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## RESPIRATORY DISEASES OF RODENTS AND RABBITS

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Private practitioners have, for years, been placed in the difficult position of diagnosing and treating disease in small, somewhat unfamiliar pets, presented in extremis by an owner with a limited budget. The diseases most commonly causing a visit to the local veterinarian are the same diseases with which laboratory animal professionals struggled for years, until suppliers of laboratory animals became the sophisticated producers that they are today. The authors of this article are all practicing laboratory animal veterinarians with additional private practice experience with the goal of sharing our experience in diagnosing and treating the most common respiratory diseases of rodents and rabbits. Additionally, necropsy descriptions are provided for those readers who may find the information valuable for husbandry and breeding in colony situations.

Certain principles of medicine apply to all species. Hypothermic, dehydrated rodents and rabbits benefit from appropriate external warmth and fluid therapy. On the other hand, the choice of antibiotics, if indicated, is more problematic in these animals, because of potentially fatal side effects of some of these drugs. Our descriptions highlight treatment indicated for the species described, with references to laboratory animal studies, where they exist, and anecdotal information as available. Several recent formularies<sup>11, 28, 37, 47</sup> provide drug doses for these species, with references—it is important to note that many of the references are to scientific studies and texts from the laboratory animal medicine field and to case reports and brief chapters in books relating anecdotal information. Unfortunately, there are no drug companies mar-

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keting products for the pet rodent or rabbit patient, and there are few controlled studies relating to treatment of disease in pet animals of these species with newer drugs. The practitioner must be particularly careful in choosing a drug and route of administration for these patients.

## HOW RESPIRATORY DISEASES AFFECT RODENTS

Respiratory diseases in rats (*Rattus norvegicus*) and mice (*Mus musculus*) may present with vague, nonspecific signs that are indistinguishable from other organ system diseases. Because of their high metabolic rates, sick rodents deteriorate rapidly and must be examined and evaluated promptly. For example:

1. Sick rats and mice often do not groom themselves as fastidiously as normal, resulting in a rough coat.
2. They are often lethargic and may separate from cage mates if group housed. Behaviorally, they are much less curious and are less likely to investigate novel areas. This may result in the owner reporting decreased interest or response to the owner or other people.
3. Nasal discharge is infrequently noted in mice even in cases of sinusitis but may be seen with some respiratory conditions in rats.
4. Audible evidence of excessive respiratory secretions (tracheal) may be heard as evidence of "chattering" as the animal breathes.
5. The character of the respiratory effort may also change but is more difficult to appreciate because of the rapid respiratory rate.

Rats, like most rodents, possess Harderian glands that surround the orbit. These glands produce a unique porphyrin pigment that is a normal component of tears; however, in times of stress in rats, the pigment may become apparent around the fur of the eyes and also on the external nares—a condition known as chromodacryorrhea. The pigment may be confused with dried blood. The presence of this red pigment is not evidence of upper respiratory disease but rather of generalized stress from environmental or husbandry problems or from dehydration.

Guinea pigs with respiratory illness often present with dyspnea that may be quite severe. Nasal and ocular discharge is common in guinea pigs, and the generalized unkempt appearance resulting from poor grooming is seen. Dehydration and anorexia may result in an appearance of weight loss, with a loss of the normal rounded abdominal contour.<sup>84</sup>

## EFFECT ON HUMANS (ZONOTIC POTENTIAL OF RODENT PATHOGENS)

Very few pathogens of rodents are zoonotic agents. Among these, only two agents involve the respiratory system, *Streptococcus pneumoniae* and Hantavirus. Although it is possible for humans to obtain pneumo-

coccal infections from rodents, *S. pneumoniae* can be isolated from between 40% and 70% of the adult human population. Because of the high rate of human infection, it is more likely for humans to infect rodents with *S. pneumoniae*. Hantavirus is an emerging disease, and wild rodents serve as reservoirs for the agent, particularly in the southwestern United States. Human infection can occur from aerosols of urine, feces, or saliva.<sup>89</sup> The infection is totally asymptomatic in the animal, with virus replication occurring within the lung prior to dissemination to the urine and saliva. Because infection can prove fatal for humans, extreme caution should be taken if there is potential for exposure to wild rodent excreta. Other than these agents, the potential for human disease to occur from respiratory agents in rodents is markedly limited.

## HOW TO DEAL WITH THE SICK RODENT OR RABBIT

It is important to observe smaller rodents, if possible, in their home cage, in order to evaluate husbandry provided by the client. Careful observation of the pet and its surroundings should precede the physical examination. An excellent description of the scheduling, history taking, and clinical examination process for small rodents has been provided.<sup>24</sup>

Traditional veterinary means of investigating respiratory disease are often impractical in small rodents. Auscultation is challenging because of the small size of the thorax and the lung fields, and it is also complicated by a rapid respiratory rate (mice, 84 to 230 breaths per minute; rats, 66 to 114 breaths per minute) and relatively small tidal volume (mice, 0.09 to 0.38 mL; rats, 0.60 to 1.25 mL).<sup>2, 49</sup> Thoracic radiographs may be difficult to produce and interpret because of the lack of experience of the practitioner with the species. Radiographic techniques have been published<sup>56, 73</sup> but must be adapted to the practitioner's situation and equipment. Culture and sensitivity of nasal or ocular discharge may be helpful but may result in a "mixed bag" of commensal organisms in mice and rats.<sup>24</sup> On the other hand, demonstration of bacteria of characteristic shape or gram-staining may be helpful in diagnosing streptococcal infections in hamsters and guinea pigs or bordetellosis in guinea pigs.

Complete blood counts (CBCs) and blood chemistries may be indicated in rodents with respiratory disease, but sampling techniques and volumes are often problematic.<sup>6</sup> There are a number of laboratories that are used routinely by animal research facilities because of their experience with rodent species (see Appendix).

## RESPIRATORY PATHOGENS IN MICE AND RATS

### Sendai Virus

#### *Clinical Presentation*

Sendai virus is a highly contagious, self-limiting RNA virus of the family Paramyxoviridae that affects mice and, to a lesser extent, rats and

other species of rodents. It is the single most clinically relevant viral respiratory pathogen in mice.<sup>1, 41</sup> Signs vary from clinically silent infections to dyspnea, respiratory distress, and death.<sup>71</sup> Severity of infection increases in the very young and in the aged, with compromised immune status, with poor husbandry conditions, and with concurrent *Mycoplasma pulmonis* infection or cilia-associated respiratory (CAR) bacillus infection.<sup>41, 69</sup>

In naive populations, the virus spreads rapidly. In this scenario, the clinical signs may be severe. In larger populations where new individuals are continually introduced, such as breeder populations, nursing pups are protected by maternal antibody. They usually become infected as young adults with a very mild infection, after which seroconversion occurs. Seroconversion provides life-long protection.

Presumptive diagnosis may be made based on the epidemiology described. Diagnosis may be confirmed by identifying gross or histologic lesions compatible with Sendai virus or by detecting Sendai virus antibody in surviving animals.

### *Pathology and Pathogenesis*

In a pure Sendai virus infection, gross pathologic findings consist of plum-colored areas of consolidation in the cranioventral lung lobes. Histologic lesions in the early stage of infection consist of necrotizing sinusitis, bronchitis, or bronchiolitis or interstitial pneumonia with a mixed inflammatory response. Bronchiolar epithelium may be hyperplastic with cells containing eosinophilic inclusion bodies and occasional syncytial cells. Later stages of infection may demonstrate squamous metaplasia of the bronchiolar epithelium.<sup>71</sup>

The virus is relatively labile in the environment and is most commonly spread via aerosols. Initial infection occurs in nasal passages and is confined to the respiratory tract. Opportunistic bacteria or other viral agents may exacerbate the infection.

### *Treatment and Control*

During the infection, supportive care provides the greatest protection. A warm, clean, nondrafty environment is required. Animals should be properly hydrated with subcutaneous or intraperitoneal lactated Ringer's solution (2 to 4 mL/100 g/d), warming the fluid prior to administration. In cases in which bacterial infection or *Pneumocystis carinii* is suspected, water supplemented with trimethoprim-sulfamethoxazole may be added. The authors routinely mix 10 mL of trimethoprim/sulfamethoxazole (240 mg/5 mL) into 1 pint of drinking water, yielding a concentration of about 1 mg/mL. Mice drinking an average of 6 to 8 mL/d<sup>45</sup> may drink up to 180 to 240 mg/kg/d of drug using this formulation. No studies of drug levels in mice have been performed, but this concentration prevents clinical problems with pneumonia in immune-suppressed mice without complications from the drugs. Caution must be observed to ensure that medicated water does not decrease water consumption.

In small populations, the virus frequently runs its course over a 2-week time frame. If no new animals are introduced, the virus is eliminated from the population within 2 weeks of infection. Animals suspected of harboring the virus should not be introduced to naive populations, such as at shows. In breeding situations, cessation of breeding for a 2- to 3-week period to halt the introduction of naive individuals may break the infectious cycle. The virus is easily killed by standard sanitizing solutions, and caging areas should be thoroughly sanitized before introducing new animals.

## ***Mycoplasma pulmonis***

### *Clinical Presentation*

Murine respiratory mycoplasmosis (MRM) is the most significant bacterial respiratory disease of rats and mice.<sup>45, 51</sup> It has also been referred to as *infectious catarrh*, *enzootic bronchiectasis*, *chronic respiratory disease* (CRD), and *chronic murine pneumonia*.<sup>12, 55</sup> The causative agent, *M. pulmonis*, is an extracellular, gram-negative bacillus that commonly affects mice and rats, and occasionally rabbits, Syrian hamsters, and guinea pigs.<sup>55</sup> Disease expression varies widely, but is typically subclinical. Under adverse conditions, such as excessive cage ammonia levels, concurrent disease, or nutritional deficiencies, the infection can cause fulminant pneumonia or otitis media. Genital tract infections may also occur in the rat. Clinical signs are generally nonspecific and may include weight loss, respiratory distress, and a rough hair coat. Respiratory sounds may also be heard, including "chattering" in the mouse, and "snuffling" in the rat. The rat may show additional signs of torticollis, infertility, and porphyrin staining around the eyes and nares.

*M. pulmonis* should be suspected with any chronic respiratory infection of rats or mice. The organism is difficult to culture, but diagnosis can be confirmed by way of commercial serology (enzyme-linked immunosorbent assay [ELISA]) or polymerase chain reaction (PCR) if needed. Microscopic lesions are characteristic and can also be used to support a diagnosis of MRM.

### *Pathology and Pathogenesis*

Gross lesions associated with *M. pulmonis* include serous to mucopurulent exudates in the nasal passages and airways, in the tympanic bullae, or in the genital tract of the female rat. Distribution of lung lesions tends to be cranioventral, and affected areas are tan to plum-colored.<sup>71</sup> In very severe cases, abscesses may be seen on the lung surface, indicative of bronchiectasis. Three characteristic microscopic lesions of *M. pulmonis* are (1) neutrophils in the airways, (2) airway epithelial hyperplasia, and (3) lymphocytic hyperplasia in the lamina propria of the submucosa. Infection by additional agents, such as Sendai

virus, CAR bacillus, or sialodacryoadenitis virus (SDAV), is very common and may complicate the pathologic findings and exacerbate the clinical disease.

### *Treatment and Control*

Virulence of *M. pulmonis* varies with the bacterial strain and the susceptibility of the mouse or rat strain. Clinical disease may not be seen until months after the initial infection. Infections become chronic and are difficult to eliminate. Seroconversion occurs but does not convey immunity.<sup>41</sup> The infection can be transmitted by aerosols and by way of the intrauterine route.

Successful treatment of infected rats was reported with the use of oxytetracycline intramuscularly, 20 mg/kg, one time daily (SID).<sup>8</sup> Symptoms associated with chronic inflammation may be alleviated by administration of dexamethasone, 0.5 mg/kg, intraperitoneally (IP). Tilmicosine, a macrolide antibiotic, was used successfully to treat mycoplasmal infections in poultry and reaches high concentrations in the lungs of affected rats at a dosage of 20 mg/kg, subcutaneously (SQ).<sup>48, 63, 64</sup> Additional control measures include assurance of a clean cage environment and adequate nutrition along with prevention of exposure to additional respiratory pathogens. The bacterium does not survive well outside the host and is susceptible to environmental conditions, particularly drying.

Once the organism has become established in a colony, it is likely to remain. With high-quality care, expression of disease can be kept at a minimum. In order to completely eliminate the organism, depopulation followed by sanitation of all associated items and replenishment with known *M. pulmonis*-free stock is required.

## **Sialodacryoadenitis Virus and Parker's Rat Coronavirus**

### *Clinical Presentation*

SDAV and Parker's rat coronavirus (RCV-P) are highly contagious, self-limiting RNA viruses of rats belonging to the family Coronaviridae. Experimental infections in mice are possible, but natural infections have not been identified.<sup>1</sup> Rats are susceptible to repeat coronaviral infections that are reduced in severity.<sup>7, 72, 90</sup> In an epidemic, there is normally high morbidity and little or no mortality.<sup>71</sup> Clinical signs may include cervical edema, photophobia, sneezing, chromodacryorrhea, corneal ulceration, and keratitis.<sup>71</sup> In breeding colonies, alterations in the estrous cycle and increased embryonic and neonatal mortality may be present.<sup>86</sup> Severity of clinical disease varies with the strain of rat,<sup>54</sup> and infections in nude (athymic) rats result in a chronic fatal disease.<sup>36</sup> Infection with SDAV enhances *Mycoplasma pulmonis* infection.<sup>76</sup>

Presumptive diagnosis may be on presentation of cervical edema

with chromodacryorrhea. The diagnosis can be confirmed by identifying gross or histologic lesions compatible with SDAV or RCV-P, detecting SDAV or RCV-P antibody in recovered animals (refer to diagnostic laboratories), or performing reverse transcriptase PCR (RT-PCR).<sup>15, 16</sup>

### *Pathology and Pathogenesis*

Gross clinical findings may include edematous parotid or submaxillary salivary glands. Histologically, during the acute phase, coagulative necrosis of the salivary glands may be identified with edema and mixed cellular infiltrate. During the recovery phase, squamous metaplasia may be seen in salivary and Harderian gland ductal and acinar tissue. Lower respiratory lesions may also be found, including tracheitis, bronchitis, bronchiolitis, and focal pneumonia.<sup>71</sup>

Initial infection occurs in nasal passages and is usually confined to the respiratory tract and associated tubuloglandular tissues. The primary site of viral replication is in the nasal mucosa. SDAV generally produces greater lesions in the glandular structures, whereas RCV-P generally produces greater lesions in the respiratory tract.<sup>5, 44</sup> The virus is relatively labile in the environment and is spread by way of contact, aerosols, and fomites; however, virally contaminated materials held at room temperature may remain infectious for up to 2 days.<sup>31</sup> Opportunistic bacteria or other viral agents may exacerbate the infection.

### *Treatment and Control*

In the face of an outbreak, affected rats should be segregated from clinically normal rats to minimize the extent of the outbreak. Supportive care as previously described is most important. Effective sanitation of caging and the surrounding environment is important in limiting the infection during the outbreak in conjunction with colony segregation. Rats are susceptible to reinfection, and periodic outbreaks in a large colony with frequent introductions of new rats may occur.

Eliminating the infection from a breeding colony can be accomplished by selecting breeding stocks that are seropositive for coronavirus.<sup>9</sup> Alternatively, one can prevent the introduction of any naive rats into the colony to maximally expose all members of the colony to the virus and allow for seroconversion. Halting breeding activity for 6 weeks, prohibiting rats from being exposed to other rats, such as at shows, and not introducing any new rats to the colony for a period of 6 weeks is recommended.

Preventing infection in large colonies can be accomplished by establishing a separate housing area (quarantine) where newly introduced rats can be maintained separately for a period of 2 weeks before introducing them to the main colony. Show animals that travel frequently and are placed in areas with high density of rats may serve as sources of infection for the colony at home.



## ***Streptococcus pneumoniae***

### *Clinical Presentation*

*Streptococcus pneumoniae* is a gram-positive diplococcus that can cause severe disease in rats. It has also been cultured from mice that had no evidence of clinical disease.<sup>26</sup> As with most diseases of rats and mice, clinical signs are nonspecific but may include dyspnea, weight loss, and breath sounds such as snuffling. *S. pneumoniae* causes acute rhinitis and can lead to fulminant bronchopneumonia.<sup>41</sup> A common presentation is otitis media. The organism can also cause septicemia in advanced cases, with septic arthritis, meningitis, orchitis, peritonitis, or infection of other organs.

The organism is easily cultured on blood agar, producing alpha-hemolysis; however, proof of respiratory tract infection does not prove disease cause, because the carrier state exists in rats just as in humans. Positive cultures obtained from blood, a body cavity, or an affected organ are more definitive proof of pneumococcal disease.

### *Pathology and Pathogenesis*

Serous to mucopurulent exudates may be found in the nasal turbinates and tympanic bullae at necropsy. In the case of septicemia, fibrinopurulent pleuritis, pericarditis, and peritonitis are common findings.<sup>71</sup> The microscopic findings mirror the gross findings, with fibrinous and neutrophilic infiltrates in a variety of locations. Pulmonary lesions may range from suppurative to fibrinopurulent bronchopneumonia, depending on the chronicity of the disease.

One of the natural hosts for the organism is humans. *S. pneumoniae* colonizes the nasopharynx and spreads to the lungs. From the lungs, the organism spreads into the pleural space and pericardium, then into the blood.<sup>41</sup> Infection may occur by way of aerosol transmission from animal to animal, human to animal, or animal to human. The organism remains viable in the environment for days but can be killed by a number of disinfectants.

### *Treatment and Control*

Antibiotic therapy with agents effective against gram-positive bacteria may be attempted. Cefotaxime administered SQ every 12 hours at 25 mg/kg was reported to be efficacious<sup>82</sup> in the treatment of pneumonia and prevention of the development of meningitis. It is important to note the high rate of carriers found in affected colonies, and treatment of the entire colony to decrease the bacterial burden may be of practical consideration.

## Cilia-Associated Respiratory Bacillus

### *Clinical Presentation*

CAR bacillus is a gram-negative, filamentous rod that can be found in most rodent species and rabbits. Clinical disease has been described in rats as identical to that of severe MRM. Signs are nonspecific and include hunched posture, rough hair coat, decreased movement, and porphyrin staining around the eyes and nares. Although primary disease with this agent was reported in rats,<sup>62</sup> it is most often found as a copathogen, commonly with *Mycoplasma pulmonis*.<sup>17</sup>

A diagnosis of CAR bacillus is difficult to achieve, but the agent should be considered in any case of chronic respiratory disease in the rat. Special staining of histopathologic samples with Warthin-Starry stain or a modified microwave Steiner silver impregnation technique<sup>62</sup> or assessment by PCR diagnostics are available through some commercial laboratories.

### *Pathology and Pathogenesis*

Grossly, lesions associated with CAR bacillus pneumonia are virtually identical to those seen with *M. pulmonis*. Microscopic lesions include chronic suppurative bronchitis with peribronchial lymphocytic cuffing.<sup>71</sup> The organism can be seen upon microscopic examination of Warthin-Starry silver-stained sections. It is a slender, silver-positive bacillus and is located between ciliated respiratory epithelial cells along the apical border. Beyond its predilection to colonize the respiratory epithelium, the pathogenesis of this organism remains unclear.

### *Treatment and Control*

Successful treatment of mice experimentally inoculated with CAR bacillus was reported by treating the drinking water with 500 mg/L of sulfamerazine.<sup>60</sup> There are no published reports of the efficacy of antibiotic treatment of clinically affected rats. The organism is quite hardy, being able to survive freeze-thaw cycles and remain virulent. Environmental removal can be achieved, however, with high-level disinfectants (e.g., chlorine dioxides), given sufficient contact time.

## Bacterial Pathogens of Secondary Significance

### *Klebsiella pneumoniae*

*Klebsiella pneumoniae* is a gram-negative bacillus that is presumed to be part of the normal flora of mice, rats, hamsters, and humans but can be an opportunistic pathogen in mice and rats. It has been suggested that infection of mice and rats may be transmitted from human handlers,

but this has not been proven. Systemic abscesses and granulomatous pneumonia have been reported in mice, and abscesses and draining fistulas have been reported in rats.<sup>43</sup>

### *Pasteurella pneumotropica*

*Pasteurella pneumotropica* is a gram-negative coccobacillus that infects mice, rats, hamsters, guinea pigs, and many other species. It is an opportunistic pathogen that most often affects the skin and adnexal structures but can also cause rhinitis or suppurative bronchopneumonia.<sup>41</sup> The clinical presentation most commonly includes a purulent conjunctivitis or periorbital abscesses. Because of its opportunistic nature, control of this agent is best handled through prevention of factors that decrease host defenses, such as malnutrition and concurrent disease.

### *Bordetella bronchiseptica*

*Bordetella bronchiseptica* is a gram-negative bacillus that is a common inhabitant of the upper respiratory tract of the guinea pig and rabbit. The organism is an opportunistic pathogen in the rat and can cause suppurative rhinitis and multifocal bronchopneumonia.<sup>71</sup> Control is achieved by prevention of exposure to host species.

Other pathogens of concern primarily in mice or rats that are immunocompromised include pneumonia virus of mice (PVM), K virus, *Corynebacterium kutscheri*, and *Pneumocystis carinii*.

## Other Respiratory Conditions

### *Neoplasia*

Primary respiratory tumors in rats are fairly uncommon. There are several tumors that may metastasize to the lungs. Lymphomas and leukemias are common in some stocks of rats, such as large granular lymphocytic leukemia of Fischer 344 rats and mononuclear cell leukemia in Wistar and Wistar-Furth rats.<sup>71</sup> Clinical signs compatible with leukemias are the presenting signs, and the lung lesions may be found secondarily.

## Conditions Confused as Respiratory

### *Chromodacryorrhea*

Chromodacryorrhea is described above in the overview of clinical signs that may be observed in the sick mouse or rat. Although present around the nares, the presence of porphyrin is not indicative of a respiratory infection. Pet owners may describe this condition as dried blood around the nose, and care should be taken to interpret this

description. Generally, chromodacryorrhea is merely a reflection of environmental stress for the animal, which may or may not represent infectious disease.

### *Malocclusion*

All rodents have continuously erupting incisors and are subject to a heritable condition of malocclusion. Overgrown incisors may result in moist facial hair, which could be confused with respiratory secretions. The condition also leads to loss of body weight, a common presentation with chronic respiratory disease. Although not respiratory in nature, this condition may be confused with respiratory conditions and is a matter of veterinary concern. Management involves trimming the incisors with scissors, toenail clippers, or the equivalent and providing a softened diet until the animal recovers. Routine trimming is necessary for the lifetime of the animal, and close monitoring of dental growth is required.

## **RESPIRATORY PATHOGENS IN GUINEA PIGS (*CAVIA PORCELLUS*)**

### ***Bordetella bronchiseptica***

#### *Clinical Presentation*

*Bordetella bronchiseptica* is the most important respiratory pathogen of guinea pigs, to the extent that this infection should always be suspected in a case of guinea pig pneumonia. The causative organism is a small, gram-negative aerobic bacillus that may be carried and shed by up to 20% of guinea pigs in infected colonies.<sup>59</sup> Clinical presentation may be sudden death without antemortem signs, or classic epizootic bronchopneumonia with inappetence, dyspnea, and nasal and ocular discharge. Secondary otitis media may be evidenced by the presence of purulent exudate in the tympanic bullae<sup>71</sup>; metritis or pyosalpinx may also be seen.<sup>75, 79</sup> If animals of mixed ages are kept together, newly exposed young animals often exhibit clinical signs of disease, whereas older inapparent carriers remain clinically unaffected.

#### *Pathology and Pathogenesis*

At necropsy, guinea pigs dying from this infection typically exhibit mucopurulent or catarrhal exudate in the trachea, lower airways, nares, and sometimes the tympanic bullae. The lung lesions are usually cranio-ventral. Although microscopic evidence of fibrinous exudation may be seen in terminal airways, gross fibrinous exudation (typical of streptococcal infection, see below) is not usually present. Whereas guinea pigs of all ages are susceptible to infection, young or stressed animals are more likely to show classic signs. The organism may be readily transmitted by the airborne route<sup>85</sup> and by direct contact or on fomites. Pets of

other species, such as rabbits, cats, and dogs, may act as the source of infection for guinea pigs within a household. In enzootically infected colonies, periodic outbreaks may be caused by immunity dropping below protective levels.<sup>59</sup>

### *Treatment and Control*

Supportive treatment with warmth, subcutaneous fluids (10 to 20 mL/kg every 12 to 24 hours) and antibiotics may be helpful for clinically ill guinea pigs. Antibiotics reported to be effective include chloramphenicol palmitate (50 mg/kg per os [PO] two to three times daily [BID-TID]), chloramphenicol succinate (30 to 50 mg/kg intramuscularly or SQ BID), enrofloxacin (2.5 to 10 mg/kg PO or SQ SID-BID), or sulfa-trimethoprim (15 to 30 mg/kg PO or SQ SID-BID).<sup>37</sup> Practitioners should avoid antibiotics that have been reported to cause gastrointestinal complications in guinea pigs, such as penicillin, erythromycin, and macrolides, including lincomycin and clindamycin.<sup>65</sup> There is a report of the successful use in guinea pigs of *Bordetella* bacterin (Bronchicine, BioCor Animal Health, Omaha, NE) that is manufactured for dogs. The authors gave 0.2 mL intramuscularly (IM), and repeated in 21 days and 6 months.<sup>81</sup> Separation from species that may be inapparent shedders of *Bordetella* organisms, such as rabbits and dogs, is strongly recommended.<sup>40</sup>

## ***Streptococcus pneumoniae***

### *Clinical Presentation*

*Streptococcus pneumoniae* is a lancet-shaped, gram-positive coccus that occurs in pairs or short chains. It causes the disease called *diplococcal* or *pneumococcal pneumonia* in a variety of species.<sup>71</sup> Guinea pigs with this infection look like animals with bordetellosis. This organism is also carried inapparently by a number of species. Clinical presentation is typically bronchopneumonia with signs of inappetence, dyspnea, and nasal and ocular discharge. Secondary sites of infection include the pericardium, the uterus, the middle ear, and the joints, resulting in pericarditis,<sup>92</sup> metritis and abortions,<sup>68</sup> otitis media,<sup>50</sup> and septic arthritis.<sup>91</sup>

### *Pathology and Pathogenesis*

The pathologic hallmark of this infection is fibrin production. Typical lesions are those of fibrinopurulent pleuritis, pericarditis, and bronchopneumonia, with thrombosis of pulmonary vessels in acute cases. Transmission is by aerosols within colonies, and up to 50% of guinea pigs in infected colonies may be carriers, with disease outbreaks occurring in times of stress caused by poor husbandry or malnutrition.<sup>71</sup> Transmission from humans, rats, and other species sharing the environment with guinea pigs is possible.<sup>59</sup>

### *Treatment and Control*

Presumptive diagnosis may be made by demonstration of diplococci on a Gram's stain of respiratory exudate. Treatments recommended include those listed for bordetellosis. Antibiotic treatment of colonies with sulfadiazine and oral tetracycline is reported to control an epizootic but not to eliminate carriers.<sup>88</sup>

## **Pathogens of Secondary Significance**

### *Cytomegalovirus*

Guinea pig cytomegalovirus (GPCMV) is a beta herpesvirus in the same subfamily as viruses of primates, cattle, pigs, horses, mice, and other species. This organism usually produces low-grade, chronic infections. Guinea pigs infected with GPCMV have been used as a model of human CMV infections, and studies of immune-suppressed animals predict that natural immune suppression could result in lung infections by this virus.<sup>58</sup>

### *Cavian Leukemia Virus*

Cavian leukemia is associated with a type C retrovirus. Lymph node enlargement and leukemia could lead to respiratory distress, which could be the primary presentation. Diagnosis is by lymph node aspiration and CBC, and treatment with chemotherapy was reported to be promising.<sup>59</sup>

Guinea pig adenovirus has recently been demonstrated as a cause of lethal pneumonia in laboratory guinea pigs<sup>24a</sup> and may be suspected to exist in the pet population as a cause of severe bronchopneumonia and death.

### *Klebsiella pneumoniae*

This nonmotile, non-spore-forming, gram-negative bacillus is reported to cause epizootics of bacterial pneumonia in guinea pigs,<sup>32</sup> with histopathologic features of fibrinous pleuritis and pericarditis that may be confused with lesions produced by *S. pneumoniae*. Culture and sensitivity of exudate should be used to distinguish the organisms and to select antibiotic treatment. The capability of *K. pneumoniae* to cause abscesses makes the organism useful in testing of therapies for large abscess cavities.<sup>57</sup>

### *Streptococcus zooepidemicus*

This gram-positive, Lancefield group C encapsulated coccus produces the disease in guinea pigs known as "lumps," primarily characterized by cervical lymphadenitis with abscesses. It was reported to cause

fibrinopurulent bronchopneumonia in young animals on occasion, with lesions similar to *Streptococcus pneumoniae*.<sup>71</sup>

## Other Respiratory Conditions

### *Neoplasia*

Primary malignant tumors are rare in guinea pigs, and the majority of pulmonary tumors reported are benign papillary adenomas.<sup>71</sup>

### *Soft Tissue Calcification*

Guinea pigs over 1 year of age may have metastatic calcification in multiple soft tissues, including the lungs. Dietary factors, such as low magnesium and high phosphorus, have been implicated.<sup>71</sup>

## Conditions Confused as Respiratory

### *Vitamin C Deficiency*

Guinea pigs have a congenital deficiency in the enzyme L-gulonolactone oxidase that is needed for synthesis of vitamin C. Improper management, such as feeding of chows made for other rodents or rabbits, or feeding guinea pig chow that is more than 3 months old, may lead to scurvy. Any guinea pig presenting with dyspnea should be checked carefully for signs of subcutaneous hemorrhages, swollen joints, and enlarged costochondral junctions that may result from hypovitaminosis C. This condition may be a stress factor in the development of bacterial pneumonia. Supplementation of vitamin C with fresh food, in drinking water, or parenterally is recommended.<sup>84</sup>

## RESPIRATORY PATHOGENS IN HAMSTERS

### Species

Most pet hamsters are Syrian or Golden hamsters, but some of the other species listed below are seen in pet shops. Clinical descriptions of problems in hamsters refer almost exclusively to Syrian hamsters, and the practitioner should extrapolate to other species with care.

- Mesocricetus auratus*—golden, Syrian hamster
- Cricetulus griseus*—Chinese, or striped hamster
- Cricetulus migratorius*—Armenian or migratory hamster
- Phodopus sungorus*—Dungarian or Siberian hamster
- Cricetus cricetus*—European hamster
- Mystromys albicaudatus*—South African hamster

It may be argued that there are no pathogens of primary significance for the respiratory system of hamsters. Bacterial respiratory infections occur with much less frequency in golden hamsters than in mice, rats, guinea pigs, and rabbits.<sup>29</sup>

### **Salmonella Infections**

Hamsters are very susceptible to salmonellosis, with reports of *S. enteritidis* serotypes *typhimurium* and *enteritidis* the most frequent isolates in this species.<sup>71</sup> Transmission is likely to be from ingestion of contaminated food or bedding, although interspecies transmission is also likely, including the danger of human disease. Pulmonary salmonellosis in hamsters was reported.<sup>39</sup>

### **Mycoplasma Infections**

*M. pulmonis* has been isolated from hamsters, but its pathogenic potential is not known.<sup>71</sup> *M. pneumoniae* was reported to be zoonotic, with demonstration of the transmission from pet Syrian hamsters to children in a classroom in Hungary.<sup>62a</sup> *M. pneumoniae* infection in hamsters was used to evaluate the potency of *M. pneumoniae* vaccines.<sup>3</sup>

### **Treatment of Bacterial Infections**

The extreme sensitivity of hamsters to develop antibiotic-induced colitis or enteritis should make any practitioner reluctant to treat this species with this class of drugs. Specific antibiotics associated with this condition, caused by overgrowth of *Clostridium difficile* and subsequent toxin production, include a wide range of drugs, some of which are advocated for treatment of the condition.<sup>80</sup> The safest antibiotics to use in hamsters are likely to be enrofloxacin, chloramphenicol, or trimethoprim/sulfamethoxazole.<sup>37</sup>

### **Sendai Virus**

Hamsters, along with mice and rats, are considered one of the natural hosts of this RNA virus of the family Paramyxoviridae, also known as parainfluenza-1. However, lesions are often subclinical and similar to those seen in rats and resistant strains of mice: mild necrotizing bronchiolitis and focal interstitial pneumonia.<sup>71</sup>

### **Other Respiratory Conditions**

#### **Neoplasia**

Spontaneous neoplasia of the respiratory tract of hamsters is rare, found in only 3% of animals surveyed in an intensive study.<sup>74</sup> Tumor



types described include polyps, bronchogenic adenomas, and bronchial carcinomas.

### *Atrial Thrombosis*

Hamsters with this disorder may present with severe dyspnea and pulmonary congestion. The condition is more common in aged females and is often associated with amyloidosis. This is a common cause of death in older hamsters and may be discovered on necropsy by appreciation of pale, adherent thrombus in the left atrium and auricle.<sup>71</sup> Treatment with cardiac drugs, including diuretics, digoxin, angiotensin-converting enzyme inhibitors, and calcium-channel blockers, may be attempted.<sup>24</sup>

## **Conditions Confused as Respiratory**

### *Malocclusion*

See discussion of this topic in the section on mice and rats.

### *Antibiotic Sensitivity*

Septic, dehydrated, painful hamsters with antibiotic-associated enteritis or colitis may present with dyspnea, a hunched appearance, and behavioral abnormalities that could be confused with respiratory disease.

## **RESPIRATORY PATHOGENS IN GERBILS (*MERIONES UNGUICULATUS*)**

As with hamsters, it is questionable if any pathogens are considered of primary significance for the respiratory system of the gerbil. No viral pathogens have been reported.<sup>38, 71</sup> Bacterial diseases of gerbils that may cause respiratory signs include *Clostridium piliforme* (formerly known as *Bacillus piliformis*), the causative agent of Tyzzer's disease. Gerbils are extremely sensitive to this agent and may be used as sentinels for the presence of it.<sup>33</sup> Although this is primarily a disease of the liver, intestines, and heart, rapid death in some gerbils may be preceded by a peracute dyspneic phase that could be mistaken for respiratory disease.

*Bordetella bronchiseptica* infects gerbils experimentally, causing severe respiratory disease, but it has not been reported as a natural infection. Caution is indicated regarding contact between gerbils and the species that may shed this organism, such as guinea pigs and rabbits.<sup>71</sup>

## Conditions Confused as Respiratory

### *Sore Nose*

This condition presents as a moist, exudative dermatitis around the nose, and possibly other parts of the body. There is a correlation between the presence of sore nose and isolation of  $\beta$ -hemolytic *Staphylococcus aureus* from the lesions.<sup>10</sup> Prevention of self-grooming of secretions from the Harderian glands (with small Elizabethan collars) can reproduce the condition.<sup>27</sup> This finding explains the experience of gerbil experts who find the problem preventable by the use of sand, kitty litter, or other dry substrate in the caging, which helps the animal to self-groom and prevent build-up of Harderian gland secretions.

## RESPIRATORY PATHOGENS IN RABBITS (*ORYCTOLAGUS CUNICULUS*)

Infectious upper respiratory disease in the rabbit is termed *snuffles*. It is the most common disease observed in pet rabbits. Snuffles typically causes nasal discharge, sneezing, and conjunctivitis. The agent most commonly associated with these symptoms is *Pasteurella multocida*; however, other agents may be responsible and are discussed below.

The most frequently observed sign of upper respiratory disease in the rabbit is nasal discharge. Exudate is generally present around the nose and on the front legs, caused by grooming. Because rabbits are such proficient groomers, staining of the fur around the face and limbs may be the only evidence of nasal discharge and rhinitis. Lower respiratory tract disease is often associated with systemic signs of anorexia, lethargy, fever (normal rabbit temperature is 101.3 to 104°F), dyspnea, tachypnea (normal respiratory rate is 30 to 60 breaths per minute), and possibly cyanosis. It should be noted that the rabbit is an obligate nasal breather, and partial occlusion of the nostrils with nasal discharge can cause significant respiratory compromise.

Thoracic auscultation should be performed on any rabbit with signs of respiratory disease. When auscultating a rabbit, the clinician should be aware that there is normally a significant amount of referred upper respiratory noise. Auscultation may reveal evidence of severe pneumonia or pulmonary consolidation. In addition, thoracic radiography should be performed to evaluate the extent of respiratory tract involvement. CBCs and serum biochemistry panels may be normal. The diagnostic test that frequently yields the most significant information for respiratory disease in the rabbit is culture and sensitivity of upper or lower airways. A nasal swab of exudate can be obtained for upper airway culture. Culture of the lower airway in a rabbit is more difficult and may involve significant risk to the already compromised patient. The amount of stress a compromised rabbit can endure is less than that of dogs and cats. This should be considered prior to examination of any

sick rabbit. A more complete discussion of laboratory diagnostic testing and interpretation for the rabbit has been published.<sup>30</sup>

## ***Pasteurella multocida***

### *Clinical Presentation*

*Pasteurella multocida* infection commonly causes sneezing and serous or mucopurulent nasal discharge (snuffles). Nasal discharge may be mild during the initial infection and go unnoticed. Recurring episodes of upper respiratory disease are common, or infection may progress from rhinitis to pneumonia. The organism may also spread systemically. The most common signs of pasteurellosis in rabbits, in descending order, are rhinitis, conjunctivitis, pneumonia, otitis media and interna, abscesses, genital tract infections, and septicemia.<sup>21</sup> None or all of these conditions may be present in a rabbit infected with *P. multocida*.

Culture and sensitivity results of nasal swabs and respiratory exudates are the best way to diagnose *P. multocida*. Serology may be used for cases when infection is suspected in organs for which cultures are not attainable (such as otitis media or interna, internal abscesses) or when culture results are negative; however, positive serology only indicates exposure to *P. multocida*, not necessarily infection. Paired samples (2 weeks apart) are needed to establish rising titers.

### *Pathology and Pathogenesis*

*Pasteurella multocida* is a gram-negative coccobacillus. Transmission occurs by aerosol, direct contact, or fomites. It is most likely to be transmitted by contact with an acutely infected animal.<sup>23</sup> The nasal/pharyngeal cavity is the initial site of colonization in the rabbit.<sup>19</sup> After nasopharyngeal colonization, hematogenous and local spread occur. The incidence of *P. multocida* infection increases with age, as does the occurrence of clinical signs.<sup>20, 34, 66</sup> Infected rabbits may carry this organism for an indefinite time without any clinical evidence of infection. The prevalence of *P. multocida* in pet rabbits is unknown but is believed to be high.

Pathologic changes associated with pasteurellosis involving the head and respiratory tract are chronic rhinitis, suppurative otitis media and conjunctivitis, and cranioventrally located acute necrotizing, fibrinopurulent bronchopneumonia with possible fibrinous pleuritis, and pericarditis.<sup>71</sup>

### *Treatment and Control*

Prior to discussing any treatment options in the rabbit, the clinician must be familiar with the potential to cause severe iatrogenic gastrointestinal disease by the use of inappropriate antibiotics that cause intestinal disruption of the normal bacterial flora (dysbiosis). The use of clinda-

mycin, lincomycin, penicillin, ampicillin, amoxicillin, amoxicillin-clavulanic acid, cephalosporins, and erythromycin was associated with enteritis.<sup>19</sup> The antibiotics commonly used in the rabbit that may be safer are trimethoprim-sulfamethoxazole, enrofloxacin, and chloramphenicol. Antibiotic administration should be discontinued and the patient re-evaluated if signs of enteritis (anorexia, soft or abnormal feces) are discovered. Recent reviews of antibiotic use in rodents and rabbits should be consulted for a more complete discussion of enteric dysbiosis.<sup>19, 42</sup>

Treatment of pasteurellosis can be difficult, because it may be disseminated throughout the body. Antibiotic therapy should be based on culture and sensitivity results. After culture samples have been obtained, empirical antibiotic treatment can begin. Enrofloxacin is commonly used and may be the best choice for treatment. Treatment should continue for at least 2 weeks and possibly longer for recurrent infections. Antibiotic therapy may lead to resolution of clinical signs, but elimination of the organism is difficult.<sup>61, 83</sup> Importantly, enrofloxacin may prevent the passage of *P. multocida* to the kits when the does are treated prior to kindling.<sup>83</sup> The client should be informed that it is very difficult to eliminate *P. multocida* from the patient and that recrudescence of clinical signs is likely.

Appropriate antibiotic therapy, good nutrition, and supportive care should all be part of the therapeutic plan. Supportive care includes maintaining hydration (60 to 100 mL/kg/d), cleaning the animal and environment, eliminating stress, and providing high-quality nutrition and oxygen therapy if needed.

Control of *Pasteurella* in pet rabbits should be based on preventing contact with other potentially infectious rabbits and control of fomites, such as people and equipment, that have come in contact with infected animals. If the *Pasteurella* status of the rabbit is unknown, it should be considered positive because of the high prevalence of this organism in conventionally housed rabbits. There has been considerable work in the development of a vaccine for *P. multocida* in the rabbit. A recent study reports 100% successful protection from death with an experimental vaccine.<sup>46</sup>

## ***Bordetella bronchiseptica***

### *Clinical Presentation*

Unlike *Pasteurella multocida*, *Bordetella bronchiseptica* is usually localized to the respiratory tract. *Bordetella* infection may present as mucoid rhinitis or pneumonia. It rarely acts as a primary pathogen; however, *B. bronchiseptica* may act as a copathogen with *P. multocida* to cause respiratory disease.<sup>21</sup> Outbreaks have been observed in which *B. bronchiseptica* is believed to be the sole agent responsible for respiratory disease.

Clinical disease, however, is relatively rare. *B. bronchiseptica* is diagnosed by identifying clinical signs and culturing the organism.

Because *B. bronchiseptica* may be a normal inhabitant of the respiratory tract of the rabbit, a relatively pure culture associated with clinical signs is necessary to confirm a diagnosis of bordetellosis. Mixed cultures of *B. bronchiseptica* and *P. multocida* probably indicate disease caused by *P. multocida*, because of its increased pathogenicity. Serology is available for *B. bronchiseptica*; however, it is probably not useful in the diagnosis of clinical cases because of the high prevalence of the organism in clinically normal animals.

### *Pathology and Pathogenesis*

*B. bronchiseptica* is a gram-negative coccobacillus. Transmission occurs by direct contact, aerosolization, and contact with fomites. The prevalence of infection in rabbit colonies is high (approximately 75%) and increases with age.<sup>19, 20, 34</sup> *B. bronchiseptica* is thought to be a potential pathogen of the respiratory tract of rabbits, especially at 4 to 12 weeks of age.<sup>71</sup> Pathologic changes associated with *B. bronchiseptica* infection are suppurative bronchopneumonia and interstitial pneumonitis.<sup>71</sup>

### *Treatment and Control*

See the section on treatment of *P. multocida* above for a discussion on appropriate antibiotic use. Treatment of *B. bronchiseptica* infections should be based on culture and sensitivity results and the provision of supportive care as discussed for *P. multocida*.

## **Calicivirus**

An RNA virus in the family Caliciviridae causes rabbit hemorrhagic disease. One recent outbreak in Iowa was responsible for the death of 25 of 27 rabbits in a rabbitry.<sup>67</sup> No other cases have been reported in the United States, but the disease has been observed in Mexico.<sup>35</sup> Clinical signs are often absent because of the acute nature of the disease; however, when present, they may consist of fever (105°F and greater), rapid respiration, cyanosis, epistaxis, anorexia, diarrhea, recumbency, and neurologic signs.<sup>13, 19</sup> Morbidity and mortality can reach as high as 90% to 100%, and death usually occurs in 2 to 3 days. The disease occurs in adult rabbits over 2 months of age, with young rabbits left unaffected.<sup>13</sup> Pathologic changes are consistent with multiorgan hemorrhage (particularly in the lungs) and disseminated intravascular coagulopathy.<sup>19</sup> Suspect cases should be reported to US Department of Agriculture Animal Plant Health Inspection Service, Veterinary Services, Emergency Programs, at telephone number 800-940-6524. A question-and-answer sheet and fact sheet are posted at the website [www.aphis.usda.gov/vs/ep/index.html](http://www.aphis.usda.gov/vs/ep/index.html).

### **Staphylococcus Infections**

*Staphylococcus aureus* is a common, commensal, gram-positive coccus of the respiratory tract of rabbits, but it has been associated with disease in the upper and lower respiratory tract. The clinical presentation and pathologic changes of staphylococcal infection usually can not be distinguished from other agents of bacterial respiratory disease, and reliance on culture and sensitivity results is necessary for diagnosis and treatment. A therapeutic plan as described above for *Pasteurella* infection should be followed.

### **CAR Bacillus**

CAR bacillus is a gram-negative filamentous rod that infects the upper respiratory tract of a variety of laboratory species. It can be found to naturally infect the upper respiratory tract of rabbits.<sup>18, 53</sup> Various studies have examined the presence of CAR bacillus in rabbits. In these studies, no gross lesions were observed, and histopathologic lesions consisted of either mild inflammatory changes to the upper respiratory tract<sup>53</sup> or no changes associated with infection.<sup>78</sup> No naturally occurring clinical disease has been reported.

### **Other Respiratory Pathogens**

Other bacterial agents have been associated with respiratory disease in the rabbit. Pulmonary thrombotic abscesses have been reported caused by *Fusobacterium necrophorum*, but the occurrence is rare.<sup>21, 77</sup> *Mycobacterium bovis*, *M. avium*, and *M. tuberculosis* have been reported in rabbits but are also considered rare.<sup>21</sup> Clinical mycobacteriosis would be similar to that seen in other species. *Francisella tularensis* (tularemia) may cause pneumonia.<sup>25</sup> Tularemia usually presents as sudden death and is considered a rare disease in domestic rabbits but is more common in wild rabbits. Tularemia is zoonotic, and appropriate precautions should be taken with a suspected case.

Other bacterial agents that have been associated with upper and lower respiratory disease in the rabbit include *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *M. bovis*, *Pasteurella pneumotropica*, *Chlamydia* spp, and *Pseudomonas aeruginosa*.<sup>19, 21, 71</sup> These agents are considered rare causes of respiratory infection in the rabbit.

Aspergillosis is rare in the domestic rabbit. *Aspergillus fumigatus*, *A. niger*, and *A. flavus* have all been associated with clinical disease and may present as cachexia and dyspnea.<sup>4</sup> Gross pathologic findings consist of pulmonary granulomas, and silver or periodic acid-Schiff (PAS) staining of affected tissue reveals septate hyphae.<sup>71</sup>

## Other Diseases Affecting the Respiratory Tract

### *Neoplasia*

Primary pulmonary neoplasia in the rabbit is rare; however, metastatic neoplasms can affect the respiratory system. The most common tumor of the rabbit is uterine adenocarcinoma, and it does metastasize to the lung. Metastasis usually occurs late in the course of the disease, within 1 to 2 years.<sup>70</sup> Radiographs should be obtained of any rabbit with uterine adenocarcinoma to determine if metastatic lung disease is present. A recent report of hypertrophic osteopathy in a domestic rabbit was found associated with metastatic uterine adenocarcinoma of the lung.<sup>22</sup>

Thymomas have been reported in the domestic rabbit and, although not involving the respiratory tract directly, may cause signs of dyspnea and hyperpnea.<sup>14, 52, 87</sup> It should be noted that the thymus of the rabbit normally remains large into adulthood.

### *Allergic Disease*

Respiratory disease manifested as rhinitis and chronic bronchitis was associated with exposure to antigens in the environment.<sup>19</sup> This fact should be considered in a differential diagnosis for upper respiratory disease not caused by infectious agents.

### *Cardiovascular Disease*

Cardiovascular disease in the rabbit should be considered for any rabbit with signs of respiratory distress. Diagnostic and treatment plans of heart disease in the rabbit are the same as for other companion animal species.

### *Heat Stress*

The rabbit is more susceptible to heat stroke than other species. Temperatures above 85°F predispose rabbits to hyperthermia. The recommended temperature range for housing rabbits is 61°F to 72°F.<sup>40</sup> Signs consistent with heat stress are tachypnea, hyperthermia, and prostration. As the condition progresses, hemorrhage may be seen from the nose and oral cavity. Prompt attention should be given to these patients to cool their body temperature. A poor prognosis should be relayed to the owners.

## CONCLUSIONS

A review of respiratory diseases of rodents and rabbits has been given, with emphasis on pathogens of primary significance. These in-

clude Sendai virus and *Mycoplasma pulmonis* in mice and rats, SDAV/RCV-P and CAR bacillus in rats, *Streptococcus pneumoniae* in rats and guinea pigs, *Bordetella bronchiseptica* in guinea pigs and rabbits, and *Pasteurella multocida* in rabbits. Treatment of individual pets should focus on supportive care with warmth, fluids, good husbandry, and antibiotics that are judged likely to help more than harm. Treatment of colonies should focus on precise diagnosis based on species-specific diagnostic techniques. Practitioners at veterinary schools or exotic animal practices are important sources of information and referral sources for individual owners. Diplomates of the American College of Laboratory Animal Medicine (<http://www.aclam.org>) or members of the American Society of Laboratory Animal Practitioners (<http://www.aslap.org>) are good sources of information relating to colony management and advanced diagnostics.

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## APPENDIX

### Laboratories with Experience in Rodent Species

AnMed Biosafe  
 7642 Standish Place  
 Rockville, MD 20855  
 Tel: (301) 762-0366  
 Fax: (301) 762-7438

Charles River Laboratories  
 251 Ballardvale Street  
 Wilmington, MA 01887  
 Tel: (508) 658-6000  
 Fax: (508) 658-7132  
<http://www.criver.com>

University of Missouri Research Animal  
 Diagnostic and Investigative Laboratory  
 1600 East Rollins  
 Columbia, MO 65211  
 Tel: (800) 669-0825  
 Fax: (573) 884-7521  
<http://www.hsc.missouri.edu/~radil/>

Microbiological Associates  
 9900 Blackwell Road  
 Rockville, MD 20850  
 Tel: (301) 738-1000

Sound Diagnostics  
 1222 NE 145th Street  
 Seattle, WA 98155-7134  
 Tel: (206) 363-0787