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Gross Pathology of Small Mammals

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A review is presented on how to perform a meaningful necropsy of the rabbit, ferret, and guinea pig. Brief descriptions of gross findings of significant diseases are provided in sufficient detail for identification in practice. Diseases are organized by organ systems affected and included based on their clinical significance, incidence, and importance in the United States.

Key words: Necropsy, gross pathology, rabbit, ferret, guinea pig, diagnostics.

One of the most intimidating challenges facing private practitioners is the task of performing a good diagnostic necropsy. Even experienced practitioners often find it difficult to apply their clinical veterinary knowledge and skills that they have acquired while performing a necropsy. Perhaps the first and most important step in overcoming these concerns is recognizing that there are a limited number of diagnostic tools that are commonly used. The appropriate collection of diagnostic samples such as cytology, skin scrapings, fecal flotation, bacterial culture, blood, histopathology, and tissue for polymerase chain reaction (PCR) or toxicologic testing is absolutely within the capabilities of every practitioner.

Second, pathology is a dynamic discipline. It is tempting to view pathology as a dogmatic specialty in which disease is unmistakable and diagnoses are definitive but there is not always a classical presentation. Becoming a skilled practitioner or pathologist requires that *patterns of disease be recognized and differential diagnoses prioritized.* A thorough and appropriate necropsy will allow the practitioner to confidently rule out important differentials.

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This article is therefore designed to provide the private practitioner a brief review of the diseases and gross findings typical of rabbits, ferrets, and guinea pigs. For a more thorough review of disease pathogenesis and clinical treatment for small exotics the reader is referred to other sources.[1-4] Because of space limitations, an emphasis has been placed on the more common or significant differentials and presentations of disease in the United States. Also because of space limitations, diseases that are unlikely to cause serious morbidity or potential mortality have often been omitted or only briefly mentioned.

Gross Necropsy Technique

Approaching a necropsy in a systematic fashion will greatly improve the chances of establishing a cause of death. Before beginning the necropsy, the clinical history (including the method of euthanasia or nature of death) should be reviewed and a list of differentials created so the practitioner is prepared to collect the necessary diagnostic samples. Before dissection the animal should be weighed and a full external physical examination performed. The veterinarian should take care to document the animal's body condition and the presence or absence of external lesions.

Animals should be necropsied as soon after death (in as fresh a state) as possible. Clients should be cautioned that postmortem bacterial overgrowth and tissue decomposition may preclude diagnostic bacterial culture, hamper PCR diagnostics, or prevent meaningful interpretation of histopathology. When a prompt necropsy is impossible the carcass should be refrigerated until necropsy can be performed. *Tissues should not be frozen before necropsy* as this will alter cellular architecture and interfere with the ability of pathologists to interpret histopathologic lesions.

A systematic approach to a necropsy includes a list of standard tissues and samples collected from each animal. During a comprehensive necropsy the practitioner should consider saving

samples of liver, lung, kidney, adrenal, heart, brain, stomach, duodenum, ileum, cecum, colon, lesioned tissue, and other tissues as indicated by the antemortem history. Some practitioners find it useful to treat the necropsy as they might a physical examination. Taking the time to note the date, animal name, sex, nature of death or euthanasia, clinical history, and a list of gross tissue findings and diagnostic samples collected will often be invaluable to you and the pathologists working on the case with you. A challenging aspect of performing a necropsy is differentiating pathology from normal or "artifact." When this distinction is unclear, color photographs should be taken, and samples saved for histopathology, culture or other diagnostic testing. A detailed description of the abnormal tissue's location, color, texture, firmness, size and shape should be recorded. This written description is not only a medical record but it is also a tool for the practitioner and consulting pathologist to use in the process of creating a list of differential diagnoses.

Beginning the Necropsy

It will be necessary to prepare a work area before beginning the necropsy (Fig 1). Although a ventilated table is preferable an examination or surgical table can be used (provided that adequate cleaning and ventilation will take place afterward). After a full history and physical examination have been performed, external samples such as skin and hair samples may be taken to screen for ectoparasites. Before entering the thoracic or abdominal cavities it is useful to thoroughly wet the animal's hair down with water, as this will decrease the amount of floating hair (esp. in the case of the rabbit) entering the field of necropsy. While wetting the animal's coat, take care to avoid contaminating the mouth, nose or other orifices from which bacterial or other diagnostic samples may be taken. If samples are to be taken for bacterial culture either sterilized instruments or a means of cleaning them (eg, gauze) followed by flaming them with alcohol over a bunsen burner or lighter should be used. Instruments used to collect PCR samples may be sterilized with a 5 minute soak in 10% bleach and blotted dry before use to avoid contaminant DNA. *Before any samples are taken a thorough examination of the associated viscera should be completed.* Samples from the gastrointestinal tract, or tissues with gross lesions should often be opened last because it will become difficult or impossible to avoid contamination of other samples. The practitioner should be ready to collect ingesta for parasitic examination and bacterial culture samples when entering the gastrointestinal tract. Remove ingesta before immersing the gut in fixative to minimize autolysis and maximize preservation of the mucosa. Finally, good tissue fixation requires adequate volumes of fixative be used (a 10:1 volume of fixative to tissue is ideal) and tissues be no thicker than 1 cm (because fixative will not penetrate more than 0.5 cm).

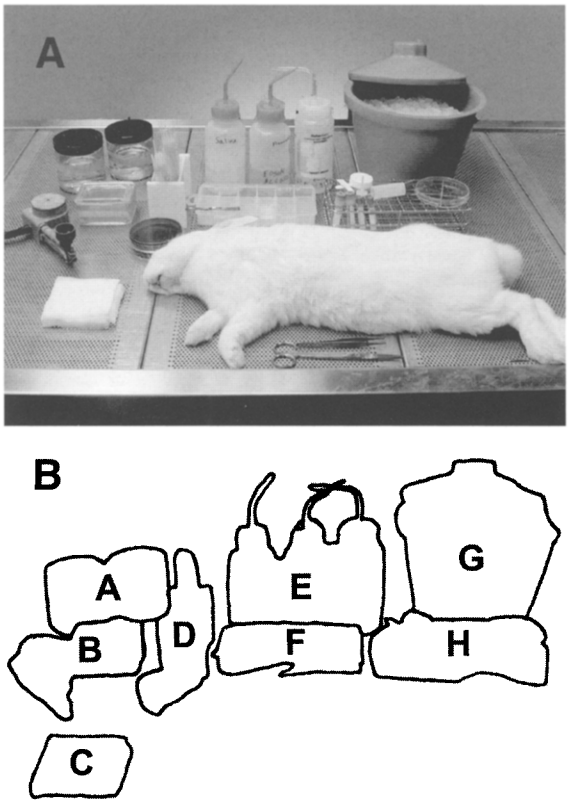

Figure 1. A and B: Materials used during a complete necropsy: A) tissue fixative; B) bunsen burner and alcohol; C) clean or sterile gauze; D) culture swabs and agar plates; E) squirt bottles with saline, alcohol, and formalin; F) instrument rinse with dilute bleach; G) ice bucket to keep PCR samples cold before freezing and shipment; and, H) blood vacutainers and fecal flotation kit. Aric Krogstad, University of Missouri.

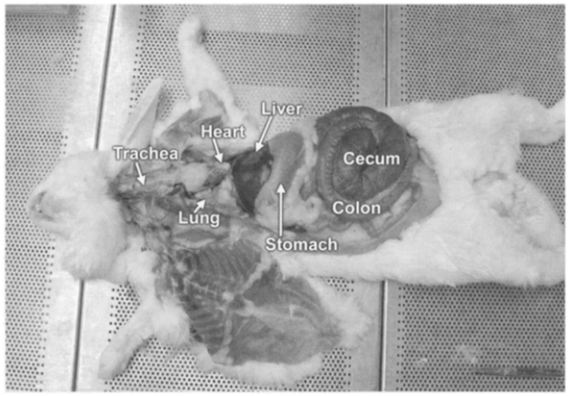

Figure 2. Normal rabbit anatomy. Aric Krogstad, University of Missouri.

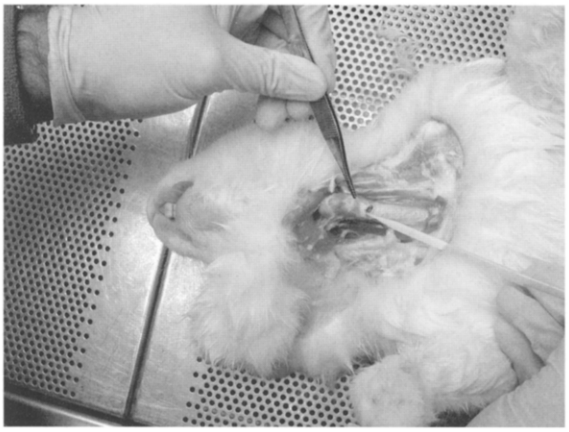

Figure 3. Nasopharyngeal swab. After sterile entry into the trachea a swab may be inserted cranially to reach the nasopharynx. Aric Krogstad, University of Missouri.

I: The Rabbit (*Oryctolagus cuniculus*)

Performing a Gross Necropsy on the Rabbit

The rabbit has several anatomical characteristics that should be considered during a thorough necropsy (Fig 2). A full examination of the oral cavity should be performed to look for proper occlusion of the incisors, peg teeth incisors, and molars. Chronic improper wear may lead to obvious malocclusion but more subtle problems such as the formation of points or hooks on the molars may cause trauma to the tongue or oral cavity mucosa. If chronic upper respiratory tract infection is suspected (see 'Diseases of the Respiratory System'), the nasal cavity should be examined for turbinate atrophy and the tympanic bullae opened to look for purulent exudate associated with bacterial otitis media (Figs 3 and 4).

The rabbit has the largest proportional stomach and cecum of any monogastric animal; the stomach is simple and has a well-developed cardiac sphincter that prohibits vomiting. Because of their habits of regular grooming and the ingestion of night feces the rabbit stomach will normally contain a certain amount of hair mixed with ingesta even after a period of fasting. This makes it more difficult to reach a clinical diagnosis of a trichobezoar obstruction on the basis of stomach contents alone. The cecum composes some 40% of the total volume of the GI tract. Normal cecal contents should not contain excessive fluid and will palpate doughy but not firm at necropsy or physical examination. The urine of normal rabbits may appear pigmented and/or cloudy because of their ability to excrete porphyrins and calcium. In cases where the urinary bladder appears thickened urinalysis, culture and histopathology are appropriate diagnostics.[2-4] A brief list of common differentials for disease by system is included in table 1.

Diseases of the Gastrointestinal System

During the examination of the oral cavity the teeth should be checked for **malocclusion** and the oral cavity examined for cuts, irregularities or ulceration. Small growths associated with **oral**

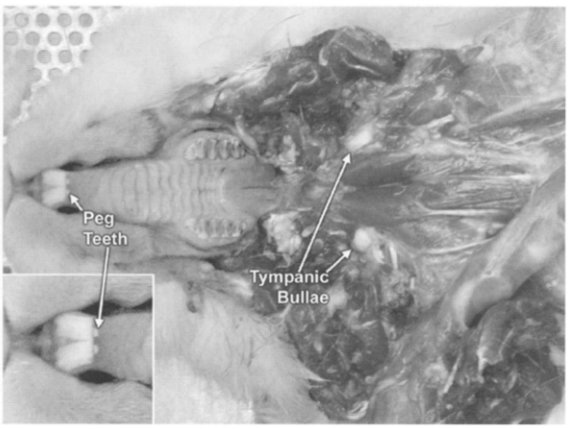

Figure 4. Tympanic bullae. Note the incisors, peg teeth, premolars, and molars as well as the intact tympanic bullae. The tympanic bullae should be cracked open and examined for exudate in suspect cases of respiratory disease. Aric Krogstad, University of Missouri.

Table 1. Differentials for Disease by Organ System in the Rabbit

Gastrointestinal	*Respiratory*	*CNS Disease/Torticollis*
Malocclusion	Pasteurella multocida	Bacterial otitis media
Oral papillomatosis	Treponema paraluis-cuniculi	Encephalitozoon cuniculi
Mucoid enteritis	Other bacterial pneumonias	Psoroptes cuniculi
Antibiotic associated enteritis		Larval migrans
Obstruction	*Genitourinary System*	
Colibacillosis	Bacterial pyometra	*Integument System*
Tyzzer's Disease	Orchitis	SQ abscesses
Salmonellosis	Treponema paraluis-cuniculi	Dermatophytosis
Proliferative enteritis	Uterine adenocarcinoma	Ectoparasites
Coronavirus and rotavirus	Urolithiasis	Myiasis
Oral papillomatosis	Listeriosis	barbering
Coccidiosis		Dewlap dermatitis
Parasitism	*Musculoskeletal System*	Pox
	Traumatic fracture	
	Vitamin E deficiency	
	Splayleg	
	Ulcerative Pododermatitis	

papilloma virus may be observed on the underside of the tongue or other areas of the buccal cavity at necropsy.[5,6] Diagnosis may be reached with a combination of history, and histopathology. These warts resolve spontaneously and are not considered a significant cause of morbidity or mortality.

Dysbiosis of gastrointestinal disease is the disruption of normal gut flora (with increased numbers of anaerobic spore forming organisms such as *Clostridium* sp. or coliforms such as *Escherichia coli*). Dysbiosis is associated with decreased dietary fiber, increased dietary carbohydrates, or other causes of altered gastrointestinal motility.[4] In all cases of gastrointestinal disease the practitioner may find it invaluable to maintain a routine during necropsy. Samples of ingesta should be saved to look for **coccidia**, bacterial aerobic and anaerobic samples may be taken to screen for pathogens, and intestinal tissue should be saved for histopathologic examination. Gastrointestinal disease associated with primary coccidial infections is most common during the postweaning period. The most pathogenic intestinal species are *Eimeria intestinalis* and *Eimeria flavescens*.[2] *Eimeria stiedae* may cause significant liver damage causing production loss and death in young rabbits.[4] Gross findings (Fig 5) highly suggestive of hepatic coccidiosis include multiple yellow to gray discolorations of the liver (0.5 to 2 cm diameter). Diagnosis can be reached with either histopathologic examination of affected tissue or wet mount preparations.[2]

The most severe presentation of **enteritis complex disease** in rabbits is **enterotoxemia.** Enterotoxemia may result from altered diet, antibiotic use, stress, or predisposition.[3] Antibiotics associated with enteritis include clindamycin, lincomycin, penicillin, ampicillin, amoxicillin, and erythromycin and a history of their use may therefore be suggestive of the etiology of enteritis complex disease.[2,4] The causative agent is an "iota-like" toxin from *Clostridium* sp. (perhaps *Clostridium spiroforme*).[7,8] Anaerobic culture is used to positively identify the organism; gram stains of the gut contents may also be used to identify the curved Gram-positive organisms. Grossly there may or may not be perineal fecal

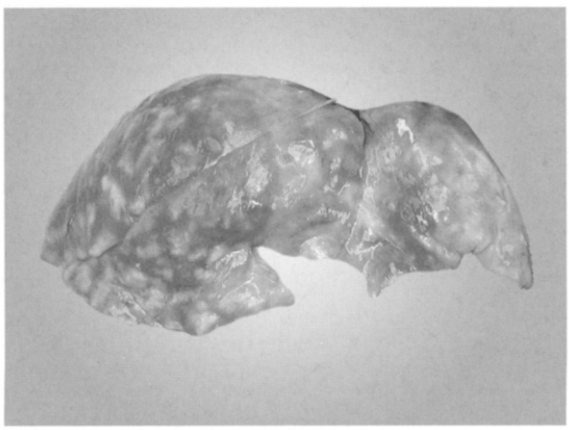

Figure 5. Rabbit liver. This liver is remarkable for the multiple nodular abscess like lesions due to coccidiosis. Lesion culture and histopathology are appropriate diagnostics. Matthew Myles, University of Missouri.

staining, increased fluid within the peritoneal cavity, or ecchymosis within the cecal mucosa, distal ileum or proximal colon. Most significantly, there will be cecal dilation with increased fluid and gas contents within the cecum and adjacent bowel.[2]

Mucoid enteropathy is a disorder most commonly attributed to high energy low fiber diets. Although the mechanism of disease is poorly understood it is clear that the cecal flora undergo significant changes in affected animals.[2] Gross necropsy findings may include distension of the stomach and small intestine with fluid and gas. The large bowel may be impacted with firm ingesta; most characteristically, the colon may be filled with abundant gelatinous mucus.[2] Gross and microscopic findings are diagnostic but screening for other enteric pathogens should be done to rule out coinfection.

Escherichia coli and *Campylobacter* sp. are other bacterial agents of rabbit enteritis. There are a well documented variety of serotypes associated with varying degrees of pathology.[4] Most strains associated with disease are considered enteropathogenic. It has been reported that neither *E. coli* nor *Campylobacter* sp. is normal flora[4] but it is not uncommon for *E. coli* to be cultured from clinically normal rabbits.[9] The possibility of coinfection with other bacterial, viral, or parasitic agents should be ruled out, especially in cases where it affects therapy for remaining animals. Histopathology of both large and small bowel is diagnostic of infection but fecal floatation and culture should be done for this reason. Gross findings most suggestive of *E. coli* infection are dehydration, perineal staining, increased fluid distension of the large bowel with the small bowel grossly normal or unaffected.

Tyzzer's disease is the result of *Clostridium piliforme* infection. The disease affects multiple age groups, with the most severely clinical signs in weanlings. Clinical signs include outbreaks of watery diarrhea, nonspecific illness, and stunted growth.[4] Gross findings include thickened and edematous cecum and colon with watery contents and debris adherent to the mucosa. Multifocal hepatic necrosis (multiple small roughly circular whitish discolorations randomly distributed in the liver) is less common and myocardial necrosis (pale white streaks) is uncommon.[2] Histopathology of affected liver, cecum, or heart is diagnostic if bacteria are found.

Proliferative enteritis is associated with *Lawsonia intracellularis.*[10] The jejunum and ileum typically have thickened mucosa with other regions of the gastrointestinal tract being spared. The mucosal surface may be eroded or proliferative and histopathology is diagnostic. Acute infection may result in diarrhea and/or death in young rabbits. In some cases Lawsonia infection can be an incidental finding with little or no apparent clinical significance so other differentials must be considered before considering it a primary pathogen.[11]

Rabbits, like many other species, are susceptible to **rotaviral enteritis**. This enteritis principally affects weanling and suckling rabbits.[12] Outbreaks of disease are likely to be more severe in the presence of *E. coli* coinfection.[13] Gross findings are largely unremarkable with most viscera being grossly normal but increased fluid contents present within the cecum. Diagnosis may be reached with a combination of electron microscopy of gut contents and histopathology of the cecum.

Multisystemic Disease

Rabbit Hemorrhagic Disease (RHD) or rabbit calicivirus is a highly pathogenic disease that is the only reportable rabbit disease in the United States. Outbreaks of disease in Iowa in 2000[14] and Utah in 2001 and the presence of endemic disease in a number of countries including Australia, Mexico, the United Kingdom, and China make this a highly significant pathogen.[2] Explosive outbreaks of disease with death in more than 90% of affected adults are possible. Central nervous system signs such as shaking, limb paddling, opisthotonus, or uncoordination may precede death. Gross findings may include hemorrhage from multiple sites including the nares, serosal surface of the intestine, or over the pericardium. Hepatomegaly or splenomegaly are consistent findings and nasal discharge may be bloody or foamy.[2,15] Diagnosis may be reached with immunohistochemistry of the liver. In the case of a suspect case of RHD the state veterinarian and USDA should be contacted immediately.

Shope fibromatosis is a poxvirus that is related to myxomatosis virus. Infection with Shope fibromatosis produces localized fibromas on the legs, feet, muzzle, periorbital region, or peri-

neum. These lesions may be large (up to 7 cm diameter in rare cases) but are generally freely mobile and self-resolving in adults but may metastasize to the bone marrow and/or abdominal viscera in young rabbits. Histopathology of masses is generally diagnostic although there are some cases in which it is very difficult to distinguish between myxomatosis or papillomatosis.[2,16] **Shope papillomatosis** is the host response to infection with a different papilloma virus; this infection typically manifests with the formation of papillomas on hairless areas such as the eyelids and ears.[2] Experimental inoculation has demonstrated that these papillomas may either progress to squamous cell carcinomas or resolve without sequelae.[17]

Diseases of the Respiratory System

Pasteurella multocida is perhaps the most common significant pathogen of rabbits. It is often referred to as snuffles because of the upper respiratory tract disease that it may cause but a variety of clinical presentations are possible including bronchopneumonia, pleuritis, pericarditis, pyometra, transmural necrotizing metritis, otitis media, abscesses or acute septicemia and death.[2,4] Transmission often occurs via respiratory or genitourinary contact. Animals suffering from chronic rhinitis may develop severe atrophy of the nasal turbinates; it is therefore appropriate to cross-section and examine the nasal cavity of rabbits with respiratory disease at the time of necropsy.[2] Suppurative otitis media associated with *Pasteurella multocida* may be present in clinically healthy animals. The middle ear is a more sensitive location for culture than the deep nasal cavity so practitioners should also crack open the tympanic bullae of rabbits with respiratory disease for gross inspection and culture. Diagnosis should be reached with culture as there are other bacteria including *Bordetella bronchiseptica, Staphylococcus,* and *Klebsiella pneumoniae* that can cause bacterial otitis or pneumonia.[2,18] ELISAs are commonly available and more sensitive indicators of host colonization than bacterial culture.[19]

Bordetella bronchiseptica is generally considered an opportunistic pathogen or copathogen in the adult but can cause respiratory disease in the juvenile or young rabbit. Lesions suggestive or consistent with Bordetellosis are suppurative bronchopneumonia. Definitive diagnosis is achieved by culture.[2]

Diseases of the Reproductive System

Uterine adenocarcinoma is a very common presentation of disease in adult rabbits, especially rabbits over 5 years of age. The incidence of neoplasia in some populations may approach 80% and be a significant cause of decreasing fecundity with age.[2,20] Grossly, there are often multiple firm masses in the uterine horns; metastasis to other organs including the lungs and viscera is common. Diagnosis is reached with histopathologic examination of affected tissue(s).

Listeriosis associated with *Listeria monocytogenes* is most commonly associated with abortion and sudden death especially in pregnant does. Miliary liver necrosis, lymphedema, and splenomegaly are the most common gross findings.[2] In cases of pregnancy the uterus may appear normal, containing dead kits, or placental pathology. Placental pathology varies with chronicity of infection. In acute cases, inflammation, hemorrhage and edema are expected but in chronic disease, the placenta may be quite friable and contain decomposing kits.[2] The bacteria may be cultured from uterus, fetuses, blood, liver, or spleen.

Staphylococcal infections associated with *Staphylococcus aureus* may result in abscesses to septicemic disease or death.[21] Suppurative lesions in the skin, mammary glands, respiratory tract, or genital system should be cultured to rule out *Staphylococcus aureus* as the etiology of disease.[2] Culture or histopathology of affected lesions may be used to confirm the diagnosis.

Diseases of the Central Nervous System

One of the more common presentations of central nervous system disease is wry neck (torticollis). The most common etiology is a bacterial otitis media associated with *Pasteurella multocida.* Significant differentials for **torticollis** include encephalitozoonosis associated with *Encephalitozoon cuniculi,* other bacterial causes of otitis media, and ear mite infestation.[22] *Encephalitozoon cuniculi* primarily affects the tissues of the CNS, liver, and kidney. Histopathology of affected tissues is diagnostic. Serology tests are

widely available but the incidence of infection and seroconversion exceeds the incidence of clinical encephalitozoonosis.[23] Kidney lesions are often the most striking findings and range from acute congestion and minimal cortical irregularity to marked irregularity and pitting in more chronic cases.[2] The rabbit ear mite, *Psoroptes cuniculi*, may cause "wry neck" as the rabbit tilts its head toward the more affected ear. Unless mites penetrate the middle ear, this parasite does not cause true otitis media or neurologic disease. In all cases of torticollis, tympanic bulla should be opened and examined for purulent material. When bullae are filled with exudative material, bacterial culture should be used for identification.

Hindlimb paralysis or paresis is most commonly the result of muscular exertion resulting in the fracture of the lumbar vertebrae. Radiographs may be used as a means of antemortem or postmortem documentation. In cases of recent lumbar fracture there will typically be an area of clearly visible hemorrhage in the paravertebral musculature.

II: The Ferret (*Mustela putorius furo*)

Performing a Gross Necropsy on the Ferret

There are several anatomical characteristics particular to the ferret (Fig 6) including their large lungs for their body size, lack of a cecum differentiating the small and large bowel, and the predisposition to develop splenomegaly with advancing age.[3,24] Setting these differences aside, the same diagnostic and interpretative skills used in other fields of veterinary medicine should be applied when performing a necropsy on an exotic pet. The clinical history of illness before death may result in the primary consideration of some differentials (see Table 2) but should not preclude the performance of a complete necropsy. This entails a systematic examination of each organ system. When obvious pathology is observed, samples should be taken with a technique designed to prevent contamination of other samples (eg, bacterial culture or PCR).

Diseases of the Gastrointestinal System

Almost 100% of adult ferrets are colonized with ***Helicobacter mustelae***. Although clinical signs are uncommon, experimental infections have been shown to result in increasingly severe gastritis with age.[25,26] *Helicobacter mustelae* has been associated with gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosal associated lymphoid tissue lymphoma.[25,27,28] A thorough necropsy would include examining the gastric mucosa for ulceration or fibrosis; abnormal tissue samples such as ulcerated or thickened stomach and duodenum should be collected for histopathologic evaluation. The gastrointestinal tract should always be examined to rule out the possibility of a **gastrointestinal foreign body** because of the tendency of ferrets to chew on a variety of household items. Culture for *Helicobacter mustelae* is an available diagnostic but the slow growing and fastidious nature of the bacteria make this a slow and labor-intensive test. PCR of the gastric mucosa is an excellent option although clients and practicing veterinarians may prefer histopathology for economic reasons.

Clostridium perfringens type A has been associated with acute abdominal distension and respiratory distress in weanling ferrets. The organism is considered ubiquitous and the mechanism of disease is not understood but it is believed that sudden dietary change and overeating are contributing factors. Diagnosis is reached with a combination of grossly distended stomach and small intestine from which *Clostridium perfringens* type A is cultured/isolated. Ingesta are accompanied by large amounts of gas with brown semifluid intestinal contents.[29] Outbreaks have been controlled with good husbandry including a restricted feeding schedule of two, rather than three, times per day.[24]

Rotaviral diarrhea can result in significant morbidity and mortality in kits less than 6 weeks of age. The diarrhea results from enterocyte loss with resulting fluid and electrolyte loss; secondary bacterial infections may significantly increase the severity of disease. Gross findings suggestive of rotaviral disease include distended small intestine with yellow fluid contents with the large intestine largely unaffected.[30] Clinical history, gross findings,

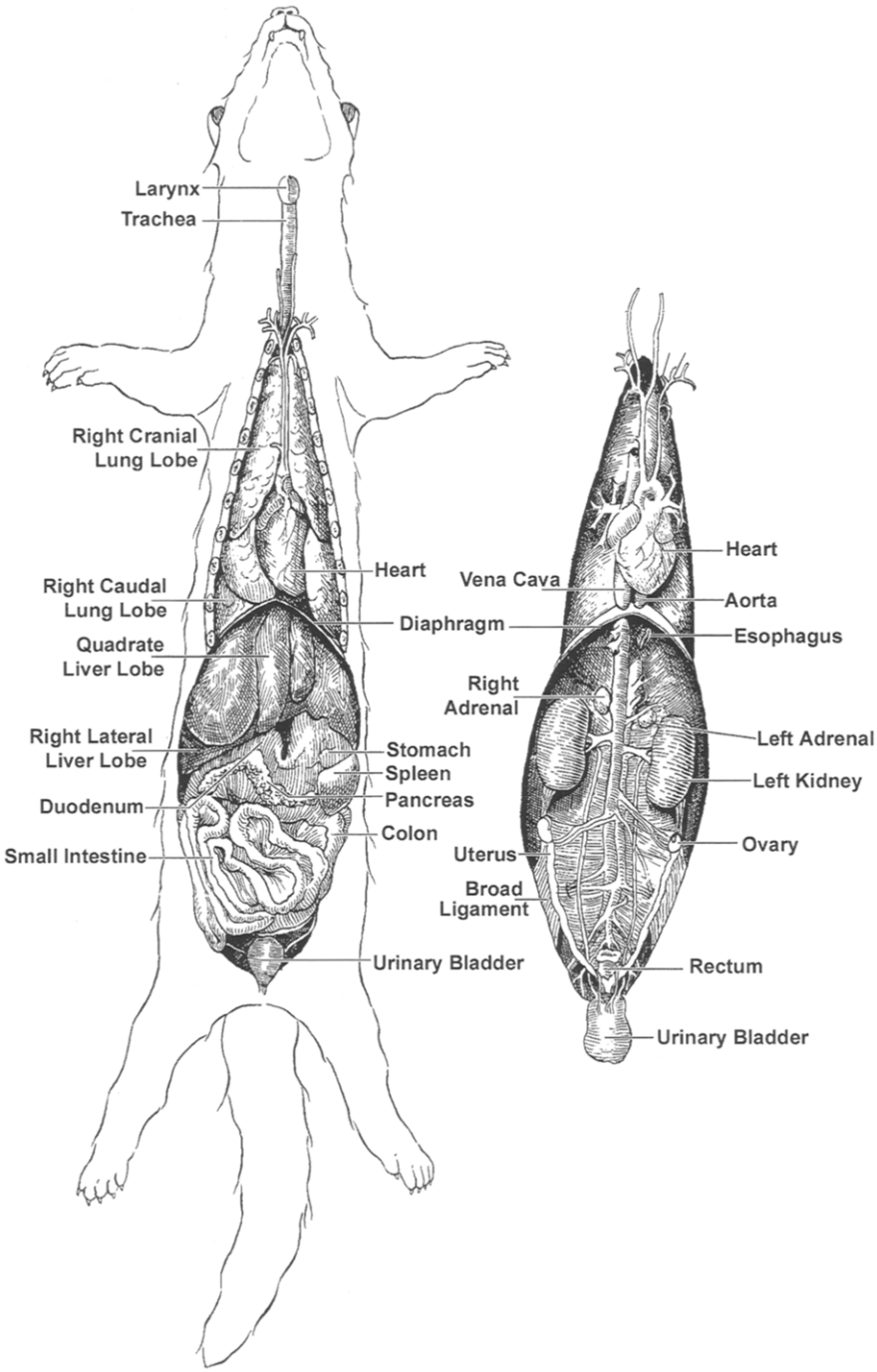

Figure 6. Ferret anatomy. Modified with permission from Hillyer and Quesenberry, Ferrets, Rabbits, and Rodents, 1997.

and histopathology of the gastrointestinal tract may be suggestive of rotaviral disease but for definitive identification fecal samples should be collected and submitted for electron microscopic evaluation. At present, there is not an ELISA available.

Epizootic catarrhal enteritis (ECE) is characterized by a high morbidity, low mortality out-

Table 2. Differentials for Disease by Organ System in the Ferret

Central Nervous System	*Gastrointestinal*	*Cardiovascular*
Canine distemper virus	Proliferative bowel disease	Cardiomyopathies
Rabies	Megaesophagus	Heartworm disease
Aleutian Disease	Gastritis/Ulceration	Infectious cardiomyopathies
Hypoglycemia	Foreign body	Myxomatous degeneration
Trauma	Eosinophilic gastroenteritis	
Systemic disease	Rotaviral diarrhea	*Genitourinary*
Neoplasia	Epizootic catarrhal enteritis	Polycystic Kidneys
Ecclampsia	Aleutian disease virus	Cystitis
Infectious meningitis/myelitis	Bacterial	Urolithiasis
Toxicity	Intestinal parasites	Prostatic hyperplasia (due to adrenal neoplasia)
Anemia	*Reproductive*	
Chronic Weight Loss	Nutritional deficiencies	*Integument*
Neoplasia	Pregnancy toxemia	Dermatophytes
Aleutian disease	Mastitis or metritis	Seasonal alopecia
Cardiovascular disease	Pregnancy toxemia	Endocrine disease
Anemia	Ovarian remnants	Ectoparasites
Gastric ulceration		Anatrichosoma sp.
Proliferative colitis		Other parasites
Salmonellosis		

break of nonspecific illness, and vomiting which later develops into profuse bright green diarrhea with abundant mucus.[31] For this reason, the disease has also been referred to as green slime disease. The disease is believed to be a transmissible gastroenteritis associated with coronavirus.[32] Clinical signs are often more severe in adults than juvenile animals. Gross lesions include green bowel contents with mucus and hyperemia of the affected portions of the small intestine.[31] Diagnosis is reached using a combination of clinical history, gross findings and the presence of coronavirus like particles in the feces.

Proliferative colitis in the ferret is associated with ***Lawsonia intracellularis***, formerly known as intracellular Campylobacter like organism (ICLO), *Campylobacter fetus* subsp *jejuni*, and *Desulfovibrio* sp.[24,33] Proliferative colitis should be a differential for any ferret with a clinical history of prolonged diarrhea with or without rectal prolapse. Typically, only the colon and rectum are affected with or without serosal or mesenteric involvement. Characteristic organisms can be identified via histopathology of the affected colon[33] or by using PCR. The division between small and large intestine is more difficult to detect in the ferret because they lack a cecum but thickened mucosa will be located in the caudal half of the intestinal tract, usually the terminal colon.

Diseases of the Central Nervous System

Aleutian Disease (ADV) is a parvovirus associated disease of mink and ferrets. Perhaps the most common presentation is an adult ferret presenting with hindlimb paresis that may be episodic or recurrent but ADV has been associated with signs ranging from neurologic disease, chronic wasting, gastrointestinal disease, latent infection without clinical signs, and sudden death.[34,35] Gross necropsy findings will be variable and sometimes absent. Young animals may develop interstitial pneumonia. Older animals suffering from chronic disease may have renal lesions (irregularity and scarring), vasculitis, or multifocal disease to consolidation of lungs. There are often characteristic microscopic liver lesions so liver samples should be taken even when the liver is grossly normal.[36] Hypergammaglobinemia, positive serologic titers, PCR, and histopathology have been used to reach a presumptive diagnosis in ferrets. Practitioners should be cautioned that although mink reliably develop hypergammaglobulinemia some ferrets with clinical ADV do not.[37]

The pathogenesis of disease is incompletely understood at this time. ADV is shed in the saliva, urine, and feces. Naïve animals acquire ADV through oro-nasal or vertical transmission. Many ferrets develop antibodies specific to ADV without developing clinical signs.[38] Whether

these findings represent a latent infection with the potential for recrudescence or host immune response and clearance of disease is unclear on an individual basis.[37] But since the seroprevalence of ADV is higher than the incidence of disease,[37] the presence of antibodies alone does not provide a definitive diagnosis; histopathologic evaluation of tissue lesions in conjunction with this test may be considered diagnostic.

Canine Distemper is a morbillivirus predominantly associated with respiratory or nervous signs in the ferret host. Other signs including a transient diarrhea have also been reported in the black footed ferret (*Mustela nigripes*)[39] but are atypical of infection in the pet ferret. Vaccination has greatly reduced the likelihood of such a presentation but distemper remains a major differential for ferrets presenting with CNS or respiratory disease.[40]

During the subacute catarrhal phase of disease, clinical signs are generally respiratory and include anorexia, pyrexia, photosensitivity, serous nasal discharge, and a pruritic rash on the chin (eventually spreading to the inguinal area). During the second neurotropic phase of disease, signs may include hyperexcitability, hypersalivation, muscular tremors, convulsions, or coma.[3,24] Gross lesions are highly variable but animals with upper respiratory discharge with or without the presence of diffuse dermatitis and footpad hyperkeratosis should be considered highly suspect (Fig 7). Diagnosis may be achieved with a good clinical history, histopathologic review and immunoflurescence of affected tissues such as the trachea, lungs, urinary bladder, and central nervous system.[40]

Rabies is a commonly considered differential for central nervous system disease. Despite this, only 23 cases of rabies in ferrets have been reported to the CDC since 1958. Recent experimental studies have demonstrated that virus variant and dose affect the host response and progression of disease.[41,42] The head of a suspect case should be shipped to the state diagnostic laboratory: diagnosis is achieved using IFA testing of brain tissue.[43]

Pancreatic islet cell tumors, or **insulinomas**, are the most commonly reported neoplasia of the ferret[24] (see multisystemic disease and insulinoma for more details). Clinical signs include ptyalism, depression, stupor, ataxia, posterior weakness, and seizures.[3] Insulinomas should be considered as a primary differential in any ferret with a history of antemortem illness that includes signs of neurologic disease.

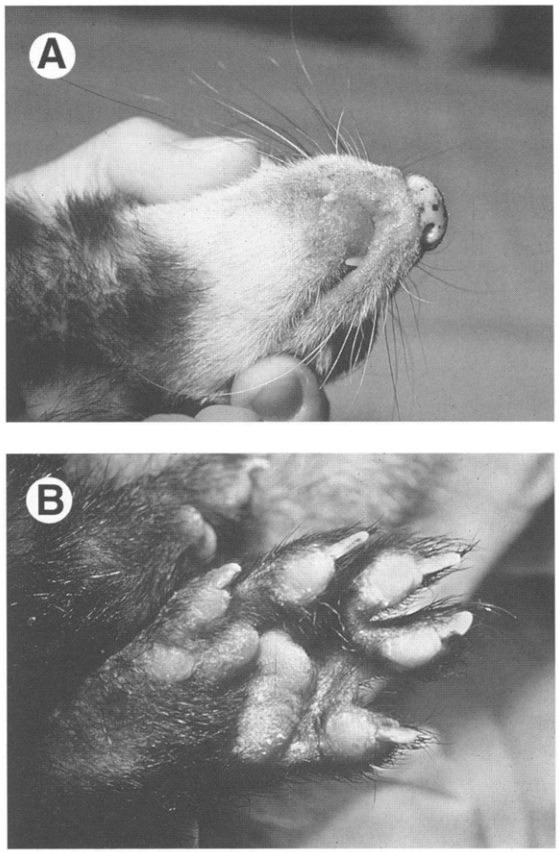

Figure 7. Canine distemper in ferrets is distinguished from other significant respiratory disease by: A) pruritic rash on chin that may spread; and, B) footpad hyperkeratosis also preceeding the neurotropic phase of infection. Donna Clemons, Covance.

Diseases of the Cardiovascular System

Cardiovascular disease in the ferret is an important differential for sudden death or chronic disease. The most common cardiomyopathies in the ferret are **dilated cardiomyopathy** (DCM) and **hypertrophic cardiomyopathy** (HCM).[44-46] Ferrets with DCM will present with chronic disease whereas ferrets with HCM may show no signs before sudden death. Both of these cardiomyopathies are grossly apparent at the time of necropsy and photographs and cardiac tissue samples should be taken to confirm the diagnosis. The most common acquired cardiovascular disease of ferrets is ***Dirofilaria immitis.***[47] Heart-

worm disease of ferrets may result in death with a very low worm burden (1 to 10 worms). Diagnosis is achieved with the visualization of adult worms at the time of necropsy. **Myocarditis** secondary to Aleutian disease virus or Toxoplasma like organism have also been reported but are uncommon differentials.

Diseases of the Respiratory System

Influenza and **canine distemper** (see diseases of the CNS) are perhaps the most commonly considered differentials for respiratory disease. Ferrets are susceptible to human influenza types A and B with type A resulting in more severe disease.[48,49] Disease spread from human to ferret and vice versa is possible, which makes influenza a potential zoonotic concern. Uncomplicated disease in adult animals is generally transient (less than 5 days till recovery) and restricted to the upper respiratory tract. Affected animals may have a mild enteritis.[50] Healthy adults will recover from uncomplicated infection but juveniles and kits suffering from disease may develop a severe diffuse interstitial pneumonia that is potentially fatal.[51] Viral isolation from nasal secretions with or without supportive histopathology of the upper respiratory tract is diagnostic of infection. Rising antibody titers from surviving animals may also be used to establish a putative etiology of disease.[52]

Endogenous lipid pneumonia (cholesterol pneumonia, subpleural histiocytosis) has been reported in the ferret. Gross findings are multiple white to yellow raised plaques on the lungs.[24] When confirmed via histopathology this is an idiopathic finding that has not been associated with clinical disease. However, these lung lesions should be differentiated from other etiologies including *Mycobacterium* sp.

In general, **bacterial pneumonias** may be due to opportunistic or synergistic pathogens in the case of primary viral disease, stress, or systemic disease. A variety of bacterial pathogens have been reported in ferrets including *Streptococcus zooepidemicus* and group C and D *Streptococcus*.[53] Gram-negative bacteria including *Escherichia coli, Klebsiella pneumoniae, Bordetella bronchiseptica,* and *Pseudomonas aeruginosa* have also reportedly been isolated from the lungs of diseased ferrets although a primary pathogenesis has not been established.

Multisystemic Disease and Neoplasia

Adrenal disease most commonly presents clinically as hyperadrenocorticism. Clinical signs associated with disease include alopecia over the tail and caudal dorsum, vulvar enlargement, muscle wasting, and pruritis.[54,55] There is also at least anecdotal evidence to suggest that hyperadrenocorticism may result in the formation of prostatic cysts with or without clinical stranguria.[56,57] These cysts may be sterile or infected and may serve as a nidus for bacterial infections of the urinary tract. Polyuria and polydipsia may be significant in some cases. Rarely, paresis results when hyperestrogenism and thrombocytopenia result in hematomyelia.[58,59] **Hyperestrogenism** may also result from prolonged estrus in an intact jill or an ovarian remnant. Diagnosis of hyperadrenocorticism is based on histopathology in conjunction with a clinical history. Gross findings may vary from very subtle to obvious adrenal enlargement and extension into adjacent tissues such as the caudal vena cava. It has been reported that more than 90% of ferrets four or more years in age had hyperplastic or neoplastic adrenal tissue.[24] It is therefore crucial for the pathologist to consider other causes of systemic disease before attributing clinical signs or death to adrenal disease alone.

Insulinomas have been widely reported in the ferret.[60,61] Any clinical history including nervous signs, lethargy, weight loss, or vomiting should lead a practitioner to include insulinoma on his/her differential list.[3,24] The clinical signs and onset of disease will vary with the severity of hypoglycemia and insulin production of a tumor. It is common for multiple pancreatic nodules to be grossly visible. Metastasis may occur to the regional lymph nodes, liver, or spleen but splenomegaly may be present without metastasis.[24] A clinical history accompanied by hypoglycemia is highly suggestive of an insulinoma but definitive diagnosis requires histopathology.

The ferret is susceptible to *Mycobacterium* sp. including *M. tuberculosis, M. avium,* and *M. bovis* but the incidence of disease is rare because of a low probability of exposure. Samples may be saved and subjected to culture and PCR for definitive identification. *Mycobacterium* sp. are potentially zoonotic agents.[62] Signs of mycobacterial disease are diverse depending on the infective strain and organ systems affected but

granulomatous lesions in the gastrointestinal or respiratory system are the most common.[24]

Pulmonary or systemic **mycosis** are uncommon differential diagnoses for the ferret. There are several cases of fungal infection in the literature but most ferrets are not environmentally exposed to mycotic spores.[63] Mycosis may result in a variety of clinical signs depending on the organ systems affected.[64,65]

The most common **neoplasia** of young ferrets is **lymphoma**. In the younger animal, there may be a mass in the anterior mediastinum and pleural effusion. This may be differentiated from pleural effusion secondary to heart failure on the basis of cytologic evaluation of the pleural fluid, histopathology of the mediastinal mass, and examination of the heart at the time of necropsy.[66] Older animals are more likely to present with multicentric disease with peripheral lymphadenopathy or splenomegaly. Adult onset lymphoma may be associated with retrovirus infection[67] and chronic *Helicobacter mustelae* gastritis may be responsible for gastric B cell lymphoma[27] but most lymphomas are considered idiopathic. For a more thorough review of lymphoma and other neoplasia the reader is referred to other material.[24]

Diseases of the Reproductive System

Pregnancy toxemia is a metabolic disorder that occurs in jills in late pregnancy with a large litter or that become anorexic while nursing an exceptionally large litter. Gross findings notably include a yellow to tan discolored liver with or without gastric hemorrhage. Histopathologic evaluation of the liver is diagnostic and clinical chemistry findings including azotemia, ketonuria, and hypoglycemia are highly suggestive.[68]

Mastitis is another cause of potential maternal death. Gangrenous mastitis may be very rapid in onset (less than 12 hours till life-threatening disease) and require antibiotic therapy and surgical resection for recovery. Bacteria most commonly associated with mastitis are Gram-positive cocci such as *Staphylococcus* sp. or *Streptococcus* sp. and coliforms such as *Escherichia coli.*[69] Care should be taken if kits are cross-fostered because of the danger of introducing pathogenic bacteria to the foster mother. Chronic mastitis causes subclinical disease in the jill but reduces milk production and results in fibrosis of affected mammary tissue.

Diseases of the Integument

***Anatrichomonas* sp.** have been identified in the subcutaneous space of ferrets. This nematode is typically found in the nape of the neck and causes a focal dermatitis. Differentials for a dermatitis affecting this region should include flea bites and biting during mating. A Trichuroidea-like egg may be identified on skin scrapings or impression smears (either clinically or during necropsy).[70] Live worms may be observed but move quickly and may be very difficult to catch. Histopathologic evaluation may be highly suggestive but definitive identification would ideally include capture and examination of a whole parasite.

III: The Guinea Pig (*Cavia porcellus*)

Performing a Gross Necropsy on the Guinea Pig

The same general skills used during a ferret or rabbit necropsy should be brought to bear on the guinea pig. A thorough history should take note of the quality of diet provided (including the vitamin C content and freshness of food), the availability of freshly changed drinking water, and the age at which sows were first bred when constructing a list of differential diagnoses (see Table 3). To an inexperienced practitioner, the large vesicular glands of the boar may resemble a uterus but a more careful examination should reveal the absence of ovaries and presence of male reproductive organs. Females that are not bred before six to eight months of age may undergo fusion of the pubic symphysis and be more prone to dystocia when later bred. Other anatomic characteristics include a long colon (60% of the digestive tract length), large adrenal glands, and large tympanic bullae. In some cases there may be pale discoloration or streaking of the cardiac tissue (a degenerative change known as **cardiac rhabdomyomatosis**). Of course, all tissues with suspect lesions should be taken and labeled for histopathology; rhabdomyomatosis is considered an incidental finding unless there are signs of cardiac failure. Multifocal coagulation hepatic necrosis is another commonly observed finding that may be a ter-

Table 3. Differentials for Disease by Organ System in the Guinea Pig

Respiratory	*Integument*	*Gastrointestinal*
Bordetella bronchiseptica	Telogen effluvian	Tyzzer's
Streptococcus pneumoniae	Barbering or bite wounds	Colibacillosis
Staphylococcus pyogenes	Dermatophytes	Coccidiosis
Adenoviral pneumonitis	Staphylococcal dermatitis	Citrobacter freundii
Citrobacter freundii	Trixacarus caviae	Wasting syndrome
other bacterial pneumonia	Protein deficiency	Clostridium sp.
Slobbers	*Reproductive*	
Malocclusion	Pregnancy toxemia	
Hypovitaminosis C	Ecclampsia/ketosis	*Musculoskeletal*
Heat Stress	Bacterial infections	Hypovitaminosis C
	Nutritional deficiencies	Hypovitaminosis E
Ocular	Dystocias	Systemic disease
Bacterial conjunctivitis	Aflatoxicosis	Osteoarthritis
Heritable cataracts	Mastitis	
Panophalmitis (Streptococcus zooepidemicus)		
Pea eye		

minal hypoxic event although differentials such as toxicity or bacterial hepatitis should be considered and ruled out. Aging sows of more than 1 year old will often have cystic ovaries. These are typically considered incidental findings although they have been associated with impaired reproductive performance with aging. Finally, many older animals have irregular pitting and granular character of the renal cortices (Fig 8). This segmental nephrosclerosis is of unclear etiology and typically considered an incidental finding although in severely affected animals renal function may become impaired.[2]

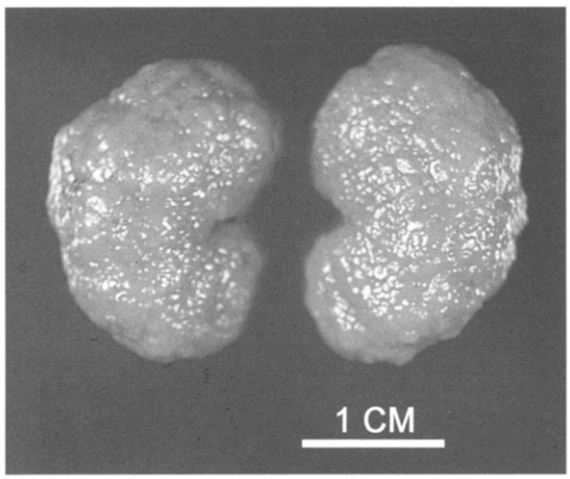

Figure 8. Chronic nephrosis in a guinea pig. Marked irregularity of cortical surfaces is commonly seen with segmental nephrosclerosis. Cynthia Besch-Williford, University of Missouri.

Diseases of the Gastrointestinal System

Gastrointestinal disease may be associated with a variety of bacterial pathogens. Bacterial dysbiosis may result from antibiotic treatment and disruption of normal flora. Dysbiosis frequently results from overgrowth of opportunistic pathogens such as ***Clostridium difficile.***[71] A history of antibiotic use combined with grossly edematous or hemorrhagic cecal mucosa are highly suggestive of antibiotic associated dysbiosis but histopathology and culture should be used for confirmation.[2] A less commonly considered differential affecting younger guinea pigs is **coronavirus like infection.** Gross lesions consistent with coronavirus like disease are enteritis mostly affecting the distal ileum and increased amounts of mucoid material in the entire gastrointestinal tract.[72] Histopathology should be performed on tissues with lesions. An incomplete understanding of disease pathogenesis and significance hampers interpretation especially since it has been demonstrated that clinically normal guinea pigs may shed coronavirus like particles.[73] Diarrhea and death may also be associated with *Cryptosporidium* sp. or *Eimeria* sp. infection.[74,75] *Cryptosporidium wrairi* typically affects juvenile animals; lesions consistent with cryptosporidiosis include watery contents in the small and large intestine. Infection with *Eimeria caviae* is associated with increased fluid and fetid contents of the large intestine.[2] Diagnosis via histopathology or mucosal scrapings may be performed and

coinfection with other enteric pathogens such as *Escherichia coli* should be considered.

Diseases of the Respiratory System

There are several major differentials for **pneumonia** in guinea pigs notably bacterial pneumonias such as ***Bordetella bronchiseptica***. Bordetella is probably the most significant respiratory pathogen of guinea pigs but may be carried as an inapparent infection in some animals.[2,76,77] The presence of gross pathology including suppurative exudate in the nares, trachea or lungs is suggestive of bacterial disease and should prompt the clinician to culture affected tissues. Lesions characterized by pleuritis or suppurative exudates in the tympanic bullae or uterus are also possible. **Diplococcal pneumonia** associated with *Streptococcus pneumoniae* may cause fibrinopurulent pleuritis, pericarditis, or peritonitis.[2] The organism may be carried in the absence of disease but culture from lesioned tissues is considered diagnostic and impression smears revealing Gram-positive diplococci may be obtained from affected animals and considered similarly diagnostic. **Adenoviral pneumonitis** is most commonly reported in experimentally manipulated or immunocompromised animals but has been reported as a primary pathogen.[78] Gross findings include consolidation of cranial lung lobes and multifocal pulmonary necrosis.[2] Histopathology of affected lung is highly suggestive of disease, especially in the absence of bacterial pathogens and in the presence of adenovirus particles (verified through electron microscopy). Cytomegalovirus infection of the respiratory tract is generally considered an incidental finding although there are rare reports of systemic cytomegalovirus disease.[79] Gross pulmonary findings associated with foreign body pneumonitis may or may not be present as incidental findings but can be recognized with the use of histopathology.

Diseases of the Genitourinary Systems

Obese sows late ingestation are predisposed to **pregnancy toxemia**. Clinical pathology findings in the metabolic form of pregnancy toxemia classically include ketosis, hypoglycemia, and hyperlipidemia.[2] Grossly, animals are well conditioned or overweight with fatty change in the liver. Death is common within one week of onset of disease. In the *circulatory form* of pregnancy toxemia the weight of the uterus obstructs blood flow in the uterine vessels and placental necrosis, hemorrhage, and death may follow.[80] Histopathology of affected uterus, placenta, and liver are diagnostic of disease.

Bacterial cystitis is a fairly common finding especially in aging sows.[81] Grossly thickened bladder mucosa with or without congestion and hemorrhage are consistent with cystitis. Histopathology, culture and examination of urinary sediment are appropriate diagnostic tools.

Diseases of the Integument

Ulcerative pododermatitis or bumblefoot is associated with a combination of suboptimal husbandry (dirty wire surfaces) and infection with *Staphylococcus* sp. Affected feet will be variably swollen, crusty, and bloody.[2] Diagnosis may be achieved with the combination of histopathology and culture. **Dermatophytosis** associated with *Trichophyton mentagrophytes* or *Microsporum canis* may cause clinical disease but are largely to be considered incidental findings at the time of necropsy.[82]

Guinea pigs are susceptible hosts to a variety of **ectoparasites** but only the sarcoptid mite, *Trixacarus caviae,* is likely to cause significant disease. Severely affected animals may become thin, extremely pruritic and lose significant amounts of hair.[83] Diagnosis may be achieved with skin scraping or histopathology of affected skin.

Suppurative lymphadenitis is a chronic suppurative inflammation of the cervical lymph nodes caused by *Streptococcus zooepidemicus.*[2] Other presentations of disease include a clinically inapparent carrier state, an acute systemic form, and a respiratory tract infection affecting tissues such as the middle ear, pericardium, or lungs.[84] Culture and histopathologic evaluation of affected tissues are used for diagnosis.

Multisystemic Disease

Scurvy due to **hypovitaminosis C** is one of the most important and widely considered differentials for disease in the guinea pig. In the absence of vitamin C supplementation, guinea pigs should be considered at increased risk of oppor-

Figure 9. Scurvy in a guinea pig. Arrows point to gross hemorrhage around patellae suggestive of hypovitaminosis C. Joe Wagner, University of Missouri.

tunistic disease. Clinical histories range from nonspecific illness and weight loss to orthopedic trauma associated with epiphyseal microfractures. Increased capillary fragility may cause ecchymosis in a variety or tissues and hemorrhage into periarticular joint spaces and costochondral junctions.[2] These gross findings (Fig 9) in combination with histopathology of affected costochondral or epiphyseal regions may be considered diagnostic.

Systemic disease associated with **salmonellosis** in the guinea pig presents in a similar fashion to disease in other species. Pinpoint foci on the liver and spleen with or without the presence of splenomegaly and suppurative necrosis of the lymphoid tissues of the gut or visceral lymph nodes are classical gross findings.[2] Histopathology alone may be highly suggestive of salmonellosis but confirmation is best achieved by culturing the blood, liver, or spleen with selective media.

Muscular dystrophy associated with **vitamin E or selenium deficiency** may be associated with muscular weakness, decreased reproductive performance, or even death.[85] Elevated creatine phosphokinase and histopathologic evaluation of affected tissue are diagnostic for disease.

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