed an interstitial lung pattern. A transtracheal wash revealed no organisms, and a fine needle aspirate of lung contained blood. The owners wanted to pursue treatment. The most likely diagnosis being mycotic, treatment with amphotericin was begun. Lack of response prompted the addition of ketoconazole to the regime. No radiographic response was evidenced two weeks later. Further radiographic consultation indicated that the lesion was too discrete for the aforementioned rule-out, and a lung biopsy was performed. After discharge, this animal was reported to be stable, but showing clinical and biochemical evidence of decreased lung compliance.

**Contributor's Diagnosis and Comments**. Multifocal interstitial pulmonary osseous metaplasia with alveolar microlithiasis. Mild multifocal emphysema (pulmonary alveolar microlithiasis).

Pulmonary alveolar microlithiasis is a rare disease, with only about 200 cases being reported in human beings. The pathogenesis is unknown, but there is a striking familial incidence. Approximately 50% of affected patients have a positive family history, with siblings being the most frequent familial association.

Human patients with pulmonary alveolar microlithiasis are usually diagnosed when chest radiographs are taken for unrelated reasons. Symptoms usually do not appear until late in the disease. The radiographs are characteristic, showing a snowstorm appearance, with apical bullae often being present. Rule-outs include miliary tuberculosis, fungal diseases, hemosiderosis associated with longstanding mitral stenosis, and the pneumonoconioses.

Although the pathogenesis of the disease is unknown, several

theories have been suggested. The first is that a local inflammatory process leads to the formation of the calculi by causing alveolar exudates which act as chelating agents to enhance the precipitation of calcium. Although an in vitro model in which hydroxyapatite has been shown to precipitate out of an unsaturated solution of calcium and phosphorus in the presence of collagen or elastin has been developed, the alveoli in alveolar microlithiasis are generally normal. Another theory is that a hyperimmune reaction to nonspecific insults at the alveolar level leads to exudation and calcification instead of reabsorption. A third theory, and one that is supported by the familial tendency, is that of an inborn error in metabolism leads to excessive alkalinity at the alveolar interface, and thus a decrease in the solubility of calcium phosphate. However, systemic calcium metabolism is normal in patients with pulmonary alveolar microlithiasis.

Recent evidence indicates that the Afghan pika (Ochotona rufescens rufescens), a lagomorph, may provide an animal model for the study of pulmonary alveolar microlithiasis in humans. Sixty pikas, ranging in age from 42 to 745 days of age, were necropsied and had an incidence of 63.3% of pulmonary alveolar microlithiasis, as evidenced by the finding of sharply outlined spherical concentric laminations or onionskin-like laminations of irregular outline.

**AFIP Diagnosis**. Lung: Mineralization, interstitial, disseminated, severe, with osseous metaplasia, interstitial fibrosis, and alveolar emphysema, English Setter, canine.

**Conference Note**. Although pulmonary alveolar microlithiasis is usually characterized by microscopic calculi located within alveolar spaces, most conference participants interpreted the location of these microliths to be interstitial. The microliths appear as well demarcated, spherical to irregularly shaped, homogeneous to concentrically laminated mineralized structures which expand the interstitium. Chemically, they have been shown to consist predominately of calcium phosphate with lesser quantities of calcium carbonate and trace amounts of other minerals. Fragments of bone, which are speculated to be sites of osseous metaplasia, have also been reported in cases of pulmonary alveolar microlithiasis in the Afghan pika. A causal relationship between the formation of bone and microlithiasis was not evident. Human cases of pulmonary alveolar microlithiasis are extremely rare. The occurrence of this condition in siblings and in successive generations suggests a familial cause in at least some cases. Interestingly, approximately one-third of the cases in people have been reported in Japan.

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**History**. This 3-week-old, Holstein bull calf was from a group of sale-barn calves that all died with similar clinical signs of scours, coughing, and respiratory distress.

**Gross Pathology**. The cranio-ventral portions of the lungs were dark red and atelectatic.

**Laboratory Results**. Intestinal tissue - fluorescent antibody test - negative for coronavirus, rotavirus, and BVD.

Lung - fluorescent antibody test - negative for $PI_3$, positive for BRSV.

**Contributor's Diagnosis and Comments**. Subacute purulent, necrotizing bronchopneumonia with mild bronchiolar epithelial hyperplasia, numerous alveolar and bronchiolar syncytial cells, and rare intracytoplasmic inclusions.

Etiologic Diagnosis: Viral bronchitis and pneumonia.
Cause: Bovine respiratory syncytial virus.

Necrotizing bronchiolitis with syncytial cells is highly suggestive of bovine respiratory syncytial virus (BRSV) infection. However, syncytia and inclusions are only present during certain stages of the disease and similar syncytia can be observed in parainfluenza infection. Definitive lesions may be obscured by secondary bacterial infections. Therefore, seroconversion, immunofluorescent staining, or virus isolation are required for confirmation. Bovine RSV is now considered to be a primary pathogen, capable of producing clinical respiratory disease and death.

Severe clinical signs including acute respiratory distress and death have been reported in animals with only consolidation of the cranioventral portion of the lungs. However, widespread pulmonary edema, hyaline membrane formation and emphysema were noted in the apparently non-infected diaphragmatic lobes. The

acute interstitial pneumonia in the diaphragmatic lobes has been compared to similar lesions observed in young children infected with a syncytial virus. Furthermore, it has been proposed that a similar immune-mediated mechanism (hypersensitivity) may be responsible for the acute interstitial pneumonia in both species.

**AFIP Diagnosis.** Lung: Bronchopneumonia, necrotizing, suppurative, subacute, diffuse, moderate, with syncytia cells and atelectasis, Holstein, bovine.

**Conference Note.** Inclusions were not evident in the section viewed in conference. Bovine respiratory syncytial virus (BRSV) is an important cause of lower respiratory tract disease in young cattle. It is a nonhemagglutinating pneumovirus of the paramyxovirus family. Herd outbreaks are usually associated with high morbidity and low to moderate mortality. Gross examination of calves that have died from BRSV infection reveals interstitial pneumonia with atelectasis and consolidation that is usually more severe in the cranio-ventral regions. Secondary bacterial infections may be superimposed on the viral pneumonia. Subpleural and interstitial emphysema and edema are often prominent in the caudo-dorsal lung lobes. It is thought that activation of complement by viral-infected cells in the cranio-ventral lung lobes generates anaphylotoxins (C3a and C5a), which travel hematogenously to the caudo-dorsal lung lobes causing mast cell degranulation, emphysema and edema. Ultrastructural studies have demonstrated that the virus infects both ciliated and non-ciliated bronchiolar epithelium, as well as type I and type II pneumocytes. Infected type I pneumocytes frequently undergo necrosis, while infected type II pneumocytes respond with hypertrophy, hyperplasia and syncytia formation, and may form the predominant alveolar lining cell in an attempt to maintain integrity of the alveoli. Occasionally, squamous metaplasia may occur in affected alveoli.

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**History**. This 1-year-old spayed female domestic shorthair cat died unexpectedly 6 days after a routine ovariohysterectomy. At necropsy the referring veterinarian noted approximately 30 ml of clear fluid in the thorax. The heart was submitted for histologic examination.

**Gross Pathology**. There were no gross lesions in the heart. Histologically, there is extensive endocardial inflammation with early fibroblast proliferation. Neutrophils predominate with lesser numbers of macrophages. In the myocardium are extensive areas of myocardial degeneration and necrosis with infiltration of neutrophils and fibroplasia.

**Contributor's Diagnosis and Comments**. Severe diffuse acute suppurative endocarditis and myocarditis with myocardial necrosis, heart, feline (endomyocarditis form of cardiomyopathy).

Endomyocarditis is a disease which is unique to cats. It is most commonly seen in young cats (under 4 years old). Cats typically present with acute respiratory distress or sudden death. Often there is a history of stress (e.g. surgery, boarding) a few days prior to onset of clinical signs. At necropsy, hearts are usually enlarged with dilated left atria. Left ventricular endocardium may be opaque with foci of hemorrhage. Histologically, there is a severe infiltration of neutrophils, lymphocytes, plasma cells and macrophages in the myocardium and endocardium. The predominant cell type varies with the age of the lesion. In older lesions there is marked fibroplasia. Lesions are typically limited to the left heart and tend to be most severe in the aortic outflow tract. Special stains are negative for organisms. The etiology of endomyocarditis is unknown.

**AFIP Diagnosis**. Heart, left ventricle: Endocarditis, acute to subacute, diffuse, moderate, with mild myocarditis, Domestic Shorthair, feline.

**Conference Note**. In the section viewed in conference, the endocardium and adjacent myocardium are expanded by edema, fibrin, hemorrhage and an infiltrate of neutrophils and macrophages. Participants reviewed the different categories of feline cardiomyopathy. Dilated (congestive) cardiomyopathy is characterized by bilateral enlargement of all heart chambers and is associated with dietary taurine deficiency. Hypertrophic cardiomyopathy is an idiopathic condition characterized by marked

hypertrophy of the ventricles, particularly the left ventricle. It may be a hereditary condition in Persian cats. A distinct hypertrophic cardiac change also occurs in cats with hyperthyroidism. Restrictive cardiomyopathy is the least common of the feline cardiomyopathies, and its etiology and pathogenesis are much less well defined. It is associated with prominent endomyocardial fibrosis resulting in reduced ventricular compliance and impaired diastolic filling. Restrictive cardiomyopathy is most common in older males and presents clinically as left-sided or bilateral heart failure. Grossly, the left ventricle is thickened with decreased volume, and the left atrium is enlarged.

In a review of 28 cats with endomyocarditis (ref. 1), lesions were characterized by marked endocardial and myocardial inflammation with degeneration and necrosis of myocardium and varying degrees of endocardial fibrosis. Over 75% of affected cats also had an interstitial pneumonia with type II pneumocyte hyperplasia. It is postulated that endomyocarditis in young cats may represent an early stage in the development of restrictive cardiomyopathy.

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**History**. This 9-month-old miniature dachshund had right heart enlargement and dyspnea. Cardiac murmur bilaterally over A-V valves.

**Gross Pathology**. The right ventricle and atrium were dilated. The lung was wet and red-purple.

**Contributor's Diagnosis and Comments**. 1. Diffuse severe pneumonia - *Pneumocystis* sp.

2. Mild multifocal myocardial degeneration.

3. Pulmonary hypertension and right ventricular dilatation (gross diagnosis).

The changes in the lung are the result of diffuse alveolar proliferation by Pneumocystis organisms with associated inflammation. The right heart dilatation is the result of pulmonary hypertension and some secondary myocardial degeneration. This syndrome has been previously reported in an article from Australia, Journal of Comparative Pathology, 1972. That article detailed six such cases involving male miniature Dachshunds, 9-12 months of age. Five of the six animals were closely related and hereditary immunodeficiency was postulated as the basis for infection.

**AFIP Diagnosis.** Lung: Pneumonia, interstitial, subacute, diffuse, severe, with type II pneumocyte hyperplasia, and intra-alveolar protozoal organisms, Miniature Dachshund, canine.

**Conference Note.** Pneumocystis carinii has been reported to cause opportunistic disease in laboratory rodents, dogs, pigs, horses, goats, nonhuman primates and humans. Infections are usually limited to the lungs of immunodeficient hosts, but occasional dissemination to regional lymph nodes and other organs may occur. Although the protozoa is only weakly stained with H&E, the appearance of alveoli filled with abundant foamy amphophilic material is very characteristic. Diagnosis can be confirmed by GMS or PAS procedures. Pneumocystis trophozoites primarily attach to type I pneumocytes, and less frequently type II pneumocytes, causing degeneration and necrosis of the alveolar lining cells. The organisms are located almost entirely extracellularly and are only rarely found within alveolar macrophages. Trophozoites can reproduce either by simple binary fission, or by forming a thick-walled cyst which undergoes a process similar to ascospore formation in yeasts. These cysts eventually rupture, releasing numerous thin-walled trophozoites. Grossly, affected lungs appear firm, pale, consolidated and fail to collapse when the thorax is opened. As in this case, concurrent right-sided cardiac dilation may result from pulmonary hypertension.

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proliferative disease in cottontail rabbits (10). This case could represent a new disease entity. According to the nature of the lesions (acute coagulative necrosis), endothelial cells are probably a primary target of the virus.

Similar disease occurrences have been reported in Western and Eastern Canada (2,3).

**AFIP Diagnoses.** 1. Spleen, red and white pulp: Necrosis, diffuse, with marked fibrin deposition, syncytia, and intranuclear inclusions, California grey rabbit, lagomorph.
2. Mesenteric fat: Necrosis and saponification, multifocal, with mild subacute inflammation.
3. Lung: Pneumonia, interstitial, fibrinonecrotic, acute, multifocal, moderate, with fibrin thrombi, syncytia, and intranuclear inclusions.

**Conference Note.** Viral hemorrhagic disease of rabbits was considered in the differential diagnosis for this case. Colonies of bacteria unaccompanied by inflammation are present multifocally within alveoli; these were interpreted to represent postmortem overgrowth. Participants speculated that DIC may have contributed to the extensive deposition of fibrin in the spleen and fibrin thrombi in the lung. Two herpesviruses have been described to occur in rabbits. Herpesvirus cuniculi has been isolated from asymptomatic rabbits, and no lesions have been associated with naturally occurring infections. Herpesvirus sylvilagus is a gamma-herpesvirus indigenous to cottontail rabbits (Sylvilagus floridanus). Experimental inoculation is reported to cause lymphoproliferative disease varying from benign lymphoid hyperplasia to malignant lymphoma. The virus has been suggested as a model of Epstein-Barr virus infection of people. The identity of the herpesvirus suspected to be the etiologic agent in this case is not known. There have been several reports from Canada of an acutely necrotizing systemic disease in Oryctolagus rabbits attributed to a herpesvirus (ref. 2 and 3). Foci of necrosis with eosinophilic intranuclear inclusions were observed in the skin, lungs and adrenal glands of the only rabbit examined histologically. Diffuse necrosis, fibrin and syncytia were also reported in the splenic red pulp.

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**History**. This dog collapsed several times over a two day period, was very anemic, and died suddenly.

**Gross Pathology**. The animal was in poor general condition and very anemic. The stomach was filled with black fluid. There was a mass measuring 4x2x3 cm in the stomach wall in the area of the pylorus, with ulceration of the mucosa and remnants of suture material on the serosal surface. Black contents were observed in the small intestine. One single white soft nodule measuring 2x2x2 cm was present in the liver.

**Contributor's Diagnoses and Comments**. Malignant granulosa cell tumor in the gastric wall with ulceration of the overlying mucosa.

The neoplasm consisted of epithelial cells, forming structures resembling granulosa cell tissue of the ovary, in some areas with Sertoli cell-like appearance.

Ovarian tissue had been implanted into the gastric wall some years earlier when the dog had been spayed. This operation, called ATOP (autotransplantation of ovarian tissue into an organ in portal circulation) was very popular in Switzerland for some years (ca 1980-1985), as it was supposed to prevent urinary incontinence in spayed bitches. First results were encouraging. However, after some years many cases showed hyperplasia of the implanted tissue causing permanent estrus. Other animals died from ulceration of the gastric mucosa (as in this case) and in a few dogs there was a transformation of the implant to malignant tumor with metastasis (in this case to the liver).

**AFIP Diagnoses**. 1. Stomach, tunica muscularis: Granulosa cell tumor, Boxer, canine.
2. Stomach: Gastritis, lymphoplasmacytic, multifocal, mild.

**Conference Note**. Ovariohysterectomy in the bitch is associated with several undesirable sequelae attributed to the loss of ovarian hormones, including urinary incontinence, obesity, and endocrine dermatoses. During the 1970s and 80s, veterinarians in several countries experimented with the use of ovarian autografts in an attempt to prevent or minimize these unwanted side effects. Production of estradiol and progesterone

by the grafted tissue was thought to reduce the symptoms of "hypogonadism". However, retrospective studies up to 5 years post-surgery revealed a wide range of complications resulting from this practice, including permanent signs of estrus, urinary incontinence, and hyperplastic and neoplastic transformation of the ovarian graft.

Granulosa cell tumor is the most common sex cord-stromal tumor of the ovary in domestic animals. Grossly, the cut surface often reveals a mixture of solid and cystic areas with hemorrhage. The histologic pattern of granulosa cell tumors may vary considerably. Although not seen in these sections, a helpful diagnostic feature of some granulosa cell tumors is a gland-like or rosette pattern reminiscent of abortive follicles and containing an ovum-like secretory globule, referred to as a Call-Exner body. Attendees believed that the pattern and morphology of the neoplastic cells in these sections closely resembled Sertoli cell tumor of the testes; this Sertoli cell tumor-like pattern is a common morphologic variant of granulosa cell tumor. Spiral-shaped bacteria morphologically compatible with Gastrospirillum are present in the gastric pits.

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