Respiratory System Diseases of Nonhuman Primates

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Chapter Outline

INTRODUCTION

The respiratory system is one of the most commonly affected systems in reports describing nonhuman primate disease, pathology, and/or clinical management. Such general papers include data pertaining to prosimians (Kohn and Haines, 1982; Brockman et al., 1988; Feeser and White, 1992), New World primates (Nelson et al., 1966; Deinhardt et al., 1967; Chapman et al., 1973; Chalmers et al., 1983; Lehner, 1984; Richter, 1984; Tucker, 1984; Abee, 1985; Kalter, 1985; Gozalo and Montoya, 1990, 1992; Potkay, 1992; Valverde et al., 1993; Weller, 1994; Baer, 1994), Old World primates (Keeling and Wolf, 1975; Kim and Kalter, 1975a; Schmidt, 1978; Ensley, 1981; Henrickson, 1984; Adang et al., 1987; Courtenay, 1988; Munson and Montali, 1990; Janssen, 1993), or primates in general (Lapin and Yakovleva, 1963; Fiennes et al., 1972a, 1972b; Martin, 1978; Benirschke, 1983; Griner, 1983; Padovan and Cantrell, 1983; Wallach and Boever, 1983; Schmidt et al., 1986; Lowenstine, 2003). Tables 9.1 and 9.2 summarize the magnitude and support the importance of respiratory disease in nonhuman primates. Respiratory system structure itself is highly complex. It has evolved to meet a variety of physiologic demands in which the basic physical requirement is intimate contact between large volumes of air and blood, which brings with it a high potential for exposure to a myriad of potentially damaging agents carried in the air or blood. An understanding of general respiratory system structure, function, and disease, as well as associated diagnostic approaches and reported respiratory problems in nonhuman primates, is essential for any individual involved in primate medicine.

RESPIRATORY SYSTEM STRUCTURE AND FUNCTION

An overview of general respiratory system structure and function can provide a foundation for understanding respiratory vulnerability and response to injury, as well as associated diagnostic and therapeutic methods. Good resources can be found in a comparative lung anatomy monograph by Parent (1992) and in pathology texts (Stookey and Moe, 1978; Dungworth, 1993; Caswell and Williams, 2007; Husain, 2010; Lingen, 2010), including a primate pathology monograph (Scott, 1992b). Additional sources include papers by Boatman et al. (1979) and Boyden (1976).

Structural and Functional Features of the Respiratory System

Upper Respiratory System

The upper respiratory system includes the nasal cavities, paranasal sinuses, nasopharynx, pharynx, larynx, trachea, and bronchi. In a number of primate species, laryngeal diverticula, also called air sacs, laryngeal sac, or throat pouch, are also present (Hill, 1960; Hilloowala, 1971; Swindler and Wood, 1982). A report by Harkema (1991) discusses comparative nasal airway anatomy, including that of primates. Upper respiratory tract function includes air exchange and filtration, separation of food and liquids from the air stream as it enters the tracheobronchial tree, vocalization, and senses of taste, smell, and hearing. This section addresses anatomy and function related to respiratory disorders.

The nasal cavities are bone-encased airways divided by the nasal septum and include osseous and cartilaginous structures, the turbinates. Nasal cavity mucosa includes four conspicuous, distinct epithelial types: stratified squamous epithelium (SE), transitional epithelium (TE), ciliated pseudostratified respiratory epithelium (RE), and olfactory epithelium (OE), as well as a recently described fifth form: lymphoepithelium (LE), which overlies nasal-associated lymphoid tissue (NALT). Respiratory epithelium (RE) includes ciliated, mucous, nonciliated columnar, cuboidal,

TABLE 9.1 Differential Diagnosis of Primate Respiratory Disease: General Diseases/Syndromes

Disease/Lesion	Etiology	Clinical Signs		Reported Species	Comments
		Respiratory	Other		
Rhinitis, nasal polyposis, and sinusitis	Viruses, allergens, irritant volatile gases, dust, very low atmospheric humidity, certain parasites	Sneezing, nasal discharge, epistaxis, open mouth breathing, occasional cough	Facial swelling, epiphora	Macaques, chimpanzees	
Epistaxis	Trauma, *Moraxella* (*Branhamella*) *catarrhalis,* see rhinitis/ sinusitis	Nasal hemorrhage		Macaques especially *M. fascicularis*	*Branhamella catarrhalis* synonyms *Moraxella catarrhalis, Neisseria catarrhalis* Zoonotic potential
Nasal cavity foreign body		Sneezing, unilateral nasal discharge, gagging, and retching	None noted in published reports	Macaques, chimpanzees	
Trachiobronchial foreign body		Paroxysmal nonproductive coughing or respiratory distress	Fever, anorexia, depression, and weight loss	Macaques, chimpanzees	
Cleft palate	Congenital anomaly	Nasal regurgitation	Trouble nursing		Susceptible to secondary bacterial or fungal rhinitis and aspiration pneumonia
Airsacculitis	*Klebsiella pneumoniae, Pseudomonas aeruginosa, Pasteurella multocida,* other Gram-negative and Gram-positive enteric organisms	Nasal discharge, intermittent cough, rapid, shallow breathing patterns	Cervical swelling, halitosis, lethargy, anorexia	Owl monkeys, pig- tail macaques, baboons, chimpanzees, pygmy chimpanzees, gorillas, orangutans	Aspiration and secondary pneumonia
Asthma	(1) Extrinsic asthma: extrinsic antigen (2) Intrinsic asthma: respiratory tract infection and inhaled irritants	Dyspnea, coughing, and wheezing; nonproductive cough or exertional dyspnea	None noted in published reports	*Macaca fascicularis,* chimpanzees	(1) May be precipitated by cold, stress, or exercise (2) Chronic disease sequelae may include emphysema, chronic bronchitis or pneumonia, or cor pulmonale and heart failure

(*Continued*)

TABLE 9.1 Differential Diagnosis of Primate Respiratory Disease: General Diseases/Syndromes—cont'd

Disease/Lesion	Etiology	Clinical Signs		Reported Species	Comments
		Respiratory	Other		
Neonatal respiratory distress syndrome	Pulmonary surfactant deficiency	Tachypnea, dyspnea	Tachycardia, cyanosis	*Macaca nemistrina*	Mechanical ventilation and oxygen toxicity can give rise to a subacute or chronic condition called bronchopulmonary dysplasia
Pulmonary edema	Left-sided or bilateral cardiac failure (cardiogenic edema), hypervolemia, acute brain injury, corrosive gases (including 80–100% oxygen), systemic toxins, endotoxins, and shock-like states	Tachypnea, dyspnea	Tachycardia, cyanosis		
Pulmonary thrombosis and embolism	Bacterial emboli, fat emboli, hypercoagulation states, endothelial damage, tumor emboli	Often clinically inapparent; dyspnea, tachypnea	Tachycardia	*Macaca fascicularis*	Types of emboli bring with them a variety of possible sequelae
Adult respiratory distress syndrome	Sepsis syndrome, gastric content aspiration, toxic fumes inhalation, oxygen toxicity, near drowning, pulmonary contusion, drugs including heroin, salicylate, and paraquat, pneumonitis (bacterial, viral), pancreatitis, multiple transfusions, fat embolism, amniotic fluid embolism	Respiratory insufficiency	Cyanosis, tachycardia and severe arterial hypoxemia that is not responsive to oxygen therapy	*Macaca nemestrina*	
Diaphragmatic hernia	Congenital, trauma	Low-grade respiratory signs, possibly associated with exercise or posture (recumbency)	Episodic gastrointestinal distress	Baboons, chimpanzees, rhesus monkeys, squirrel monkeys, golden lion tamarins	Presence of subclinical hernia may be unmasked by the development of secondary problems (see text)

TABLE 9.2 Differential Diagnosis of Primate Respiratory Disease: Infectious Diseases

Etiology	Disease	Clinical Signs		Reported Species	Comments, Including Zoonotic Potential
		Respiratory	Other		
Virus diseases					
Respiratory syncytial virus	Chimpanzee coryza	Rhinorrhea, cough, sneezing	Fever	Chimpanzees, bonnet macaques	(1) Infections in very young animals may lead to lower respiratory tract involvement, principally bronchitis; can predispose to pneumococcosis, pertussis, or other bacterial infections (2) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans
Paramyxovirus - 1 (parainfluenza - 1), PMV-2, and PMV-3 (parainfluenza 2, 3)		Upper respiratory signs: mild serous or occasionally purulent nasal exudate	Systemic illness and death (associated with severe interstitial pneumonia)	Marmosets, chimpanzees, gorillas, orangutans, macaques, African green monkeys	(1) Predisposes to pneumococcosis, pertussis, or other bacterial infections (2) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans
Measles (rubeola)	Measles	Rhinorrhea, cough	Maculopapular rash, fever, conjunctivitis, depression, dehydration, facial edema	New World and Old World monkeys and apes	(1) Gastrointestinal lesions or immunosuppression rather than respiratory disease can be the most important sequelae (2) Zoonotic potential: risk of human to nonhuman primate infection plus monkey to human transmission
Influenza A and B	Influenza	Rhinorrhea, dyspnea, tachypnea, cough, sneezing	Depression, fever, lethargy, anorexia	Capuchins, squirrel monkeys, owl monkeys, macaques, baboons, gibbons, chimpanzees	(1) Most reports are for experimental infection. Gibbon infection was a spontaneous outbreak (2) Sequela can include pneumococcal super-infection with lethal outcome (3) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans
Human metapneumovirus		Nasal discharge, cough	Mortality	Chimpanzees, cynomolgus macaques (experimental)	(1) Histology (experimental, macaques) (2) Anthropozoonosis causing outbreaks in free-ranging chimpanzees. All monkeys and apes likely susceptible
Adenoviruses		Nasal discharge, cough tachypnea	Conjunctivitis, and erythema, skin rash, facial edema, cyanosis, diarrhea	Macaques	(1) Histology: bronchiolar and alveolar epithelium necrosis and enlarged nuclei filled with amphophilic to basophilic inclusions (2) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans

(Continued)

TABLE 9.2 Differential Diagnosis of Primate Respiratory Disease: Infectious Diseases—cont'd

Etiology	Disease	Clinical Signs		Reported Species	Comments, Including Zoonotic Potential
		Respiratory	Other		
Herpesvirus simiae	B virus infection	Purulent nasal exudate	Oral ulcers, splenomegaly, hepatomegaly	Bonnet monkeys	(1) Histology: hemorrhagic interstitial pneumonia (2) Endemic simian type D retrovirus infection (SRV- 1) also present in the affected population (3) Zoonotic potential: infection in humans can be fatal
Herpesvirus SA8 and *Herpesvirus papio-2*.		Not noted in published reports	None noted in published reports	African green monkeys, baboons	(1) Histology: necrotizing bronchiolitis and interstitial pneumonia (2) No known zoonotic potential
Varicella-zoster-like herpesviruses		Not noted in published reports	Vesicular rash	Macaques, African green monkeys, patas monkeys, great apes	(1) Histology: pulmonary edema and alveolar septa necrosis with marked fibrin exudation (2) Zoonotic potential: minimal risk of human to nonhuman primate infection (3) Human varicella can infect apes
Rhinoviruses		Sneezing, rhinorrea, often clinically inapparent	Not noted in published reports	Chimpanzees	(1) Experimental inoculation in other species has been unsuccessful (2) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans
SARS coronavirus	Severe acute respiratory syndrome	Dyspnea	Fever, lethargy, death	Rhesus and cynomolgus macaques, common marmosets, African green monkeys (experimental)	A human disease. No spontaneous nonhuman primate cases, but virus has broad host range. Important model systems
Simian immunodeficiency virus (SIV)	Retroviral giant cell pneumonia	Generally no specific respiratory signs	Anorexia, weight loss, inactivity	Macaques	(1) Histology: histologic examination reveals thickening of alveolar septa, marked exudation of macrophages, lesser amounts of proteinaceous material, and large numbers of syncytial giant cells (2) Lentiviruses of cercopithecine monkeys are indigenous to African monkeys of the genera *Cercopithecus, Cercocebus, and Papio* (*Mandrillus*). Very low pathogenicity in African species (3) Zoonotic potential: rare reports of human seroconversion; no associated human disease reported, closely related to HIV-2

Bacterial diseases					
Mycobacterium tuberculosis, and *M. bovis*	Tuberculosis	Usually clinically inapparent, cough with pulmonary parenchymal loss, dyspnea with advanced disease	Low-grade fever, weakness, weight loss	New World and Old World monkeys, apes. Fewer reports in prosimians	Zoonotic potential: risk of human to nonhuman primate infection. Usual subclinical nature plus potential disease severity make this a disease routinely screened for in nonhuman primate populations and associated humans
Streptococcus pneumoniae	Pneumococcal infection	Cough, dyspnea	Anorexia, weakness, facial edema	Macaques, great apes	(1) Lesions include lobar pneumonia, bronchopneumonia, empyema, and upper respiratory infection (middle ear, sinuses) as well as severe meningitis or brain abscesses (2) Clinical disease associated with the presence of other predisposing problems, such as stress, inclement weather, or viral respiratory infections (3) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk of primate to humans
Streptococcus equi var. *zooepidemicus*	Upper respiratory infection	Purulent rhinitis progressing in some case to pneumonia with respiratory distress	Conjunctivtis, pharyngitis, lethargy	Rhesus macaques	Transmissible within group, but not to groups in nearby cages
Klebsiella pneumoniae		Nasal discharge, congestion	Fever, anorexia, weight loss, unexpected death without clinical signs	Macaques, chimpanzees	(1) Lesions include pneumonia (lobular or lobar), urinary tract infection, and miscellaneous septic lesions, including sinusitis, meningitis, and otitis (2) Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans
Bordetella pertussis	Whooping cough	Coughing, sneezing, nasal discharge	Peripheral lymphocytosis, malaise, weight loss, mild fever, subcutaneous emphysema, convulsions	Chimpanzees	Zoonotic potential: risk of human to nonhuman primate infection. Minimal risk to humans
B. bronchiseptica		Bilateral mucopurulent nasal discharge, occasional dyspnea	Torticollis, seizures, mild fever, sudden death	Prosimians, New World and Old World monkeys	(1) Generally, cases have occurred in association with potentially weakened pulmonary defenses (stress, virus, age, etc.) (2) Zoonotic potential: common part of respiratory mucosa microflora. Minimal risk to humans

(*Continued*)

TABLE 9.2 Differential Diagnosis of Primate Respiratory Disease: Infectious Diseases—cont'd

Etiology	Disease	Clinical Signs		Reported Species	Comments, Including Zoonotic Potential
		Respiratory	Other		
Nocardia sp.	Nocardiosis	Productive cough	Fever	Macaques, orangutans	(1) Signs associated with pulmonary nocardiosis are often nonspecific and even subclinical until late in the disease course (2) Zoonotic potential: not transmitted between individual animals or humans. Can be found as a primary infection, but often is noted as an apparent opportunist
Pasteurella multocida or *P. hemolytica*	Pasteurellosis	Dyspnea	Anorexia, lethargy	Goeldi's monkeys, owl monkeys, patas monkeys	(1) Predisposing factors include stress induced by such factors as transportation, crowding, climatic changes, or respiratory viral infections (2) Zoonotic potential: common part of respiratory mucosa microflora. Minimal risk to humans
Pseudomonas aeruginosa		Air sacculitis, distension of air sacs, cough, nasal discharge, halitosis, pneumonia	Enteritis	Orangutans, Old World monkeys	(1) In humans a cause of both nosocomial and community acquired pneumonia. Infants, elderly, and individuals with cystic fibrosis or immune suppression most susceptible. (2) Environmentally acquired (3) Pneumonia-enteritis complex
Mycotic diseases					
Coccidioides immitis	Coccidioidomycosis	Often clinically inapparent, cough, dyspnea	Fever, weakness, weight loss, convulsions, urine retention, diarrhea	Ring-tailed lemurs, macaques, baboons, gorillas, all species likely susceptible	(1) Geographic restriction in U.S. "Lower Sonoran life zone" and has occurred in outdoor-housed laboratory and zoo primates (2) Zoonotic potential when handling infected tissue, via parenteral inoculation or inspiration of aerosolized infectious material (fresh tissues pose less threat)
Histoplasma capsulatum	Histoplasmosis	Similar to coccidioidomycosis	Similar to coccidioidomycosis	Squirrel monkeys, de Brazza's monkeys	Zoonotic potential when handling infected tissue, via parenteral inoculation or inspiration of aerosolized infectious material
Cryptococcus neoformans, C. gattii	Cryptococcosis	Dyspnea	Neurologic signs, depression, death without prior clinical signs	Douc langurs, proboscis monkeys, purple-faced langur, squirrel monkey, Allen's swamp guenon	(1) Clinical signs usually unapparent and when present, nonspecific (2) Meningitis is a very common complication

Pneumocystis carinii	Pneumocystis pneumonia, pneumocystosis	Dyspnea, nonproductive cough	Fever, anorexia	Marmosets, owl monkeys, macaques, chimpanzees, many other species	(1) Associated with SIV infection in macaques (2) Considered an opportunist in immune-compromised hosts (3) Human infection is a distinct species *P. jirovecii*. Epidemiologic and experimental data support the occurrence of airborne, possible horizontal, transmission in humans and animals, including nonhuman primates
Blastomyces dermititidis	North American blastomycosis	Labored breathing, harsh cough	Depression, anorexia	Rhesus macaques	(1) Uncommon: one report in the literature (2) Endemic in southern and midwestern parts of the U.S. (3) Association with moist environments and bird and bat droppings
Parasitic diseases					
Toxoplasma gondii	Toxoplasmosis	Found acutely moribund with audible rales and fluid, blood, or foam coming from the nares and mouth	Anorexia and lethargy, diarrhea	Prosimians, New World and Old World monkeys	Infection is most devastating in New World monkeys and prosimians and can occur in outbreaks
Taenia sp.	Cysticercosis	Usually incidental findings at necropsy	Not reported	Red-ruffed lemurs, macaques	Should be included in the differential diagnosis for space-occupying pulmonary lesions
Echinococcus granulosus, E. multilocularis.	Hydatidosis, cystic and alveolar echinococcosis	Usually incidental findings at necropsy	Not reported	Baboons, Japanese macaques	(1) Should be included in the differential diagnosis for space-occupying lung lesions (2) Alveolar (*E. multilocularis*) reported in outdoor housed research monkeys (3) Wild canids are definitive host
Mesocestoides sp.	Tetyrathyridiosis	Usually incidental findings at necropsy	Not reported	Cynomolgus monkeys	Should be included in the differential diagnosis for space-occupying lesions
Filaroides sp. *Filariopsis* sp.	Pulmonary nematodiasis	Generally clinically inapparent, occasional coughing, pulmonary hemorrhage	Not reported	Marmosets, squirrel monkeys, cebus monkeys, howler monkeys, cynomolgus monkeys	More common in wild-caught primates
Anatrichosoma cutaneum or A. cynomolgi	Nasal nematodiasis	Usually subclinical	Creeping eruptions and subcutaneous nodules	Rhesus monkeys, cynomolgus monkeys, patas monkeys, vervets, talapoin monkeys, mangabeys, baboons, gibbons	Diagnosis by nasal swabs and fecal exams

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TABLE 9.2 Differential Diagnosis of Primate Respiratory Disease: Infectious Diseases—cont'd

Etiology	Disease	Clinical Signs		Reported Species	Comments, Including Zoonotic Potential
		Respiratory	Other		
Strongyloides stercorialis	Strongyloidiasis	Cough, hemoptysis	Diarrhea, death	Apes, especially orangutans	(1) Anthropozoonosis (2) Enteric hyperinfection and pulmonary migration leading to intra-alveolar hemorrhage and secondary bacterial pneumonia (3) Most fatalities in infants and juveniles, but can occur in adults
Dinobdella ferox, Limnatus africana	Nasal annelids	May be asymptomatic, epistaxis, asphyxiation	Restlessness, anemia, weakness, sometimes death	Macaques	(1) Clinical problems relate to numbers of leeches present (2) Usually only a problem in countries of origin
Pneumonyssus sp. *Pneumonyssoides* sp.	Pulmonary acariasis	Usually subclinical, severe infections may have associated cough and dyspnea	Not reported	Woolly monkeys, howler monkeys, macaques, douc langurs, proboscis monkeys, chimpanzees	(1) Most severe in the Asian colobine monkeys (2) Complications of lung mite infection include pneumothorax and pulmonary arteritis
Rhinophaga sp.	Nasal acariasis	Not reported	Not reported	Rhesus monkeys, baboons, orangutans, chimpanzees, gorillas	

and basal cells. Olfactory epithelium (OE) is composed of olfactory sensory cells, sustentacular cells, and basal cells. Most of the nasal mucosa epithelial lining is composed of RE, which has many similarities, structurally and in response to injury, to tracheal and bronchial epithelium. Lamina proprial serous, mucus, and mixed tubuloalveolar glands contribute to nasal secretions. The paranasal sinuses are continuous with the nasal cavity and have similar mucosal lining as in the nasal cavity. The morphology and extent of the sinuses varies amoung species and between individuals within a species (Takahashi 1984; Preuschoft et al., 2002; Smith et al., 2010).

The nasopharynx is also supported by surrounding bony structures, with a submucosal layer of striated muscle and two layers of fascia. It is lined by RE, with zones of SE. Lymphoid nodules are present throughout the nasopharyngeal submucosa. The Eustachian (auditory) tubes extend from the nasopharynx to the middle ears and are similarly lined by RE. Laryngeal, tracheal, and bronchial patency is maintained by hyaline cartilage plates and rings. Spaces between the cartilages are made up of fibroelastic membranes, termed the annular tracheal ligament. The ends of incomplete tracheal rings are joined by smooth muscle, the trachealis. It is not unusual for tracheal ring ossification to occur in older animals. The laryngeal mucosa includes SE from the vestibule to the oral margin of the vocal cords, whereas the posterior lumen is lined by RE. Laryngeal diverticula, the air sacs, are lined by stratified cuboidal and ciliated pseudostratified columnar epithelium. The air sacs pass over the external surfaces of the trachea, thyroids, salivary glands, and skeletal muscle in the neck region (Figure 9.1) and, in some species (orangutans (*Pongo* sp.) and gorillas (*Gorilla* sp.)), even extend over the clavicles and into the axillae (Figure 9.2). In chimpanzees (*Pan trogylodytes*) the air sacs are described as being of unequal size (Swindler and Wood, 1982). The air sac

FIGURE 9.2 Air sac (laryngeal diverticula). Orangutan (*Pongo pygmaeus*). Dorsal view of larynx (*ex situ*) showing location of internal ostia/ lateral vestibules (saccules) (top) and ventral view (bottom) showing location of ostia into the air sacs. *(Zoological Society of San Diego, ZSSD)*

opening in monkeys is usually single, on the midline at the base of the epiglottis. In the apes, there are paired openings directed laterally from the lateral ventricles. The air sac adventitia is quite vascular and includes abundant adipose tissue, nerves, and sparce, flat bands of skeletal muscle. The function of the air sacs is uncertain, but they are thought by many to serve as a resonating or amplifying apparatus for phonation (de Boer, 2009). Another hypothesis is that they act as a "rebreathing apparatus" during phonation (Hewitt et al., 2002).

The trachea and bronchi are lined by pseudostratifled respiratory epithelium that includes ciliated, mucous, and nonciliated cells. Nonciliated cells include serous, basal, and neuroendocrine cells. The tracheal and bronchial mucosa also includes lymphocytes, globular leukocytes, and intraepithelial nerve fibers. The submucosa contains connective tissue, blood vessels, lymph channels, nerves, glands, and occasional focal or diffuse lymphocyte infiltrates.

A stereotypic pattern of repair follows injury to the tracheobronchial epithelium. Normal RE exists in a state of low-level turnover. Ciliated cells are terminally differentiated, with little or no regenerative capacity. When epithelial injury occurs, the ciliated cells are sloughed and replaced

FIGURE 9.1 Cervical air sac. Old World monkey (Francois langur, *Trachypithecus francoisi*). The angle of the jaw and mandibular salivary gland are visible on the left. *(UC Davis, Veterinary Medical Teaching Hospital, VMTH)*

by nonciliated cell types, primarily mucous cells and nonciliated cells, with basal cells providing a smaller contribution. The mucous and nonciliated cells regenerate themselves and undergo differentiation into ciliated cells and other epithelial types. Prolonged injury results in squamous metaplasia.

Approximately 50% of total airway resistance occurs in the nasal cavities. The nasal mucosa functions to warm and humidify inspired air, as it includes a large surface area and has extensive submucosal vascular plexuses, particularly in the turbinates and nasal septum. Nasal plexus hyperemia can cause a significant decrease in nasal airway caliber, resulting in increased airflow resistance. Of the remaining airflow resistance, approximately 80% is present in the first four to seven bronchial tree divisions, in which airflow is rapid. Relatively small amounts of bronchoconstriction or air wall edema and inflammation can cause large increases in overall respiratory resistance and ascultable airway sounds.

A key upper respiratory tract function involves the removal of larger particles and water-soluble gases via the mucous lining. Depending on the material, this occurs via inertial impaction, gravitational sedimentation, diffusion, or a combination of these. Inertial impaction occurs primarily in the nasal passages and pharynx at points of air stream change in direction and turbulence. Gravitational sedimentation and diffusion take place primarily in the lower respiratory system and are discussed later in relation to the vulnerability and formation of certain lesions in those areas. Virtually all particles greater than 10 μm in diameter are deposited above the nasopharynx, as are a large percentage of inhaled particles smaller than 10 μm. This deposition is associated with initial replication of many viral and bacterial agents in the upper respiratory epithelium and lymphoid tissue before they spread systemically or are redistributed into the lower respiratory tract after nebulization and inspiration.

The mucociliary blanket consists of a mucus layer with physical properties of a viscoelastic gel, which lies over a watery sol into which the cilia project and beat. The gel–sol mucus layer is derived from surface mucous cells and submucosal glands that include both serous and mucous secretory cells. The mucociliary blanket moves toward the pharynx at a velocity of 5–15 mm/min. These secretions and deposited materials are subsequently cleared when they are swallowed after they reach the pharynx. When circumstances result in airway secretion volume that is greater than can be cleared by normal mucociliary clearance, coughing is an important mechanism that aids in the movement of this additional material. Well-developed lymphoid tissue in the tonsillar and dorsal nasopharyngeal regions provides the opportunity for immune response to the variety of antigens deposited there, but also provides a route for primary infection by organisms such as *Mycobacterium paratuberculosis* and *Brucella* spp. (Dungworth, 1993). The transport and deposition of particles from the mucociliary blanket provide a mode of spread for diseases such as tuberculosis and a variety of helminth eggs and larvae. Normal mucociliary function depends on intact, functional ciliated epithelium and the normal viscous properties and quantity of secretions. Problems with one or more of these can predispose to infection.

Additional activity of the tracheobronchial mucosa includes the metabolism of a number of endogenous and xenobiotic compounds, the synthesis and secretion of neutral endopeptidase, interferon, lysozyme and lactoferrin, and the synthesis and secretion of immunoglobulins (Ig), primarily IgA, by nasal and bronchial-associated lymphoid tissue (NALT and BALT). Clara cells (nonciliated epithelial cells) have high cytochrome P450 monooxygenase activity, which can activate a number of xenobiotic compounds into pulmonary toxins. Tracheobronchial epithelial cells metabolize arachidonic acid to eicosanoids, including prostaglandin E_2 and hydroxyeicosatetraenoic acid (12-HETE), which may regulate local smooth muscle tone and vascular flow. Neutral endopeptidase is an enzymatic regulator of airway neuropeptides such as substance P and neurokinin A, which in turn can stimulate increased vascular permeability and airway smooth muscle contraction. Following injury and interaction with cytokines, bronchial epithelial cells can also upregulate the expression of intercellular adhesion molecule-1. Intracellular adhesion molecule-1 promotes adhesion and migration of circulating neutrophils and monocytes into airways during an inflammatory reaction. Interferon is a nonspecific compound that can help limit local viral infection, whereas lysozyme and lactoferrin have selective antibacterial activity. The presence of pathogen-specific secretory IgA on the respiratory mucosa is one of the most important components of immunity to respiratory pathogens. Finally, normal bacterial flora in the nose and nasopharynx are important in that they specifically adhere to receptors on cilia and epithelial surfaces, preventing adherence and colonization by more virulent organisms.

Lower Respiratory System

The lungs make up the lower respiratory system. They are generally divided into multiple lobes on each side, with differences in lung lobation among the different primate groups (Parent, 1992; Scott, 1992b). The right lung in prosimians, New World monkeys, and many Old World species has four lobes. A few prosimians and Cebidae have three right lobes as do the great apes, which lack the accessory (azygous) lobe. The left lung of smaller and more "primitive" species consists of two lobes, whereas the larger Old World species generally have three, and great

apes generally have two. An interesting exception to this lobation is the orangutan, which has a single lung lobe on each side. An important anatomic variation of note is the right superior bronchus site of origin. In some species (e.g., orangutan and bonobo), it branches from the trachea proximal to the main tracheal bifurcation at the carina, increasing the possibility for accidental obstruction during tracheal intubation, leading to atelectasis of the right cranial lung lobe (Robinson and Janssen, 1980). The bronchi progressively branch and decrease in diameter, eventually becoming bronchioles, the last generation of which is termed the terminal bronchiole. The branching airways are accompanied by a double arterial supply, the pulmonary and bronchial arteries. Bronchioles are distinguished from bronchi by the absence of cartilage and submucosal glands within their walls. Each terminal bronchiole opens to the functional unit for gas exchange, the acinus. An individual acinus includes respiratory bronchioles, alveolar ducts, alveolar sacs, alveoli, and associated blood vessels.

With no cartilage in the bronchiole walls, bronchiole patency is dependent on the attachment of interalveolar septa to a thin connective tissue layer in the bronchiolar wall. As lung volume increases, the radially arranged interalveolar septa pull on the bronchiolar wall, with a resulting maximal bronchiolar luminal diameter during maximum volume. This process is reversed with expiration, such that small bronchioles may collapse at low volume. Airflow out of the pulmonary acinus supplied by the collapsed bronchiole ceases without sufficient collateral ventilation. The thin walls, collapsibility, and small diameter of bronchioles make them much more susceptible than bronchi to pathologic processes occurring in the surrounding alveolar parenchyma. Similarly, inflammatory processes originating in bronchioles are likely to spread to adjacent alveoli. The small lumens increase the likelihood for bronchioles to become obstructed by inflammatory exudate. Although the resistance to airflow in individual bronchioles is high, the total cross-sectional area of all bronchiolar generations is considerably larger than that of the bronchi. Consequently, pathologic processes that affect small numbers of bronchioles can be clinically inapparent with regard to signs of airway obstruction. Clinically apparent disease usually occurs only when a large percentage of bronchioles are affected.

Proximal generation bronchioles are generally lined by epithelium similar to that in the distal bronchi. Distal, small caliber bronchioles are lined by simple columnar to cuboidal epithelial lining that is made up almost entirely of ciliated cells and nonciliated bronchiolar (Clara) cells. The nonciliated cells have regenerative capacity as described earlier with regard to respiratory epithelial response to injury. Clara cells have a high concentration of cytochrome P450 monooxygenase enzyme systems, making them particularly sensitive to toxic injury by xenobiotic compounds.

The alveolar parenchyma includes capillary endothelium, type I and type II alveolar epithelial cells, and alveolar macrophages, as well as fibroblasts and other interstitial cells. Covering approximately 93% of the alveolar surface, type I alveolar epithelial cells are squamous cells across which gas exchange occurs. They are vulnerable to injury by a variety of agents, with little ability to adapt to injury. Injured type I cells usually quickly slough from the basement membrane. Type II alveolar cells are cuboidal cells, making up approximately 7% of the alveolar septum surface area. They have a number of key functions, including pulmonary surfactant production, differentiation to type I cells during normal turnover, and rapid proliferation to cover the exposed alveolar basement membrane in response to type I cell damage and loss. Type II cells also synthesize a variety of matrix components, including fibronectin, type IV collagen, and proteoglycans. They also metabolize arachidonic acid to form eicosanoids, including prostaglandin E_2, which influences the function of other alveolar cell types. Finally, type II cells can express major histocompatibility complex (MHC) I receptors and function as antigen-presenting cells.

The lungs represent the largest capillary bed in the body. Alveolar capillary endothelial cells are the initial permeability barriers between capillary lumen and pulmonary interstitium, with important transport functions for solutes, water, and gases. Among their many metabolic functions are uptake and clearance of serotonin, norepinephrine, prostaglandins E and F, bradykinin, hormones, and drugs. Endothelial cells have angiotensin-converting enzyme activity, converting angiotensin I to angiotensin II. They are sensitive to toxic damage by xenobiotic compounds, due to cytochrome P450 monooxygenase activity. Endothelial cells upregulate cell adhesion molecules when exposed to a number of mediators, including leukotriene B_4, as well as cytokines such as tumor necrosis factor and interleukins 1−8. This facilitates attachment and migration of neutrophils and other leukocytes into the interstitium and alveoli.

Alveolar fibroblasts are connective tissue cells with heterogenous morphology and varying protein synthetic activity, contractile function, and cell and matrix interactions. The alveolar interstitial matrix includes elastic and collagen types I, III, IV, V, and VI, with a predominance of types I and III. Other pulmonary fibroblast products include laminin, fibronectin, glycosaminoglycans, and proteoglycans. This admixture of intercellular matrix components contributes to the mechanical properties of the lung.

Four macrophage populations are present in the lungs. These include alveolar macrophages, interstitial macrophages, pulmonary intravascular macrophages (which are thought to be of minor importance in primates), and

dendritic cells. Alveolar macrophages are a key pulmonary defense against agents that reach the alveoli after bypassing upper respiratory tract defenses. Derived from blood monocytes, alveolar macrophages undergo a maturation step in the interstitium before they migrate into the alveolar lumen, except in inflammatory states, during which they migrate directly into the alveolus. The wide variety of alveolar macrophage functions starts with phagocytosis and killing of infectious agents and degradation of other phagocytosed particles. They also have a key role in inflammatory, immune, and repair process control, mediated through their release of cytokines and a variety of regulatory molecules. Among the macrophage-produced cytokines are interleukin-1, tumor necrosis factor, interferon α and γ, and histamine-releasing factor. Inflammatory mediators released by alveolar macrophages include leukotriene B_4 and C_4, platelet-activating factor, and thromboxane A_2. Macrophage-associated control and regulation of repair processes come through the release of cytokines such as transforming growth factor β and α, fibroblast growth factor, insulin-like growth factor, and platelet-derived growth factor. Finally, alveolar macrophages have a role in cellular and humoral immune responses as antigen-presenting cells.

Dendritic cells are present in the alveolar interstitium and airway lamina propria. They are bone marrow-derived leukocytes with enhanced antigen-presenting capacity. These cells lack phagolysosomes, have a very irregular, folded nucleus, and numerous long, irregular dendritic processes. They normally express high levels of MHC class I and II molecules and common leukocyte antigen. They lack many of the cytoplasmic surface markers of mononuclear phagocytes and do not efficiently phagocytize particles. Pulmonary intravascular macrophages (PIMs) are unique mononuclear phagocytes that have been found in the lung of certain species, including cattle, sheep, pigs, goats, cats, and humans, though they are of less importance in humans than the other mentioned species. They are present in alveolar capillary lumens as large mature macrophages, attached to endothelium via membrane adhesion complexes. These highly phagocytic cells play a role in the clearance of circulating bacteria and particles as they pass through the pulmonary circulation, fulfilling the same role as Kupffer cells of the liver. They release a variety of inflammatory mediators in association with this clearance process, thus contributing to acute pulmonary inflammation.

Inspired particles that are not removed in the upper respiratory tract are deposited in the lower respiratory tract via gravitational settlement and diffusion. Gravitational settlement is proportional to particle size and density and generally occurs in the relatively still air of the most distal parts of the respiratory system. Diffusion involves particles less than 0.3 μm in diameter and requires minimal flow as occurs in the alveoli. With decreasing size of particles (less than 10 μm), an increasing proportion pass into the deep lung. Many of these are subsequently exhaled; however, droplet nuclei and other irritant or infectious particles approximately 1−2 μm in diameter tend to deposit at the bronchiolar-alveolar junction. This phenomenon is associated with the sudden drop of the air stream linear velocity to zero at this point, due to the abrupt increase in the airspace cross-sectional area. It is a major factor in the apparent vulnerability of the bronchiolar-alveolar junction to damage by inhaled irritant and viruses.

Alveolar macrophage phagocytosis is the key to alveolar defense against small-sized particles. Although phagocytosis can occur within a relatively short time (e.g., 4 h after alveolar deposition of bacteria), the physical removal of particulates from alveoli is inefficient compared to particles deposited on the mucociliary blanket. Depending on particle physical nature and irritant characteristics, it can take several days to months or longer for 50% clearance of particles. Macrophage-phagocytosed particles are either inactivated or sequestered as the macrophages move toward the bronchioles and onto the mucociliary blanket. If not phagocytized, particles within the alveoli tend to be cleared with the alveolar lining liquid as it moves centripetally to the bronchioles or it may penetrate the pulmonary interstitium. The latter tends to occur more with increased particulate load. Interstitial penetration is generally by endocytosis across alveolar type I epithelial cells. Particles within the interstitium are removed with lymph flow and are phagocytosed by interstitial macrophages. Peribronchiolar and perivascular clusters of particle-laden macrophages are associated with lymphatics, with some eventually moving to local lymph nodes.

The alveolar-lining liquid contains a variety of factors that are important for helping to maintain alveolar sterility and to protect against tissue damage, lmmunoglobulin G is the primary immunoglobulin in the liquid. Both IgG and surfactant are important opsonizing factors that enhance phagocytosis by alveolar macrophages. Lysozyme, lactoferrin, and complement are additional factors with roles in pathogen control. Catalase and the glutathione peroxidase system, which help protect against reactive oxygen radical-associated injury, and α_1-antitrypsin, which contributes to protection against acute lung injury and development of alveolar emphysema, are important humoral components of the pulmonary-lining liquid.

Pulmonary Circulatory and Lymphatic Systems

The pulmonary circulation receives the entire output of the right ventricle via the pulmonary artery. It is a low-pressure system made up of densely anastomosing capillaries in the alveolar septa. The bronchial artery, originating from the

aorta, is the second blood source in the dual pulmonary blood supply. The pulmonary artery carries systemic venous blood to the pulmonary parenchyma for gaseous exchange in the alveolar capillaries. The pulmonary arteries generally run parallel to the bronchi and bronchioles, with a similar branching pattern. With their origin in the aorta, the bronchial arteries supply oxygenated blood to the airways and supporting pulmonary connective tissue, including the pulmonary artery vasa vasorum. Bronchial artery branches are closely associated with bronchial and bronchiolar walls. Venous drainage of the lungs occurs primarily through the pulmonary veins, with just a small amount of blood returning through the bronchial veins. Normal pulmonary and cardiac functions are closely interdependent. This is evident with the observation that cardiovascular diseases can result in impaired respiratory function in association with pulmonary edema and congestion, whereas chronic pulmonary diseases that interfere with pulmonary blood flow can affect normal heart function and systemic circulation causing "cor pulmonale."

The dual supply, extensive anastomosis and function as a capillary bed through which the entire right ventricle output flows, provides a mechanism for efficient filtration and trapping of emboli while minimizing the potential damage due to vascular obstruction. Particulate trapping by pulmonary intravascular macrophages (PIMs) is not thought to occur in primates, and trapping in capillaries is, therefore, merely mechanical (Brain et al., 1999). Common particulates and emboli entering the lungs include bacteria, fungi, protozoa, endogenous fat, normal cells (e.g., megakaryocytes), or abnormal cells (usually neoplastic). Other emboli can include fragments of thrombi, helminth parasites for which the respiratory system is a natural or accidental habitat, and even parasitic ova. Rare emboli that may be found in the lung circulation include epidermal fragments and hair inadvertently introduced into the blood during injections or intervertebral disc nucleus pulposis fragments. This blood filter function of the pulmonary circulation can be both beneficial and a source for additional problems. The trapping of emboli serves to prevent them from reaching the systemic circulation and causing infarction in major organs such as heart, brain, and kidneys. Problems can occur as it serves to set up the lungs themselves as sites of spreading infection, tumor metastasis, and pulmonary thromboembolism.

Pulmonary lymphatic drainage occurs through a subpleural network as well as through perivascular and peribronchial lymph channels. The lymph flow is centripetal, eventually draining through hilar (tracheobronchial) lymph nodes. In addition, direct lymphatic connections are known to exist between lower lung lobes and the diaphragmatic and coeliac lymph nodes in humans. Such connections could provide a potential route for the extension of pathologic processes between the thorax and the abdomen. Lymphatic channels are not demonstrable in alveolar septa.

APPROACH TO THE PATIENT WITH RESPIRATORY DISEASE

Signs of Respiratory System Disease

Sneezing and Nasal Discharge

Sneezing and nasal discharge are primary signs of sinus, nasal, and nasopharyngeal disorders. The approach to the veterinary patient with sneezing and nasal discharge is reviewed by McKiernan (1995). With persistent disease, sneezing may decrease, whereas nasal discharge may increase in volume and change character.

Sneezing is an involuntary airway reflex that is an important protective respiratory system defense mechanism. Among the many primary causes of sneezing are congenital anomalies (e.g., cleft palate, cilial defects), inflammatory conditions (e.g., allergy), and infections (e.g., virus, bacteria, fungi, parasites). Other direct causes include mechanical and chemical stimuli (e.g., foreign bodies, environmental dusts, odors, or pollutants) and simple trauma.

Nasal secretions normally are cleared via the mucociliary apparatus toward the nasopharynx. When material appears at the external nares (nasal discharge), it can be due to excessive secretion and/or decreased clearance ability (e.g., due to obstruction). Extranasal disease can cause nasal discharge as well, as noted later.

The character of the nasal discharge provides important clues about the primary medical condition. The type of discharge can be serous, mucoid, mucopurulent, purulent, blood-tinged, overtly bloody (epistaxis), and/or may include food particles. Most nasal and sinus diseases start with a serous discharge but with persistence of the primary cause can progress to mucoid, mucopurulent, and frankly purulent. The presence of blood can be associated with a number of conditions, including focal irritation/inflammation, erosion or ulceration, mucosal capillary trauma associated with violent sneezing, or as part of a systemic disease such as thrombocytopenia or other coagulopathy. Whether the discharge is initially unilateral or bilateral can help in suggesting the type of disease process. For example, a unilateral discharge could be associated with upper arcade dental disease, nasal foreign body, nasal tumor, or mycotic infection or parasites. When a nasal discharge is bilateral from the onset, it may suggest viral or bacterial infection, allergy, environmental agents (e.g., dust, smoke), or extranasal disease (such as pneumonia, esophageal stricture, megaesophagus, and cricopharyngeal disorders).

Dyspnea and Tachypnea

Dyspnea is the presence of labored or difficult breathing. The assessment of respiratory rate, rhythm, and character is used to determine whether an inappropriate degree of breathing effort is present. Dyspnea is further characterized as exertional, paroxysmal (suddenly recurring or intensified), or continuous, with differences due to the cause and extent of the abnormality. Tachypnea, an increased rate of breathing, is not necessarily an indication of respiratory disease, as it occurs in a number of normal physiological states, such as exercise, hyperthermia, anemia, or anxiety. Orthopnea indicates difficulty breathing while recumbent, such that orthopnic animals tend to maintain an upright position. The cardinal importance of normal respiratory function to homeostasis is reflected in the occurrence of dyspnea and tachypnea when any of a number of systems is involved, including respiratory, cardiovascular, hematologic, and nervous systems, as well as certain metabolic disorders. The general approach to the dyspneic veterinary patient is reviewed by Turnwald (1995).

A variety of disorders associated with dyspnea involve airway obstruction at one or more sites, with the source of obstruction being within the lumen (e.g., thick secretions, exudates, or foreign bodies), within the airway wall (e.g., inflammation or tumors), or externally compressing the airway (e.g., mass lesions). Enlargement of pharyngeal and, in apes, lingual tonsils can cause significant obstruction (Figure 9.3). Obstruction above the thoracic inlet tends to result in increased inspiratory effort, whereas lower airway obstruction is often associated with increased expiratory effort. In either case, presentation of obstructive disease may include tachypnea. A second set of disorders associated with dyspnea functionally limit normal lung expansion and include pulmonary parenchymal disease, as well as disorders of the pleura, the pleural space, diaphragm, peritoneum, or peripheral nerves. Such disorders, termed restrictive respiratory disorders, often are associated with rapid, shallow breathing patterns. Some conditions can have both obstructive and restrictive elements.

Among the problems associated with dyspnea that are not primary respiratory disorders are certain neurological, metabolic, and hematological (anemia) disorders. Nervous system disorders include brain disease, spinal cord, and peripheral neuropathies. The respiratory effect of brain disease varies with the anatomic distribution of the lesion. Tachypnea may be present, and breathing depth may be more or less than normal. An increase in breathing rate and depth occurs as respiratory compensation for metabolic acidosis. The level of anemia-associated hypoxia that leads to dyspnea varies among individuals and in association with the rate of onset of anemia, with acute onset hypoxia more often causing respiratory changes than slower onset disorders. As with compensation for metabolic acidosis, breathing rate and depth are generally increased in anemia-associated dyspnea.

Cough

Excess secretions and foreign bodies can be cleared from the tracheobronchial tree by coughing, which involves explosive expiratory effort. Coughing can be reflexive or voluntary. Cough is triggered by foreign materials and inflammatory stimulation of airway cough receptor nerves. The end result of the cough sequence is an intratracheal airflow rate that approaches the speed of sound, producing efficient shearing forces and subsequent movement of material up the airways to the pharynx. When cough is chronic, algorithms used in the diagnosis of chronic cough in humans can be used (Brashers and Haden, 2000).

Diagnostic Procedures in Respiratory Disease

A diagnostic plan always should start with a good history and physical examination. Radiographic imaging is the third common information source upon which the differential diagnostic list for respiratory disease is initially established. The results of these primary steps can help suggest a logical progression for further diagnostic workup, with varying degrees of invasiveness and need for equipment and technical support and ability. Decisions made in further pursuing the diagnostic plan must take into account variable sensitivity and specificity of each procedure and their associated interpretation problems and diagnostic value. Diagnostic algorithms have been developed in both veterinary and human medicine to guide the diagnostic process (Devakonda et al., 2010).

FIGURE 9.3 Laryngeal obstruction. Western lowland gorilla (*Gorilla gorilla gorilla*). Obstruction due to mucopurulent exudate from sinuses and enlargement of pharyngeal and lingual tonsils. *(UC Davis, VMTH)*

Physical Examination and History

History and signalment can give useful diagnostic clues due to the prevalence of certain disorders in association with the specific circumstances. Congenital conditions, e.g., cleft palate, pectus excavatum, and diaphragmatic hernia, are more likely to be associated with clinical signs in young animals. Middle-aged or older animals are more likely to have neoplastic or chronic disorders (e.g., chronic dental disease as a cause of nasal disease). Conditions associated with husbandry include environment (indoor *vs.* outdoor housing), with differing potential for air pollutant, allergen, or foreign body exposure, trauma, and so on. The geographic origin and housing history can indicate potential for parasitism (wild caught and outdoor housed) or exposure to geographically restricted organisms (e.g., coccidioidomycosis, histoplasmosis, blastomycosis). A previous medical history can reveal problems (trauma, surgery, dental disease, allergy, etc.) that could subsequently have led to the current presenting respiratory problem. Information about vaccination history (e.g., measles vaccination) and response to previous medical treatments (e.g., antibiotic responsiveness can occur with tooth abscesses or foreign bodies but generally not in association with neoplastic disease or mycotic infection) can be helpful as well in formulating and refining a differential diagnosis list. Other important information can include the duration and progression of signs, evidence of exercise intolerance, and the involvement of other body systems (e.g., mouth, eyes, regional lymph nodes).

A comprehensive physical examination of a patient with respiratory signs involves observation, palpation, auscultation, and, at times, percussion. The physical examination should assess the animal in general, with particular emphasis on the upper and lower respiratory tracts and the cardiovascular system, as respiratory and cardiovascular disorders can frequently lead to similar signs. Elements of observation include the presence of discharges, deformities, or other lesions and the presence of sneezing or coughing. The breathing pattern character (rate and rhythm, effort during inspiration and expiration) and the intensity and quality of respiratory sounds (wheezing, crackles) are additional important factors to note. Features of importance regarding nasal discharge include discharge characteristics and whether it is unilateral or bilateral. Open mouth breathing in an otherwise calm, unstressed animal may be a sign of bilateral nasal obstruction, complete nasopharyngeal obstruction, or severe lower respiratory tract disease. Cyanosis occurs in severely affected animals. General systemic signs such as weight loss, anorexia, and depression can occur at the same time and may be the only sign(s). Hypoxia and acute hypercapnea can be associated with disturbances in mentation and even coma.

Important aspects of the physical examination of animals with other evidence of nasal involvement include assessment of nasal airflow, and examination of nose, face, oral cavity, regional lymph nodes, and eyes. Airflow assessment techniques can include visually comparing the size of condensation formed by airflow out of either nostril onto a smooth cool surface such as a glass slide or ophthalmoscope base and/or listening to or feeling the airflow out of each nostril while the other one is occluded. The nasal, sinus, and oral regions should be palpated for evidence of distortion or swelling. Percussion and transillumination can be additional helpful techniques for the evaluation of possible sinus filling. A careful oral examination is essential for the assessment of possible nasal cavity problems. This would include examination of the hard palate (defects, swellings), soft palate (ventral depression associated with nasopharyngeal swelling), oral mucosa in general (trauma, erosions, ulcers, plaques, petechiae), palatine and glossal tonsils, teeth, and periodontia. Local lymph nodes (submandibular, retropharyngeal) may be enlarged in association with neoplasia and/or chronic inflammation/infection. Ocular findings that can relate to rhinitis include conjunctivitis and, to a lesser extent, chorioretinitis.

For assessment of dyspneic animals, thoracic auscultation is crucial, including evaluation of thoracic pulmonary and heart sounds and respiratory sounds directly over the trachea, larynx, and nose. The latter steps can help localize the site of a lesion, with sounds generally more intense near their site of origin. Swollen cervical lymph nodes or other cervical soft tissue structures can be the cause of tracheal narrowing and associated respiratory difficulty. Palpation and ballottement are important in the diagnosis of laryngeal air sac infections.

Laboratory tests (CBC, serum chemistry, urinalysis, and more specific tests such as a coagulation panel) are an important aspect of the overall workup of an animal with respiratory signs. These can help focus the diagnosis on an etiology (e.g., viral *vs.* bacterial pneumonia) or a process (e.g., anemia, thrombocytopenia, coagulopathy, or metabolic acidosis associated with renal failure or diabetes).

Radiography and Other Imaging Techniques

Radiography is a generally available diagnostic technique that can provide valuable information for localizing and initially characterizing respiratory system lesions (Silverman, 1975). It also often provides clues for the selection of subsequent diagnostic procedures. Positioning can be very important, with the most useful views being those that can help differentiate which side is affected, while minimizing the overlap of structures of interest. For nasal radiographs, such features as loss of symmetry, increase or decrease in

nasal cavity density, bone abnormalities, and the presence of foreign bodies are some of the more frequently occurring changes with nasal disease. Tracheal radiographs are evaluated for variation in diameter and course. At times, contrast studies are needed in cases of suspected tracheal rupture or fracture or to help visualize suspected radiolucent foreign bodies. Thoracic radiographs are generally made with the animal in erect or sitting position, with exposure timed to coincide with near peak inspiration. Use of the lateral decubitus position may be helpful for revealing small pleural effusions not evident with the upright position. Many pulmonary diseases can have a variety of possible radiographic patterns, with no pattern specific enough to establish a diagnosis. However, some patterns (e.g., lobar consolidation or multifocal nodularity) are more often associated with certain diseases (Rawlings and Splitter, 1973; Silverman et al., 1975, 1976; Odkvist and Schauman, 1980; Robinson and Bush, 1981; Stills and Rader, 1982; Gillett et al., 1984; Marcella and Wright, 1985; Wolff et al., 1989; Karesh et al., 1990; Goldberg et al., 1991; Devakonda et al., 2010).

Other special imaging techniques can be helpful (Friedman, 1994). Computed tomography (CT) and magnetic resonance imaging (MRI) can provide additional detail for skull internal structure in particular and are becoming more available at regional diagnostic facilities. Computed tomography can be particularly useful in determining the extent of an upper respiratory problem, including whether it has extended into epidural areas or the brain itself (Cambre, 1986). Both CT and MRI can be used for studies of nasal and sinus lesions with good consensus between the two modalities (Drees et al., 2009). CT has proven useful for diagnosis of air sacculitis as well as sinusitis in orangutans (Steinmetz and Zimmerman, 2011). For thoracic imaging, CT is useful for characterizing pleural disease (e.g., differentiating fluid from tumor); with contrast injections, differentiating tissue masses from vascular structures; and identifying small parenchymal nodules. Lewinsohn et al. (2006) describe the usefulness of CT imaging in conjunction with IFN-γ ELISPOT testing (see below) for accurately assessing the extent and progression of TB in individual rhesus macaques (*Macaca mulatta*). Magnetic resonance imaging has the potential to provide fine definition of mediastinal and pleural lesions. Early use of these highly sensitive techniques is somewhat compromised because little base line information is available to indicate how many "normal" individuals have small, previously undetected parenchymal lesions. Also, it is not yet known how to differentiate the specific types of lesions (e.g., inflammatory or neoplastic). Pulmonary scintigraphy provides the opportunity to further differentiate and locate various disease processes (e.g., inflammation, neoplasia) using radionucleotides with affinity for certain cells types (Karesh et al., 1990).

Skin and Serologic Testing

Skin tests for specific antigens are available, including tuberculosis, coccidioidomycosis, histoplasmosis, blastomycosis, trichinosis, toxoplasmosis, and aspergillosis. Intradermal tuberculosis skin testing using mammalian old tuberculin (MOT) is commonly used in nonhuman primates as an important part of preventive medicine programs (Henrickson, 1984; Southers and Ford, 1995; Kramer et al., 2011) (see also under tuberculosis). Tuberculin testing of nonhuman primates provides a good example of the potential variability in sensitivity and specificity when performing skin tests in general (Chaparas et al., 1975; Kaufmann and Anderson, 1978; Kuhn and Selin, 1978; McLaughlin and Marrs, 1978; Janssen et al., 1989; Dillehay and Huerkamp, 1990; Wells et al., 1990). As with skin testing antigens, a number of potentially useful serologic tests have been developed that include a variety of respiratory pathogens. Using appropriate serologic tests can help avoid the use of more extensive/invasive diagnostic procedures. Sensitivity, specificity, and the specific types of available serologic tests (e.g., enzyme-linked immunosorbent assay (ELISA), agar gel immunodiffusion, indirect immunofluorescence, latex agglutination) vary within institutions, however, requiring close interaction with the responsible laboratory for test result interpretation. With regard to TB diagnostics, recent new techniques (Lin et al., 2008), including interferon gamma releasing assays (Desem and Jones, 1998; Vervenne et al., 2004), lymphocyte activation assays (Parsons et al., 2009), and serologic assays (Khan et al., 2008) are being developed. These assays are generally best used in addition to the tuberculin skin test as part of a comprehensive response to apparent positive tuberculin skin tests within designated animal populations.

Endoscopy

Rhinoscopy and bronchoscopy provide the opportunity for direct visualization of the areas, biopsy of suggestive or obvious lesions, removal of foreign bodies, and regional lavage, brushing, or even biopsy of the lung for culture and cytology. For anterior rhinoscopy, a variety of equipment can be used, from an otoscope to a rigid pediatric arthroscope to a flexible fiberoptic endoscope (FOE). Flexible fiberoptic technology has tremendously improved the ability to perform these procedures (Strumpf et al., 1979; Muggenburg et al., 1982; Moser, 1994; McKiernan, 1995). The flexible FOE is composed of fiberoptic bundles that provide both illumination and visualization pathways. One or more small channels traverse the FOE, through which instruments can be passed, fluids delivered, and suction applied with retrieval of cells for cytology (Tate et al., 2004). An FOE is most useful for posterior rhinoscopy, although a dental mirror may provide some visualization of the nasopharynx. The major

contraindication for endoscopic examination, particularly in the lower respiratory system, is lack of experience, which both reduces the diagnostic and therapeutic potential and increases the risks (e.g., hypoxia, laryngospasm, and bronchospasm, pneumothorax, and biopsy-associated hemorrhage). Thomas et al. (2006) describe the use of human nasal cannulas during bronchoscopy procedures as an aid in maintaining adequate oxygen delivery in pig-tailed macaques.

Pleuroscopy, thoracoscopy, and mediastinoscopy are procedures that can yield important information and samples (Moser 1994). These techniques can involve the use of rigid or flexible devices. As with rhinoscopy and bronchoscopy, operator experience is a key to minimizing risks and maximizing diagnostic and therapeutic potential.

Nasal Flushing, Transtracheal Aspiration, Bronchioalveolar Lavage, and Thoracentesis

Forceful nasal flushing with saline can yield samples useful for the cytological assessment of nasal cavity cytology. Transtracheal aspiration (TTA) is a useful technique for sampling the lungs and lower airways for cytology and culture, avoiding the potential contamination of the pharyngeal flora (Moser, 1994; Dysko and Hoskins, 1995). In this technique, a 17- or 19-gauge intravenous catheter and needle set are aseptically placed into the tracheal lumen through the skin and between tracheal cartilage rings. Once in the lumen, the needle is with drawn, and a sample of sterile saline is introduced via the catheter then immediately aspirated back into the same syringe. Approximately 4 ml is often recovered from an initial instillation of 10−15 ml (Stills et al., 1979).

Bronchioalveolar lavage (BAL) can be practiced with or without an FOE (Gundel et al., 1992). It is generally performed by lightly wedging an FOE into a distal airway, gently irrigating the airway with saline, and then retrieving the fluid through the biopsy port of the endoscope by manual or mechanical suction for cytology and possible culture. The recommended amount of fluid for lavage of macaque lungs varies, but aliquots of 25−50 ml have been used. Retrieval of BAL fluid and cells can be improved by use of a 70-cm section of sterile tubing between the biopsy channel port and the 25-cc syringe used for aspiration (Singletary et al., 2008). Thoracentesis should be performed to sample pleural fluid for all pleural effusions of uncertain etiology and can be indicated for relief of effusion-associated symptoms as well (Dysko and Hoskins, 1995).

Conventional and Molecular Microbiology and Biopsy

Fluid samples obtained in any of the previously mentioned techniques should be examined by cytology and with stains to highlight bacteria (Wright-type, Gram, and possibly acid-fast stain). Samples should minimally be saved in transport medium (refrigerate) for possible culture, which would be indicated if evidence of inflammation is found in the cytology sample. Culture techniques should be based on the cytology and physical examination findings, including aerobic culture minimally, but also potentially anaerobic (e.g., with an inflammatory pleural effusion) or mycobacterial culture (e.g., granulomatous inflammation with or without acid-fast organisms). Pharyngeal and nasal cultures must be interpreted in light of the fact that these sites are not normally sterile and "normal" nasopharyngeal flora can include potential pathogens that may not be the inciting agent in the problem under investigation.

Pathogen detection by molecular techniques is an invaluable aid in the diagnosis of individual cases or outbreaks of respiratory disease and can be utilized on lavage samples, swabs, or tissue biopsies. Commercially available and research lab-based multiplex polymerase chain reaction (PCR) and "gene chips" are used in human medicine to simultaneously screen for several different bacterial (e.g., ResPlex IT Assay™ (Qiagen)) or viral respiratory pathogens (e.g., NGEN respiratory virus analyte-specific assay™ (Nanogen, San Diego, CA) and ResPlex II™ assay (Genaco Biomedical Products, Inc., Huntsville, AL)) many of which also affect nonhuman primates (Li et al., 2007; Benson et al., 2008). Samples collected for molecular detection must be handled appropriately. Immediate snap freezing of swabs or tissues at −80°C is suitable for detection of viral, bacterial, and/or fungal DNA, while preservation in media such as RNAlater™ (Ambion, Applied Biosystems) or FineFIX™ (Milestone Medical) is necessary for ideal preservation of RNA (important for many of the respiratory viruses) (Gazziero et al., 2009; Casale et al., 2010). Formalin fixation, if prolonged for more than a few hours, can substantially diminish the ability to amplify diagnostically useful nucleic acid sequences.

A variety of biopsy techniques are used for respiratory system sampling. For nasal cavity lesions (McKiernan, 1995), these can include the use of plastic catheters (e.g., shortened urinary catheters) cut to a sharp tip to obtain a core samples, endoscopic cup forceps used to obtain a pinch biopsy, or more invasive procedures such as nasal and sinus trephination or rhinotomy. For lung biopsy, both closed and open approaches are used. Closed biopsies are obtained via a fiberoptic endoscope (transbronchial) or a percutaneous cutting needle. Using an FOE provides the opportunity for multiple biopsies in one procedure; however, care must be taken when sampling close to the pleural surface. Even though performed with fluoroscopic or CT guidance, cutting needle techniques have a relatively high potential for complications due to pneumothorax and/or bleeding. Open lung biopsy approaches include

thoracotomy and, to a lesser extent, thoracoscopic techniques. These procedures are relatively safe and allow direct visualization of the optimum biopsy site and the opportunity to obtain a sample of adequate size. All specimens obtained via biopsy should be processed for pathologic examination and should be cultured and or collected appropriately for molecular diagnostics (see above). Imprint cytology from biopsy material can be useful in the diagnosis of neoplastic and some infections (e.g., *Penicillium, Cryptococcus, Herpesvirus*). Final diagnosis should, nevertheless, generally be based on histopathologic findings. Pathologists reviewing respiratory samples need to be aware that chronic cough can induce inflammatory changes in airways irrespective of the underlying disease process (Irwin et al., 2006).

Routine 10% neutral buffered formalin is the fixative of choice for most biopsy specimens. Immersion of the biopsy in a minimum of 10:1 formalin to tissue volume is recommended, and biopsy specimens should be no more than 1 cm thick. Instillation of the fixative into the main bronchus improves fixation and allows for expansion of alveoli to *in vivo* volumes in larger specimens such as lung lobe resections (or whole lungs at necropsy). Formalin fixation allows for paraffin embedding, application of a wide variety of histochemical stains, and also for immunohistochemistry and nucleic acid retrieval for molecular diagnostics, providing the fixed tissue is embedded as soon as possible (Grizzle, 2009). Formalin fixation is relatively rapid with a penetration rate of about 1 mm/hour (Hewitt et al., 2008). Other aldehyde- and non-aldehyde-based fixatives are used in some institutions. If molecular diagnostics are anticipated, a portion of the biopsy can be snap frozen or placed in special media as mentioned above for pathogen detection. Clinicians should consult with their pathology laboratory and with investigators about fixative selection.

Gas Exchange Assessment

The most definitive measure of gas exchange between alveolar spaces and blood is arterial PaO_2 and $PaCO_2$. Blood gas analysis, including arterial and/or venous oxygen, carbon dioxide, and pH, as well as total serum carbon dioxide and bicarbonate concentrations, can give additional information regarding the extent of hypoxemia and acidosis. These data are more easily obtained than is generally thought and can provide important information for the assessment and supportive treatment of seriously ill animals (Rosenberg, 1995). In comparing arterial and venous blood gas levels, venous samples provide a great deal of useful information, with greater ease in sample procurement. Differences in arterial and venous sample pH and PCO_2 levels are magnified in animals with hypovolemia or other systemic circulatory disturbances (King and Hendricks, 1995).

Pulse oximetry provides an indirect measure of hemoglobin oxygen saturation percent (SaO_2) as well as pulse rate using a technique involving absorption of two wavelengths of light by hemoglobin in pulsatile blood in a skin or mucosal fold. Differential absorption of the two light wavelengths by oxygenated and nonoxygenated hemoglobin allows calculation of the percent of hemoglobin that is saturated with oxygen. It is important to be aware of certain issues when interpreting pulse oximetry data (Weinberger and Drazen, 1994). First, the oxyhemoglobin saturation curve becomes flat above arterial PaO_2 60 mmHg (corresponding to an $SaO_2 = 90\%$), such that the oximeter is relatively insensitive to changes in PaO_2 above this level. The curve position and relationship between PaO_2 and SaO_2 can also change in relation to temperature, pH, and the erythrocyte concentration of 2,3-diphosphoglyceric acid (2,3-DPG). Second, low tissue perfusion can make the oximeter signal less reliable or even unobtainable. Third, the two wavelengths of light do not detect other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin, such that SaO_2 determined by the pulse oximeter in the presence of significant amounts of either of these hemoglobin forms is unreliable. Finally, the often-used goal of $SaO_2 \geq 90\%$ does not reflect CO_2 elimination and thus does not ensure that $PaCO_2$ levels are clinically acceptable.

Other Pulmonary Function Testing

Some commonly used pulmonary function tests in human medicine, e.g., spirometry for quantification of respiratory rate, tidal volume, and lung compliance, are not generally clinically useful due to difficulties involving the need for anesthesia in most animals as compared to the need for voluntary maneuvers from human patients to obtain these data. In certain research situations, however, including toxicology and infectious disease research, some such tests are carried out under controlled circumstances. Reports available in the literature regarding such work include those by Besch et al., (1996), Binns et al., (1972), and Liu and DeLauter (1977).

Postmortem Assessment

Thorough gross examination of the entire respiratory tract is necessary for the recognition and appropriate sampling of lesions as well as of unaffected tissue. Postmortem examination of the lungs can include varying degrees of complexity (Tyler et al., 1985) depending on the diagnostic and/or research needs. The presence of discrete lesions, characteristics of airway mucus coat, and the presence of airway edema or hemorrhage should be noted, as well as the characteristics of the lung parenchyma (color and consistency, including the presence of consolidation, atelectasis, or scarring). Tissue may be taken for microbial studies. Removal of the lungs prior to fixation is important

for overall assessment and sampling of the unfixed tissue, including microbiology sample selection.

Tyler et al. (1985) describe a variety of fixatives and fixation techniques for lungs, each with its own advantages and disadvantages. This includes a discussion of fixation by immersion versus intratracheal infusion versus vascular perfusion fixation via the pulmonary artery. Neutral buffered 10% formalin is the standard fixative for light microscopic assessment; however, some newer formalin-free preservatives provide for good histologic detail while better protecting and preserving antigens and nucleic acids for immunohistochemistry and molecular detection of pathogens (see above). For electron microscopy, a variety of other fixatives are more suitable, generally containing paraformaldehyde, glutaraldehyde, or mixtures of the two with phosphate or cacodylate buffer (e.g., Karnovsky's fixative). Fixation of tissue slices by immersion generally provides adequate samples for the assessment of microscopic morphology. Infusion of fixative via the airways provides for the rapid fixation of larger volumes of tissue, and the expanded air spaces allow for the easier interpretation of lesion orientation and alveolar epithelial and interstitial changes. Tracheal perfusion fixation disadvantages include the possibility that cellular exudates and inhaled particles may be translocated to other areas in the lung during the infusion process. With generalized disease processes, the use of immersion fixation of lung slices for some samples, combined with inflation via airways for other lobes, can provide a good compromise.

UPPER AIRWAY DISEASES

Nose, Nasal Sinuses, Nasopharynx, and Trachea

Rhinitis, Nasal Polyposis, and Sinusitis

Normal nasopharyngeal microflora plays an important protective role against potential pathogens by excluding adherence to and subsequent colonization of the mucosa by more virulent organisms. This adherence is specific, via bacterial adhesins to sugar-containing epithelial surface-binding sites. In circumstances of mucosal injury, the usually nonpathogenic normal flora occasionally can produce problems itself. Mucosal injury can also compromise the attachment sites for normal flora, providing an opportunity for attachment and colonization by pathogenic organisms. Immune compromise, as with certain systemic immunodeficiency or nonspecific stress-associated immune dysfunction, can contribute to immune dysfunction in the nasal cavity and subsequent infection. Finally, prolonged antibiotic therapy can adversely affect normal bacterial flora populations, promoting conditions for opportunistic organisms, including fungi.

Viruses are the primary agents of nasal mucosal damage. Allergens are also a relatively common problem. Other injurious agents include irritant volatile gases, dust, and very low atmospheric humidity as well as certain parasites. Rhinitis generally results from an interaction between viruses or other injurious agents and bacteria or fungi.

Rhinitis can be differentiated according to time course, e.g., acute to chronic, and in relation to morphology. Morphologic categories include serous, catarrhal (mucous), purulent, ulcerative, pseudomembranous, hemorrhagic, or granulomatous inflammation. The course of acute rhinitis generally includes an initial serous response, which can progress to catarrhal then purulent inflammation. The presence of pseudomembranous, ulcerative, or hemorrhagic inflammation indicates very severe mucosal damage. A hallmark of chronic rhinitis is proliferative change, although atrophy is also a potential manifestation. Rhinitis can lead to a number of potential complications, the most common of which is sinusitis. Bronchopneumonia associated with the aspiration of nasal exudate can also occur. Finally, intracranial lesions such as thrombophlebitis, abscessation, or meningitis can occur due to reflux blood flow via the diploic veins, which are valveless.

In serous rhinitis, the mucosa is swollen and variably hyperemic. The swelling is associated with mild respiratory discomfort and subsequent sneezing and snuffling. Thin, clear seromucin secretion is present. Microscopically, the secretion contains small numbers of leukocytes and epithelial cells. There is mucosal epithelial cell hydropic degeneration and cilia loss, and goblet cells and submucosal glands are hyperactive. The lamina propria has edema and mild inflammatory cell infiltration. With time (hours to a few days), changes in glandular secretion and early bacterial infection lead to more severe hyperemia, edema, and swelling. Epithelial cell desquamation and increased leukocyte emigration result in a catarrhal to purulent discharge. Both epithelial regeneration and ulceration may be present. Acute rhinitis is often self-limiting, with treatment directed at palliative measures, such as the use of oral nasal decongestants and/or antihistamine preparations. In the case of allergic rhinitis, environmental management to control allergen exposure and allergen desensitization are also potential measures for control/prevention. Finally, if possible (e.g., with a well-trained great ape), topical corticosteroid sprays are available and potentially very effective.

Chronic rhinitis follows repeated attacks of acute rhinitis, whatever the cause, and generally is complicated by superimposed bacterial infection. This is probably the result of multiple interacting factors, including the compromise of local defense mechanisms, further infection by usually nonpathogenic flora, and self-sustaining inflammation caused by interactions of the infiltrating mixed inflammatory cells and associated inflammatory mediators and

cytokines. Chronic rhinitis can result in atrophic rhinitis, which is characterized by foul odor and epistaxis with nasal obstruction, and results in the presence of crusting, debris, and necrosis of normal tissues and turbinates. Causes include various types of infection, however, many cases, even in humans, are idiopathic (Wood and Douglas, 2010). Treatment requires management of the underlying disease and can include the use of saline nasal douches.

Nasal polyp formation occurs in association with chronic or recurrent inflammation (e.g., allergic rhinitis). The polyps, which are sessile or, with increased size, pedunculated, may be localized or diffusely distributed. The overlying mucosa may be hyperplastic, metaplastic, or ulcerated. The subepithelial tissue is edematous and contains mixed inflammatory cells, which can include neutrophils, eosinophils, plasma cells, and lymphocytes. Subepithelial fibrosis occurs with time. Polyps may impair nasal cavity airflow and slow or obstruct sinus drainage. Treatment includes surgical removal and treatment of the underlying cause for inflammation (e.g., allergic rhinitis).

Allergic rhinitis has been reported in an adult female chimpanzee (Halpern et al., 1989; Dumonceaux et al., 1997) and Japanese macaques (*M. fuscata*) (Sakaguchi et al., 1992, 1999). The report of pollinosis in Japanese macaques (Sakaguchi et al., 1992) describes specific serum IgE to allergens from Japanese cedar trees and refers to reports indicating pollinosis in both wild and captive Japanese macaques throughout Japan. The tested monkeys had clinical signs of sneezing, rhinorrhea, pruritus, and epiphora. The chimpanzee had a long history of upper respiratory tract allergic disease, first confirmed and treated after a 12-year history of clinical signs. Seasonal (March through fall) signs included nasal discharge, impacted nares, open mouth breathing, facial swelling, bilateral epiphora, and an occasional cough. Annual tuberculin tests were negative, and previous hematology, serum chemistry, throat cultures, and thoracic radiographs had no significant abnormalities. A variety of antibiotic regimes produced equivocal results. Initial symptomatic treatment with prednisolone, followed by use of the oral antihistamine terfenadine, 60 mg twice daily, reduced the severity of upper respiratory disease. Both intradermal skin testing and serum IgE (IgE FAST-plus™: fluorescent allergosorbent test) allergy tests indicated specific allergies to a number of species of local trees and grasses. Signs recurred within five years, with increased severity and persistence. Switching to a second antihistamine, loratidine, 10 mg orally once a day, produced only a temporary response. A purulent nasal discharge initially improved with oral cephalexin, 500 mg b.i.d., but then recurred and was unresponsive to an additional antibiotic regimen. Further workup at that time revealed the presence of multiple bilateral nasal polyps. These polyps, plus purulent material and plant fibers resembling hay, were removed from the nasal cavities.

The animal was subsequently started on an oral desensitization regimen, similar to investigational techniques for humans (Sjövall, 1990; Korzeniowska-Zuk, 1992). The combination of endoscopic surgery and immunotherapy eliminated clinical signs during the initial part of the subsequent allergy season, at the time of the report (Dumonceaux et al., 1997).

Additional reports of nasal polyposis in chimpanzees exist (Nichols, 1939; Jacobs et al., 1984). In the report by Jacobs et al. (1984), the cause for the polyposis in a 15-year-old female chimpanzee did not appear to be allergy related, as signs suggestive of allergic respiratory tract disease had not been observed, and radioallergosorbent test (RAST) results were negative for the presence of IgE to common aeroallergens. The polyps were first diagnosed when the animal was 10 years old during evaluation for a purulent nasal discharge. Left untreated, the animal appeared to tolerate the polyps over the next five years, with apparent increasing nasal obstruction to the point that continuous open mouth breathing was necessary. At that time she successfully delivered her second infant and subsequently was sedated prior to transport to a new local. During sedation, respiratory tract compromise occurred, with subsequent cardiac and respiratory arrest and death.

Sinusitis usually is preceded by acute or chronic rhinitis, but occasionally arises in association with tooth root abscesses that extend into the maxillary sinuses. Edema associated with nasal mucosal inflammation contributes to the potential conditions for sinusitis by impeding sinus secretion outflow. Mucocele is a condition in which mucous secretions accumulate without bacterial invasion. When the accumulated material is purulent exudate, the condition is termed sinus empyema. The associated bacterial flora in empyema usually consists of normal mixed oral microflora. Fungi cause particularly severe forms of chronic sinusitis, such as mucormycosis, which is particularly prevalent in individuals with diabetes. Sinusitis often is clinically inapparent unless it has caused facial deformity or a fistula in the overlying skin. The sinus proximity to the brain carries with it increased potential for severe complications, including local osteomyelitis and spread into the cranium and brain. Sinusitis treatment is directed at the primary disease cause (e.g., tooth root abscess, foreign body) and associated infection when present (antibiotics, antifungal therapy) but may also require surgical curettage and drainage.

A case of ethmoiditis/sinusitis has been reported in an 8-month-old mother-raised orangutan (*Pongo pygmaeus*) (Cambre, 1986). The animal presented initially with bilateral exophthalmos and supraorbital swelling, then developed weight loss, depression, and lack of vigor. Physical examination included aspiration of the swellings, which yielded caseous suppurative material with rare Gram-negative rods. *Escherichia coli* was isolated in pure culture.

The response to antibiotic therapy was equivocal. A CAT scan revealed bilateral ethmoiditis, left maxillary sinusitis, bilateral extraconal intraorbital infection, and apparent epidural inflammation. Surgical debridement and drainage was performed, followed by a 6-week period of intravenous antibiotic therapy to treat a mixed bacterial infection. Microscopic appearance of the tissues was compatible with chronic inflammation of the ethmoids, sinus mucosa, bone, and dura. The animal recovered completely, with CAT scan confirmed resolution, and was returned to his parents after four months of separation.

Epistaxis

Epistaxis in individual animals is most commonly caused by trauma. A variety of other causes and associated conditions exist, including allergic rhinitis, sinusitis, nasal polyps, and a number of infections, such as acute viral infections, typhoid fever, nasal diphtheria, pertussis, and malaria. Severe bleeding may occur with congenital vascular anomalies and with thrombocytopenia, clotting factor deficiency, hypertension, and renal failure.

Epistaxis in nonhuman primates has been reported in association with both benign and very severe infections. In particular, viruses such as simian hemorrhagic fever virus and filoviruses can cause generalized bleeding disorders and may present with epistaxis and nasal discharge (Centers for Disease Control, 1990). Occasional outbreaks of acute, self-limiting epistaxis, termed "bloody-nose syndrome," have been reported in groups of cynomolgus macaques (*Macaca fascicularis*) (Cooper and Baskerville, 1976; Olson and Palotay, 1983; Van de Woude and Luzarraga, 1991).

Clinical signs among the reports of bloody-nose syndrome included epistaxis, nasal discharge, sneezing, and eyelid swelling. One report (Olson and Palotay, 1983) also noted supraorbital palpebral bullae associated with cellulitis, whereas another (Van de Woude and Luzarraga, 1991) included wheezing. In all three reported outbreaks, *Branhamella catarrhalis* (currently classified as *Morexella catarrhalis*, and formerly *Neisseria catarrhalis*) was isolated from a number of animals. The report by Van de Woude and Luzarraga (1991) included transmission studies that supported the role of *B. catarrhalis* as an upper respiratory pathogen in cynomolgus macaques causing a syndrome similar to the previously reported bloody-nose syndrome. Antibiotic therapy (penicillin) in that report resulted in diminished clinical signs within 24 hours, although it was noted that some β-lactamase-resistant strains have been recorded in the human literature. Other factors thought to contribute to the severity of clinical disease include concurrent viral or bacterial disease, stress (e.g., recent transport), and/or low humidity. Although no apparent human infection was noted among animal care staff in any of the three reports, *M. catarrhalis* is a recognized human respiratory and otic pathogen, supporting the potential for zoonotic and anthropozoonotic transmission of this organism (Murphy and Parameswaran, 2009). In a similar note, human *M. catarrhalis*-associated disease has comparable fall/winter seasonality as noted in reports of bloody-nose syndrome in macaques. In a more recent study it was found that *M. catarrhalis* could be cultured from 1/5 healthy rhesus macaques and was isolated from 33/33 with bloody-nose syndrome (Bowers et al., 2002). Isolation of the organism was favored by trypticase soy agar with 5% sheep blood at room temperature.

Foreign Body

In the veterinary literature, most intranasal foreign bodies are of plant origin, deposited as a result of inhalation. Other foreign bodies may enter the nasal cavity via palatine defects, self-insertion, or retrograde reflux via the internal nares. Initial signs suggesting intranasal foreign body include sudden onset vigorous and persistent sneezing. Unilateral nasal discharge and obstruction can be suggestive of a foreign body. If the foreign body is dislodged, mild inflammation may still be present for several days. With time, if the foreign body remains in place, sneezing may subside, and the clinical presentation is characterized by the presence of chronic nasal discharge with potential complications such as bacterial and possible fungal infection. A foreign body in the posterior nasal cavity may result in nasopharyngeal drainage that causes gagging and retching. Vegetative foreign bodies are not apparent with radiology. Rhinoscopy provides the opportunity for both recognition and removal of foreign body material. Occasionally, rhinotomy may be necessary.

Signs associated with trachiobronchial foreign body can vary depending on the degree of airway obstruction, lodging site, the length of time it has been present, and the irritant/inflammation-producing potential of the object. Often there is initial acute, severe, paroxysmal nonproductive coughing or respiratory distress. If the initial period of coughing and respiratory distress is missed, a relatively long period of time may pass, during which an occasional cough or slight wheezing may be apparent. At some point, relatively nonspecific systemic signs may occur, including fever, anorexia, depression, and weight loss, which are generally associated with the presence of pneumonia. Radiography of the thorax and neck may reveal soft tissue or mineral density, but this is relatively uncommon. With time, an inflammatory tissue response, including localized bronchial or parenchymal densities, may become more apparent. Definitive diagnosis is generally made with bronchoscopy. If animals with recurrent pneumonia are examined with radiography early after antibiotic initiation and within one week of completion of treatment, focal radiodense areas may indicate the lodging site of the

foreign body. Plant derived (e.g., grass awn) foreign bodies can be particularly troublesome due to difficulty in detection and their potential for migration. Tissue migration can lead to such complications as bronchopulmonary abscess, pneumothorax, pyothorax, discospondylitis, or signs due to penetration of other organs. Treatment consists of foreign body removal and appropriate antibiotic therapy for secondary bacterial infection. Bronchoscopic removal is generally preferred, although a surgical approach may be necessary in some cases.

Marcella and Wright (1985) reported on the intratracheal presence of a 1×1 cm rock in an adult female rhesus monkey. The animal presented with an occasional dry, nonproductive cough that had increased in frequency over a 2-week period. Radiographs revealed an irregularly shaped radiodense object at the tracheal bifurcation. Using a flexible bronchoscope, the object was identified as a triangular, wedge-shaped rock and removed. Coughing decreased immediately after the procedure and ceased one week after bronchoscopy.

In another report (Odkvist and Schauman, 1980), a 15-year-old multiparous female chimpanzee initially was noted to have signs of fatigue and malaise, with reduced appetite, rapid weight loss, episodes of apparent pain, and cough. A few months later, she had a spontaneous abortion during the third month of pregnancy. Subsequent medical workup included thoracic radiography, which revealed a radiopaque foreign body in the right main stem bronchus. With bronchoscopy, the right bronchus at the carina was observed to have swollen mucosa with overlying crusts and contained a dark foreign body covered with purulent discharge. Removal of the crusts and suction made it possible to identify a firmly embedded metallic foreign body, which was extracted. The foreign body consisted of two pieces of 3-cm-long wire resembling fencing material. The animal recovered without complication.

Developmental Anomalies

Cleft Palate

Cleft palate occurs alone or with other defects, and is related to the need for integration of a number of embryonic processes for the development of normal facies and oral cavity. The palate is formed, except for a small rostral contribution from the frontonasal process, from bilateral ingrowth of the maxillary process lateral palatine shelves, which fuse with each other and with the nasal septum. Failure of this fusion generally results in a central, unilateral, or bilateral defect in the hard and/or soft palate. Neonates with palatine defects commonly have trouble nursing, show nasal regurgitation, and are susceptible to secondary bacterial or fungal rhinitis and aspiration pneumonia. Treatment is via corrective surgery. Reports of cleft palate in nonhuman primates are summarized by Wilson (1978), including cleft palate in two "marmosets" (*Saguinus fusicollis*) (Hill 1953−1955; Kraus and Garrett, 1968) and cleft lip and palate in a rhesus monkey (Swindler and Merrill, 1971). A cleft palate and choanal atresia were diagnosed in a neonatal gorilla that died at five days of age (Siebert et al., 1998).

Upper Respiratory Neoplasia

Respiratory system tumors are relatively infrequent in nonhuman primates (Lowenstine, 1986; Beniashvili, 1989). Nasopharyngeal tumors of various kinds have been described, with epithelial tumors occurring most frequently. Of particular note is the apparent propensity for nasal, nasopharyngeal, and oral carcinoma in marmosets (*Callithrix jacchus*) (Baskerville et al., 1984; Betton, 1984; McIntosh et al., 1985). This high rate of occurrence has been suspected to be associated with an underlying oncogenic virus infection, as occurs in Epstein−Barr virus (EBV) associated nasopharyngeal carcinomas of humans. McIntosh et al. (1985) looked for, but were unable to detect, EBV-antibodies in their study. The initial presentation of these animals is facial swelling, with or without nasal discharge, and visual impairment. These signs are relatively common in marmosets, usually related to abscesses of the upper canines, but, at least in marmosets, nasal carcinoma is also important to keep high on the differential diagnostic list. These tumors have a high potential for pulmonary metastasis.

Among other primate species, two reports not included in the reviews by Beniashvili (1989) and Lowenstine (1986) also highlight epithelial tumors, including nasal papillary adenocarcinoma in a Taiwanese macaque (*M. cyclopis*) (Brown et al., 1977) and a nasal cavity carcinosarcoma in a bonnet macaque (*M. radiata*) (Slayter, 1988). The bonnet macaque presented with unilateral left lower eyelid swelling, epiphora, and nasal discharge. The Taiwanese macaque presented with left maxilla swelling. Biopsy was used for diagnosis in both animals. The tumor recurred after attempted surgical excision in the Taiwanese macaque. Both animals were euthanized. In each case, pulmonary metastasis had occurred. Based on radiographic monitoring of the Taiwanese macaque, metastasis was a late development, with metastatic nodules not detected until one year after the initial diagnosis was made. In a more recent review of neoplasia in cynomolgus macaques, a single case of exophytic nasal adenoma was diagnosed, but no further details were given (Kaspereit et al., 2007).

Larynx and Air Sacs

Airsacculitis

Laryngeal air sacs are present in many primate species and are reported sites of infection for owl monkeys (*Aotus* sp.) (Giles et al., 1974), pig-tailed macaques (*M. nemestrina*)

(Brown and Swenson, 1995), baboons (*Papio* sp.) (Lewis et al., 1975; Gross, 1978), chimpanzees (Strobert and Swenson, 1979), pygmy chimpanzees (bonobo, *P. paniscus*) (Brown and Swenson, 1995), gorillas (Hastings, 1991), and orangutans (Guilloud and McClure, 1969; Clifford et al., 1977; Cambre et al., 1980; McManamon et al., 1994; Lawson et al., 2006) (Figure 9.4). The report by Hastings (1991) details the recognition and successful treatment of air sac infection in a wild, free-ranging mountain gorilla (*Gorilla beringei beringei*). The potential complications of this infection, including fatal bronchopneumonia and sepsis, make it extremely important to monitor animals for signs of air sac infection and to promptly treat such infections when they occur.

Nonspecific clinical signs for airsacculitis include halitosis, lethargy, and anorexia, as well as such respiratory signs as nasal discharge, intermittent cough, and rapid, shallow breathing patterns. The latter signs tend to occur with progressive disease and are indications of lower respiratory system involvement. At times the only sign is the presence of cervical swelling, corresponding to air sac distension. The variable consistency of air sac exudate (liquid to consolidated and tenacious) can make diagnosis by palpation and ballottement extremely difficult in some cases. Radiography may reveal an air−liquid interface in the air sac. For problematic cases, endoscopy, aspiration (with or without irrigation), and ultrasound have been useful for confirmation of airsacculitis.

Although the owl monkey report (Giles et al., 1974) found *Klebsiella pneumoniae* to be a primary cause of airsacculitis in that species, reports of airsacculitis in other primate species have characterized the infections as mixed, including Gram-negative and Gram-positive enteric organisms (*Proteus vulgaris, P. morganii, Pseudomonas aeruginosa, Escherichia coli,* streptococci, *Staphylococcus* spp., *Aerobacter cloacae*, etc.). Sensitivity testing is essential for optimal therapy. McManamon et al. (1994) note that chronically infected air sacs may be compartmentalized, with different bacterial populations in different compartments, and recommend separate cultures of each compartment.

The goal of treatment is to clear infection, prevent aspiration and secondary pneumonia, and prevent recurrence (Brown and Swenson, 1995). Infection severity and time course, as well as primate species (and air sac anatomy), are important variables in the choice and effectiveness of the treatment technique. Systemic antibiotics alone or in combination with simple exudate aspiration are not effective in the treatment of even simple air sac infection. The presence of secondary pulmonary infection is an important indication for systemic antibiotic use. A 1- to 2-week period of repeated closed irrigation and drainage with saline, followed each time with local antibiotic instillation, can be effective for mild infection. Gross (1978) describes the effectiveness of surgical air sac ablation in a baboon. This is much more difficult, if not impossible, in great apes, in which the air sacs extend into the axillary region and, in male orangutans, even around the mandible toward the ears and cheeks. Severe or persistent infections require open drainage. Successful control of chronic, progressive air sac infection in animals has been achieved using intermittent reevaluation, drainage, and antibiotic therapy in some animals and surgical intervention creating a transient stoma or permanent air sac marsupialization in others (Strobert and Swenson, 1979; Hill et al., 2001). Chronic air sac marsupialization prevents extensive exudate accumulation, but chronic aspiration of small amounts of exudate can continue, leading to chronic pulmonary infection or immune complex glomerulonephritis. Brown and Swenson (1995) and McManamon et al. (1994) briefly describe a promising technique to eliminate the occurrence of secondary pneumonia in orangutans with chronic or recurrent airsacculitis through surgical closure of the paired ostia between the larynx and air sacs.

LOWER RESPIRATORY TRACT DISEASES

Bronchi and Bronchiolar Disease

Asthma

Asthma is a disease in which episodic, reversible bronchoconstriction occurs in response to any of a variety of stimuli. This generalized bronchoconstriction results in the clinical hallmarks of asthma, including dyspnea, coughing, and wheezing. A less common presentation of asthma involves intermittent episodes of nonproductive cough or exertional dyspnea. Most asthmatics are asymptomatic between attacks; however, a subset of individuals with chronic disease may develop emphysema, chronic bronchitis or pneumonia, or cor pulmonale and heart failure.

FIGURE 9.4 Chronic airsaccultitis. Sumatran orangutan (*Pongo abelii*) female. Ventral view of opened airs sacs with tenacious, "peanut butter-like" exudate. *E.coli*, hemolytic *E.coli* and *Pseudomonas aerugenosa* were cultured. *(UC Davis VMTH)*

A classification for asthma generally includes two basic types: extrinsic and intrinsic. Extrinsic asthma is associated with a type I hypersensitivity reaction induced by exposure to an extrinsic antigen. Subclassification of extrinsic asthma includes atopic asthma, which is precipitated by specific allergens; "occupational" asthma, which is precipitated by exposure to chemicals; and allergic bronchopulmonary aspergillosis, which is associated with the *Aspergillus* colonization of airways followed by development of *Aspergillus*-specific IgE. Intrinsic asthma is associated with such precipitating factors as respiratory tract infection and inhaled irritants. All types of asthma may be precipitated by cold, stress, or exercise, and patients with one form may also be likely to experience asthma associated with another form.

Specific clinical diagnosis of asthma is based on pulmonary function testing that demonstrates reversible airway obstruction or increased airway responsiveness. In human medicine, reversible airway obstruction is determined by measuring the 1-second forced expiratory volume (FEV_1), with reversible airway obstruction defined as a 15% or greater increase in FEV_1 following two puffs of a β-adrenergic agonist. Increased airway responsiveness can be diagnosed by demonstrating increased airway responsiveness to challenge with histamine, methacholine, or isocapnic hyperventilation of cold air. In veterinary medicine, techniques to test lung compliance and resistance are being used experimentally for the assessment of airway obstruction in a variety of conditions (King and Hendricks, 1995). For allergy-associated asthma, nonspecific tests that support the possibility of hypersensitivity include blood eosinophil count and quantitative serum IgE levels, as well as skin testing and serum IgE (IgE FAST-plus™: fluorescent allergosorbent test (3M Diagnostics)) tests for various specific antigens. Radiographs that demonstrate hyperinflation are also not, in and of themselves, diagnostic.

Gross morphologic changes with asthma include the presence of lung hyperinflation, often with small areas of atelectasis. Bronchi and bronchioles are occluded by thick, tenacious mucous plugs. Microscopically, numerous eosinophils and Charcot−Leyden crystals are present. The latter are crystalloid collections made up of eosinophil membrane protein. The mucous plugs contain whorls of shed epithelium. Other findings include bronchial epithelium basement membrane thickening, bronchial wall edema, and an inflammatory infiltrate that includes 5−50% eosinophils, submucosal gland hyperplasia and bronchial smooth muscle hypertrophy. With time, emphysematous changes may occur, and bronchitis may be present due to secondary bacterial infection.

The most successful method for treating asthma is through environmental modification, eliminating specific agents that cause the condition, such as the type of cage bedding. In addition, desensitization, as described earlier for allergic rhinitis, provides an additional possibility for specific treatment. Nonspecific treatment is directed toward relieving bronchoconstriction and reducing airway inflammation. To control severe inflammation, systemic corticosteroids are used. Drugs used for bronchodilation include oral albuterol, aminophylline, and theophylline. Topical (inhalant) drug preparations are used in human practice for chronic asthma control and prevention. These include bronchodilators (e.g., albuterol), corticosteroids (e.g., beclomethasone), and mast cell stabilizers (e.g., cromolyn sodium).

Asthma has been recognized in chimpanzees (Janssen, 1993) and has been experimentally induced and studied in susceptible cynomolgus and rhesus macaques (Gundel et al., 1992). Inhalant allergy and asthma in chimpanzees and bonobos have been characterized by nonspecific chronic respiratory disease with an increased susceptibility to bacterial pneumonia, often with associated problems, including rhinitis and chronic sinusitis. Treatment for such animals is reported to include long-term antibiotic therapy to eliminate chronic infections and antihistamines or bronchodilators for dyspneic episodes. Experimental work with cynomolgus macaques involved exposure of animals to inhaled *Ascaris suum* extract as part of a study of the pathogenesis of the acute- and late-phase bronchoconstriction recognized in human asthmatics. Some animals exhibited an acute bronchoconstriction in response to the allergen, as well as the less common (among human asthmatics) delayed bronchoconstriction, providing a valuable model for the pathogenesis of the delayed response. Other models include house mite dust exposure in cynomolgus and rhesus (Schelegle et al., 2001; Van Scott et al., 2004) and ozone exposure in rhesus (Plopper et al., 2007).

Eosinophilic Bronchitis

Eosinophilic bronchitis without asthma is recognized in humans as a cause of corticosteroid responsive chronic cough without the airway reactivity that characterized true asthma (Gonlugur and Gonlugur, 2008). The etiology is undetermined, but some cases have been associated with work place exposure to aerosols or particulates. A single case of fatal eosinophilic bronchitis has been described in a rhesus macaque (Christal et al., 2008). The 3-year-old, outdoor-housed animal was found in severe respiratory distress and was euthanized. No gross lesions were noted, but on histology bronchioles were filled with mucus, sloughed epithelium, and macrophages while the walls were heavily infiltrated by mixed inflammatory cells in which eosinophils predominated. The diagnosis of asthma was excluded because of the absence of smooth muscle hyperplasia and mural mast cell infiltration.

Lungs

Atelectasis and Fetal Distress

Atelectasis refers to incomplete lung expansion (congenital-neonatal atelectasis-atelectasis neonatorum) or to collapse of a previously inflated lung (acquired atelectasis). Complete atelectasis occurs in lungs of stillborn animals (fetal atelectasis), as they have never been aerated. The fleshy, dark reddish-blue lungs do not float. Alveoli are lined by rounded epithelial cells, and alveolar lumens contain fluid, sloughed epithelial cells from aspirated amniotic fluid, and sometimes bright yellow meconium particles. Andrews (1974) describes how careful assessment of the alveolar lumen components can provide important evidence of the circumstances of fetal death, including fetal distress and possible placentitis. Large numbers of squamous cells in alveolar lumens (small numbers are normal in the term fetus), especially if meconium is also present, are evidence of amniotic fluid aspiration during exaggerated respiratory movements of the distressed fetus.

Patchy congenital atelectasis in neonates may be associated with incomplete expansion and/or acquired atelectasis of a briefly aerated lung. Incomplete expansion can be associated with weak respiratory movement due to general debilitation or central nervous system damage. Other possible causes include laryngeal dysfunction, airway obstruction, and lung or related thoracic structure anomalies. The gross appearance of patchy atelectasis is of dark red areas of variable size that are depressed below the surface of the surrounding aerated lung. These areas are flabby rather than consolidated as with inflamed lung. Microscopically, the alveolar walls are closely apposed, with only small amounts of fluid, epithelial debris, and alveolar macrophages present.

The presence of extensive neonatal atelectasis is a feature of neonatal respiratory distress syndrome (RDS) or hyaline membrane disease (HMD). The fundamental defect in RDS is a deficiency of pulmonary surfactant, often associated with inadequate surfactant production by type II epithelial cells due to fetal immaturity (pre-term births) or to more specific metabolic derangement of their surfactant synthesis, such as might occur with fetal hypothyroidism and, possibly, hypoadrenocorticism. The high levels of insulin in diabetic mothers can counteract the effects of endogenous corticosteroids, which are particularly important for the induction of surfactant formation in the fetal lung, resulting in a higher risk for RDS in the infants of diabetic mothers. Other factors can contribute to RDS, such as fetal asphyxia, decreased pulmonary arterial blood flow, amniotic fluid aspiration, and inhibition of surfactant by fibrinogen, other edema fluid constituents, or components in aspirated amniotic fluid, particularly meconium. An additional contributing factor comes with the need for oxygen therapy and mechanical ventilation in these patients. High concentrations of oxygen for prolonged periods can cause toxic pulmonary changes. In particular, mechanical ventilation and oxygen toxicity can give rise to a subacute or chronic condition called bronchopulmonary dysplasia (BPD). Fetal and neonatal atelectasis, as well as RDS, are reported as causes of perinatal and neonatal death in infant *Macaca nemistrina* (Morton et al., 1979). Primates also provide experimental models of RDS (HMD) and BPD (Coalson et al., 1982; Escobedo et al., 1982; Hessler et al., 1985; Coalson, 1988), as well as meconium aspiration as a cause of RDS (Block et al., 1981; Carey, 1988). Macaques, especially pig-tailed and rhesus, have been used extensively in studies of lung development, effects of prematurity, and efficacy of various therapeutic modalities such as glucocorticoids (Bunton and Plopper, 1984; Avdalovic et al., 2009).

Affected lungs in RDS are largely atelectic. They are heavy, fleshy, often edematous, and generally sink in fixative. Cream-colored or red foam is often present in airways and exudes from cut surfaces. Characteristic microscopic changes include alveolar septal congestion, variably collapsed or fluid-filled alveoli, and the presence of acidophilic hyaline membranes that line terminal bronchioles, alveolar ducts, and random, usually proximal, alveoli. Focal hemorrhage and interstitial edema are also common. Persistent respiratory distress occurs with BPD. In bronchopulmonary dysplasia lesions include epithelial hyperplasia and squamous metaplasia in large airways, plus thickened alveolar walls, with peribronchial and interstitial fibrosis.

Treatment of RDS must approach the basic defect, inadequate pulmonary exchange of O_2 and CO_2, as well as deal with secondary problems of metabolic acidosis and circulatory insufficiency. This requires close monitoring of heart and respiratory rates, blood gases, and pH, as well as provision of general support to maintain blood glucose levels, blood pressure, and temperature. It is necessary to provide increased oxygen levels, often with respiratory assistance via mechanical ventilation (Hermansen and Lorah, 2007). For immature lungs, it is now possible to provide exogenous surfactant intratracheally, a measure that is extremely helpful in allowing a minimization of the degree and time of mechanical ventilation assistance. Minimizing mechanical ventilation can help avoid potential problems, including barotrauma, oxygen toxicity, nosocomial pneumonia, tracheal stenosis, and deconditioning of respiratory muscles. The added complication of meconium aspiration, with associated inflammation and neutralization of surfactant, has led to further intervention, including pulmonary lavage with surfactant solutions to wash out inflammatory products and replace affected surfactant as well as the use of extracorporeal membrane oxygenation (ECMO).

Acquired atelectasis most commonly occurs due to airway obstruction, as would occur with the presence of mural inflammation, exudates, parasites, aspirated foreign material, granulomas, or tumors. Compression can also cause atelectasis, as with pleural or intrapulmonary space-occupying lesions including hydrothorax, hemothorax, pneumothorax, exudative pleuritis, and mediastinal and pulmonary tumors. Contraction atelectasis occurs when fibrosis of pleura or parenchyma prevents expansion. Recognition and treatment of the primary problem can lead to the resolution of acquired atelectasis. Artifactual massive atelectasis occurs when animals die while being maintained with 80–100% oxygen in intensive care settings. Oxygen is rapidly absorbed into tissues causing the lungs to be devoid of gas at the time they are examined postmortem.

Circulatory Disturbances and Vascular Lesions

A variety of circulatory disturbances can affect the lungs, including problems involving pulmonary vessels or the heart, as well as pulmonary vascular changes secondary to primary pulmonary disease. Functionally, the most important consequence of these problems is hypoxemia due to ventilation/ perfusion mismatching. Attenuation of alveolar capillaries associated with emphysema or pulmonary fibrosis can lead to pulmonary ischemia. Pulmonary arterial obstruction can lead to pulmonary congestion due to the presence of the dual pulmonary blood supply (pulmonary and bronchial arteries) and extensive collateral circulation. Active hyperemia is a component of acute inflammation and occurs with a variety of problems that cause acute pulmonary injury. Pulmonary congestion occurs with multiple problems, including left-sided or bilateral cardiac failure, and conditions that lead to the redistribution of blood from systemic to pulmonary circulation. Such redistribution commonly occurs terminally and can also be caused by acute hypothalamic damage.

Pulmonary Edema

Pulmonary edema is a very common pulmonary abnormality associated with increased capillary hydrostatic pressure, increased air–blood barrier permeability, or a combination of both. Pulmonary edema is most often due to increased microvascular hydrostatic pressure, as occurs in association with left-sided or bilateral cardiac failure (cardiogenic edema) and also can occur with hypervolemia, as with excessive fluid therapy. Decreased plasma oncotic pressure due to hypoproteinemia or hyponatremia, as might occur with enteropathies or fluid therapy dilution, can also lead to pulmonary edema. In addition, acute brain injury can lead to pulmonary edema (neurogenic edema) due to increased microvascular pressure associated with catecholamine release-caused pulmonary hypertension followed by increased capillary permeability.

Damage to alveolar type I epithelium and capillary endothelium leads to rapid onset edema with a higher protein concentration than in cardiogenic forms. Among the agents that cause such damage are corrosive gases (including 80–100% oxygen), systemic toxins, endotoxins, and shock-like states. Many of the toxic or shock-like states that lead to pulmonary injury-associated edema can cause abnormalities associated with acute interstitial pneumonia and acute respiratory distress syndrome (ARDS, see below).

Pulmonary Thromboembolism

As a capillary bed through which the entire right ventricular output flows, the pulmonary circulation is situated to catch emboli originating in the systemic venous circulation. Various possible types of emboli bring with them a number of possible outcomes. Bacterial emboli can cause acute pulmonary edema and interstitial pneumonia. Infected thrombi can generate septic emboli, which can cause thromboembolism, arteritis, multiple abscessation, and sometimes suppurative pneumonia. Tumor emboli can lead to metastatic neoplastic foci. Fat emboli can occur in association with bone fracture and with hepatocyte rupture in severe hepatic lipidosis, lodging in pulmonary capillaries and appearing as a large empty capillary distention in paraffin-embedded sections. An incidental finding associated with intravenous injections is hair emboli. This has been described by Kast (1994).

Pulmonary thrombosis can occur with blood stasis, in hypercoagulation states, or in association with endothelial damage. Pulmonary embolism and endarteritis can also predispose to thrombosis. DiGiacomo et al. (1978) report a case of pulmonary arteriosclerosis and thrombosis in a cynomolgus macaque. The animal was found dead. A saddle thrombus was present at the initial bifurcation of the pulmonary artery, with complete occlusion of the left pulmonary artery. Microscopic examination revealed generalized pulmonary arteriosclerosis, with intimal and medial thickening (endothelial hyperplasia, subendothelial fibrosis, and medial smooth muscle hyperplasia). Cause and pathogenesis for this condition were not determined. A similar case has been reported by Ulland (1968). Diagnosis of pulmonary thromboembolisms is usually a postmortem event, however, pulmonary angiography techniques have been described for use in experimental settings (Neeman et al., 2004).

Pulmonary Hemorrhage

Pulmonary hemorrhage can occur by vascular rhexis or diapedesis. It can result from insults as coarse as chest trauma or as subtle as microvascular endothelial damage. It may reflect a primary pulmonary problem or a systemic problem such as clotting disorders. Pulmonary hemorrhage may be occult or result in hemoptysis; it may be focal,

multifocal or diffuse. Diffuse alveolar hemorrhage is a potentially life-threatening condition characterized by cough, hemoptysis (absent in a third of human patients), dyspnea, anemia, and diffuse radiographic pulmonary infiltrates. In humans it results from "alveolar capillaritis" (inflammation directed toward and damaging the capillaries), other forms of acute alveolar damage (see ARDS), coagulopathies, and heart disease (left-sided heart failure) (Lara and Schwartz, 2010). In nonhuman primates, pulmonary hemorrhage is often a reflection of viral diseases, such as the hemorrhagic diseases (Ebola filoviruses, Simian hemorrhagic fever arterivirus, varicella-like viruses, etc.) or acute alveolar damage secondary to infections or experimental interventions such as marrow transplantation (Gray, 2003; Hukkanen et al., 2009).

Pulmonary Arteriopathy/Pulmonary Hypertension

Pulmonary hypertension is a progressive syndrome in which there is median hypertrophy, intimal thickening or plexiform change in muscular arteries and arterioles of the lung (Dorfmuller et al., 2003). The exact etiopathogeneis of this syndrome in humans is not fully elucidated; however, endothelial injury and vascular reactivity, probably mediated by inflammatory cytokines, are thought to play a role, along with a possible genetic susceptibility. The syndrome occurs in human AIDS patients and can be induced by monocrotaline in rodent models. An occlusive arteriopathy has been described in macaques infected naturally and experimentally with simian immunodeficiency virus (SIV) (Chalifoux et al., 1992) or SHIV-nef viral constructs (Sehgal et al., 2009). Cytomegalovirus infection of pulmonary vascular endothelium has been implicated in some of the cases in AIDS patients and SIV-infected macaques (Yanai et al., 2006). Clinical signs of pulmonary hypertension include respiratory insufficiency manifest as dyspnea on exertion, progressive right-sided heart failure (due to cor pulmonale), and eventual death (Hegewald et al., 2007). There is no cure, and treatment options are limited, but vasodilation with calcium channel blockers offers relief in a small percentage of humans (Arunthari et al., 2010).

Lung Inflammation — Pneumonia

Pulmonary inflammation varies according to the type of initiating agent and the route of entry, distribution, and persistence. Pneumonia in nonhuman primates is often associated with abnormal respiration (Robel-Tillig et al., 2003) and can be clinically difficult to diagnose when cough or altered respiration are not present. A useful morphologic classification that gives clues regarding pathogenesis and possible etiology focuses on the initial site of involvement and pattern of spread. Three categories in this classification scheme are bronchopneumonia, lobar pneumonia, and interstitial pneumonia.

Initiation of inflammation by agents arriving via an aerogenous route generally results in bronchopneumonia, usually originating at the bronchioalveolar junction, often as an extension of bronchial inflammation. Such inflammation often is located in cranioventral lung regions in quadrapedal species and in the lower lobes in humans and more bipedal or upright-stanced nonhuman primates. Bacteria are the major cause of clinically significant bronchopneumonia, often in association with predisposing factors such as viral infection or severe stress. Lobar pneumonia is basically similar to bronchopneumonia, with the key differentiation being the presence of extensive consolidation with uniform parenchymal involvement as opposed to a recognizable bronchiolar orientation.

Interstitial pneumonia is characterized by diffuse or patchy damage to alveolar septa. Inflammatory features generally include an early exudative response, followed by proliferative and fibrotic responses. The acute injury is caused by or associated with such conditions as severe viral pneumonia (which often begins at the bronchiolar-intersitial junction as "bronchointersitial pneumonia"), chemical lung injury, acute pancreatitis, shock, and septicemia. Interstitial pneumonia is generally associated with a hematogenous exposure route, although aerogenous exposure to very high concentrations of toxic gases can also produce severe diffuse damage. An exception to the often diffuse nature of hematogenous exposure occurs with chemicals that are not themselves toxic, but which are metabolized into toxic metabolites by localized cells such as Clara cells, which in turn are the only cells that are injured.

Pneumoconioses, initiated by inhalation of particulate matter, involve a chronic progressive process that starts with aerogenous exposure; however, they often are not clinically apparent until after the initially terminal bronchiole-oriented process of granulomatous inflammation or fibrosis has spread into adjacent parenchyma.

Pulmonary abscesses occur in association with focal residues of severe suppurative inflammation of bronchopneumonia, or with septic emboli. Those arising from suppurative pneumonia often are oriented cranioventrally, whereas hematogenous sources often lead to multiple, widely distributed abscesses. Direct traumatic penetration of the lung and aspiration of foreign bodies such as plant awns are also recognized causes of pulmonary abscess.

Adult Respiratory Distress Syndrome

Adult (acute) respiratory distress syndrome (ARDS) is a term that is applied to acute, diffuse alveolar damage and infiltrative lung disease with severe life-threatening respiratory insufficiency, tachycardia, cyanosis, and severe arterial hypoxemia that is not responsive to oxygen therapy. Severe pulmonary edema is generally present, lung compliance is decreased, and a diffuse alveolar infiltrative

pattern is apparent in thoracic radiographs. Adult respiratory distress syndrome is associated with a variety of etiologic agents, including (1) gastric content aspiration; (2) inhalation of toxic fumes; (3) oxygen toxicity; (4) near drowning; (5) pulmonary contusion; (6) drugs including heroin, salicylate, and paraquat; (7) pneumonitis (bacterial, viral); (8) sepsis syndrome; (9) pancreatitis; (10) multiple transfusions; (11) fat embolism; and (12) amniotic fluid embolism. The syndrome often occurs in the context of the systemic inflammatory response syndrome (SIRS) associated with a "cytokine storm" of acute phase inflammatory mediators (Hukkunan et al., 2009). Naturally occurring cases have been reported in two macaques, one with post-operative sepsis and the other with neurogenic trauma (Fremont et al., 2008). The authors have seen similar cases in New World and Old World primates, usually secondary to severe systemic bacterial infections such as yersiniosis (Figure 9.5).

Nonhuman primates have been important models for ARDS, particularly with regard to pathophysiologic mechanisms (Balis et al., 1974; Holcroft et al., 1977; Campbell et al., 1984; Revak et al., 1985; Hangen et al., 1987; Schlag et al., 1992; Drake et al., 1993; Taylor et al., 1994). In addition to diffuse pulmonary damage, secondary compromising of pulmonary surfactant also generally occurs. The complexity of ARDS, pathophysiology contrasts with neonatal respiratory distress syndrome, in which the primary problem involves inadequate pulmonary surfactant production associated with lung immaturity, along with the highly compliant nature of the infant chest wall. Despite the variety of potential causes, ARDS, clinical characteristics, pathophysiologic derangement, and general supportive measures are similar. Untreated ARDS is almost uniformly fatal. With the current level of treatment, prognosis is still poor, with mortality in humans of 50−60%. Treatment includes mechanical ventilatory support and identification and treatment of the primary

problem. For sepsis-associated ARDS, identification of the source of infection and responsible organism(s) is necessary. Treatment of the pulmonary injury focused on the variety of possible bacterial products, and factors involved in the injury and inflammatory process have been proposed and are subjects of clinical trials, but no single clear-cut strategy exists. These strategies include use of such things as antibodies to endotoxin and a variety of chemokines, as well as the administration of exogenous surfactant and judicious use of corticosteroids. Modalities such as ECMO and ventilation, as described for neonatal respiratory distress syndrome (above) are also used.

Pulmonary Neoplasia

Reviews of neoplasia in nonhuman primates note a low relative prevalence of primary pulmonary tumors most of which were malignant epithelial tumors (Giddens and Dillingham, 1971; Lowenstine, 1986; Beniashvili, 1989). Among the case reports of spontaneous primary pulmonary tumors in nonhuman primates are multiple peripheral carcinoid tumors in the lungs of a rhesus monkey (Giddens and Dillingham, 1971); a bronchial adenoma in a lion-tail macaque (*M. silenus*) (Griner, 1983); a bronchioalveolar neoplasm of a possible type II alveolar epithelium origin in a bonnet macaque (Nicholls and Schwartz, 1980); a bronchogenic squamous cell carcinoma in a Sykes monkey (*Cercopithecus mitis stuhlmani*) (Suleman et al., 1984); and a clear cell carcinoma in a pig-tailed macaque (Tsai and Giddens, 1985). An additional report describes squamous cell carcinoma of the prepuce and penis of a rhesus monkey with metastasis to the lungs (Hubbard et al., 1983).

A more recent review of spontaneous neoplasms in cynomolgus macaques reported 33 animals with neoplasms (<1% of necropsied animals) of which six involved the lung and airways (Kaspareit et al., 2007). These included: two pulmonary squamous cell carcinomas, one bronchoalveolar carcinoma, two bronchiolar papillomas, and one chondromatous hamartoma.

Among descriptions of experimental induction of pulmonary neoplasia is the occurrence of pulmonary epidermoid carcinoma in an owl monkey (*Aotus trivirgatus*) that had been inoculated intratracheally 350 days earlier with 7,12-dimethylbenz[a]anthracene (DMBA) and *Herpesvirus saimiri* (Giddens, 1974). Allen et al. (1970) described an 18-year-old rhesus monkey with multiple small carcinoids (bronchial adenomas) in the lung, associated with exposure to 1100 roentgens of X-irradiation between the ages of 2 and 6 years. Death in this animal, which also had four other unrelated tumors in other areas of the body, was due to the effects of severe diarrhea. Squamous (epidermoid) carcinoma of the lung occurred in two of six galagos (*Galago crassicaudatus panengiensis*) that

FIGURE 9.5 Severe acute alveolar damage (ARDS) secondary to *Yersinia pseudotuberculosis* septicemia and shock. Old World monkey (*Allenopithecus nigriveridis*). (UC Davis, VMTH)

received a weekly intratracheal instillation of 3−15 mg of benzo[*a*]pyrene combined with an equal weight of powdered ferric oxide over a 67- to 69-week period (Crocker et al., 1970). A single bronchial fibrosarcoma has been reported in a rhesus monkey that died due to pulmonary fibrosis nine years following experimental inhalation of plutonium-239 (Hahn et al., 1987).

DISORDERS OF THE DIAPHRAGM, PLEURA, AND MEDIASTINUM

Bauer and Woodfield (1995) provide a detailed review of the variety of problems in veterinary medicine associated with the diaphragm, pleura, and mediastinum.

Diaphragm

The most common disorder of the diaphragm is diaphragmatic hernia. This term refers to disorders in which abdominal viscera encroach on or enter the thoracic cavity via a diaphragmatic defect. The abdominal viscera may be free in the pleural space or be contained within a hernial sac. The herniation can occur at any level and may be congenital or acquired. Reports of congenital diaphragmatic hernia are summarized by Wilson (1978), including cases in a baboon fetus (Hendrickx and Gasser, 1967), a chimpanzee (McClure, 1972), a rhesus and a cynomolgus monkey (Dalgard et al., 1975), and a squirrel monkey. The relatively common occurrence of congenital retrosternal diaphragmatic defects has been documented in the endangered golden lion tamarins (*Leontopithecus rosalia*) being captive-bred for release back into the wild in Brazil (Montali, 1993).

Diaphragmatic hernia may present as an acute, subacute, or chronic disorder. A vague history of episodic gastrointestinal distress may be present. There may be low-grade respiratory signs, possibly associated with exercise or posture (recumbency). Signs may be progressive and intensify over time. The presence of a subclinical hernia may be unmasked by the development of secondary problems, including: (1) gastric dilatation of a herniated stomach, with subsequent lung compression and dyspnea; (2) intrathoracic splenic torsion; (3) intrathoracic bowel obstruction; and (4) cholangitis or cholangiohepatitis secondary to liver lobe incarceration. Definitive diagnosis is difficult, with radiography being the most useful technique, particularly contrast studies (barium swallow, contrast pleurography, contrast peritoneography, etc.). Treatment involves surgical correction (Randolph et al., 1981).

Pleura

The pleura consists of a membrane of mesothelial origin. It covers the surface of the chest wall (parietal pleura),

mediastinum, and lung (visceral pleura). The pleural cavity is a potential space that contains a few milliliters of fluid, which provide lubrication during respiratory motion. This fluid is serum-like, with a total protein level of 0.3−4.1 g per deciliter. The pleural space can be imaged radiographically with CT scans being more sensitive than flat films (Heffner et al., 2010).

Numerous processes can affect the pleural surface, often causing accumulation of fluid within the pleural space and/or adhesions between the visceral and parietal pleura. Pleural inflammation and effusions in humans are often associated with pain (pleurisy), which may be difficult to assess in nonhuman primates (Kass et al., 2007). Apparent respiratory difficulty is the most common sign occurring with pleural effusion. The primary problem causing pleural effusion may contribute to other signs, including cough or fever. Diagnostic techniques range in invasiveness and potential diagnostic yield. Generally, more invasive techniques are needed for specific diagnosis. The clinical situation helps dictate whether the early use of invasive diagnostic procedures is appropriate, with a more serious clinical condition supporting the earlier use of invasive techniques (Medford et al., 2010; Mishra and Davies 2010).

A variety of problems can produce pleural effusion (English and Leslie, 2006). Pleural effusions can be classified as transudates or exudates, serous, chyous (containing lymph), hemorrhagic, or suppurative, or combinations which can be diagnosed by fluid analysis and cytology (Porcel, 2010). Congestive heart failure, both right-sided and biventricular, is a major cause of serous pleural transudates which may progress to more inflammatory exudates over time. This condition can coexist with other disorders, including neoplasia, parapneumonic effusion, and pulmonary embolism or thrombosis. Pleural tumors are usually metastatic tumors, although spontaneous malignant mesothelioma has been reported in an adult female olive baboon (*Papio anubis*) (Fortman et al., 1993). Pleural tumors generally produce effusion via the obstruction of pleural lymphatics, although other secondary mechanisms may also contribute to or cause the effusion. Spontaneous chylothorax is a reported complication of intravenous catheters in rhesus macaques (Olson and Anver, 1979).

Pleural effusions can occur as a secondary effect of pneumonia (parapneumonic effusion), characterized as serous or hemorrhagic, sterile effusions or suppurative exudates as direct extension of inflammation from the interior of the lung. Pneumonia due to *Streptococcus pneumoniae* is notorious in this regard. Empyema, or pyothorax, is the accumulation of infected purulent exudate (pus) within the pleural space. Three routes for thoracic invasion of microbial agents include (1) hematogenous or lymphatic; (2) spread from an adjacent structure, e.g., severely affected lung, ruptured esophagus, or mediastinitis; or (3) direct introduction via penetrating

trauma, foreign bodies, thoracentesis, or surgery. An example of the second route has been reported for an African green monkey (*Chlorocebus* sp.) (Stills and Rader, 1982). The occurrence of empyema is a medical emergency and treatment should be initiated immediately, including the possible use of tube thoracostomy to achieve effective drainage (Carter *et al.*, 2010).

Mediastinum

The mediastinum is the central (midline) portion of the thoracic cavity. It contains all of the extrapulmonary structures of the cranial and caudal thoracic cavity, including esophagus, trachea, thymus, lymph nodes, nerves, and major blood vessels. Signs of mediastinal disease are often nonspecific and vary in association with lesion size, location, pathologic consequences, and peripheral vascular signs. Space-occupying lesions, such as thymic lymphoma or thymoma, can produce obstruction of the vena cava, with associated cranial edema and swelling. Respiratory signs may occur in relation to airway or pulmonary parenchymal compression or mass effect limiting expansion of the lungs. Signs of upper airway obstruction, changes in vocalization, and stridor may be the primary clinical signs. Mediastinal inflammation (mediastinitis) can result from extension from cervical abscesses, pulmonary hilar lymphadentitis or other inflammatory processes within the thoracic cavity. Interestingly, mediastinitis is reported to occur in almost a third of cynomolgus monkeys with experimental inhalation anthrax (Vasconcelos et al., 2003).

VIRAL DISEASES

In the human primate, respiratory viral infections in the form of the "flu" and the "common cold" are familiar and annoying conditions caused by agents of several genera, including rhinoviruses (Picornaviridae; Rhinovirinae), adenoviruses, paramyxoviruses (including respiratory syncytial virus and parainfluenzaviruses 1, 2, 3 (also called paramyxoviruses viruses 1, 2, and 3)), metapneumovirus, and orthomyxoviruses (influenza A and B) (see Table 9.2). Nonhuman primates are also susceptible to many of these infections, although only in the apes, and especially the chimpanzees (*Pan troglodytes* and *P. paniscus*), are colds a common and regular problem. Much of the work on the natural history of simian respiratory viral infections dates from the 1960s and 1970s, although nonhuman primates are still used as animal models in the study of influenza and the newly described human metapneumovirus. Many viruses can affect both the upper and lower respiratory tract. In the lungs they tend to cause a bronchointerstitial pneumonia in which the initial attack causes widespread damage to the terminal bronchioles and alveolar ducts. Bronchiolitis obliterans, in which there is fibrous repair and occlusion of bronchioles by fibrous plugs, is a potential, but rare, sequela to viral infections or other insults (e.g. toxins, aspirated gastric content) to this location (Aguerre et al., 2010).

Paramyxoviruses

Respiratory Syncytial Virus/Chimpanzee Coryza Agent

Several species of nonhuman primates can be infected experimentally with RSV, including *Cebus* spp., *Saimiri* spp., *M. mulatta*, *M. radiata* and *P. troglodytes.* However, only the chimpanzee develops significant clinical illness (Belshe et al., 1977; Clarke et al., 1994; Simoes et al., 1999) and is therefore an essential animal model for understanding this potentially devastating disease of young children. Chimpanzees are often naturally infected and were the species from which this agent was initially isolated in 1956 (Morris et al., 1956). In one serosurvey, 100% of the chimpanzees tested had antibodies (Kalter, 1983). RSV has also been detected during respiratory disease outbreaks in free-ranging, human habituated chimpanzees (Kondgen et al., 2008). Whether the virus was of human or chimpanzee origin has not been fully established. Other great apes (*Gorilla gorilla gorilla, G. Gorilla beringi, Pongo pygmaeus, Pongo abelii,* and *Pan paniscus*) are also often seropositive, but the association with clinical disease is uncertain.

Signs most commonly reported in chimpanzees are rhinorrhea or coryza (hence the name chimpanzee coryza agent), coughing, and sneezing. Initial infections in very young animals may lead to lower respiratory tract involvement, principally bronchitis. In older animals or individuals that have been previously exposed, the infection is limited to the upper respiratory tract. As in humans, reinfection appears to be common. The disease is usually self-limiting but can predispose to pertussis or other bacterial infections such as *Streptococcus pneumoniae* (Gustavsson et al., 1990; Szentiks et al., 2009). Clinical diagnosis relies on demonstration of a rising antibody titer, virus isolation, or molecular detection of viral RNA.

Lesions of RSV infection have been described in the experimental bonnet macaque model (Simoes et al., 1999). Although the animals remained afebrile after intratracheal inoculation, and showed no clinical signs of illness, inflammatory lesions consisting of bronchointerstitial pneumonia and virus replication could be demonstrated in the epithelium of bronchi, bronchioles, and alveoli and in macrophages. Multinucleated syncytial cells without inclusion bodies were seen in the terminal bronchiolar and

alveolar epithelium. Highest viral titers were in the lower portions of the lungs.

Parainfluenza Viruses 1, 2, and 3 (PIV-1, PIV-2, and PIV-3)

Parainfluenza viruses (PIV) are in the family Paramyxoviridae and were formerly called paramyxovirues (PMV) a term that is now restricted to the related avian paramyxoviruses. Parainfluenza viruses 1 and 3 are currently placed in the genus *Paramyxovirus* along with murine PIV-1 (Sendai virus), bovine PIV-3, and simian parainfluenza virus 10 (SPIV 10). Parainfluenza virus 2 is placed in the genus *Rubelavirus* along with the avian paramyxovirues, mumps, and simian parainfluenza viruses 5 and 41 (SV 5, SV 41). The susceptibility of many nonhuman primates, including callitricids, cebids, cercopithicines, and pongids, has been established by virologic and serologic studies and by experimental inoculation. Outbreaks of PIV-1 or Sendai-like virus have been reported in marmosets associated with fatal pneumonia (Murphy et al., 1972; Flecknell et al., 1983). In one outbreak in common marmosets (*Callithrix jacchus*) there was high morbidity (69/91) with lower mortality (10/69) (Flecknell et al., 1983; Sutherland et al., 1986). Clinical presentation included upper respiratory signs of mild serous, or occasionally purulent, nasal exudate or systemic illness and death. In animals that died or were euthanized, the main finding was diffuse pulmonary consolidation and edema with histologic evidence of acute interstitial pneumonia. Histopathologic lesions were not well described. The upper respiratory tracts were contaminated with hemolytic *E. coli, Staphylococcus aureus, Klebsiella pneumoniae*, and *Neisseria* spp., but only one of eight animals necropsied had bacteria in the lungs (*K. pneumoniae*).

Fatal pneumonia due to "PMV-1" has also been reported in "marmosets" (actually tamarins, *Saguinus* sp.) (F. Deinhardt et al., 1967) and patas monkeys (*Erythrocebus patas*) (Churchill, 1963). Parainfluenza type 3 has been incriminated in predisposing chimpanzees to serious pneumococcal pneumonia (Jones et al., 1984). Several species of nonhuman primates (chimpanzees, African green monkeys, squirrel and owl monkeys, and pig-tail and rhesus macaques) have been used as experimental models for PIV vaccine development (Durbin et al., 2000). Both Sendai-virus (murine PIV-1) and human PIV-1 replicate in the upper and lower respiratory tract of chimpanzees and African green monkeys (AGMs) (Skiadapolous et al., 2002). HPIV-1 also replicates in the nasal cavity and trachea of squirrel monkeys, owl monkeys, pig-tail macaques, and rhesus, while HPIV-2 only replicates well in the nasopharynx of chimpanzees and AGMs and the trachea of AGMs and squirrel monkeys. When PIV-3 was inoculated into AGMs and rhesus, virus was shed in the nasopharynx with lower replication in the trachea of rhesus than AGMs.

Serologic evidence for "PMV-1, -2, and -3" exposure has been found in many species of primates but seems most common in great apes. Among 31 gorillas and chimpanzees tested for paramyxoviruses as part of battery screening, the seroprevalence was 0 for PMV-1, 39% for PMV-2, and 52% for PMV-3 (Kalter and Heberling, 1990). Serious respiratory disease outbreaks among chimpanzees in Africa were associated with human PIVs in addition to RSV (Kondgen et al., 2008). Orangutans are also susceptible. It is likely that these infections often represent anthropozoonoses, as infection in the human population is very high. In the great apes this infection is usually self-limiting but can be fatal if complicated by secondary bacterial infections.

Measles (Rubeola)

The measles virus is classified in the family Paramyxoviridae, genus *Morbillivirus*. The natural host is the human primate; however, it is broadly infective for nonhuman primates, including New World and Old World monkeys and apes and is a cause of significant outbreaks in laboratory and zoo-housed primates (Lowenstine, 1993b; Willy et al., 1999; Bailey and Mansfield, 2010). Little work has been done in prosimians. Exposure to humans remains the major risk factor in the development of measles in nonhuman primates (Jones-Engel et al., 2006). The portal of entry of this highly contagious anthropozoonotic virus is generally considered to be respiratory, but the disease is systemic with initial infection and viremia being associated with dendritic reticular cells and lymphocytes and, later, infection of epithelia and other cells (de Swart, 2008). Gastrointestinal disease or immunosuppression, rather than respiratory disease, are often the most important sequelae to the infection, however, "giant cell interstitial pneumonia" also occurs and can be fatal. In New World monkeys there may be no respiratory involvement at all, with hemorrhagic gastroenteritis being the main clinical sign.

Clinical signs in macaques include conjunctivitis, chemosis, rhinorrhea, rash, depression, and dehydration. Animals may be leukopenic and are immune compromised (Wachtman and Mansfield, 2008). Diagnosis is based on serology, virus isolation (from lymphocytes), viral RNA detection, immunostaining of conjunctival smears or other cytologic material, and histopathology. Morbidity is high and mortality is variable. It is highest in New World monkeys, Asian colobines, and young animals.

Lesions in the respiratory tract are a bronchointerstitial pneumonia typically centered on the small bronchioles or respiratory ducts (Figure 9.6). There is a desquamation of bronchiolar epithelium and alveolar lining cells along with an increase in bronchoalveolar macrophages. Indistinct intranuclear and cytoplasmic inclusion bodies and
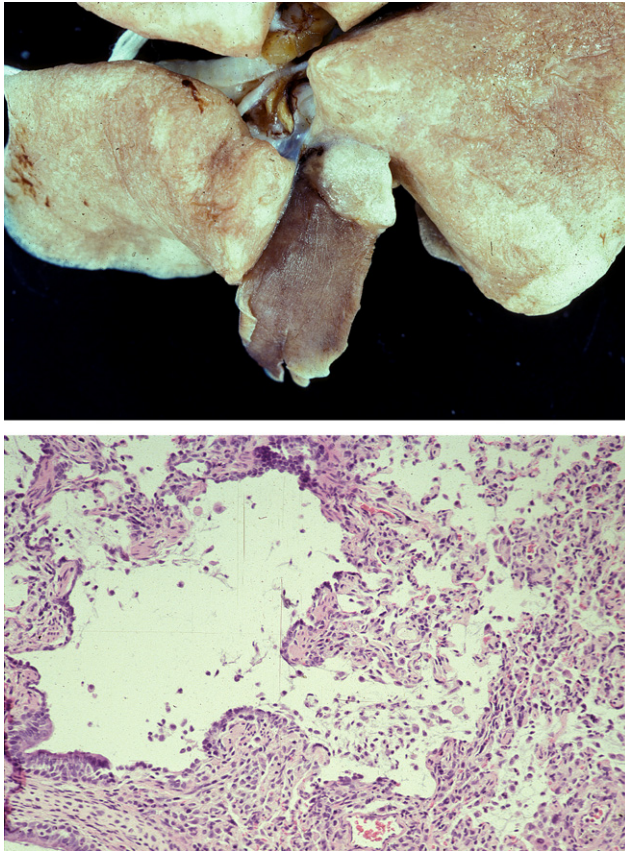
FIGURE 9.6 **Measles. Rhesus macaque (*Macaca mulatta*).** Lobar consolidation due to bronchial obstruction (top). Histological appearance of typical viral bronchointerstitial pneumonia centered on a terminal airway (bottom). *(CNPRC)*

multinucleated giant cells may occur, especially as type II pneumocyte hyperplasia ensues (Lowenstine, 1993b). The laryngeal air sacs may also be involved. Secondary bacterial infections and superimposed bronchopneumonia may occur.

Prevention is by vaccination. Because of the prohibitive cost of human measles vaccines, a canine distemper-measles vaccine (Vanguard D-M®) was compared to results of vaccination with a standard human vaccine (Attenu-vax®). Two doses of the distemper-measles vaccine conferred excellent immunity to challenge with a rhesus adapted strain of measles virus (Christie et al., 2002).

Human Metapneumovirus

Metapneumoviruses (MPV) are RNA viruses of the family Paramyxoviridae, subfamily Pneumovirinae (along with RSV) and genus *Metapneumovirus*. Human MPV was first recognized as the cause of respiratory infections in children in the Netherlands in 2001 (van den Hoogan et al., 2001). It is now considered to occur worldwide with different strains circulating in different geographical areas.

Naturally occurring human metapneumoviruses (hMPV) have been documented in chimpanzees in the wild

(Kaur et al., 2008) and in captivity (unpublished data) and in wild gorillas (Palacios et al., 2011). HMPV was demonstrated to have been associated with at least one outbreak of fatal respiratory disease in free-ranging chimpanzees in Africa. Morbidity ranged from 34 to 98% with mortality of 5−7% in the three outbreaks reported (Kaur et al., 2008). Mortality was highest in infants. Signs included coughing, sneezing, nasal discharge, respiratory difficulty, and lethargy.

Cynomolgus monkeys have proven to be useful models for hMPV pathogensis (Kuiken et al., 2004). Lesions included lymphocytic rhinitis and tracheitis with decilia-tion, erosion, and increased numbers of alveolar macro-phages. The virus replicates in ciliated epithelium and type 1 pneumocytes. Though infection in macaques produces transient immunity, a vaccine is not yet available (van den Hoogen et al., 2007). Vaccination trials in cynomolgus have demonstrated an adverse immune effect of vaccination with formalin inactived hMPV and immunity of short duration in other candidate vaccines (de Swart et al., 2007; Herfst et al., 2008).

Orthomyxoviruses: Influenza Viruses

That both influenza A and B have been described in nonhuman primates is not surprising given the wide host range of these viruses (Renegar, 1992). What is surprising is the relatively few reports of active spontaneous disease. Serologic screening of primate colonies and collections has revealed that exposure to influenza A is more common than exposure to influenza B (Kalter and Heberling, 1978, 1990).

Much of our knowledge of the effects of flu viruses in nonhuman primates comes from experimental inoculations that have been carried out in New World monkeys (*Cebus* spp., *Saimiri* sp., and *Aotus* sp.), Old World monkeys (*Macaca mulatta, M. fascicularis, Papio* spp.), and apes (*Hylobates* sp. and *Pan troglodytes*). Squirrel monkeys are one of the animal models of choice for vaccine and thera-peutic studies (Renegar, 1992); they and capuchins have also been used for pathogenesis studies. In capuchins, the severity of disease varied with the route of inoculation (intratracheal more severe than intranasal) and strain of virus (A/Victoria/3/75 more pathogenic than A/New Jersey/76). The incubation period was 3−5 days, although virus could be recovered on day 1. Clinical signs included depression and dyspnea in the worst cases, and rhinorrhea in the less severely affected animals. Radiographic evidence of pneumonia was more evident on lateral than anterior−posterior projections and was most evident in middle and lower (caudal) lobes. Pathologic findings in animals killed at days 4 to 6 included gross evidence of tracheal hyperemia and patchy pulmonary consolidation. Histologically there was a loss of ciliated cells, erosion,

hemorrhage, and mononuclear inflammation in tracheal and bronchial epithelium accompanied by squamous metaplasia. Extension into the parenchyma was characterized by thickening of alveolar septa by mononuclear cells and exudation of fibrin. Upper respiratory lesions were limited by mild submucosal inflammation (Grizzard et al., 1978).

A study in squirrel monkeys highlighted the significance of pneumococcal superinfection in causing lethal outcomes in influenza virus infections (Berendt et al., 1975). Clinical signs of "flu" in these monkeys were fever, coryza, tachypnea, dyspnea, coughing or sneezing, lethargy, and anorexia. Signs were least severe in animals inoculated with *Streptococcus pneumoniae* alone and most severe in animals sequentially infected with influenza virus and *S. pneumonia.* Although mortalities occurred in all groups, they were most numerous in the dually infected animals. Lesions in the virus-infected animals were similar to those described in capuchins with the exception of the presence of neutrophils (post-inoculation day 6). In sequentially infected animals the lungs were grossly consolidated with pleural exudate. Histologically the pneumonia was fibrinopurulent and necrotizing.

Human influenza virus strains generally produce mild respiratory disease in cynomolgus monkeys (Rimmelzwaan et al., 2003; van Riel et al., 2007). In contrast, the highly pathogenic H5N1 strain of avian influenza and the 1918 pandemic strain cause very severe disease due to acute alveolar damage or ARDS (see above) and subsequent systemic effects of multiorgan dysfunction syndrome (MOBS) (Kuiken et al., 2003; Rimmelzwaan et al., 2003; Feldmann and Kawaoka, 2007; Kobasa et al., 2007). Cynos have also been used in influenza vaccine development.

There is one well-documented outbreak of influenza A in a colony of gibbons (*Hylobates lar lar*) in Southeast Asia in which morbidity was about 30% and mortality about 10% (Johnsen et al., 1971). This outbreak was initiated by experimental inoculation but spread to involve uninoculated contact animals. Clinical signs reported were anorexia, depression, serous to suppurative nasal exudate, coughing, and gastrointestinal signs. In many animals the signs were short-lived and self-limiting. Two of the animals that died had no premonitory upper respiratory signs. Gross lesions in gibbons included posterior pulmonary consolidation, congestion, and edema. Microscopically, the lungs of animals without secondary bacterial infections had evidence of bronchointerstitial pneumonia centered on small bronchioles. Sloughing of epithelium was evident and in one animal was accompanied by early proliferative bronchiolitis. Exudation of erythrocytes, fibrin, and alveolar macrophages was evident in the parenchyma. The presence of marked neutrophilic exudation was associated with secondary bacterial pathogens.

Adenoviruses

Adenoviruses have been readily isolated from many species of nonhuman primates; however, clinical disease is less common (Espana, 1974). Conjunctivitis and rhinitis have been described in patas monkeys and macaques infected with SV17, macaques infected by SV15, and chimpanzees infected with SV32. Pneumonias in macaques have been associated with SVll, SV15, SV20, and SV37. "Pneumoenteritis" has been described in African green monkeys and baboons infected with V404 and V340. Adenoviral pneumonia has also been described in a juvenile chimpanzee (Butchin et al., 1992). Adenoviral pneumonia in macaques may be secondary to recrudescence of latent infection in the face of immunosuppression caused by retroviruses (King, 1993a; Lowenstine, 1993a).

Clinical signs depend on the host and strain of virus. Many of the reports have been in juvenile or infant monkeys. Acute respiratory infections in macaques with signs of skin rash, conjunctivitis, facial edema and erythema, nasal discharge, and cough were attributed to adenoviruses based on isolation of SV15 and SV32 and histologic evidence of necrotizing pneumonia with basophilic inclusions in which adenovirus-like particles were identified by electron microscopy (Espana, 1971, 1974). In another report (Boyce et al., 1978), clinical signs in infant rhesus included tachypnea, cough, and cyanosis unresponsive to oxygen. Gross lesions in neonatal monkeys were limited to the lungs and consisted of consolidation, gray discoloration, and failure to collapse. There was necrosis of bronchiolar and alveolar epithelium and enlarged nuclei filled with amphophilic to basophilic inclusions. Cowdry type A eosinophilic inclusions were less common. Exudate consisted of necrotic cellular debris, fibrin, alveolar macrophages, and low numbers of neutrophils. The diagnosis was based on electron microscopy.

An outbreak of fatal adenovirus-associated pneumonia (mortality rate of 83%) has been seen in titi monkeys (*Callicebus* spp.) at one of the national primate research centers (Chiu, 2010). Descriptions of the epidemiology, pathology, and virus molecular characterization have not yet been published.

Herpesviruses

Simian alphaherpesviruses are associated with systemic disease during which the lungs may become involved. Pneumonic involvement as a primary "complaint" is less common, but has been reported.

Herpesvirus simiae

Herpesvirus simiae (herpes B, B virus, cercopithecine herpesvirus I, macacine herpesvirus) is an alpha herpesvirus of the genus *Simplexvirus* that is enzootic in Old

World monkeys of the genus *Macaca*, principally rhesus. In most macaque groups the infection is endemic and of low pathogenicity. Overt disease in rhesus and cynomolgus macaques is usually limited to oral, labial, or genital vesicles and ulcers.

Systemic, clinical disease occurs in the face of immune suppression or due to cross-species transmission. An outbreak of respiratory herpesvirus infection was described in bonnet monkeys (*Macaca radiata*) (Espana, 1973). Clinical signs included purulent nasal exudate. No oral ulcers were observed. Morbidity was 50% and about 50% of affected animals died. Grossly the lungs were consolidated, and foci of hemorrhage were observed. There was also splenomegaly and hepatomegaly with multifocal necrosis. Histologic lesions were those of a hemorrhagic interstitial pneumonia. Inclusion bodies were seen in the livers. The virus was subsequently determined to be *Herpesvirus simiae.* Periodic epizootics of herpesvirus infections were seen subsequent to the original report and respiratory disease was often a manifestation, although oral ulcers and encephalitis were seen as well. In retrospect, this colony of bonnet monkeys was found to have an endemic simian type D retrovirus infection (SRV-1), which may have allowed for recrudescence and severe manifestion of the herpesvirus infection. This contention is corroborated by a report of fatal herpesviral bronchopneumonia in two elderly female bonnet monkeys, which had been severly stressed by the introduction of an aggressive male to the group (Scharf et al., 2008).

Herpesvirus SA8/Herpesvirus Papio-2

Herpesvirus SA8 of African green monkeys and Herpesvirus papio-2 of baboons are closely related alphaherpesviruses that are also related to B virus. Herpesviral pneumonia was reported in two zoo-born perinatal Gelada baboons (*Theropithecus gelada*) (Ochoa et al., 1982). The animals died without clinical signs having been recognized. Gross lesions included large areas of pulmonary consolidation and pulmonary hemorrhage. Necrotizing bronchiolitis and interstitial pneumonia were present with many basophilic, Cowdry type A inclusion bodies. Similar inclusions were also seen in brain, kidney, and spleen. Herpesviral particles were demonstrated by electron microscopy, and the infection was suspected to be SA8; however, in retrospect it is more likely that the culprit was *Herpesvirus papio*. Spontaneous herpesviral pneumonia was also reported in a hand-reared neonatal olive baboon (*Papio anubis*), which developed severe necrotizing pneumonia associated with intranuclear inclusion bodies in epithelium and endothelium (Wolf et al., 2006).

Herpesviral tracheobronchopneumonia has been produced experimentally in newborn yellow baboons (*Papio cynocephalus*) inoculated intratracheally (Brack et al., 1985). Clinical disease was not described, but terminal illness developed within two days of inoculation. Tracheal and bronchial epithelium was affected initially followed by bronchiolar involvement and spread to the parenchyma. Lesions were hemorrhagic and necrotizing.

Varicella-Zoster-Like Herpesviruses

Varicella-like viruses are cell-associated herpesviruses of the genus *Varicellovirus*, related to the human virus (Varicella-Zoster, HHV-2) that causes "chicken pox" and "shingles." Several simian varicella-zoster-like alphaherpesviruses have been isolated from Old World monkeys (Gray, 2003). Macaques are the presumed natural hosts for many of these agents. Disease in these species is often self-limiting while fatal disseminated disease, including pneumonia and encephalitis, has been seen in naturally and experimentally infected African primates, including African green monkeys and patas monkeys (Iltis *et al.*, 1982). Intratracheal inoculation produced systemic disease with viremia and a vesicular rash in African green monkeys. Pulmonary lesions included edema and petechial hemorrhages have been described. Histologically, pulmonary edema and necrosis of alveolar septa with marked fibrin exudation was seen (Dueland et al., 1992).

Rhinoviruses: Picorniviridae, Rhinovirinae

The susceptibility of chimpanzees to natural and experimental infection with human rhinoviruses has been documented (Dick and Dick, 1974), but the infection is often clinically inapparent or mild. Attempts at experimental inoculation in other species have been limited but unsuccessful. Species inoculated included *Papio doguera*, *P. hamadryas*, *Theropithecus gelada*, *Macaca mulatta*, *M. arctoides*, *Cercopithecus aethiops*, *Erythrocebus patas*, *Cebus albifrons*, and *Saimiri sciureus*. Gibbons (*Hylobates lar*) proved somewhat susceptible. Based on serosurveys, natural infection of chimpanzees with human rhinoviruses is considered to be rare. Clinical signs and lesions have not been described.

Retroviruses

Several different retrovirus infections have been described in nonhuman primates. Of the exogenous or pathogenic retroviruses, only infections with simian type D retroviruses (SRV) and simian immunodeficiency viruses (SIV) have been associated with respiratory tract lesions. In infections with SRV the lesions encountered are due to secondary opportunistic infections (Lowenstine, 1993a). Similar infections may also be seen in SIV-infected animals; however, SIV also causes a primary retroviral

pneumonia in macaques (Baskerville et al., 1992; King, 1993a).

Simian Immunodeficiency Virus

Lentiviruses of cercopithecine monkeys are indigenous to African monkeys of the genera *Cercopithecus, Chlorocebus, Cercocebus*, and *Papio* (*Mandrillus*). The viruses are of very low pathogenicity in African species. In Asian macaques, however, these viruses cause devastating disease characterized by immune dysfunction, wasting, opportunistic infections, and primary retroviral pneumonia and encephalitis. Historically, many macaques were infected by accidental iatrogenic exposure by direct contact with African species and through exposure to other infected macaques (Lowenstine et al., 1992; Aprtei et al., 2006). In most vivaria, natural SIV infection of macaques is rare to nonexistent (Daniel et al., 1984). However, macaques are commonly experimentally infected as models for human HIV infection.

Primary retroviral pneumonia is a common finding in experimentally infected rhesus (Baskin et al., 1989; Baskerville et al., 1992; King, 1993a). Clinical signs are nonspecific, including anorexia, weight loss, and inactivity. Grossly, the lungs fail to collapse and are diffusely or patchily discolored tan to cream or yellow, sometimes with pleural opacification. They are spongy to slightly firm on palpation with minimal free exudate on cut surface (Figure 9.7). Histologic examination reveals thickening of alveolar septa, marked exudation of foamy macrophages, lesser amounts of proteinaceous material, and large numbers of syncytial giant cells. The pneumonia is readily differentiated from measles giant cell pneumonia by the absence of inclusion bodies in the SIV pneumonia giant cells and the diffuse alveolar involvement as opposed to the measles orientation around small bronchioles (i.e., no necrotizing bronchiolitis).

FIGURE 9.7 Simian immunodeficiency virus giant cell pneumonia. Experimentally infected rhesus macaque. Lungs do not collapse and are firm, "styrofoam-like," on palpation. *(CNPRC)*

Coronaviruses

SARS (Severe Acute Respiratory Syndrome) Coronavirus

Coronaviruses are enveloped single-stranded RNA viruses long known to be enteric pathogens of domestic animals, such as cats (FeCoV), dogs (CaCoV), cattle (BCoV), and swine (TGEV). Coronavirus particles have been detected in the feces of both healthy and diarrheic baboons, chimpanzees, macaques, and "marmosets," but these viruses and their disease potential have not been fully examined (Smith et al., 1982). In 2002, a severe respiratory disease outbreak occurred in human primates, beginning in China and spreading via air travel to other Asian countries, Canada, and Europe, causing international concern and panic (reviewed by Nagata et al., 2010). The infection was traced to masked palm civets (*Paguma larvata*) in a live animal market, and several other species in the market were found to be positive including raccoon dogs (*Nyctereutes procyonoides*). Other studies, however, showed that, although the virus has a broad host range, the most likely natural hosts of the SARSCoV are bats of the genus *Rhinolophus*. Although spontaneous nonhuman primate cases have not been reported, SARS is included in this chapter because cynomolgus and rhesus macaques, African green monkeys, and common marmosets can be infected experimentally and serve as important animal models (Haagmans and Osterhaus, 2006). In affected humans, severe interstitial pneumonia progresses to ARDS. The presenced of multinucleated viral-induced syncytial cells is a hallmark. Adults and elderly are more severly affected than children with a case fatality rate approaching 10%. Lesions in nonhuman primates variably reflect the human disease, but interstitial pneumonia with giant cell formation has been described in cynomolgus monkeys and common marmosets (Kuiken et al., 2003; Greenough et al., 2005).

BACTERIAL DISEASES AND AGENTS

Normal Respiratory Flora

The normal respiratory flora of nonhuman primates has been incompletely studied. Bacteria generally isolated from the nose and pharynx of healthy rhesus include: *Hemophilus, Neisseria, Moraxella*, Alpha and Beta hemolytic Streptococci, *Staphlococcus* spp., *Staphylococcus aureus*, diphtheroids, *Kingella* spp., and rod-shaped Gram-positive and Gram-negative bacteria. Alpha streptococci, *Hemophilus* sp., and *Staphylococcus* sp. were the most common (Bowers et al., 2002). In another study Carrier et al. (2009) also found that species of staphylococci and streptococci were the most common orophayrngeal isolates from rhesus; however, *Strep. pneumoniae* was not

demonstrated in any of the 24 animals. Stills et al. (1979) demonstrated, by culture of transtracheal aspirates, that *Bordetella bronchoseptica* was carried by 23% of cynomolgus macaques but was not present in throat swabs.

Tuberculosis

Tuberculosis is a disease of major concern in primate colonies, both for its potential devastating effect on captive primate populations (Renquist and Whitney, 1978; Henrickson, 1984; Lehner, 1984) and for its zoonotic potential (Dannenberg, 1978). In addition, the continued global human health threat caused by *Mycobacterium tuberculosis* (Corbett et al., 2003) is the stimulus for multiple, continuing studies using nonhuman primate models of tuberculosis. These studies are part of worldwide efforts to better characterize infection-related immunological response in order to establish improved diagnostics and possible effective vaccines (Capuano et al., 2003; Vervenne et al., 2004; Lewinsohn et al., 2006). Although most notably a problem among Old World primates, it occurs naturally in New World monkeys as well (Hessler and Moreland, 1968; Leathers and Hamm, 1976; Alfonso et al., 2003). Prosimians are also susceptible. The disease is generally associated with infection by the organisms *Mycobacterium tuberculosis* and *M. bovis* (Hessler and Moreland, 1968; Renner and Bartholomew, 1974; Thoen et al., 1977; Kaufmann and Anderson, 1978; McLaughlin, 1978; Tarara et al., 1985; Ward et al., 1985; Wolf et al., 1988; Keet et al., 1996; Martino et al., 2007; Panarella and Bimes, 2010); however, a number of other *Mycobacterium* species have occasionally been reported in association with clinical pulmonary disease (King, 1993b; Chege et al., 2008). Nontuberculous mycobacterial infection is also recognized in nonhuman primates, usually associated with agents belonging to the *Mycobacterium avium-intracellulare* complex, but also reported in association with *M. paratuberculosis.* Surveillance and diagnostic techniques for tuberculosis are important preventive health procedures for captive primate colonies (Kaufmann and Anderson, 1978; Kuhn and Selin, 1978; McLaughlin and Marrs, 1978; Renquist and Whitney, 1978; Montali and Hirschel, 1990; Southers and Ford, 1995; Desem and Jones, 1998; Kahn, et al., 2008; Lin et al., 2008; Parsons et al., 2009; Kramer et al., 2011). Interpretation of surveillance results can vary for individual animals, depending on the state of disease or *Mycobacterium* exposure, and has been a particular problem with orangutans (Chaparas et al., 1975; Kaufmann and Anderson, 1978; Kuhn and Selin, 1978; McLaughlin and Marrs, 1978; Calle et al., 1989; Dillehay and Huerkamp, 1990; Wells et al., 1990). For orangutans, a high rate of positive tuberculin reaction (60% of those tuberculin tested) generally has been associated with exposure to a variety of nontuberculous *Mycobacterium* species, including *M. fortuitum, M. terrae,*

M. nonchromogenicum, M. avium, and *M. cheloni* (Calle et al., 1989; Wells et al., 1990), with no evidence of mycobacterial disease.

Mycobacteria are aerobic, slightly curved or straight, occasionally beaded, rod-shaped bacilli that stain (poorly) with Gram's stain, but stain positively with acid-fast staining (e.g., Ziehl−Neelsen stain, Fite−Faraco stain). Culture of these organisms requires special media and techniques to destroy contaminating nonacid-fast bacteria. Tuberculosis is extremely rare in natural populations of nonhuman primates that are remotely situated away from human populations. Infection in captive populations is generally thought to be related to the transmission of disease from humans to animals (Cappucci et al., 1972). Tuberculosis is a particularly contagious and potentially fulminant disease in macaques, especially in rhesus monkeys (King, 1993b; Walsh*, et al.*, 1996). Differences in clinical course, lesions, and disease pathogenesis between rhesus monkeys and cynomolgus monkeys have been recognized and compared with regard to potential models of human tuberculosis (Walsh et al., 1996; Langermans et al., 2001; Capuano et al., 2003). Rhesus monkeys are reported to develop fulminant disease even in low-dose experimental infection, while with low-dose experimental infection, cynomolgus monkeys tend to show a disease spectrum, including chronic, slowly progressive disease and even chronic clinically inapparent infection. Strict quarantine procedures and routine tuberculin testing of nonhuman primates and animal care personnel have contributed to a marked reduction in the occurrence of tuberculosis in captive nonhuman primate populations.

Transmission of tuberculosis occurs most commonly via respiratory exposure to infected aerosols, although ingestion of infected materials and subsequent gastrointestinal infection are also recognized. Disease pathogenesis, reviewed by Dannenberg (1978) and King (1993b), involves phagocytosis of organisms by tissue-resident macrophages. Variability in macrophage ability to kill the organisms exists, leading to diverse possibilities for infection outcome and lesion morphology. When organisms are able to survive phagocytosis and replicate intracellularly, the macrophage is eventually killed. Successful intracellular killing of mycobacteria by macrophages leads to processing of the agent and antigen presentation for immune response by T lymphocytes. The T cells, as well as peripheral blood monocytes, are recruited to the infection site by various macrophage-derived cytokines. Further activation of mononuclear phagocytes occurs in these sites in response to mycobacterial products and cytokines released by the reactive lymphocytes. The activated macrophages phagocytize the bacteria and tend to transform into immobile epitheliod cells, forming epithelioid granulomas. A subset of macrophages remains mobile and

may eventually move to regional lymph nodes and other tissues, where, if intracellular killing has not been complete, the infection and associated inflammatory response continue. Additional processes that contribute to the classical morphology of tuberculous lesions include fusion of macrophages to form multinucleate Langhans-type giant cells and promotion of potentially encapsulating fibrosis by various mediators.

A spectrum of gross lesions is recognized in nonhuman primates with tuberculosis. Lesions may be inapparent or may include widely disseminated, 1.0−10.0-cm, yellow-white, focal to confluent granulomas affecting all major organs. Large granulomas in the lung may be cavitary, a result of drainage of caseous exudate into adjacent airways. Among the most commonly affected organs are lungs, tracheobronchial lymph nodes, spleen, liver, kidney, intestine, and mesenteric lymph nodes.

Microscopic variation is influenced by the time course and extent of disease and probable host factors (genetics, immune dysfunction, etc.). Early lesions may be widely scattered microscopic granulomas made up of circumscribed collections of epithelioid cells and an occasional Langhans' giant cell. Some of these lesions may include central neutrophil aggregates. Such small lesions may initially be confined to lung or intestinal tract, in association with the initial route of infection. The tubercle is the "classic" lesion of advanced tuberculosis. It includes a central core of acellular necrotic debris, surrounded by a zone of epithelioid cells and scattered Langhans-type, multinucleate, giant cells. At times the core is calcified. The tubercle periphery is generally made up of variable amounts of fibrous connective tissue and infiltrating lymphocytes. Acid-fast special stains can reveal acid-fast bacilli in the epithelioid and multinucleate giant cells, although in some cases many tissue sections must be examined to find tubercle bacilli (paucimicrobial infection).

Differential diagnosis of microscopic lesions seen with tuberculosis includes other granulomatous disease, including certain foreign bodies (e.g., kaolin), mycotic, protozoan, and parasitic organisms. Definitive diagnosis relies on identification of a specific mycobacterial species from the lesions, using isolation and/or polymerase chain reaction (PCR). Speciation by PCR can be performed on isolates and on DNA extracted from formalin-fixed paraffin embedded tissues (Ghossien et al., 1992). In the absence of culture or PCR, the presence of acid-fast bacilli in granulomas or tubercles in microscopic sections only confirms the diagnosis of a mycobacteriosis. Among the lesions assessed for differential diagnosis, those caused by *Nocardia* can be confused, particularly because of the partial acid-fast nature of *Nocardia*; however, *Nocardia* organisms stain Gram positive and are beaded and branching, making differentiation relatively easy.

When tuberculosis is diagnosed in a population of animals, it is extremely important that the outbreak be controlled. All animal movement within the colony should be halted, and animals previously housed in the same room with the infected animal(s) should be located. These animals should be tested biweekly with intradermal mammalian old tuberculin (MOT) for a minimum of five consecutive negative tests. This is necessary because detecting infected animals early post-infection can be difficult. The nature of the intradermal tuberculin skin test, which measures delayed-type hypersensitivity, is not sensitive under conditions of recent infection and generally does not become positive until at least a short time after the infected animal has begun to shed organisms (Clarke, 1968; Henrickson, 1984). In addition, other possibly immune-suppressive circumstances can produce anergy, leading to false-negative results, e.g., recent (within four weeks) immunization with modified live virus measles vaccine (Staley et al., 1995; Panarella and Bimes, 2010). Panarella and Bimes (2010) also discuss variables that can modify the sensitivity of intrapalpebral skin testing for tuberculosis, including the following important points: (1) sedation allowed for increased ability to find positive reactors through closer examination and palpation (animals with scores of one to three on the standard five-point scale); (2) location of the injection may be crucial—with guidelines calling for injection placement as close as possible to the eyelid edge. This latter point is based on review of facility practices in the described outbreak which showed that TB test injections had been being placed in the middle of the eyelid, leading to the authors' speculation that mild swelling may have been more difficult to detect than if the tuberculin was placed at the eyelid edge. Under certain circumstances, abdominal intradermal skin testing has been performed in conjunction with or rather than intrapalpebral skin testing. Capuano et al. (2003) report that results with abdominal intradermal testing were among monkeys and did not necessarily correlate with the concurrently administered palpebral test and remark that primate health care personnel should reconsider the use of this technique as part of a confirmatory follow up to positive intrapalpebral testing. Recent new techniques (Lerche et al., 2008; Lin et al., 2008), including interferon gamma releasing assays (Desem and Jones, 1998; Jones, 1998; Vervenne et al., 2004), lymphocyte activation assays (Parsons et al., 2009), and serology assays (Khan, *et al.*, 2008), are being developed. These assays are generally best used in addition to the tuberculin skin test as part of a comprehensive response to apparent positive tuberculin skin tests within designated animal populations.

When screening animals in quarantine, or as part of an ongoing preventive health program (Southers and Ford, 1995; Kramer et al., 2011), positive test results may occur. Some of these results may be equivocal. In such cases, or

in cases such as those involving potentially false-positive reactions in orangutans, additional tests may be performed. In the meantime, no animals should be moved into or out of the group. Additional tests can include some of the tests mentioned above, using different types of tuberculin (e.g., purified protein derivatives), as well as the employment of a variety of other procedures including gastric and bronchial lavage with cytology (for acid-fast organisms) and culture or PCR, as well as thoracic radiography.

The combination of the high level of risk to a colony, and the difficulty in achieving successful treatment, often results in the decision to euthanize positive-reacting animals. This makes it possible to eliminate the potential for infection spread. In some cases, usually due to the value of the individual animal, treatment is carried out. For decades the standard and most effective treatment for humans has involved regimens that include isoniazid and rifampin for 9–12 months, with a favorable outcome in 99% of patients (Daniel, 1994). Drug toxicity is an important factor in the choice of therapeutic agents. Drug-associated hepatitis is of greatest concern. Serum enzymes and other blood tests predicting liver disease are not helpful as monitors of toxicity and are not recommended. Discontinuation of medication at the onset of jaundice generally leads to the resolution of drug-associated hepatitis.

The global emergence of multidrug resistant tuberculosis in humans, fueled in part by the AIDS epidemic, has led to the development of combination chemotherapy regimens and a push for development of new anti-mycobacterial drugs (Neurmberger et al., 2010). Even with drug-susceptible strains of MTb, a prolonged course of drug therapy is always necessary due to the long generation time of mycobacteria and their extended periods of metabolic inactivity.

Reports of treatment in nonhuman primates document the use of a multiple drug regimen such as isoniazid, rifampin, and ethambutol (Wolf et al., 1988) or streptomycin and isoniazid (Ward et al., 1985) over a period that minimally lasts 9 to 12 months and up to 30 months in one report included in a summary by Wolf et al. (1988). Treatment must be carried out in conjunction with culture and sensitivity testing, as supported by the failure of combined isoniazid and *p*-aminosalicylic acid therapy to resolve tuberculosis in orangutans due to drug resistance of the particular organism (Haberle, 1970). Ward et al. (1985) used a treatment period of six months, and one animal out of 195 exposed animals (48 became tuberculin reactive) subsequently developed tuberculosis. If animals are being treated, it is important to be aware that the tuberculin reaction can be masked when animals are undergoing chemotherapy (Clarke and Schmidt, 1969; Dillehay and Huerkamp, 1990).

Pneumococcal Infection

Streptococcus pneumoniae is found in nasal secretions of up to 60% of normal human adults during winter months. This Gram-positive coccus is the cause of 90–95% of lobar pneumonia in humans and can be rapidly fatal. In addition, it is also a cause of bronchopneumonia, empyema, and upper respiratory infection (middle ear, sinuses), as well as severe meningitis or brain abscesses. Severe infections can lead to pneumococcal bacteremia. Similarly, it has been reported to cause up to 95% of pneumonia cases in one report of nonhuman primate respiratory disease (Fiennes and Dzhikidze, 1972); however, *S. pneumoniae* does not appear to be part of the normal flora of nonhuman primates. In rhesus, after experimental inoculation, *S. pneumoniae* can be recovered for a maximum of 11 days. In the face of concurrent inoculation with influenza virus, *S. pneumoniae* persists for up to 99 days (Berendt et al., 1974). These data suggest that *S. pneumoniae* in nonhuman primates is anthropozoonotic. The presence of unique clones of *S. pneumoniae* in wild chimpanzees dying during a respiratory disease outbreak suggests, however, that nonhuman primate specific strains may occur (Chi et al., 2007).

Outbreaks of *S. pneumoniae*-associated respiratory disease in nonhuman primates are usually associated with the presence of other predisposing problems, such as stress, inclement weather, or viral respiratory infections such as RSV, PIV-3, and influenza (Berendt et al., 1975; Jones et al., 1984; Szentiks et al., 2009). In nonhuman primates, the main lesion is lobular to lobar, fibrinous and suppurative bronchopneumonia that may progress to lobar consolidation. Secondary pleuritis and epicarditis and pulmonary arterial thrombosis secondary to vasculitis can be seen (Figure 9.8). Septicemia leading to meningitis and, more rarely, encephalitis is a common sequel in infant great apes

FIGURE 9.8 **Acute lobar and bronchopneumonia with pleuritis. Rhesus monkey (*Macaca mulatta*).** Presumed *Streptococcus pneumoniae*. (CNPRC)

and macaques. Corneal ulcers, peritonitis, otitis media are also reported. The presence of large numbers of paired Gram-positive cocci in smears of exudates supports the diagnosis of *S. pneumoniae* infection.

Streptococcus pneumoniae is usually sensitive to penicillin, such that use of long-acting penicillin during an outbreak can decrease morbidity. Valuable populations of vulnerable animals may benefit from immunization with pneumococcal polysaccharide (Centers for Disease Control, 1989).

Other Gram-Positive Bacterial Pneumonias

Streptococcus equi *Subsp.* zooepidemicus

Streptococcus equi subsp. *zooepidemicus* is a β-hemolytic, group C streptococcus that causes disease in animals and humans. It is primarily associated with infections in horses, though it also is found as a commensal on the mucous membranes of the nasopharynx, tonsils respirator tract, and genitals of healthy horses and cattle. In other species, including pigs, sheep, cattle, and goats, it has been associated with mastitis, as well as other infections. The latter hosts can be the source for human infection. Human infection can lead to pharyngitis, septicemia, meningitis, purulent arthritis, and endocarditis.

There have been rare reports of *Streptococcus equi* subsp. *zooepidemicus*-associated disease in nonhuman primates. Callitrichid deaths have been reported, with the infection source likely infected horse meat that was being fed to armadillos in the same exhibit (Montali, 1997; Schiller et al., 1989). Mätz-Rensing et al. (2009), describe a *S. equi* subsp. *zooepidemicus* respiratory disease outbreak in a group of rhesus monkeys. In this outbreak, over a 1-month period, six adult animals in a group of 45 died with a short disease course that included signs of severe upper respiratory tract infection and conjunctivitis (in four animals) and sudden death without clinical signs in two animals. All six animals had severe inflammation in the upper respiratory tract and lungs, characterized by moderate to severe purulent tonsillitis and pharyngitis, purulent lymphadenitis, and severe fibrinopurulent pleuropnuemonia. Other lesions included fibrinopurulent epi- and pericarditis, severe purulent endometritis in one pregnant female (with associated abortion), and mild splenitis and hepatitis in four animals. One animal also had purulent encephalomeningitis. The inflammation was associated with with clusters and chains of Gram-positive cocci, which were present within extracellular spaces and within macrophages. The cause of death in all cases was septicemia.

Staphylococcus aureus

Staph. aureus is a major cause of secondary bacterial pneumonias in community-acquired pneumonias in children and in institutional settings such as nursing homes. It is also an important pathogen in aspiration pneumonia in debilitated individuals and in ventilator-aquired nosocomial pneumonias (Husain, 2010). It is a rarely reported cause of pneumonia in nonhuman primates, but has been seen in immune-suppressed stump-tailed macaques (*Macaca arctoides*) naturally infected with SIVstm (Lowenstine et al., 1992). The infection is usually pyogenic with localized abscessation.

Enterobacteriacea: Gram-Negative Bacterial Pneumonias

Klebsiella pneumoniae

Klebsiella pneumoniae is a common enterobacterium that causes a disease spectrum that includes severe pneumonia (lobular or lobar), enteritis, urinary tract infection, and miscellaneous septic lesions, including sinusitis, meningitis, and otitis. In humans it is an unusual part of pharyngeal and oral microflora, but is recognized in up to 20% of hospital patients. Pneumonia in *K. pneumoniae* infections is generally a bronchopneumonia, with a tendency for abscess formation and pleuritis. Septicemic pneumonia secondary to enteritis (pneumo-enteritis complex) also occurs. The exudate associated with *Klebsiella* is typically gelatinous, especially in infections with hypermucoviscosity strains. In hematoxylin and eosin (H&E) and Gram-stained sections, the organism has a characteristic evenly spread distribution and a thick clear capsule. Inflammation in Klebsiella pneumonia may be histiocytic as well as suppurative due to inhibition of neutrophil influx by capsular mucopolysacchrides. Although often associated with acute pneumonia, this may be followed by persistent, chronic infection, including chronic bronchitis, bronchiectasis, and pulmonary abscesses. Hypermucoviscosity strains are recognized as an emerging casue of community-acquired pneumonias in humans along with a syndrome of liver abscesses. This phenotype may be more virulent. Pneumonia and pleuritis associated with similar strains have been reported in sea lions (Jang et al., 2010). In nonhuman primates invasive hypermucoviscosity phenotype *Klebsiella pneumoniae* has been reported as a cause of systemic disease consisting of abdominal, pulmonary, and/or cerebral abscesses in a laboratory colony of African green monkeys (Twenhafel et al., 2008), but not as a primarily pneumonic syndrome.

Klebsiella respiratory infections have been recognized in lemurs, New World and Old World monkeys, and apes (Good and May, 1971; McClure et al., 1986; Gonzalo and Montoya, 1991). Eichberg (1985) reported an outbreak of *K. pneumoniae* infection in a group of nursery-housed infant chimpanzees. The disease began with nasal discharge. Two animals died, including one that had no

recognized signs of clinical illness. The first animal that died had congestion, fever, anorexia, and weight loss along with the nasal discharge. Treatment with tetracycline was unsuccessful. Postmortem lesions in this animal were restricted to the lungs, including consolidation and pleural adhesions. Microscopic lesions were of diffuse severe bronchopneumonia. Gross lesions in the second animal included multifocal subepicardial hemorrhage and mild pulmonary edema, with scattered multifocal yellow-gray lesions in all lobes and scattered subpleural petechiae. Histologic examination revealed lesions compatible with septicemia, including moderate to severe pneumonia. Culture in each case yielded pure cultures of *K. pneumoniae*, for which gentamycin was the drug of choice. Other animals were treated with gentamycin and the disease was rapidly cleared. Based on findings that many normal adult chimpanzees had positive throat and rectal cultures for *K. pneumoniae*, it was presumed that very young chimpanzees were immunologically compromised and at risk for clinical disease. Following this outbreak, strict husbandry and nursery management procedures were instituted, including restricted access, routine sanitation procedures for equipment and nursery enclosures, and use of protective clothing by nursery caretakers.

Fox and Rohovsky (1975) present two cases of *K. pneumonia* infection in rhesus monkeys. The animals were involved in experimental work that included use of an atherogenic diet. Each case had meningitis, one had severe bronchopneumonia, and the other's lesions were compatible with septicemia, including pneumonia. Other reports of *K. pneumonia* in nonhuman primates were reviewed, and the occurrence of high mortality and frequent multiple drug resistance in the isolated organisms was discussed. Rapid identification and antibiotic sensitivity are keys for successful treatment in *K. pneumonia* outbreaks. *Klebsiella* has been identified as a cause of airsacculitis in owl monkeys (Giles et al., 1974) and in mixed infections in orangutan airsacculitis (see above). Vaccination reduced mortality in owl monkey infants due to Klebsiella "pneumo-entereitis complex" and septicemia from 20% per annum to 4% (Obaldia, 1991).

Escherichia coli *and* Pseudomonas *spp.*

Gram-negative coliform pneumonia can occur via inhalation/ aspiration or septicemic spread and is usually an indicator of an underlying disease process such as immune suppression or viral pneumonia. Gram-negative bacterial pneumonias are often part of a pneumonia-enteritis complex (Kim and Kalter, 1975a) (Figure 9.9). *Pseudomonas aerogenosa* and related organisms can occur as nosocomia infections. This agent, along with *E. coli*, is often found in association with other bacteria in laryngeal airsacculitis (see above).
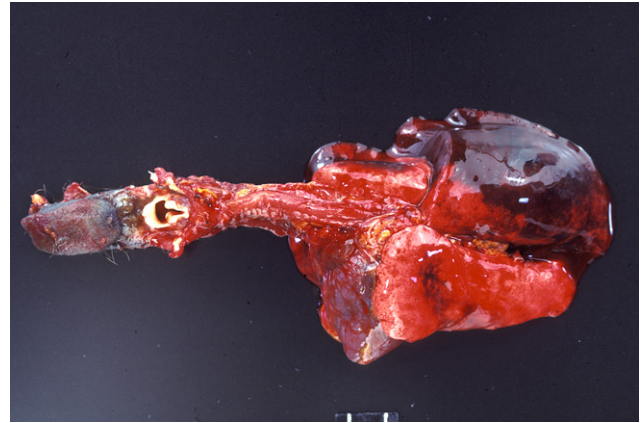

FIGURE 9.9 **Lobar hemorrhagic pneumonia,** *Pseudomonas aeruginosa*. **Titi monkey (***Callicebus* **sp.).** Pneumonia-enteritis complex. *(CNPRC)*

Bordetella

Bordetella bronchiseptica

Bordetella bronchiseptica is an obligate parasite of the upper respiratory tract of a number of animal species, including primates. It is the documented cause of pneumonia and upper respiratory disease in prosimians (Kohn and Haines, 1977), New World primates (Baskerville et al., 1983), and Old World primates (Graves, 1970; Klein et al., 1987). Generally, these cases have occurred in association with potentially weakened pulmonary defenses (stress, virus, age, etc.).

Kohn and Haines (1977) described the occurrence of *B. bronchiseptica* interstitial pneumonia, pleuritis, middle ear infection, and meningitis in lesser bushbabies (*Galago senegalensis*). The first animal presented with torticollis and later developed seizures. Necropsy findings included middle ear infection, meningitis, and interstitial pneumonia. A second animal died unexpectedly the day following this necropsy and a third animal died 12 days later. Both the latter animals had severe pulmonary consolidation, and one also had severe fibrinopurulent pericarditis and pleuritis. Microscopic examination of the lungs in all animals revealed a mixed inflammatory infiltrate with an interstitial distribution, without apparent bronchial involvement.

Bordetella bronchiseptica-associated disease is documented by Baskerville et al. (1983) in a colony of common marmosets that had initially been established as *B. bronchiseptica* free. Bilateral mucopurulent nasal discharge was noted in animals of all ages. Cough was not recognized, and animals often remained bright and alert, with occasional signs of dyspnea when handled. Affected animals had mild fever. Over a 3-month period, 16 animals died out of a colony of 156 animals. Fifteen of the deaths occurred in animals less than 12 months old, whereas the other death

occurred in a 5-year-old animal. Deaths occurred suddenly, with typical gross lesions consisting of pneumonia and pleuritis and two animals with pericarditis. Microscopic lung lesions were coalescing acute purulent bronchopneumonia. Animals were treated with oxytetracycline, with clinical recovery in adults after several days. Despite clinical recovery, *B. bronchiseptica* was still present in the nasopharynx of these animals eight weeks later. Nasal cultures of the entire colony yielded positive cultures for *B. bronchiseptica* in 71 of the 156 animals. Because of the fulminant nature of the disease in the young animals, initiation of treatment was too late to prevent mortalities.

Graves (1970) reported the occurrence of fatal *B. bronchiseptica* pneumonia in a group of six African green monkeys (vervets, *Chlorocebus aethiops*) over a 6-month period after the arrival of a total of 25 animals. In experimental studies of simian type D retrovirus serotype 1 (SRV-1) infection in rhesus monkeys, *B. bronchiseptica* pneumonia occurred in three out of 22 animals that died with simian AIDS (KGO and LJL, unpublished data) (Figure 9.10). *Bordetella bronchiseptica* pneumonia had not otherwise been a recognized problem at the California National Primate Research Center.

Bordetella pertussis

Whooping cough is an acute, highly communicable respiratory disease of human primates caused by *Bordetella pertussis*, a small pleomorphic Gram-negative coccobacillus. The organism has a strong tropism for bronchial epithelial brush border, to which it attaches and grows in tangled colonies without tissue invasion (McAdam and Sharpe, 2005). The characteristic lesions and signs (enhanced cough reflex, peripheral lymphocytosis, malaise, weight loss, mild fever) are thought to be related to exotoxin

FIGURE 9.10 *Bordetella bronchiseptica,* **bronchopneumonia and cytomegalovirus interstitial pneumonia. Rhesus monkey (*Macaca mulatta*).** The macaque had a primary simian retrovirus-1 infection. Cytomegalovirus-associated lesions include hilar edema and multifocal hemorrhage. *(CNPRC)*

production. These signs persist as long as the toxin is present within cells, even after the bacteria are gone. Immune protection and recovery are based on the production of secretory IgA, which inhibits bacterial adhesion and subsequent proliferation. The disease has a 7−10-day incubation period, at the end of which there is a "catarrhal" period of coughing and sneezing, followed by the onset of the characteristic violent paroxysmal coughing. Occasional complicating problems include subcutaneous emphysema and convulsions associated with hypoxia and constant coughing. Lesions of established whooping cough are of laryngotracheobronchitis. In severe cases this can include bronchial mucosal erosion, hyperemia, and copious mucopurulent exudate. Mucosal lymph follicles and peribronchial lymph nodes are enlarged and hypercellular, paralleling the marked peripheral lymphocytosis seen in complete blood count data. Immunization has traditionally been provided as part of the DPT (diphtheria, pertussis, tetanus) vaccination; however, complications in both humans and in at least one infant chimpanzee (Southers and Ford, 1995) associated with the pertussis component have raised a cautionary note to the routine use of DPT. ADT vaccine is now available and could be considered as an alternative in conjunction with policies regarding immunization for employees and that prevent potential contact with children.

An epizootic of whooping cough has been described in a group of zoo common chimpanzees (Gustavsson et al., 1990). Clinical signs and epidemiologic data were compared to an outbreak of respiratory syncytial virus infection that occurred in the same group earlier in the same year. During the whooping cough outbreak, which started in early August, animals exhibited cough and some exhibited nasal catarrh. Following this period, animals developed drawn-out paroxysmal coughing fits and associated dyspnea. The coughing gradually decreased and eventually ceased during September.

Pasteurellosis

Pasteurellae are strict animal parasites, generally inhabiting the nasopharyngeal and oral mucous membranes. Pasteurellosis can be caused by *Pasteurella multocida* or *Mannheimia (*formerly *Pasteurella*) *haemolytica.* It may occur as peracute or acute septicemia, or may be less acute, and causes signs associated with the primary organ of infection. It often occurs when local and systemic defense mechanisms are impaired. Predisposing factors include stress induced by such factors as transportation, crowding, and climatic changes or by the damaging effects of respiratory viral infections.

Reported cases in nonhuman primates include outbreaks in Goeldi's monkeys (*Callimico goeldii*) (Duncan et al., 1995), owl monkeys (*Aotus trivirgatus*) (Benjamin and Lang, 1971), and baboons (Bronsdon and DiGiacomo,
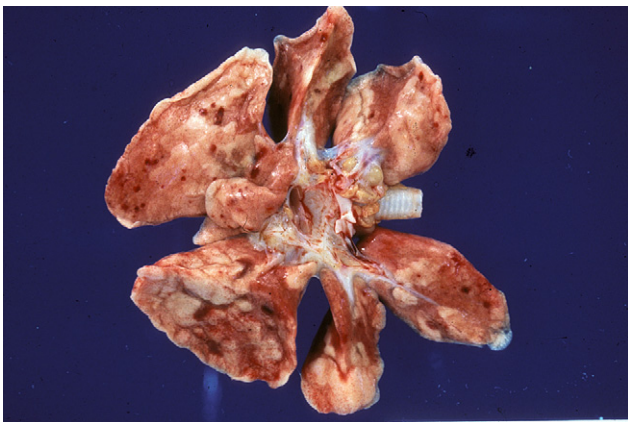
1993), as well as a case in a patas monkey (Okoh and Ocholi, 1986). Possible predisposing conditions included the presence of lingual gongylonemiasis in the Goeldi's monkeys, recent acquisition and transport of the owl monkeys, and the onset of cold, rainy seasonal weather for the patas monkey. The Goeldi's monkeys had a clinical history of a long-term increase in salivation, with no other signs prior to the death of three out of four animals over an 8-hour period. The owl monkeys were received in poor condition and were anorexic and lethargic, with one animal found dead three days after arrival and two more animals dead three days later. Respiratory difficulty had been noted in the patas monkey for two weeks prior to her death, during which she appeared to improve with penicillin−streptomycin therapy. Lesions in all three supported the occurrence of acute bacteremia, with pulmonary involvement that included the presence of fibrinopurulent interstitial inflammation associated with fibrinous thrombi and bacteria in pulmonary vessels. *Pasteurella multocida* was isolated from the Goeldi's monkeys and the owl monkeys, whereas "*P. hemolytica*" was isolated from the patas monkey.

Haemophilus influenzae

Haemophilus influenzae is a Gram-negative non-motile rod that is part of the normal pharyngeal flora in humans. It is reported as an infrequent cause of respiratory disease in nonhuman primates by Good and May (1971). It was an historically important cause of respiratory disease in children in the U.S. prior to the onset of vaccination and still remains an important cause of otitis and pneumonia in infants and children in areas where vaccination is not available. It is considered to be an opportunistic pathogen with disease occurring secondary to viral infection or immune suppression and including bacteremia, meningitis, and pneumonia. Two recent reports of normal bacterial flora in rhesus macaques did not isolate *H. influenza* from the animals in those studies (Bowers et al., 2002; Carrier et al., 2009). When *H. influenza*-related disease has been reported in nonhuman primates it often characterized by septicemia with or without pneumonia. The lesions occurring with septicemia, besides pneumonia, can include septic arthritis and meningitis (Scheifele et al., 1980; Dawkins, 1982). Experimentally, nonhuman primates (macaques) have been used as models of human infection (Scheifele et al., 1979) or to study the immune response to vaccines (Vella and Ellis, 1991). Occasional naturally occurring cases have appeared in zoo-housed apes (L.J. Lowenstine, unpublished).

Francisella tularensis

Tularemia (rabbit fever), caused by *F. tularensis*, is a disease affecting a broad range of mammalian species including human and nonhuman primates. The agent is distributed throughout the temperate Northern Hemisphere and is endemic in parts of North America, Europe, and Asia (Thomas and Schaffner, 2010). Carried by rabbits and rodents, it is therefore most often reported in outdoor-housed nonhuman primates in zoos and vivaria. The agent can also be spread by insect vectors (flies and ticks), by direct contact or wound contamination with infected tissues or blood, and by inhalation or ingestion of infected exudates and contaminated water. In humans, there are several disease manifestations: (1) ulceroglandular, affecting skin with regional lymphadenitis; (2) oropharyngeal; (3) glandular; (4) pulmonic; (5) typhoidal (enteric); (6) occuloglandular and; (7) septicemic/systemic. Nonhuman primate infections have been reported in prosimians, New World and Old World monkeys, and apes, and most have been presumed to be due to ingestion of an infected small mammal (Mätz-Rensing et al., 2007; Ketz-Reily et al., 2009; Lowenstine, unpublished). Most reported infections were septicemic, but pneumonic cases have occurred as either part of systemic disease or due to presumed inhalation (Figure 9.11). Rhesus have been used as a model for pneumonic tularemia, which is considered to be a potential agent of bioterrorism (Schriker et al., 1972). Pulmonary lesions can vary from bronchopneumonia to interstitial and can range from predominantly histiocytic, to pyogranulomatous to necrotizing and suppurative. Organisms are difficult to identify with H&E and tissue Gram stains and are best demonstrated by culture, immunohistochemistry or PCR. Treatment consisting of doxycycline at 5 mg/kg, intravenously followed by treatment p.o., was successful in the orangutan cases (Ketz-Reily et al., 2009).

Nocardiosis

Nocardiosis is an infrequent disease in nonhuman primates that must be differentiated from cases of tuberculosis.

FIGURE 9.11   Tularemia, interstitial pneumonia secondary to septicemia. Squirrel monkey (*Saimiri sciureus*). *(UC Davis, VMTH)*

Nocardiae are found worldwide as soil-dwelling, saprophytic organisms. They are Gram-positive, weakly acid-fast-positive, long, filamentous (1 µm diameter) aerobic organisms that frequently aggregate in branching chains, growing extracellularly in tissue. Culture requirements are less exacting than *Mycobacterium* sp., as they grow in common culture media and under aerobic conditions.

Nocardial infection occurs in a variety of species, including humans and nonhuman primates (Klumpp and McClure, 1993). The disease is not transmitted among individual animals or humans. It can be found as a primary infection, but is more often opportunistic, occurring in cases of chronic illness or with other states that may have associated immune dysfunction. In humans, it appears as pulmonary or skin infection. Cases reported in nonhuman primates also include extrapulmonary infection with lesion distribution supporting the likelihood of an oral infection route (Liebenberg and Giddens, 1985).

Clinical signs associated with pulmonary nocardiosis are often nonspecific and even subclinical until late in the disease course. Fever and productive cough occur. Late dissemination may include sequelae such as meningitis and cerebral abscess. Nocardia may not be suspected until after more common bacteria have been excluded and the response to antibiotics has proven unsuccessful. Antimicrobial testing for *Nocardia* species may not be clinically relevant, such that choice of effective antibiotic should generally be based on published clinical experience. Recommended treatment most often includes the use of long-term sulfonamide or minocycline. In addition to sulfonamides and minocycline, most aminoglycosides, fusidic acid, and some newly developed lactam antibiotics are active against most *Nocardia* strains (Filice, 1994). Increased efficacy has been suggested when sulfonamide is combined with streptomycin or trimethoprim (Liebenberg and Giddens, 1985). It is unknown whether combination therapy is actually more effective than single agent therapy (Filice, 1994). The potential for increased efficacy must be weighed against the increased risk for toxicity.

Pulmonary lesions often include multinodular to diffuse consolidation, as well as abscessation and cavitation. Other reported lesions include fibrinous pleuritis or empyema and nodules and abscesses in peritoneum, liver, kidney, brain, and subcutis. Microscopically, lesions frequently contain central areas of necrotic debris, bacteria, and neutrophils. Granulation or fibrous connective tissue often surrounds this lesion center, with a mixed inflammatory infiltrate that includes neutrophils, lymphocytes, plasma cells, macrophages, epithelioid cells, and multinucleate giant cells. Bacteria are generally not readily apparent with H&E staining but can generally be located with either Gram or methenamine silver stain. Occasionally norcardia will form large colonies surrounded by host response (Splendore-Hoeppli phenomenon), often termed "sulfur granules." This feature has resulted in the potential for misdiagnosis of nocardiosis as actinomycosis, actinobacillosis, or botryomycosis (staphylococcosis). Definitive diagnosis is dependent on isolation and identification of the organism.

Pulmonary nocardiosis in an outdoor-housed adult male orangutan (*Pongo pygmaeus*) was associated with a history of recurrent upper respiratory infection signs over a 22-month period (McClure et al., 1976). The episodes were considered to be not severe enough to warrant examination and treatment. A terminal episode occurred in which the animal was found lethargic and severely dyspneic, with epistaxis. Gross lesions included extensive chronic pneumonia and pleuritis, as well as air sac infection. Microscopic lesions were similar to those generally described with nocardiosis, including the presence of occasional granules made up of bacteria. Brown and Brenn stains revealed Gram-positive, branched filamentous organisms. These were acid-fast-negative with a variety of acid-fast stains, leading to an initial diagnosis of actinomycosis. Microbiology resulted in culture of *Nocardia asteroides*.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is an important cause of community-acquired pneumonias in children and adults in the U.S. and is also the cause of "military recruit," "primary atypical," and "walking" pneumonias (Waites et al., 2008). The only known natural host is the human primate, but this organism is also suspected to cause pneumonia in nonhuman primates including Old World monkeys and apes, and has been demonstrated experimentally to infect macaques and chimpanzees, which are used for studies of pathogenicity and vaccine development. Like all mycoplasmas, *M. pneumoniae* is a small, Gram-negative organism that lacks a cell wall and is placed in the class Mollicutes. It is both an extracellular and facultative intracellular parasite. Transmission is by respiratory droplets and inhalation after which the organisms attach to the upper and lower respiratory mucosa causing pharyngiti, tracheobronchitis, and pneumonia. Attachment to the ciliated border of respiratory epithelium, via a specialized attachment organelle, can lead to altered ciliary movement and deciliation. Cell cytotoxicity is due to production of hydrogen peroxide by the organism. Grossly lesions consist of patchy lobar, unilateral, or bilateral consolidation. Histologically there is mixed inflammation and mucosal edema with erosions in the trachea, bronchi, and bronchioles; in the lungs it is centered on respiratory bronchioles and alveolar septa causing thickening and exudation of protein rich edema and inflammatory cells (macrophages and lymphocytes with fewer plasma cells and neutrophils) (Atkinson et al., 2008). The lesions are similar to those seen in viral respiratory infections and resemble a localized ARDS lesion, complete with hyaline membranes (see

above). Indeed *M. pneumoniae* infection may precipitate full-blown ARDS and can occur concurrently with respiratory viral infections and predispose to other secondary bacterial pneumonias. Much of the damage caused by *M. pneumoniae* is due to host immune response and cytokine release. Diagnosis in humans is often made by assumption, and definitive diagnosis by culture can be difficult due to the finicky nature of the organism and its slow growth rate in vitro. Evidence of seroconversion has also been used. Sputum Gram stains are negative, which helps rule out pneumococcal pneumonia. Molecular (PCR) detection, directed toward the organism or as part of a multiplex or "gene-chip" approach, is increasingly being adopted for definitive diagnosis. Treatment with tetracyclines (e.g., doxycycline) or macrolide antibiotics (e.g., azithromycin, erythromycin) is usually effective, though resistant strains have been reported. Protective immunity is short-lived and recurrent or recrudescent episodes of mycoplasma respiratory disease can occur.

Reports of infection in nonhuman primates have been primarily on experimental infections. Rhesus can be infected, but without clinical signs (Friedlaender et al., 1976). There was no transmission between infected and control animals, although the organism persisted in infected rhesus for up to 50 days. Chimpanzees are the animal model of choice and are preferable to rodent models because they develop clinical signs that mimic the disease in humans, including rhinorrhea, pharyngitis, persistent cough, fever, and radiographic lung lesions (Barile et al., 1987, 1993). Infection was by direct instillation into a main bronchus; however, two control chimps became accidentally infected suggesting that horizontal transmission may occur in this species. The agent could be recovered for 28−68 days from the oropharynx, similar to findings in humans. Positive serology was noted in wild mountain gorillas (*Gorilla beringei beringei*) during a suspected measles respiratory disease outbreak (Hastings et al., 1991). It is likely that this infection is under-diagnosed in nonhuman primates and it will be interesting to see if the application of "gene-chip" molecular diagnostics will help increase our understanding of the role of *M. pneumoniae* in nonhuman primate respiratory disesase (Benson et al., 2008).

MYCOTIC DISEASES

Mycotic infections of nonhuman primates have been reviewed by Migaki (1986).

Coccidioidomycosis

Coccidioides immitis and *Coccoidioides posadasii* are dimorphic fungi that grow as saprophytes in endemic geographic areas, including arid regions of California (*C. immitis*), Arizona, and Texas, as well as in similarly arid portions of northern Mexico, Central America, and South America (*C. posadasii*). They naturally infect a variety of wild rodent species (Pappagianis, 1985), and high concentrations of the fungus may be found in rodent burrows. Vegetative growth occurs in these areas after rains, with dispersion of spores (arthroconidia) by the wind after the soil dries. Other activity that disturbs the contaminated soil, such as construction or agricultural, also can increase the possibility of spreading the infective spores. Very severe dust storms have resulted in epizootics of disease, and cases may occur in areas geographically associated with, but not normally recognized as, endemic sites of *C. immitis/posadasii* growth, as the windblown spores are carried miles away from their original source.

Coccidioidmycosis is primarily a respiratory disease, with inhalation of arthrospores as the mode of infection. It is not transmitted via the respiratory route from animal to animal. The tissue form is not generally considered to be pathogenic, although ingestion of infected mouse cadavers by other mice, rats, or hamsters has produced infection (Pappagianis, 1985). Occasional human cases with sporulation in tissues antemortem have been documented. These latter findings support the use of appropriate precautions when handling diagnostic or postmortem material to avoid parenteral exposure or aerosolization and possible inhalation. Over time, it is likely that many animals and humans in endemic areas are exposed and possibly infected, with relatively few clinically apparent cases. When present, clinical signs in those with pulmonary disease may include fever and cough, and in humans have been noted to include pleuritic pain and hypersensitivity-type skin lesions (erythema nodosum, erythema multiforme). In a small percentage of individuals, more generalized disease occurs, with signs such as continued fever, chills, night sweats, weakness, and weight loss. Diagnostic workup can include radiology (Silverman et al., 1975), as well as serology, biopsy, and culture or molecular detection of the organism (Pappagianis, 1985; Sauabolle, 2007). Treatment involves the use of antimycotic agents, such as amphotericin B, ketoconazole, fluconazole (Graybill et al., 1985, 1990; Pappagianis, 1985; Ampel 2010) and posaconazole (Herrin et al., 2005). Vaccines are not yet available, but cynomolgus macaques are being used as models for vaccine development (Johnson et al., 2007).

Gross pulmonary lesions include focal gray-white foci of consolidation as well as more diffuse consolidation. Local lymph node enlargement may also occur. When disseminated disease is present, there is more diffuse pulmonary involvement, with multifocal involvement of other tissues, including lymph nodes, spleen, bones, liver, meninges, and adrenals. The host inflammatory reaction depends on the phase of the organism that is present. Inflammation in acute and fulminant lesions includes

a marked neutrophilic response, which generally occurs in response to arthroconidia and endospores. A granulomatous reaction takes place in response to the presence of the classical tissue-phase stage of *C. immitis* growth; the thick-walled spherule (sporangium), which measures 10−70 µm in diameter and has a thick, double-contoured wall. Endospores are produced in large numbers within the spherules and generally are 2−5 µm in diameter. They are released into the tissues when a spherule ruptures. The presence of all phases of fungal growth within an infection site can lead to a lesion morphology that includes foci of neutrophilic aggregation in association with endospores, as well as extensive fibrosis with epithelioid cells, giant cells, lymphocytes, and neutrophils, often in association with spherules. When infection is well contained by the host, the granulomatous response predominates and numbers of organisms are small, making detection and etiologic diagnosis more difficult.

There are multiple reports of coccidioidomycosis occurring in nonhuman primates (Pappagianis, 1985), and it is presumed that all taxa are likely susceptible. In each reported case, as well as in more recent reports (Burton et al., 1986; Graybill et al., 1990; Bellini et al., 1991; Johnson et al., 1998), the affected animals either resided in endemic areas or had originated from endemic areas. Review of great ape mortality in North American zoos identified gorillas as being very susceptible to disease (Benirschke and Adams 1980; L.J. Lowenstine, unpublished). The report by Burton et al. (1986) describes coccidioidomycosis in a ring-tailed lemur (*Lemur catta*) that had been relocated to a zoo in Oklahoma from a zoo in Phoenix. The initial clinical presentation of that animal was unilateral corneal opacity, followed three months later by convulsions, urine retention, and diarrhea. Within a week the condition of the animal continued to deteriorate, with dyspnea and radiologically apparent pleural effusion. Exploratory laparotomy revealed peritonitis as well, and the animal was subsequently euthanized. Pathological workup revealed the presence of multifocal granulomatous inflammation in multiple tissues including the retina, lungs, liver, kidney, and chest wall associated with thick-walled spherules compatible with *C. immitis* infection. Culture and serology confirmed the diagnosis.

Graybill et al. (1990) document the occurrence of coccidioidomycosis in a free-ranging group of more than 200 Japanese macaques (*M. fuscata*) in Dilley, Texas. The report further deals with the use of fluconazole in efforts to treat animals with coccidioidomycosis. Four gravely ill monkeys died within one month of starting treatment, whereas eight animals showed rapid improvement with an oral regimen of approximately 2−3 mg/kg/day, given as caramel candy into which the drug had been mixed. Therapy was successful when given over a prolonged period of time (minimum of 13 months in this group); however, at the time of publication, only one animal in this group of eight had actually had treatment discontinued without a recurrence of clinical disease. Two animals that had therapy interrupted at two months relapsed but showed improvement again after resumption of therapy. The deaths of two other monkeys that had initially responded to therapy were directly related to a temporary interruption of the fluconazole supply. The authors discuss the potential benefit of higher doses and provide a review that includes initially mixed results in human trials. Finally, they reference earlier work that demonstrated great effectiveness of a liposomal preparation of amphotericin B, which could be administered just once or twice weekly and produced remission in treated animals (Graybill et al., 1985), but which could not be used in the field situation in which the free-ranging macaques were involved.

In a case report of disseminated coccidioidomycoses with CNS involvement in a 4-year-old, zoo-housed chimpanzee, posaconazole at 50 mg/kg daily for approximately 24 months was effective, where as fluconazole previously given at 10 mg/kg daily for six months had failed to cause clinical improvement or decrease serum titers (Herrin et al., 2005). This chimp had to be euthanized because of intractable diarrhea and weight loss, but there was no evidence of active coccidioidomycosis at time of necropsy.

Histoplasmosis

Histoplasmosis, caused by *Histoplasma capsulatum*, is a mycotic disease with a number of similarities to coccidioidomycosis, including (1) the occurrence of granulomatous pulmonary disease that can resemble tuberculosis, (2) fungus species characteristics that include thermal dimorphism (hyphae with spores at room temperatures, yeast-type growth at body temperature), and (3) a tendency for geographic localization (Ohio and Mississippi rivers and the Caribbean for *Histoplasma* and United States southwest and far west plus Mexico for *Coccidioides*). Histoplasmosis occurs generally by ingestion or inhalation of contaminated dust, which is often associated with pigeon, chicken, or bat feces-contaminated areas. *Histoplasma* exists in the infected individual as an intracellular parasite of the monocyte-macrophage system, with subsequent potential for dissemination throughout the reticuloendothelial system. Diagnosis can be made with a delayed-type hypersensitivity skin test or by morphologic identification in affected tissue specimens with confirmation by culture or molecular diagnostics. Treatment is as for other systemic mycotic infections.

There are few reports of histoplasmosis due to *H. capsulatum* in nonhuman primates (Migaki, 1986). Systemic histoplasmosis occurred in a de Brazza's monkey (*Cercopithecus neglectus*) in Kenya (Frank, 1968), with extensive renal involvement and less affected liver and lungs. This

was presumably due to *Histoplasma duboiseii* the causative agent of African histoplasmosis, which has also been identified as causing locally invasive cutaneous and osteolytic lesions in imported baboons housed in a colony in Texas (Butler and Hubbard, 1991). Bergeland et al. (1970) report a squirrel monkey with *Histoplasma*-associated granulomatous pneumonia, hepatitis, and splenitis. The animal died two months after being purchased from a Minneapolis pet shop. Disseminated histoplasmosis has also been reported as an opportunistic infection in an SIV-infected rhesus monkey (Baskin, 1991a).

Cryptococcosis

Cryptococcus neoformans and *Cryptococcus gattii* are yeast-like fungi that are found in soil throughout the world and occur in particularly high frequency in old pigeon nests and droppings (*C. neoformans*) or associated with certain trees or wood products (*C. gattii*). Cryptococcosis due to *C. neoformans* generally occurs as an opportunistic primary respiratory infection via inhalation, more often affecting the nasal passages than the lungs. The pulmonary infection frequently remains mild or subclinical while the fungus spreads to other organs, including the central nervous system, skin, liver, spleen, adrenals, and bones. Meningitis is a very common complication in human cases. In humans the disease usually occurs as an opportunistic infection, but infection in normal individuals also occurs, often in association with overwhelming exposure. *C. gattii* is more often associated with pulmonary cryptococcosis and occurs in immunologically competent individuals (Dewar and Kelly, 2008). This species of Cryptococcus was initially described in Australia and tropical countries, but has expanded its range to the west coast of Canada and the U.S. in recent years, as evidenced by cases in humans, domestic animals, and free-ranging and captive wild animals (Byrnes et al., 2010).

Clinical signs of cryptococcosis are usually inapparent and, when present, nonspecific. Most infected humans present with meningoencephalitis and associated symptoms, including headache, nausea, staggering gait, dementia, irritability, confusion, and blurred vision (Li and Mody, 2010). Reports of nonhuman primates have included signs such as marked depression in an Allen's swamp monkey (*Altenopithecus nigroviridis*) (Barrie and Stadler, 1990) and a lion-tailed macaque (Miller and Boever, 1983), seizures several days before death in a purple-faced langur (*Presbytis senex vetulus*) (Migaki, 1986), and a mandibular mass in a squirrel monkey (Roussilhon et al., 1987). Leaf-eating monkeys (colobines) seem to be susceptible, especially proboscis monkeys (*Nasalis larvatus*) in which nodular pulmonary and meningeal lesions predominated (Griner, 1983).

Diagnosis of pulmonary cryptococcosis can be suggested with radiography (Feigin, 1983) or computerized tomography (Barrie and Stadler, 1990), but requires biopsy or culture for confirmation. Serological tests can also prove useful (Gazzoni et al., 2009). The radiographic appearance and microscopic morphology can vary depending on the immune function of the host (Feigin, 1983; McAdam and Sharpe 2005). In immunocompromised patients, gelatinous fungal masses may exist with minimal to no inflammation. Inflammatory infiltrates even in immune competent patients may often contain relatively few cells, consisting of a mixture of macrophages, lymphocytes, and plasma cells, although granulomatous inflammation with epithelioid and giant cells occurs as well, particularly in lung lesions. In section and cytologic specimens, the yeast has a characteristic very wide capsule. The capsule remains unstained in H&E-stained sections and stains positively with periodic acid-Schiff (PAS), mucicarmine, or alcian blue. Use of India ink in cytologic specimens is a negative staining technique that reveals the distinctive thick capsule as a clear halo around the yeast.

Cryptococcosis treatment in humans and nonhuman primates has included the use of amphotericin B alone or in combination with flucytosine, and fluconazole alone or combined with flucytosine (Roussilhon et al., 1987; Barrie and Stadler, 1990; Shirley and Baddley 2009). *C. gattii* responds similarly to *C. neoformans* to antifungals such as isavuconazole, posaconazole, and voriconazole, while some isolates demonstrated reduced susceptibility to fluconazole (Thompson et al., 2009). Barrie and Stadler (1990) describe marked improvement in response when fluconazole was substituted for amphotericin B.

Pneumocystis spp.

Pneumocystis spp. are important opportunistic respiratory pathogens, the environmental sources of which are as yet unknown. Analysis of ribosomal RNA gene sequences, mitochondrial proteins, major enzymes (thymidylate synthase, dihydrofolate reductase), and cell wall components (include glucans) provides evidence that *Pneumocystis* is a fungus rather than its previous classification as a protozoan (Stringer, 2002). In humans, the agent formerly known as *P. carinii* has been renamed *P. jirovecii* and is considered to be highly species specific. *Pneumocystis* isolated from nonhuman primates are still considered to be *P. carinii*. Though further speciation is likely, in one study, no nonhuman primates were found to be infected with *P. jirovecii* (Demanche et al., 2001; Guillot et al., 2004). Most normal children are seropositive to *Pneumocystis* by the time they are 3 to 4 years old. *P. jirovecii* pneumonia occurs in premature or malnourished infants, children with primary immunodeficiency diseases, patients receiving immunosuppressive therapy, and people with AIDS. Epidemiologic and experimental data support the occurrence of airborne, possibly horizontal transmission in humans and animals, including nonhuman primates

(Vogel et al., 1993; Demanche et al., 2005). There is debate about whether *Pneumocystis* can be transmitted vertically in humans, and there is one mention of twin stillborn common marmosets with the infection (Demanche et al., 2003). Clinical signs associated with pneumocystis pneumonia in humans and nonhuman primates include dyspnea, fever, anorexia, and nonproductive cough (Chandler et al., 1976; Pyrgos et al., 2009; Catherinot et al., 2010). Radiographic findings often include bilateral diffuse pulmonary infiltrates ("white-out"). Because the clinical and radiographic findings are nonspecific, etiologic diagnosis depends on identification of the organism itself. Bronchoalveolar lavage fluid is the key material for testing and the organisms are generally made apparent using such traditional stains as methenamine silver, toluidine blue, or cresyl echt violet, which stain the cell wall. Specific immunostaining or molecular probe techniques (PCR) are also available. Grossly, affected lungs fail to collapse and are regionally pale pink to tan with a firm styrofoam-like consistency similar to the appearance of SIV giant cell pneumonia (Figure 9.12). Rarely, a nodular form with extension to extrapulmonary pleural surfaces is seen (Yanai et al., 1999). The typical microscopic lesion is a diffuse or patchy pneumonia. Alveolar spaces contain variable amounts of amphophilic, foamy amorphous material that resembles proteinaceous edema fluid, but which is composed of *Pneumocystis* and cellular debris as demonstrated by electronmicroscopy (Baskerville et al., 1991). Variable degrees of interstitial thickening are often present due to edema, minimal to mild mixed inflammatory cell infiltrates, and fibrosis. Neutrophils are present early in the course of experimental infection and true granulomatous pneumonia is rare, but can be seen (Board et al., 2003; Hartel et al., 2010). Type II pneumocyte hyperplasia may also be present. Organisms can be identified in histological sections using the stains mentioned above and by immunohistochemistry (Baskerville et al., 1991).
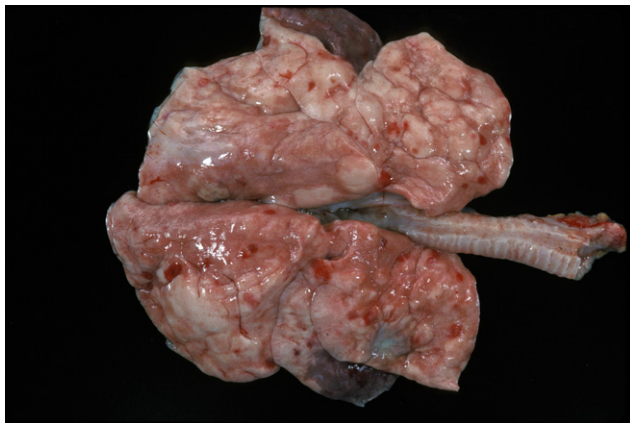

FIGURE 9.12   *Pneumocystis carinii* **pneumonia, SIV-infected rhesus.** Lungs do not collapse and are firm to spongy on palpation.

The mainstay of treatment for pneumocystis pneumonia is trimethoprim−sulfamethoxazole (TMP−SMX) 1920 mg three times daily (approximately equivalent to TMP 15 mg/kg/day−SMX 75 mg/kg/day) for 21 days (orally or i.v.). However, lower doses (TMP−SMX 960 mg four or three times daily (approximately TMP 10 mg/kg/day−SMX 50 mg/kg/day)) may be equally efficacious and have less severe side-effects (Thomas et al., 2009). Pentamidine is frequently used but is more toxic than TMP−SMX. Other drugs used for second-line treatment include clindamycin and primaquine or dapsone and trimethoprim, which are administered orally. These drugs are as effective as pentamidine, with much lower toxicity (Helweg-Larsen et al., 2009).

Spontaneous *P. carinii* infection has been reported in several nonhuman primate species. Carriage rates among 83 individuals of 26 species of zoo-housed primates were examined using postmortem lung tissue and were determined to be 28.6% in New World species and 20.0% in Old World monkeys (Demanche et al., 2003). A serologic survey comparing wild *vs.* laboratory-born Japanese and cynomolgus macaques in Japan revealed that exposure/infection was much higher in those animals brought in from the wild (54.9% of wild cynomolgus and 40% of Japanese monkeys *vs.* 9.4% of lab-born cynos) (Fujita et al., 1996). Other reports include endemic infection in a "marmoset" colony (*Saguinus* spp.) (Richter et al., 1978), infection in two aged owl monkeys (*A. trivirgatus*) and two young chimpanzees (Chandler et al., 1976), infection in cynomolgus and Japanese macaques (Matsumoto et al., 1987; Demanche et al., 2003, 2005; Kling et al., 2009), and in red-bellied tamarins (*Saguinus labiatus*) (Kobayashi et al., 1999). Although no systematic study of gibbons or great apes has been conducted, mild histological lesions of pneumocystosis were identified in a zoo-housed gorilla infant (L.J. Lowenstine, unpublished). Richter et al. (1978) describe a retrospective survey of lungs from 441 callithricids (*Saguinus* spp.) for the occurrence of *Pneumocystis*. Fifty of the animals had histologically detected *Pneumocystis*, with just two animals that were thought to have associated clinical disease. The most-affected age groups were the 7−12-month group and aged animals (approximately 4 years plus). In the report by Chandler et al. (1976), one of the owl monkeys had no concurrent disease, whereas the other had been experimentally inoculated with *Treponema pallidum* 44 months before death. The chimpanzees in the same report each had an underlying myeloproliferative malignant neoplasm (erythroleukemia; McClure et al., 1974). A retrospective survey of macaque necropsies by Matsumoto et al. (1987) revealed low rates (7.7%) of *Pneumocystis* in Japanese macaques (*M. fuscata*), 4 out of 52; crab-eating macaques (*M. fascicularis*), 1 out of 13; and none detected among 35 rhesus monkeys. All of the affected animals were

relatively young (four juveniles, 7 to 22 months, and one young adult). Of the infected macaques, just two of the Japanese monkeys were thought to have clinically significant *Pneumocystis* infection; one was 16 months old and the other apparently an infant (body weight listed at 490 g).

Other reports of *P. carinii* in nonhuman primates include descriptions of the lesion and a relatively high rate of infection among macaques infected with SIV (Baskerville et al., 1991; Furuta et al., 1993, 1997; Vogel et al., 1993). Furuta et al. (1993) found Pneumocystis pneumonia in three of five SIV-infected rhesus monkeys and suggest that this represents reactivation of latent *Pneumocystis* infection. In the report by Vogel et al. (1993), 44 of 85 terminally ill, SIV-infected rhesus monkeys and 2 of 22 SIV-infected animals in earlier stages of SIV infection had detectable *P. carinii*. Clinically significant *P. carinii* infection increased from zero in the first two years of SIV infection to >50% during the fourth year of virus infection. Epidemiologic data, in this report, strongly supported the horizontal transmission of *Pneumocystis* as opposed to reactivation of latent infection. Description of the lesions included the orientation of *P. carinii* infection centered on terminal airways in 59% of the infected animals.

North American Blastomycosis

Blastomyces dermitiditis, the cause of North American blastomycosis, is a dimorphic soil fungus endemic to the Mississippi and Ohio river valleys and the Great Lakes region of the United States and Canada. Blastomycosis had been described in humans and domestic animals, primarily dogs (Brömel and Sykes, 2005). Infection is by aerosolization of spores from disturbed soil and usually results in multifocal pyogranulomatous pneumonia. Skin is a frequent site of dissemination while spread to bone, genitourinary tract, and brain occurs less often (Saccente and Woods, 2010). Diagnosis relys on identification of the characteristic broad-based budding yeast on cytology, in histological sections, or by culture (Patel et al., 2010). Itraconazole is generally effective and can be used in place of the more toxic amphotericin B (Bradsher, 2008).

There is a single case report of granulomatous pneumonia and disseminated blastomycosis in an 8-year-old, male rhesus macaque that had clinical signs of depression, anorexia, labored breathing, and a harsh cough (Wilkinson et al., 1999). The animal died six days after clinical signs were first noted. Gross lesions consisted of military pulmonary nodules of pyogranulomatous pneumonia in which organisms morphologically compatible with *B. dermatiditis* were visualized in impression smears and histological sections. Similar lesions were also found in the spleen and brain. The animal had been housed indoors for several years but had spent its early life house outdoors at a facility near the Mississippi river delta. That facility, however, had seen only one case of blastomycosis in 18 years.

PROTOZOAN DISEASES

Toxoplasmosis

Toxoplasmosis is the only significant respiratory protozoanosis of nonhuman primates. *Toxoplasma gondii* is a protozoan parasite of the Apicomplexa subphylum, which also includes coccidia. Like other apicomplexans, toxoplasma has a two-host life cycle. The only known definitive hosts are members of the cat family (Felidae). Intermediate hosts include essentially all other warm-blooded animals, including nonhuman primates. Sexual reproduction of the parasite takes place in the intestinal tract of the felid and unsporulated oocysts are shed in the feces. Sporulation takes place in the environment, and it is the sporulated oocytes that are infectious. Intermediate and definitive hosts become infected by ingesting the sporulated oocytes or by ingesting an infected definitive or intermediate host in which tissue cysts (bradyzoites) are present. Transplacental infection is an important cause of fetal death in humans and has been demonstrated experimentally in macaques (Schoondermark-Van de Ven et al., 1993). *T. gondii* has a worldwide distribution and is ubiquitous in almost every ecosystem from the Arctic to the tropics.

Laboratory-housed primates may become infected through ingestion of feed stuffs contaminated with cat feces, infected food items that might be offered (e.g., raw ground meat, especially horse meat or sheep heart), or vermin, especially mice that might be caught and eaten (Anderson and McClure, 1993). Paratenic hosts, such as earthworms and cockroaches, which can be found in vivarial and exhibition settings, may transport infective oocysts (Chinchilla et al., 1994; Bettiol et al., 2000). Horizontal transmission in squirrel monkeys has been documented and confirmed experimentally. In these cases, respiratory secretions from dying cage mates were thought to spread infectious zooites to other monkeys through inhalation or ingestion (Furuta et al., 2001; Carme et al., 2009).

Among nonhuman primates, infection has been documented in prosimians, New World monkeys, and Old World monkeys (Anderson and McClure, 1993), but it is the New World monkeys and prosimians in which infection is most devastating and in which it has occurred in outbreak form. In New World monkeys, especially the cebids such as squirrel monkeys (*Saimiri* sp.) (Anderson and McClure, 1982; Cunningham et al., 1992), capuchins (*Cebus* sp.), and woolly monkeys (*Lagothrix* sp.), toxoplasmosis is manifest as severe respiratory distress or as sudden death. Animals may be found acutely moribund with audible rales and fluid, blood, or foam coming from the nares and mouth (Epiphanio et al., 2003). There may be nonspecific

premonitory signs of anorexia and lethargy. Diarrhea may also be present and occasionally is the main presenting sign (Bouer et al., 1999). In Old World monkeys, the infection is often self-limiting, inapparent, and may be seen in the context of immune suppression (Lowenstine et al., 1992). Tissue cysts without inflammation are an occasional incidental finding in macaques and apes, but encephalitis may ensue in immune-suppressed animals.

Gross lesions include marked pulmonary congestion and edema (Figure 9.13), white or bloody froth in the trachea, and hilar (tracheobronchial) lymphadenopathy. The lungs fail to collapse when the pluck is removed. Mesenteric lymphadenopathy, overt enteritis, and other lesions reflecting the systemic and fulminating nature of the infection may also be seen.

Histologically, the catholic tropism of the organism becomes apparent. The tachyzoites excyst in the small intestine where they cause intestinal necrosis and are swept into the systemic circulation via lymphatics and blood vessels. Necrosis of pancreas and mesenteric lymph nodes is common. Hepatic and splenic multifocal acute necrosis results from dissemination via the portal circulation. Necrosis of the lung capillaries and endothelial cells results in the profound pulmonary edema. In animals that survive a few days, type II pneumocyte hyperplasia may be evident. Cerebral edema and necrosis have also been reported. Individual tachyzoites can be seen in histologic sections but are best demonstrated in impression smears. Tissue cysts with bradyzoites can be found in areas of acute necrosis. If the primate is less severely affected, bradyzoite tissue cysts can be found in heart and skeletal muscle and brain.

The organisms are PAS negative, but with a PAS-positive cyst margin. They are Gram-negative. Differential diagnosis in a nonhuman primate would include microsporidiosis, which may also be found in nervous tissue, and

FIGURE 9.13 **Toxoplasmosis.** Acute diffuse interstitial pneumonia and pulmonary edema. Cotton-top tamarin (*Saguinus oedipus*). *(UC Davis, VMTH)*

possibly *Neospora* spp., which have been recognized to experimentally infect nonhuman primate (rhesus) infants (Barr et al., 1994). Definitive diagnosis can be made in tissue section and confirmed by immunohistochemistry or electron microscopy.

Treatment in fulminating cases is often futile as the infection is widely disseminated by the time clinical signs are noted. The treatment of choice in human patients is pyramethamine plus sulfadiazine and folinic acid in a prolonged course (4−6 weeks), which is effective only against the tachyzoite stage (Montoya and Liesenfeld, 2004). Toxicity is relatively common in humans. Possible substitute drugs for sulfadiazine include dapsone (diaminodiphenyl sulfone), clindamycin, spiramycin, or clarithromycin. The agent hydroxynaphthoquinone is thought to be effective against bradyzoite-containing cysts and has provided prolonged remission of toxoplasmosis in an rodent experimental model (Ferreira et al., 2006). A white-throated capuchin monkey with neurological signs was successfully treated with clindamycin and trimethaprim-sulfamethoxazole, which resulted in improvement within three days and complete clinical resolution within two weeks (Fiorella et al., 2006).

METAZOAN PARASITES

Toft (1986) provides a comprehensive and useful review of parasites in nonhuman primates. Metazoan parasites found in respiratory system include (larval) cestodes, nematodes (metastrongylids, strongyloides), annelids (leeches), and arthropods (mites), as detailed later.

Cestodes

Nonhuman primates can be intermediate hosts for several cestode species. Those associated with the respiratory system are most commonly "bladder"-type larvae of taeniid cestodes, including the genera *Taenia* (cysticercosis) and *Echinococcus* (hydatid cyst). There is one report of tetrahyriidial larvae resembling *Mesocestoides* sp. (Guillot and Green, 1992) and another of sparganosis (Chai et al., 1997). The presence of such larvae generally causes no clinical signs or ill effects and is usually an incidental finding at necropsy. However, cyst location, number, size, death, and/or rupture may lead to significant clinical problems. Such infection should be included in the differential diagnosis for space-occupying lesions recognized in wild and/or free-ranging nonhuman primates. The zoonotic risks associated with such larvae increase the importance of recognition of this as a potential problem.

Cysticercosis

Cysticercosis cysts occur in herbivorous or omnivorous animals. The adult tapeworms (genus *Taenia*) parasitize

a variety of carnivorous and omnivorous birds and mammals. The oval, translucent cysts contain a single invaginated scolex with four suckers. The cysts have been found in the abdominal and thoracic cavities, muscle, subcutaneous tissue, and central nervous system. Viable cysts generally have little or no associated host reaction, although clinical problems may be associated with the space-occupying effect of the cyst. Inflammation occurs in association with cyst death. Diagnosis depends on finding the characteristic bladder-shaped structure in the tissues, with species identification based on the scolex hook size and structure.

Wolff et al. (1989) report the presence of cysticercus pneumonitis and pleuritis in a red-ruffed lemur. The condition was initially recognized with full-body radiographs taken during quarantine screening procedures. A mineralized density and a soft tissue density were recognized in the left ventrocaudal thorax and left dorsocaudal lung, respectively. Exploratory thoracotomy revealed an extrapleural bilobed firm mass in the left ventral pleural space, attached via fibrous adhesions to the left caudal lung lobe, and a 1.0-cm encapsulated nodule within the dorsal margin of the left caudal lung lobe. These were excised. An intact cysticercus with armed scolex and a larval remnant with associated mixed inflammation (eosinophils, plasma cells, neutrophils) were found by microscopic examination of the pulmonary nodule. The extrapleural mass contained degenerate remnants of calcified larval cestodes and fibrinous exudate. The animal recovered uneventfully and was later released from quarantine. Severe disseminated cystocercosis was also reported in a zoo-housed black lemur in which one lung was obliterated by multiple cystacerci associated with atelectasis, edema, and moderate mixed inflammation (Dyer and Grieve, 1998). The organisms were identified as *Cysticercus longicollis*, the larval form of the canine tapeworm *Taenia crassiceps*.

Hydatidosis

Hydatidosis (cystic and alveolar echinococcosis) results from infection by the larval stages of *Echinococcus* sp. cestodes, *E. granulosus*, and *E. multilocularis,* respectively. Adult *Echinococcus* sp. are parasitic in the small intestine of canids. The larval stage has been found in a wide variety of species, including various wild and domestic herbivores, as well as nonhuman primates and humans. Hydatid cysts are large, and unilocular (*E. granulosus*) or multilocular (*E. multilocularis*). The cyst wall inner layer is composed of germinal epithelium from which multiple brood capsules develop. Multiple scolices develop from the wall of each brood capsule. Hydatid cysts may be located in the abdominal cavity, liver, lungs, subcutis, or brain, or disseminated throughout the body. Death due to anaphylactic shock has been reported associated with hydatid cyst rupture. Free scolices from ruptured cysts will produce additional cysts that may implant locally or spread systemically by lymphatics. Diagnosis of hydatid disease includes imaging studies, e.g., radiology or ultrasonography, as well as serological tests such as the Casoni intradermal skin test, indirect hemagglutination, or western blotting (Goldberg et al., 1991; Sato et al., 2005). Species identification is based on morphology of the detached scolices in the cyst fluid or on cyst wall morphology, which is laminated hyaline in *E. granulosus*.

Echinococcosis in a wild-caught baboon (*Papio anubis*) has been reported by Goldberg et al. (1991). The condition was discovered using thoracic radiography during quarantine screening, which revealed multiple fluid-filled cysts in the thoracic cavity. The animal was clinically normal, with normal hematology and serum biochemistry profiles. Indirect hemagglutination testing for *Echinococcus* was negative, a finding that occurs in approximately 50% of human patients with isolated pulmonary *Echinococcus* lesions. The animal was euthanized due to the interference the lesions would have in the intended research study, and necropsy confirmed the presence of *Echinococcus granulosus* cysts on the pleural surface of the left caudal and right middle lung lobes. Although treatment was not carried out with this animal, the report discusses the potential therapeutic approaches in similar cases, which include the use of chemotherapy and/or surgery. Generally, surgical procedures involving resection, enucleation, or evacuation of echinococcal cysts are the recommended treatments for human disease. During such surgery, scolicidal agents (e.g., silver nitrate, hypertonic saline) have been injected into the cyst to help reduce the risks of accidental spillage of cysts and the subsequent spread of the condition. Promising chemotherapeutic approaches involve the use of benzimidazole carbamate compounds (e.g., albendazole) over extended periods (Yamano et al., 2009; Santivanez and Garcia 2010).

Additional cases of hydatid disease have been seen in a thick-tailed galago (*Otolemur crassicaudatus*), a ring-tailed lemur (*Lemur catta*), and rhesus macaques, one of which had a primary lung cyst with subsequent spread to the abdomen (Palotay and Uno, 1975). Several cases of "alveolar echinococcosis" due to *E. multilocularis* also have been reported in nonhuman primates, most of which had either primary or concurrent pulmonary involvement (Garcia et al., 2002; Yamano et al., 2009). Long-term albendazole was efficacious in treatment of some of the Japanese macaques in the outbreak described by Yamano et al. (2009). A detailed account of imaging studies performed on two of these macaques was described by Kishimoto et al. (2009), which demonstrated mineralization of many of the lesions.

Tetyrathyridiosis

Infection by larval stages of the cestode genus *Meso-cestoides* produces a condition referred to as tetrathyridiosis. Adult *Mesocestoides* infect various bird species and domestic and wild mammalian carnivores. The larvae, or tetrathyridia, have been found in the coelom or peritoneum of vertebrates, including snakes, lizards, mice, dogs, and cats, as well as in nonhuman primates which serve as secondary intermediate hosts. The primary intermediate hosts are invertebrates such as ants and orbatid mites. Guillot and Green (1992) report the presence of multiple *Mesocestoides* sp. tetrathyridia-like larvae in the lungs of a cynomolgus monkey (*Macaca fascicularis*) that died due to respiratory arrest within several hours following recovery from a surgical procedure. The animal had been apparently clinically healthy up to the time it died. Multiple 1- to 3-mm-diameter cysts were recognized in all lung lobes during necropsy. Two other case of pleural and pulmonary mesocestoidiasis have been reported, one in a wild-caught pig-tailed macaque which was euthanized because of experimental SIV and the other in a long-term captive, wild-caught, female vervet monkey (Fincham et al., 1995; Sasseville et al., 1996). In both cases, chronic pleural fibrosis was associated with either encysted (in the macaque) or free tetrathyridia. In the macaque, there were multiple opaque grayish cysts encasing whole tetrathyridia and yellow solid nodules consisting of fibrous capsules with varying amounts of granulomatous inflammation. In both cases the infection was considered to be incidental.

Sparganosis

Spargana, mesocestode pleurocercoid larval stages of *Spirometra* sp., are an infrequent cause of pulmonary nodules and eosinophilic pleuritis in humans (Ishii et al., 2001; Iwatani et al., 2006). The definitive hosts for these parasites are various carnivores. Reptiles and amphibians are secondary intermediate hosts and infection of human and nonhuman primates occurs through ingestion of the invertebrate first intermediate host (copepods) or the secondary hosts. Most typically the ingested larvae travel to the subcutis or muscle fascia, but migration to the brain, lung, and other organs has been described. The spargana can apparently replicate within the secondary or aberrant hosts (i.e., human and nonhuman primates). Cases have been identified in wild-caught baboons and African cercopithecines such as blue and golden monkeys (*Cercopithecus mitis* ssp.) (Chai et al., 1997; Nobrega-Lee et al., 2007; Lowenstine, unpublished). Lesions consist of the grossly visible encysted worms, which have a variably elongated segmented body with a terminal bulb. Histologically these are accompanied by varying degrees of inflammation, which is sometime predominantly eosinphilic.

Nematodes

Pulmonary Nematodiasis

Pulmonary nematodiasis, due to infection with meta-strongylid lungworms of the genera *Filaroides* and *Filariopsis*, has been recognized commonly in New World monkeys (callithricids, squirrel monkeys, cebus monkeys, and howler (*Alouatta* sp.) monkeys) (Toft, 1986; Wolff, 1993) (Figure 9.14). Lung lesions can also be associated with the normal or abnormal "migration" of nematodes, often larvae, within pulmonary vascular lumens, including: the occurrence of filarioid nematode-associated verminous vasculitis in a cynomolgus monkey following recent ivermectin treatment (Kornegay et al., 1986); *Dirofilaria immitis* in rhesus monkeys (Baskin, 199lb); intravascular pinworms (*Enterobius* sp.) in a common chimpanzee with fatal enterobiasis (Zhang et al., 1990); and pulmonary strongyloidiasis in apes and human primates (DePaoli and Johnson 1978; Jayaprakash et al., 2009).

The very slender and fragile adults of metastrongylid lungworms are located in terminal bronchioles, respiratory bronchioles, and alveoli. Larvae are produced by the viviparous female, are coughed up, swallowed by the host, and passed in the feces. The rest of the life cycle is not known (Toft, 1986). Infection is generally clinically inapparent, although occasional coughing, and even pulmonary hemorrhage, have been reported (Wolff, 1993). Antemortem diagnosis is made by finding larvae in nasopharyngeal mucus or in feces. Various drugs used for treatment include fenbendazole, albendazole, or levamisole (Wolff, 1993). However, in an outbreak in a group of wild-caught white-faced capuchins only alabendazole at 15 mg/kg orally for 14 days cleared the infection when previoius treatments with ivermectin, fendendazole, thiabendazole, mebendazole, and pyrantel pamoate had failed (Lee et al., 1996).

Gross lesions in New World monkeys are small, elevated, subpleural, pink to gray, sometimes

FIGURE 9.14 **Pulmonary nematodiasis, squirrel monkey (*Saimiri sciureus*), etiology: *Filaroides gordius*.** *(UC Davis, VMTH)*

hyperpigmented, nodules. Microscopically, multiple profiles of coiled nematodes with characteristic features of metastrongles often containing filarid larvae are seen. Some alveolar septal loss is present, and epithelial changes, including atrophy and/or hyperplasia, as well as focal bronchiolar squamous metaplasia, occur. Localized chronic mixed inflammation is also often present, with mild interstitial fibrosis (Brack et al., 1974).

In the report by Kornegay et al. (1986), an apparently healthy cynomolgus monkey died two hours after routine inhalation anesthesia and femoral catheter implantation. Seventeen days before the surgery the animal had been treated with ivermectin for gastrointestinal parasites prior to quarantine release. Gross necropsy findings included patchy raised areas of pulmonary hemorrhage and consolidation. Filarioid nematodes (*Edesonfilaria malayensis*) were present in pulmonary blood vessels and in multifocal cysts on visceral and parietal pleural surfaces, as well as in the urinary bladder wall. Microscopically, there was verminous vasculitis, pulmonary infarcts, and pneumonia. The condition of the parasites themselves was compatible with parasite death due to the earlier drug treatment. The report postulates that parasitic emboli led to pulmonary infarction and severe inflammation and that this condition contributed to death following anesthesia due to pulmonary function compromise.

Zhang et al. (1990) describe a case of fatal enterobiasis in a 5-year-old chimpanzee from the Qingdao Zoo in China. The animal became clinically ill, with anorexia and diarrhea. Fecal examination noted erythrocytes and inflammatory cells, and the animal was treated with ampicillin, dexamethasone, and other unnamed drugs over a 14-day period, at which time it died. Numerous pinworms were noted in the bloody stool before death. Death was associated with disseminated intravascular coagulation. In addition to extremely large numbers of pinworms (*Enterobius* sp.) in the colon, which also contained multifocal ulcers to which worms were attached, pinworms were found microscopically in the mesenteric lymph nodes and lymphatic vessels, hepatic veins, and pulmonary vessels.

Strongyloidiasis is another enteric parasitism that often has pulmonary manifestations, which may ultimately lead to the death of the animal (Olsen et al., 2009). The culprit is the human parasite *Strongyloides stercorialis*, which differs from the similar parasites of New World (*S. cebus*) and Old World (*S. fulleborni*) monkeys in that only *S. stercorialis* causes internal reinfection (autoinfection) and extremely large parasite burdens (hyperinfection). The life cycle is complicated, involving alternate parasitic and free-living generations but no intermediate hosts. Parasitic females reproduce only female eggs by parthenogenesis in the duodenmum and upper jejunum. Sexual differentiation of larvae is regulated by extrinsic factors. The eggs hatch in the host large intestine to rhabdidoid larvae and may be passed out in the feces or stay in the lower intestine. Development through two molts to the infective third stage filariform larvae may occur in the ground or in the host (autoinfection). Larvae excreted in feces alernately develop into free-living male and female sexual stages producing rhabdidiform larvae, which may perpetuate the free-living population or may develop into infectious filariform larvae. The filariform larvae can penetrate the colon (in autoinfection) or the skin of a new host. They migrate via the venous circulation or lymphatics to the heart and then to the lung capillary bed where they molt to postfilariform fourth stage larvae and break out into the alveoli. They move up the respiratory tract to the larynx amd pharynx and are swallowed. They burrow into the mucosa of the upper intestines develop into adult females and the cycle begins again.

When the filariform and fourth stage larvae are in the lungs and break out into alveoli, marked pulmonary hemorrhage and edema can occur. They also can introduce intestinal flora to the blood stream and lungs causing a bacterial interstitial pneumonia. Clinical signs include cough and dyspnea and occasionally blood tinged respiratory secretions. Vomiting and diarrhea due to the effects of the parasites on the GI tract are usually present as well. Grossly, the lungs do not collapse and are red, wet, and heavy. Histologically, the larval nematodes are visible in pulmonary capillaries and free in the alveoli and are accompanied by hemorrhage and edema. Ape species are most often victims of autoinfection and strongyloidiasis is the most significant cause of death in juvenile orangutans in zoos in North America (Lowenstine et al., 2008).

Nasal Nematodiasis

Nasal mucosal nematodiasis, due to infection with anatrichosomatid nematodes *Anatrichosoma cutaneum* or *A. cynomolgi*, occurs in both Asian and African Old World nonhuman primates, including rhesus monkeys, cynomolgus monkeys, patas monkeys, vervets, talapoin monkeys (*Miopithecus* sp.), mangabeys (*Cercocebus* sp.), and baboons (Toft, 1986). The adults are small and slender, with the males lying in the lamina propria and the females in the stratified squamous epithelium of the nasal mucosal epithelium. The bipolar, embryonated eggs are laid in tunnels within the stratified epithelium and are shed either in nasal secretions or in the feces after being swallowed.

Infection is usually subclinical. Diagnosis is made via use of nasal mucosal scrapings or swabs, which contain the characteristic eggs (Conrad and Wong, 1973). Postmortem microscopy of nasal mucosal sections may reveal adult worms. Microscopic lesions include mucosal epithelial parakeratotic hyperplasia, with underlying mixed inflammation (neutrophils, histiocytes, and lesser numbers of eosinophils and lymphocytes) (Stookey and Moe, 1978). The life cycle and transmission method are not known.

Annelids

The leech, *Dinobdella ferox*, is distributed throughout southern Asia and is a frequent parasite of the nasal cavities of macaques in this region (Pryor et al., 1970; Toft, 1986). A similar leech, *Limnatus africana*, occurs in Africa. The life cycle of *D. ferox* is direct. The hermaphroditic adults lay eggs attached in a cocoon to objects on the surface of the water. The immature leeches hatch out and remain at the pond surface, gaining entry through the host oral or nasal cavity as the host drinks. The leeches attach to the upper respiratory tract mucosa (nasal passages, nasopharynx, larynx) and suck blood for a period of a few days to many weeks. During this period they grow and mature, then detach and drop out through the nostrils. Adult leeches are not parasitic.

Clinical problems relate to numbers of leeches present. Infection involving few parasites may be asymptomatic; however, heavy infection is associated with restlessness, epistaxis, anemia, weakness, asphyxiation, and sometimes death. Microscopic lesions contain mild, focal, chronic inflammation, with increased mucus production. Recognition and identification of the parasite in its typical anatomic location within the host are the bases for diagnosis. Treatment (Stookey and Moe, 1978) involves removal of the leeches. In military dogs in southeast Asia, nasopharyngeal leech infestation was a significant problem. These animals were treated by flushing the nares with 15−20% alcohol while under anesthesia, with an endotracheal tube in place. The flushing continued until all of the leeches were detached and washed out into the oral cavity.

Arthropods

Respiratory acariasis in nonhuman primates includes the occurrence of pulmonary acariasis and of nasal acariasis, as reviewed by Kim (1980) and Toft (1986).

Pulmonary Acariasis

A number of species of lung mites, genus *Pneumonyssus*, cause pulmonary acariasis in Old World monkeys and great apes, and a similar species, *Pneumonyssoides* sp., causes similar infection in some New World monkeys, including woolly monkeys and howler monkeys. In association with their widespread use in biomedical research, most reports regarding this condition describe *Pneumonyssus simicola* infection in macaques. *Pneumonyssus simicola* occurs in up to 100% of wild or imported rhesus monkeys. Transmission appears to require close association with infected animals. Raising newborns away from infected animals can prevent infection.

In rhesus monkeys, pulmonary acariasis is usually a subclinical infection, although it may predispose to secondary infection due to bronchiolar epithelial changes and impaired mucociliary clearance (Kim, 1980). Severe infections may have associated cough and dyspnea, but animals with heavy infections may exhibit no signs prior to finding infection during necropsy (Stookey and Moe, 1978). Tracheobronchiolar lavage is the most useful technique for antemortem diagnosis (Furman et al., 1974; Joseph et al., 1984), although false-negative results may occur. Treatment with a single subcutaneous dose of ivermectin (200 mg/kg) was effective in killing lung mites in infected rhesus monkeys (Joseph et al., 1984), with a progressive decrease in mite-associated inflammatory changes following treatment.

Gross lung mite lesions are discrete, ovoid, pale yellow to gray/tan cystic foci, usually only a few millimeters in diameter. Occasionally, bullae are present. The lesions are present throughout the lung parenchyma (Figure 9.15). They have a small central lumen, which often contains one or more mites. Fibrinous or fibrous adhesions are often present between visceral and parietal pleura. Microscopically, the lesions consist of dilated, thickened bronchioles (chronic bronchiolitis and bronchiectasis) with epithelial erosion or ulceration, often with sections of mite within the lumen, and with a surrounding zone of mixed inflammatory cells (lymphocytes, eosinophils, and macrophages). The macrophages frequently contain characteristic birefringent crystalline golden brown to black pigment. The pigment is thought to be a product of the mite (Andrade and
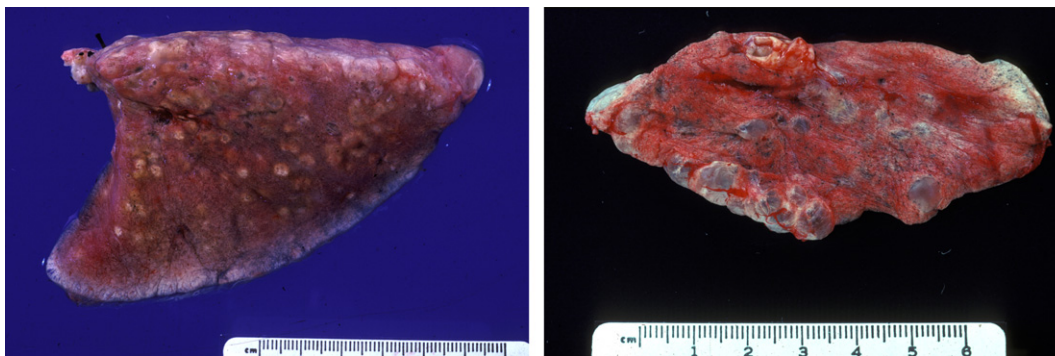

FIGURE 9.15 **Pulmonary acariasis (lung mites),** *Pneumonyssus simicola.* Rhesus macaques (*Macaca mulatta*). (Left) Left caudal lung lobe, multifocal mite-associated nodules apparent on the pleural surface. (Right) Multiple bullae secondary to lung mites.

Marchevsky, 2007). The pathology of lung mite infection in baboons and chimpanzees is similar to that described for the rhesus monkey (McClure and Guilloud, 1971; Kim and Kalter, 1975a, 1975b).

Reported complications of lung mite infection in rhesus monkeys include pneumothorax (Rawlings and Splitter, 1973) and pulmonary arteritis (Woodard, 1968). Massive infections and resulting death have been reported for other primate species, including the douc langur (*Pygathrix nemaeus nemaeus*), proboscis monkey (Robinson and Bush, 1981; Griner, 1983), and pig-tailed macaque (Stone and Hughes, 1969).

Nasal Acariasis

Nasal mites of the genus *Rhinophaga* have been described from the upper skull and olfactory mucosa of Old World monkeys (rhesus monkeys, baboons, *Cercopithecus* sp.) and great apes (orangutan, gorilla, and bonobo) (Toft, 1986; L.J. Lowenstine, unpublished). Mucosal polyps in the maxillary sinuses of the chacma baboon (*Papio ursinus*) are associated with *Rhinophaga papinosis* infection (McConnell, 1977). A very long mite, *Rhinophaga elongata*, also is found in the nasal mucosa of chacma baboons, with its anterior end embedded deeply in a raised nodule. *Rhinophaga dinolti* occurs in the lungs and nasal cavities of rhesus monkeys, but without reported lesions (Toft, 1986). Pneumonitis and excessive mucus production are associated with the presence of *Rhinophaga cercopitheci* in several guenon species (*Cercopithecus ascanius*, *C. mitis*) (Toft, 1986).

ACKNOWLEDGMENT

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