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CHAPTER 9

Respiratory System, Mediastinum, and Pleurae[1]

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Diseases of the respiratory system (respiratory apparatus) are some of the leading causes of morbidity and mortality in animals and a major source of economic losses. Thus veterinarians are routinely called to diagnose, treat, and implement health management practices to reduce the impact of these diseases. In companion animals, diseases of the respiratory tract are also common and, although of little economic significance, are important to the health of the animals and thus to clinicians and pet owners. In the past few years, animal shelters have been recognized as a major risk factor for respiratory diseases in dogs and cats, a comparable situation to what is reported in human beings with nosocomial infections.

Structure and Function

General Structure

To facilitate the understanding of the structure and function, it is convenient to arbitrarily divide the respiratory system into conducting, transitional, and gas exchange systems (Fig. 9-1).

Conductive System

The conducting system includes nostrils, nasal cavity, paranasal sinuses, nasopharynx, larynx, trachea, and extrapulmonary and intrapulmonary bronchi, all of which are largely lined by pseudostratified, ciliated columnar cells, plus a variable proportion of secretory goblet (mucous) and serous cells (Figs. 9-2 and 9-3 and E-Fig. 9-1).

Transitional System

The transitional system of the respiratory tract is composed of bronchioles, which are microscopic structures that serve as a transition zone between the conducting system (ciliated) and the gas exchange (alveolar) system (see Fig. 9-1). The disappearance of cilia in the transitional system is not abrupt; the ciliated cells in the proximal bronchiolar region become scarce and progressively attenuated, until the point where distal bronchioles no longer have ciliated cells. Normal bronchioles also lack goblet cells but instead have other types of secretory cells, notably Club cells (formerly Clara cells) and neuroendocrine cells. Club cells, also referred to as secretory bronchiolar cells, contain numerous biosynthetic organelles that play an active role in detoxification of xenobiotics (foreign substances), similar to the role of hepatocytes (Fig. 9-4). Club cells are also critical stem cells in the repair and remodeling of not only the bronchioles but also of most of the respiratory tract. In addition, Club cells contribute to the innate immunity of the lung by secreting protective proteins (collectins) and pulmonary surfactant (see Fig. 9-4, *B*). In carnivores and monkeys, and to a much lesser extent in horses and human beings, the terminal portions of bronchioles are lined not only by cuboidal epithelium but also by segments of alveolar capillaries. These unique bronchioloalveolar structures are known as respiratory bronchioles (Fig. 9-5; also see Fig. 9-1).

Exchange System

The gas exchange system of the respiratory tract in all mammals is formed by alveolar ducts and millions of alveoli (Fig. 9-6; also see Fig. 9-1). The surface of the alveoli is lined by two distinct types of epithelial cells known as type I (membranous) pneumonocytes and type II (granular) pneumonocytes (Fig. 9-7).

All three—the conducting, transitional, and exchange systems of the respiratory system—are vulnerable to injury because of constant exposure to a myriad of microbes, particles and fibers, and toxic gases and vapors present in the air. Vulnerability of the respiratory system to aerogenous (airborne) injury is primarily because of (1) the extensive area of the alveoli, which are the interface between the blood in alveolar capillaries and inspired air; (2) the large volume of air passing continuously into the lungs; and (3) the high concentration of noxious elements that can be present in the air (Table 9-1). For human beings, it has been estimated that the surface of the pulmonary alveoli is approximately 200 m^2, roughly the area

[1]For a glossary of abbreviations and terms used in this chapter, see E-Glossary 9-1.

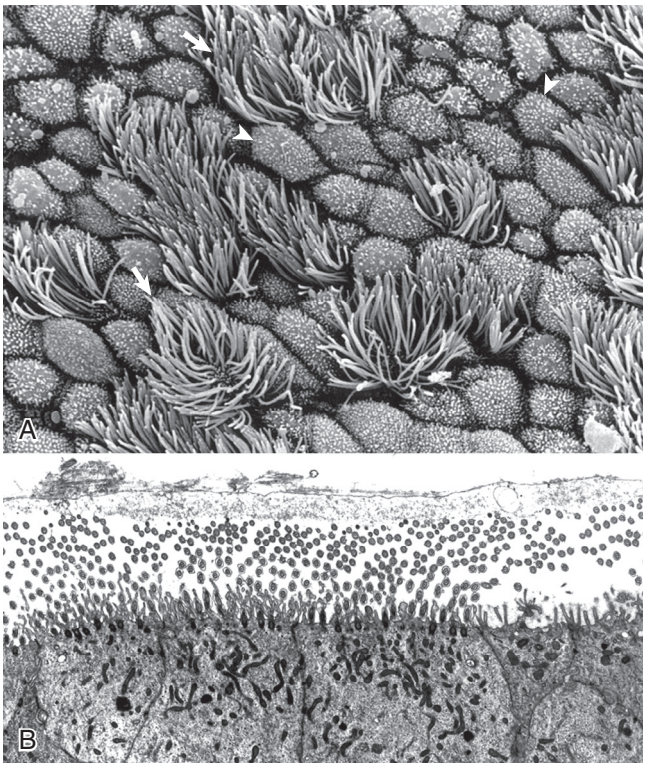
E-Glossary 9-1 Glossary of Abbreviations and Terms

ABPEE–Acute bovine pulmonary edema and emphysema
AHS–African horse sickness
AHV-4–Asinine herpesvirus 4
AHV-5–Asinine herpesvirus 5
AIDS–Acquired immunodeficiency syndrome
AIP–Atypical interstitial pneumonia
ALI–Acute lung injury
APCs–Antigen-presenting cells
Apx–*Actinobacillus pleuropneumoniae* RTX toxin
ARDS–Acute respiratory distress syndrome
BAL–Bronchoalveolar lavage
BALT–Bronchial-associated lymphoid tissues
BLAD–Bovine leukocyte adhesion deficiency
BCoV–Bovine coronavirus
BoHV-1–Bovine herpesvirus 1
BOOP–Bronchiolitis obliterans organizing pneumonia
BPIV-3–Bovine parainfluenza virus 3
BRD–Bovine respiratory disease
BRDC–Bovine respiratory disease complex
BRSV–Bovine respiratory syncytial virus
C3a–Complement fragment 3a
C3b–Complement fragment 3b
C5a–Complement fragment 5a
CAE–Caprine arthritis encephalitis
CAEV–Caprine arthritis encephalitis virus
CaHV-1–Canid herpesvirus 1
CAV-1–Canine adenovirus type 1
CAV-2–Canine adenovirus type 2
CC10–Club cell 10-kDa protein
CD4–Cluster of differentiation 4
CD8–Cluster of differentiation 8
CD40–Cluster of differentiation 40
CDV–Canine distemper virus
CID–Virulence-associated protein
CIRD–Canine infectious respiratory disease
CIV–Canine influenza virus
Cl–Chlorine
CNS–Central nervous system
CO_2–Carbon dioxide
COPD–Chronic obstructive pulmonary disease
CPIV-2–Canine parainfluenza virus 2
CPXV–Cowpox virus
CRCoV–Canine respiratory coronavirus
DIC–Disseminated intravascular coagulation
ECM–Extracellular matrix
EHV-1–Equine herpesvirus 1
EHV-4–Equine herpesvirus 4
EHV-5–Equine herpesvirus 5
EIPH–Exercise-induced pulmonary hemorrhage
ELAM–Endothelial adhesion molecule
ENTV-1–Enzootic nasal tumor virus 1
ENTV-2–Enzootic nasal tumor virus 2
EVA–Equine viral arteritis
EVR–Equine viral rhinopneumonitis
FAS–Apoptosis stimulating fragment
FCV–Feline calicivirus
FECV–Feline enteric coronavirus
FeHV-1–Felid herpesvirus 1
FeLV–Feline leukemia virus
FIP–Feline infectious peritonitis
FIPV–Feline infectious peritonitis virus
FIV–Feline immunodeficiency virus
FVR–Feline viral rhinotracheitis
GMS–Grocott-Gomori's methenamine silver
H&E–Hematoxylin and eosin
HeV–Hendra virus
H_2O_2–Hydrogen peroxide
H_2S–Hydrogen sulfide
IAD–Inflammatory airway disease
IBP–Infectious balanoposthitis
IBR–Infectious bovine rhinotracheitis
ICAM–Intercellular adhesion molecule
IFN-γ–Interferon-γ
IgA–Immunoglobulin A
IgBP–Immunoglobulin-binding proteins
IgE–Immunoglobulin E
IgG–Immunoglobulin G
IgM–Immunoglobulin M
IL-1–Interleukin-1
IL-2–Interleukin-2
IL-4–Interleukin-4
IL-5–Interleukin-5
IL-6–Interleukin-6
IL-8–Interleukin-8
IL-9–Interleukin-9
IL-10–Interleukin-10
IL-13–Interleukin-13
IP-10–Interferon-inducible protein
IPV–Infectious pustular vaginitis
IRDS–Infant respiratory distress syndrome
JSRV–Jaagsiekte sheep retrovirus
LIP–Lymphoid interstitial pneumonia
LOS–Lipooligosaccharide
LPS–Lipopolysaccharide (endotoxin)
M cell–Microfold cell
MAS–Meconium aspiration syndrome
MFO–Mixed function oxidases
MIP-2–Monokine-inducible protein 2
NH_3–Ammonia
NK cell–Natural killer cell
NKA–Neurokinin A
NKB–Neurokinin B
NO–Nitric oxide
NO_2–Nitrogen dioxide
O_2–Oxygen
O_2•–Superoxide radical
O_3–Ozone
OH•–Hydroxyl radical
OIE–World Organization for Animal Health
OPP–Ovine progressive pneumonia
PAF–Platelet-activating factor
PAS–Periodic acid–Schiff
PCR–Polymerase chain reaction
PCV2–Porcine circovirus 2
PCVAD–Porcine circovirus–associated disease
PDNS–Porcine dermatitis and nephropathy syndrome
PEH–Progressive ethmoidal hematoma
PI3–Parainfluenza virus 3
PMWS–Postweaning multisystemic wasting syndrome
PRCoV–Porcine respiratory coronavirus
PRD–Porcine respiratory disease
PRDC–Porcine respiratory disease complex
PRRS–Porcine reproductive and respiratory syndrome
PRRSV–Porcine reproductive and respiratory syndrome virus
PTE–Pulmonary thromboembolism
RAO–Recurrent airway obstruction
ROS–Reactive oxygen species
RNS–Reactive nitrogen species
RSV–Respiratory syncytial virus
RTX–Repeats-in-*toxin*

Continued

E-Glossary 9-1 Glossary of Abbreviations and Terms–cont'd

SARS–Severe acute respiratory syndrome
SARS-CoV–Severe acute respiratory syndrome coronavirus
sER–Smooth endoplasmic reticulum
SIRS–Systemic inflammatory response syndrome
SIV–Swine influenza virus
SO_2–Sulfur dioxide
SPAOPD–Summer pasture-associated obstructive pulmonary disease
SPF–Specific pathogen free
spp.–Species
SRLV–Small ruminant lentivirus
ssp.–Subspecies
SuHV-1–Suid herpes virus 1
TGF-α–Transforming growth factor-α
TGF-β–Transforming growth factor-β
T_H2–Helper T lymphocyte 2
TLR–Toll-like receptor
TME–Thrombotic meningoencephalitis
TNF-α–Tumor necrosis factor-α
TTW–Transtracheal wash
VAP–Virulence-associated protein
VCAM–Vascular cell adhesion molecule
VMV–Visna/maedi virus
WHO–World Health Organization



E-Figure 9-1 Ultrastructural Morphology of Respiratory Mucosa. A, Normal bronchial mucosa, bronchus, rat. The mucous layer was removed before fixation to expose the external surface of the epithelium. Mucosa consists of ciliated cells and nonciliated secretory cells. Ciliated cells have numerous slender cilia *(arrows)*. Nonciliated secretory cells have a dome-shaped surface with abundant microvilli *(arrowheads)*. The proportion of ciliated to nonciliated cells varies depending on the level of airways. Ciliated cells are more abundant in proximal airways, whereas secretory cells are more numerous in distal portions of the conducting and transitional systems. Scanning electron micrograph. Carbon-sputter coating method. **B,** Normal ciliated epithelium, trachea, cow. This trachea was specially fixed to preserve the mucous layer, which consists of an internal, clear, hypophase-fluid layer (not visible here) surrounding microvilli and kinocilia and an external mucous epiphase at the level of the tips of the kinocilia (cut in both transverse and longitudinal section here). TEM. Uranyl acetate and lead citrate stain. (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** from Sims DE, Westfall JA, Kiorpes AL, et al: *Biotech Histochem* 66:173-180, 1991.)

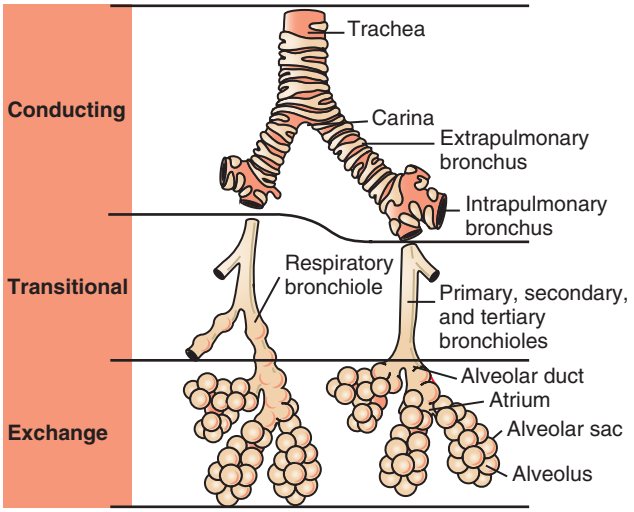


Figure 9-1 Airways From the Trachea to the Alveoli. Conducting, transitional, and exchange components of the respiratory system. The transitional zone (bronchioles) is not as equally well developed in all species. (Adapted from Banks WJ: *Applied veterinary histology*, ed 3, St. Louis, 1993, Mosby.)

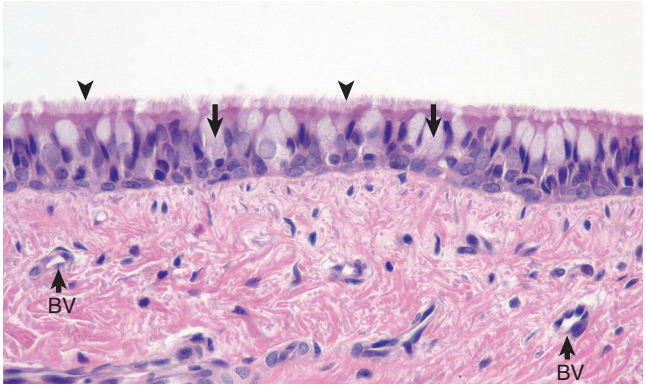


Figure 9-2 Normal Mucosa, Trachea, Dog. Mucosa consists of ciliated and nonciliated secretory cells. Goblet cells have a pale staining cytoplasm *(arrows)*. The proportion of ciliated to nonciliated cells varies depending on the level of airways. Ciliated cells *(arrowheads)* are more abundant in proximal airways, whereas secretory cells are proportionally more numerous in distal portions of the conducting and transitional systems. The submucosa of the conducting system (nasal to bronchi) has abundant blood vessels *(BV)*. H&E stain. (Courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

of a tennis court. The alveolar surface of the equine lung is estimated to be approximately 2000 m^2. It has also been estimated that the volume of air reaching the human lung every day is approximately 9000 L. Lungs are also susceptible to blood-borne (hematogenous) microbes, toxins, and emboli. This fact is not surprising because the entire cardiac output of the right ventricle goes into the lungs, and approximately 9% of the total blood volume is within the pulmonary vasculature. The pulmonary capillary bed is the largest in the body, with a surface area of 70 m^2 in the adult human; this area is equivalent to a length of 2400 km of capillaries, with 1 mL of blood occupying up to 16 km of capillary bed.

Normal Flora of the Respiratory System

The respiratory system has its own normal flora (microbiota), as does any other body system in contact with the external environment. If a sterile swab is passed deep into the nasal cavity of any healthy

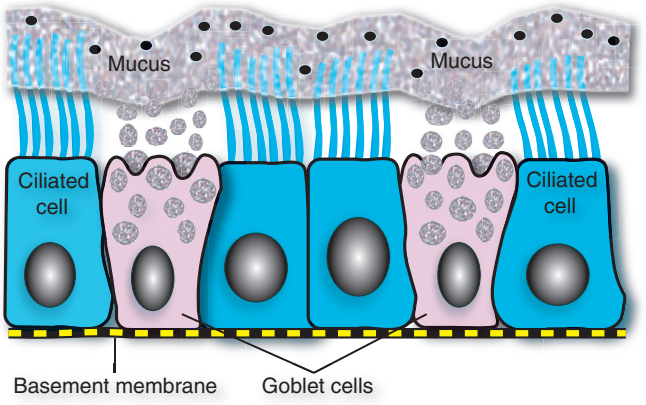


Figure 9-3 Mucociliary Apparatus of the Conducting System. Both ciliated and goblet cells rest on the basement membrane. Mucus produced and released by goblet cells forms a carpet on which inhaled particles *(black dots)* are trapped and subsequently expelled into the pharynx by the mucociliary apparatus. (Courtesy Dr. A. López, Atlantic Veterinary College.)

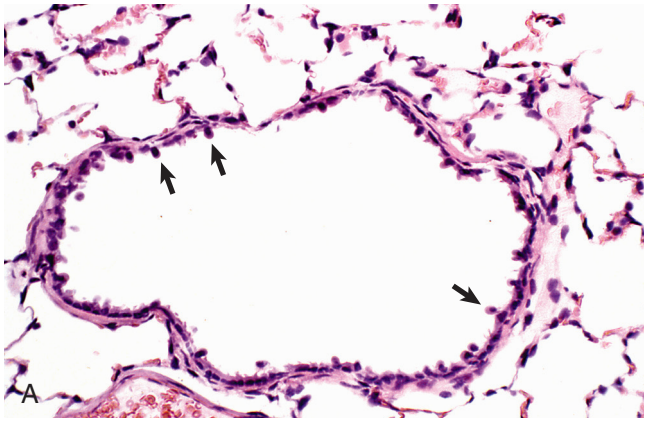
animal and cultured for microbes, yeasts, and fungi, many species of bacteria are recovered, such as *Mannheimia* (*Pasteurella*) *haemolytica* in cattle; *Pasteurella multocida* in cats, cattle, and pigs; and *Bordetella bronchiseptica* in dogs and pigs. The organisms that constitute the normal flora of the respiratory tract are restricted to the most proximal (rostral) region of the conducting system (nasal cavity, pharynx, and larynx). The thoracic portions of the trachea, bronchi, and lungs are considered to be essentially sterile. The types of bacteria present in the nasal flora vary considerably among animal species and in different geographic regions of the world. Some present in the nasal flora are pathogens that can cause important respiratory infections under some circumstances. For instance, *Mannheimia* (*Pasteurella*) *haemolytica* is part of the bovine nasal flora, yet this bacterium causes a devastating disease in cattle—pneumonic mannheimiosis (shipping fever). Experimental studies have established that microorganisms from the nasal flora are continuously carried into the lungs via tracheal air. Despite this constant bacterial bombardment from the nasal flora and from contaminated air, normal lungs remain sterile because of their remarkably effective defense mechanisms.

Dysfunction/Responses to Injury and Patterns of Injury

Conductive System (Nose, Paranasal Sinuses, Larynx, Trachea, and Bronchi)

The conducting portion of the respiratory system is lined by pseudostratified columnar ciliated epithelium (most of the nasal cavity, paranasal sinuses, part of the larynx, and all of the trachea and bronchi), olfactory epithelium (part of the nasal cavity, particularly ethmoidal conchae), and squamous epithelium (nasal vestibulum and parts of the larynx). The pattern of injury, inflammation, and host response (wound healing) are characteristic for each of these three types of epithelium independent of its anatomic location.

Pseudostratified ciliated epithelium, which lines most of the nasal cavity and nasopharynx, part of the larynx, and all of the trachea and bronchi, is exquisitely sensitive to injury. When these cells are irreversibly injured, whether caused by viral infection, trauma, or inhalation of toxic gases, the ciliated cells swell, typically lose their attachment to underlying basement membrane, and rapidly exfoliate (Fig. 9-8). A transient and mild exudate of fluid, plasma proteins, and neutrophils covers the ulcer. In the absence of



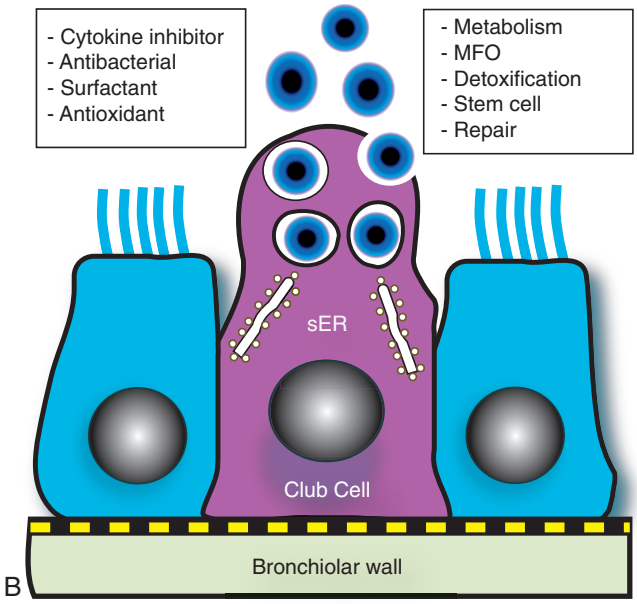


Figure 9-4 Normal Bronchiole, Rat. A, Bronchiole showing a thin wall composed of a basement membrane, smooth muscle, and connective tissue. On the luminal surface of the bronchiole, note dome-shaped Club (Clara) cells *(arrows)* protruding into the lumen. H&E stain. **B,** Schematic representation of a Club cell showing abundant smooth endoplasmic reticulum *(sER)* and cytoplasmic granules, which are extruded into the bronchiolar lumen. *MFO,* Mixed function oxidases. (Courtesy Dr. A. López, Atlantic Veterinary College.)

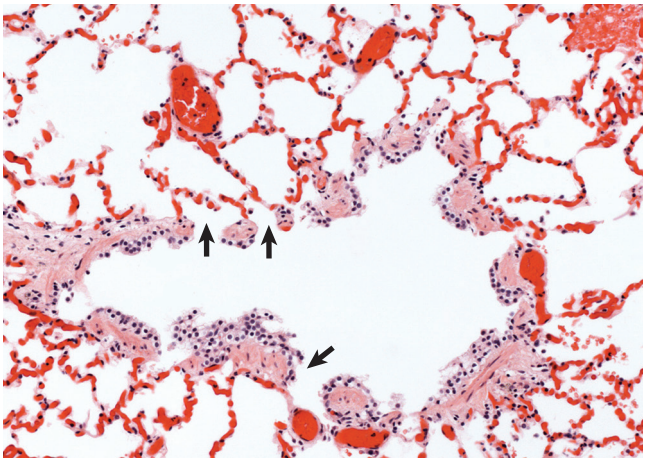


Figure 9-5 Normal Respiratory Bronchiole, Dog. The wall of the bronchiole is covered by ciliated epithelium, which is supported by smooth muscle and connective tissue. Terminally, the wall becomes interrupted, forming lateral communications between the bronchiolar lumen and alveoli *(arrows)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

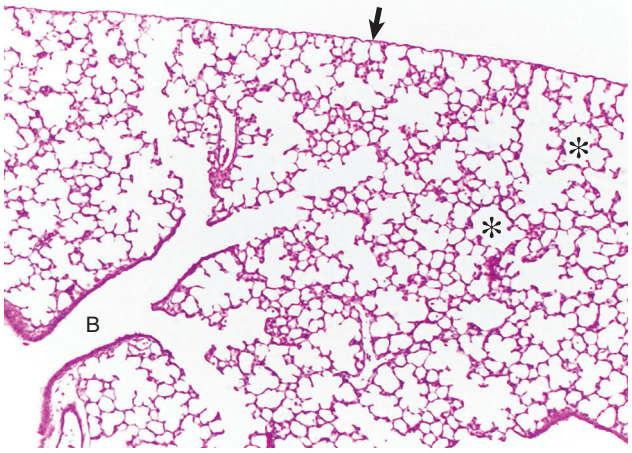


Figure 9-6 Lung, Rat. Lungs were fixed by intratracheal perfusion of fixative to retain normal distention of airways. Note the dichotomous branching of the bronchioles *(B)* that terminate as alveoli *(asterisks)* and the thin visceral pleura *(arrow)* covering the surface of the lungs. H&E stain. (Courtesy Dr. J. Martinez-Burnes, Atlantic Veterinary College.)

complications or secondary bacterial infections, a specific type of progenitor cells known as basal cells or *nonciliated secretory cells* (preciliated cells), which are normally present in the mucosa, migrate to cover the denuded basement membrane and undergoes mitosis, eventually differentiating into new ciliated epithelial cells (see Fig. 9-8). Cellular migration, proliferation, and attachment are regulated by locally released interleukins (IL-1β, IL-2, IL-4, and IL-13), growth factors, integrins and extracellular matrix (ECM) proteins such as collagen, and fibronectin. The capacity of ciliated epithelium to repair itself is remarkably effective. For example, epithelial healing in an uncomplicated ulcer of the tracheal mucosa can be completed in only 10 days. This sequence of cell degeneration, exfoliation, ulceration, mitosis, and repair is typically present in many viral infections in which viruses replicate in nasal, tracheal, and bronchial epithelium, causing extensive mucosal ulceration. Examples of transient infections of this type include human colds (rhinoviruses), infectious bovine rhinotracheitis (bovine herpesvirus 1), feline rhinotracheitis (felid herpesvirus 1), and viruses of the canine infectious respiratory disease (CIRD) group such as canine adenovirus 2 (CAV-2) and canine parainfluenza virus (CPIV).

If damage to the mucociliary blanket becomes chronic, goblet cell hyperplasia takes place, leading to excessive mucus production (hypersecretion) and reduced mucociliary clearance, and when there is loss of basement membrane, repair is by fibrosis and granulation tissue (scarring). In the most severe cases, prolonged injury causes squamous metaplasia, which together with scarring causes airway obstruction and an impediment to mucociliary clearance. In laboratory rodents, hyperplastic and metaplastic changes, such as those seen in nasal polyps and squamous metaplasia, are considered a prelude to neoplasia.

The second type of epithelium lining the conducting system is the sensory olfactory epithelium, present in parts of the nasal mucosa, notably in the ethmoidal conchae. The patterns of degeneration, exfoliation, and inflammation in the olfactory epithelium are similar to those of the ciliated epithelium, except that olfactory

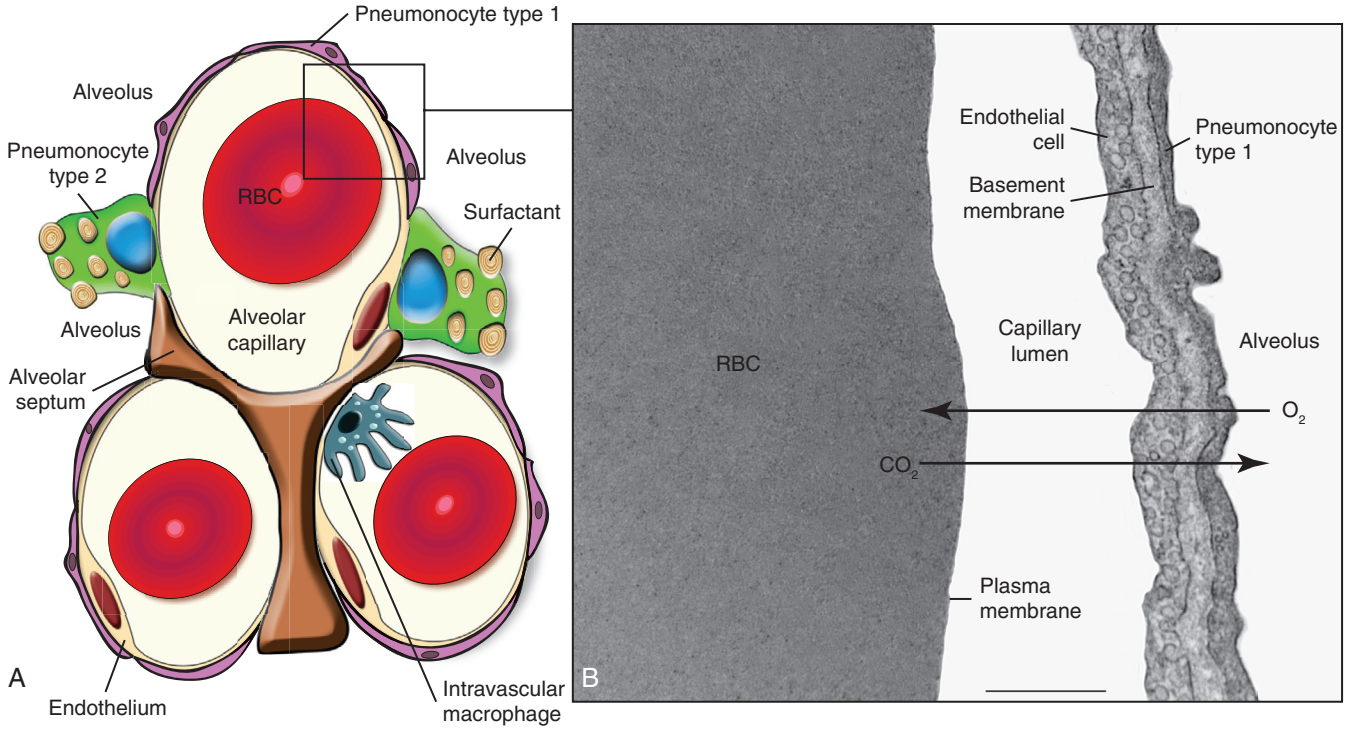


Figure 9-7 The Blood-Air Barrier. A, In this schematic diagram, note the thin membrane (blood-air barrier) separating the blood compartment from the alveoli. Type I (membranous) pneumonocytes are remarkably thin and cover most of the alveolar wall. Note the endothelial cells lining the alveolar capillary. Alveolar interstitium supports the alveolar epithelium on one side and the endothelium on the other side of the blood-air barrier. Type II (granular) pneumonocytes appear as large cuboidal cells with lamellar bodies (surfactant) in the cytoplasm. A pulmonary intravascular macrophage, a component of the monocyte-macrophage system, is depicted on the wall of an alveolar capillary. A red blood cell *(RBC)* is present inside the lumen of the alveolar capillary. **B,** Alveolar wall. The blood-air barrier consists of cytoplasmic extensions of (1) type I (membranous) pneumonocytes, (2) a dual basal lamina synthesized by type I pneumonocytes, and (3) cytoplasmic extensions of endothelial cells. TEM. Uranyl acetate and lead citrate stain. Bar = 500 nm (0.5 μm). (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** courtesy Dr. A.G. Armien, Diagnostic Ultrastructural Pathology Service, College of Veterinary Medicine, University of Minnesota.)

Table 9-1 Common Pathogens, Allergens, and Toxic Substances Present in Inhaled Air

Category	Agents
Microbes	Viruses, bacteria, fungi, protozoa
Plant dust	Grain, flour, cotton, wood
Animal products	Dander, feathers, mites, insect chitin
Toxic gases	Ammonia (NH_3), hydrogen sulfide (H_2S), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), chlorine (Cl)
Chemicals	Organic and inorganic solvents, herbicides, asbestos, nickel, lead

epithelium has only limited capacity for regeneration. When olfactory epithelium has been irreversibly injured, olfactory cells swell, separate from adjacent sustentacular cells, and finally exfoliate into the nasal cavity. Once the underlying basement membrane of the olfactory epithelium is exposed, cytokines are released by leukocytes and endothelial cells, and inflammatory cells move into the affected area. When damage is extensive, ulcerated areas of olfactory mucosa are replaced by ciliated and goblet cells or squamous epithelium, or by fibrous tissue, all of which eventually cause reduction (hyposmia) or loss of olfactory function (anosmia). Repair of the olfactory epithelium is slower and less efficient than repair of the respiratory epithelium. Neurons in the olfactory mucosa have the unique ability to regenerate, a fact that is being explored as a potential source of new neurons in the treatment of spinal cord injury.

Squamous epithelium, located in the vestibular region of the nose (mucocutaneous junction), is the third type of epithelium present in the nasal passages. Compared with ciliated and olfactory epithelia, nasal squamous epithelium is quite resistant to all forms of injury. The pharyngeal mucosa, composed of squamous epithelium, has similar patterns of necrosis and inflammation as the oral mucosa (see Chapter 7).

Bronchi

The patterns of necrosis, inflammation, and repair in intrapulmonary bronchi are similar to those previously described for the nasal and tracheal epithelium. In brief, injury to ciliated bronchial epithelium may result in degeneration, detachment, and exfoliation of necrotic cells. Under normal circumstances, cellular exfoliation is promptly followed by inflammation, mitosis, cell proliferation, cell differentiation, and finally by repair (Fig. 9-9 and see Fig. 9-8). Depending on the type of exudate, bronchitis can be fibrinous, catarrhal, purulent, fibrinonecrotic (diphtheritic), and sometimes granulomatous. When epithelial injury becomes chronic, production of mucus is increased via goblet cell hyperplasia (chronic catarrhal inflammation). This form of chronic bronchitis is well illustrated in habitual smokers who continually need to cough out excessive mucus secretions (sputum). Unfortunately, in some cases, excessive mucus cannot be effectively cleared from airways, which

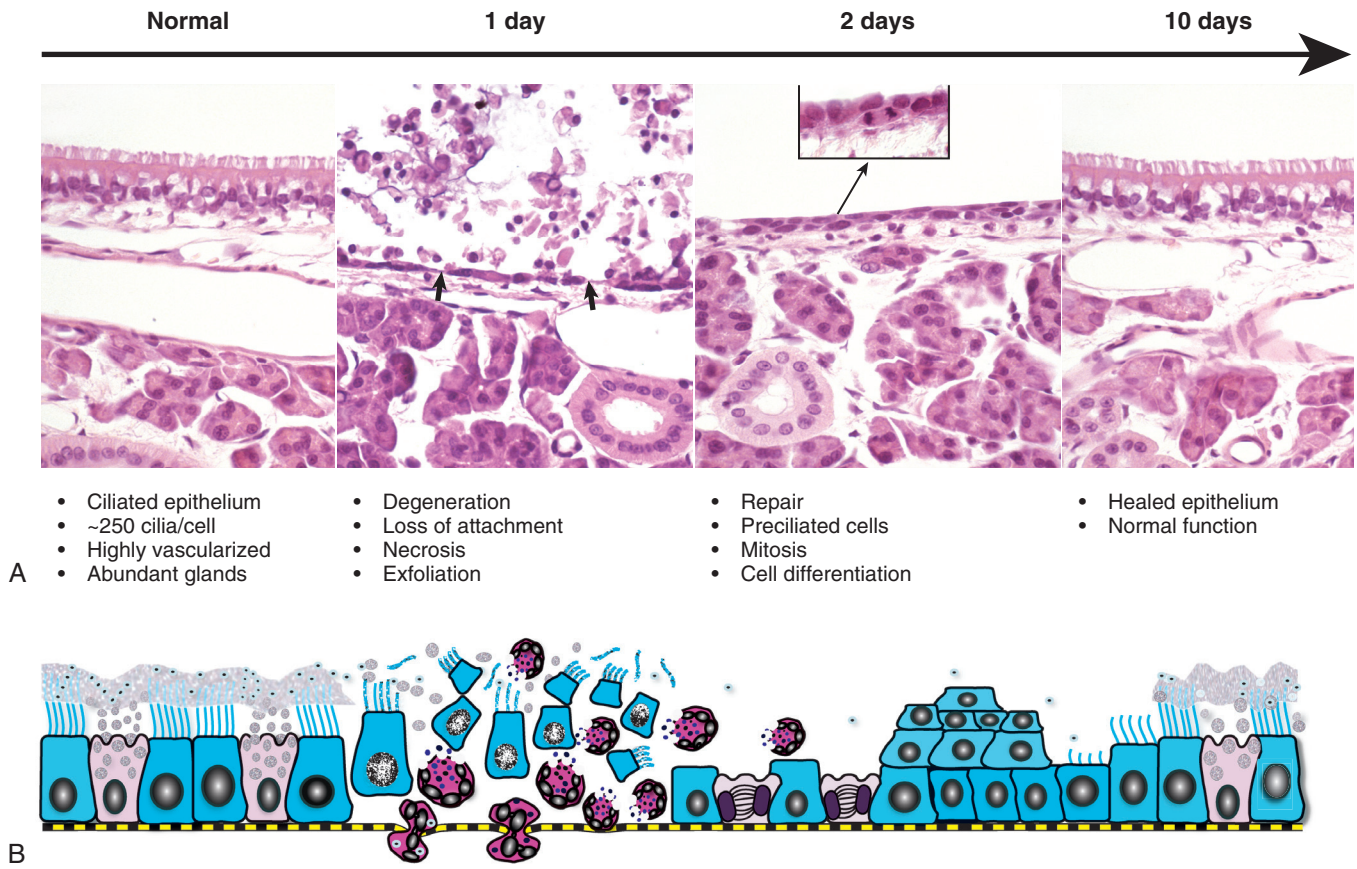


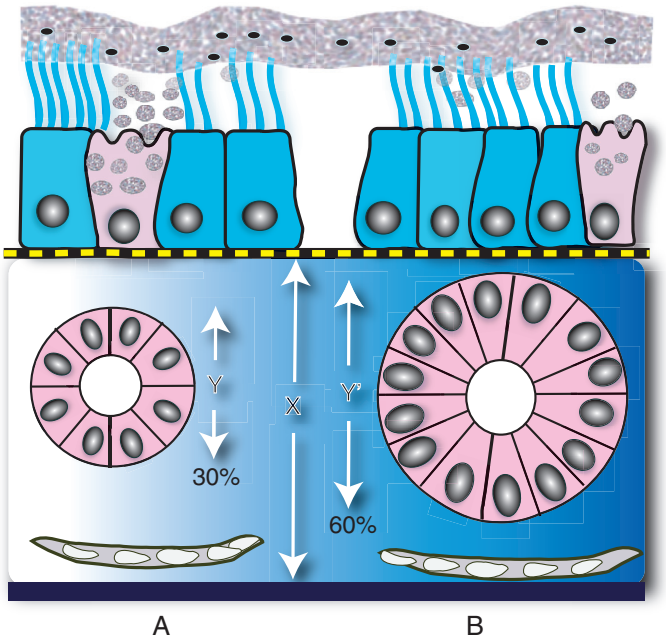
Figure 9-8 Normal and Injured Nasal Epithelium Following Exposure to Air Containing an Irritant Gas (Hydrogen Sulfide), Nasal Concha, Rats. A, Normal ciliated epithelium composed of tall columnar cells with numerous cilia. Day 1: Note detachment and exfoliation of ciliated cells, leaving a denuded basement membrane *(arrows)*. This same type of lesion is seen in viral or mechanical injury to the mucosa of the conducting system. Two days after exposure, the basement membrane is lined by rapidly dividing preciliated cells, some of which exhibit mitotic activity *(inset)*. Ten days after injury, the nasal epithelium is completely repaired. H&E stain. **B,** Schematic representation of the events of injury and repair in the respiratory mucosa of the conducting system. Blue cell, ciliated mucosal epithelial cell; pink cell, goblet cell; red cell, neutrophil. (**A** from López A, Prior M, Yong S, et al: *Am J Vet Res* 49:1107-1111, 1988. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

leads to chronic obstructive bronchitis and emphysema (see Fig. 9-9). Chronic bronchial irritation causes squamous metaplasia of highly functional but vulnerable ciliated epithelium to nonfunctional, but more resistant, squamous epithelium. Squamous metaplasia has a calamitous effect on pulmonary clearance because it causes a structural loss and functional breakdown of portions of the mucociliary escalator. Hyperplasia of bronchial glands occurs frequently in chronic bronchitis, which translates to an increase of the Reid index (bronchial-gland to bronchial-wall ratio) (E-Fig. 9-2). This index is less than 30% in the healthy human lung and in the lungs of most domestic species, except for cats, which generally have an index higher than 40%. The term *airway remodeling* encompasses all the structural changes that accompany chronic bronchitis such as hypertrophy and hyperplasia of smooth muscle, submucosal glands, and goblet cells; fibrosis; and increased bronchial vascularity.

Bronchiectasis is one of the most devastating sequelae to chronic remodeling of the bronchi. It consists of a pathologic and permanent dilation of a bronchus with rupture of the bronchial wall as a result of obstruction or chronic inflammation. Destruction of walls occurs in part when proteolytic enzymes and oxygen radicals released from phagocytic cells during chronic inflammation degrade and weaken the smooth muscle and cartilage (chondromalacia) that help to maintain normal bronchial diameter (Fig. 9-10). Bronchiectasis may be saccular when destruction affects only a small localized portion of the bronchial wall or cylindrical when destruction involves a large segment of a bronchus. Grossly, bronchiectasis is manifested by prominent lumps in the lungs (bosselated appearance or having rounded eminences) resulting from distention of bronchi with exudate, which results in a concurrent obstructive atelectasis of surrounding parenchyma (Fig. 9-11). The cut surfaces of dilated bronchi are filled with purulent exudates; for this reason, bronchiectasis is often mistaken for pulmonary abscesses. Careful inspection, usually requiring microscopic examination, confirms that exudate is contained and surrounded by remnants of a bronchial wall lined by squamous epithelium and not by a pyogenic membrane (connective tissue) as it is in the case of a pulmonary abscess. The squamous metaplasia further interferes with the normal function of the mucociliary escalator.

Transitional System (Bronchioles)

The epithelial lining of the bronchiolar region (transitional zone) is exquisitely susceptible to injury, particularly to that caused by some respiratory viruses (bovine parainfluenza virus 3, bovine respiratory syncytial virus, adenovirus, or canine distemper virus), oxidant gases (nitrogen dioxide [NO_2], sulfur dioxide [SO_2], or ozone [O_3]), and toxic substances (3-methylindole or paraquat). The precise explanation as to why bronchiolar epithelium is so prone to injury is still not clear, but it is presumably due in part to (1) its high vulnerability to oxidants and free radicals; (2) the presence of



E-Figure 9-2 **Bronchial Hyperplasia (Reid Index).** The Reid index is the relative size of the bronchial gland *(Y)* in relation to the thickness of the bronchial wall *(X)*. **A,** Normal bronchial gland; the gland size is approximately 30% of the bronchial wall ($X/Y \times 100$). The Reid index for the healthy bronchus of human beings and domestic animals is less than 30% except for the cat, which can have a normal Reid index of 50% to 60%. **B,** Bronchial gland hyperplasia; the gland size is greater than 60% of the bronchial wall ($X/Y' \times 100$). The Reid index generally increases in chronic bronchitis and chronic obstructive pulmonary disease (COPD). (Courtesy Dr. A. López, Atlantic Veterinary College.)

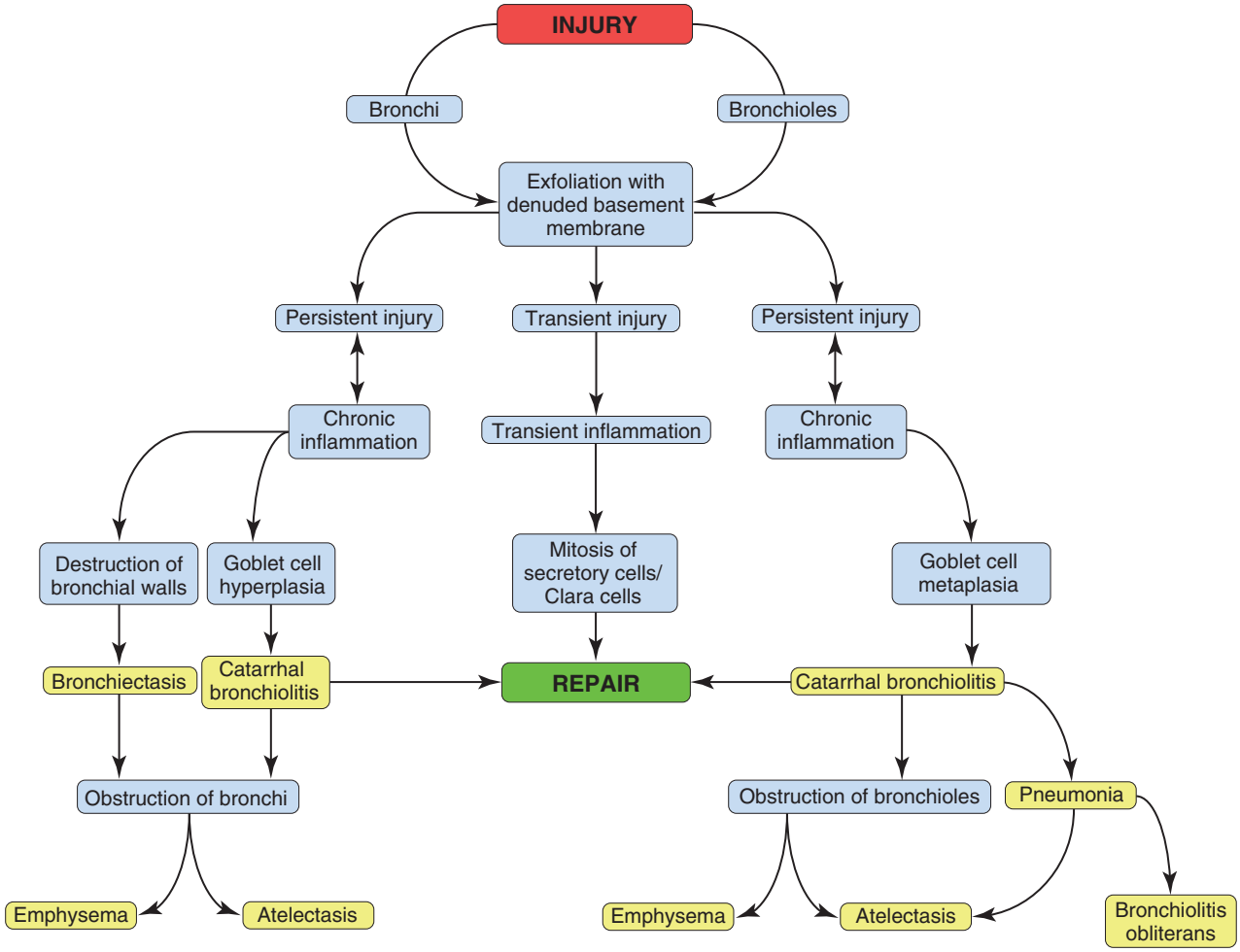


Figure 9-9 Patterns of Host Response and Possible Sequelae to Bronchial and Bronchiolar Injury. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Club (Clara) cells rich in mixed function oxidases, which locally generate toxic metabolites (see Fig. 9-4); and (3) the tendency for pulmonary alveolar macrophages and leukocytes to accumulate in this region of the lungs. Depending on the types of injury and inflammatory response, bronchiolitis is classified as necrotizing, suppurative, catarrhal (mucous metaplasia), or granulomatous.

Repair in Acute and Mild Bronchiolar Injury

Once injury to bronchiolar ciliated cells becomes irreversible, the cells degenerate and exfoliate into the bronchiolar lumen, leaving a denuded basement membrane. Repair in the bronchiolar region is similar to, but less effective than, that in the tracheal or nasal mucosa. Under normal circumstances, recruited phagocytic cells remove exudate and cell debris from the lumina of affected bronchioles, thus preparing the basement membrane to be repopulated with new, undifferentiated cells originating from a rapidly dividing pool of Club (Clara) cells. After several days, these proliferating cells fully differentiate into normal bronchiolar cells.

Repair in Acute and Severe Bronchiolar Injury

In severe acute injury, such as that caused by aspiration pneumonia or by highly pathogenic microorganisms, exudate attaches and cannot be removed from the basement membrane of bronchioles. The exudate becomes infiltrated by fibroblasts, which form small nodular masses of fibrovascular tissue that develop into well-organized, microscopic polyps inside the bronchiolar lumen. The external surface of the exudate eventually becomes covered by ciliated cells. This lesion is referred to as *bronchiolitis obliterans*, and the polyps may become so large as to cause airflow impairment (Fig. 9-12 and see Fig. 9-9).

Repair in Chronic Bronchiolar Injury

In mild but persistent bronchiolar injury, goblet cells normally absent from bronchioles proliferate from basal cells, resulting in goblet cell metaplasia and causing a profound alteration in the physicochemical properties of bronchiolar secretions (Fig. 9-13). The normally serous bronchiolar fluid released by Club (Clara) cells becomes a tenacious material when mucus produced by goblet cells is added. As a result of increased viscoelasticity of the mucus, bronchiolar secretions cannot be removed effectively by ciliary action, leading to plugging and obstruction of distal airways. Under such conditions, often grouped as chronic obstructive pulmonary disease, coughing is required to clear mucus from obstructed bronchioles. Pulmonary emphysema and atelectasis are further sequelae to bronchiolar metaplasia and mucous hypersecretion blocking or partially blocking the lumens of these bronchioles. These two inflation abnormalities are characteristically present in chronic obstructive pulmonary disease (COPD), which is called "recurrent airway obstruction (RAO or "heaves") in horses (see Recurrent Airway Obstruction, under Disorders of Horses). Peribronchiolar

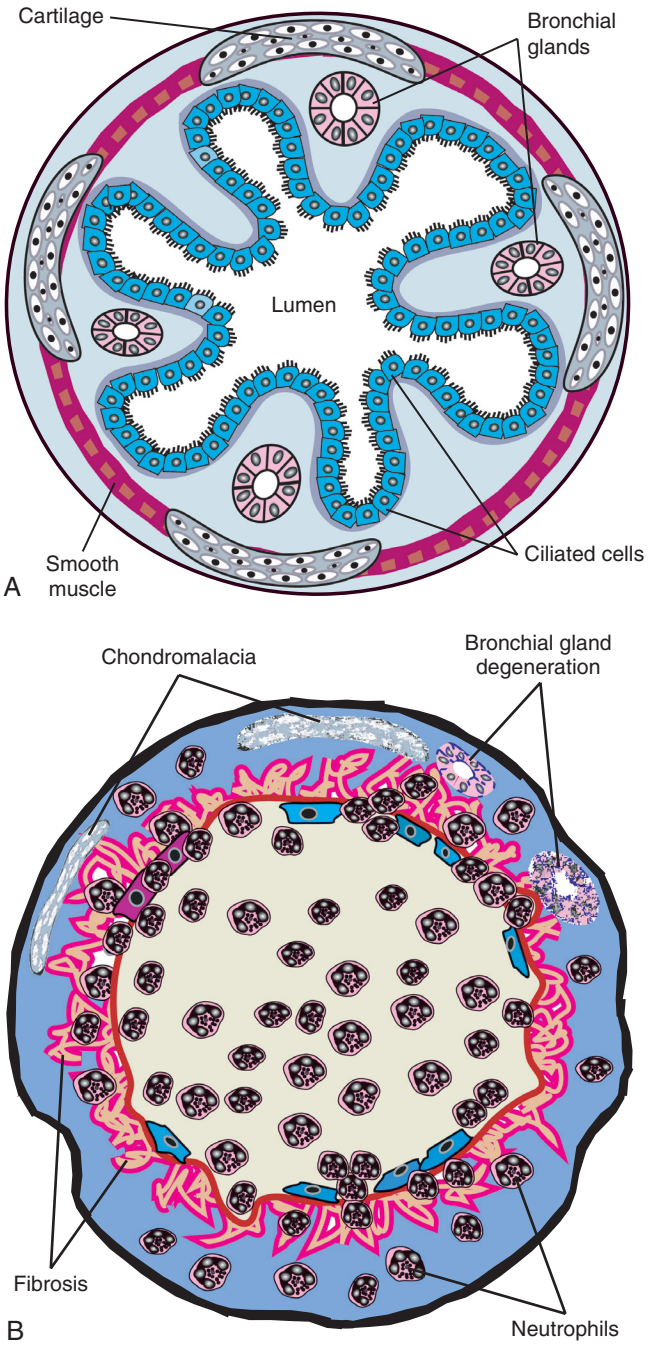


Figure 9-10 Schematic Illustrations of Bronchiectasis. A, Normal bronchus showing mucosa, submucosa, bronchial glands, and cartilage. **B,** Bronchiectasis. The affected bronchus is dilated and has lost its normal projections of the mucosa into the lumen. Note the inflammation, loss of mucosa, destruction of bronchial wall, and fibrosis with atrophy of cartilage and bronchial glands. (Courtesy Dr. A. López, Atlantic Veterinary College.)

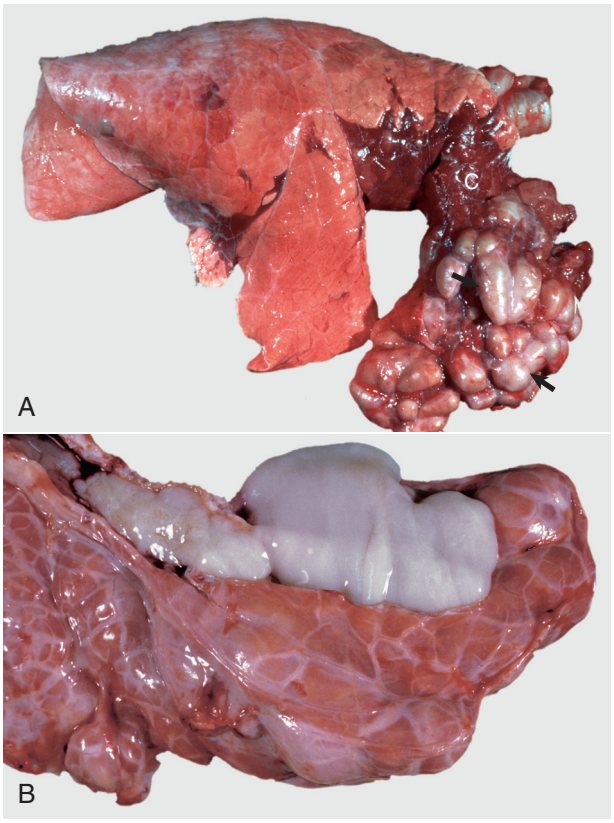


Figure 9-11 Severe Bronchiectasis with Chronic Bronchopneumonia, Right Lung, Calf. A, Note the segmentally distended (bosselated) bronchi *(arrows)* supplying the ventral portion of the cranial lung lobe. The lumens of affected bronchi are filled with purulent exudate. The surrounding lung parenchyma supplied by these bronchi is atelectatic *(C)*. Bronchiectatic bronchi resemble pulmonary abscesses, but unlike abscesses, which are composed of pyogenic exudate within a fibrous capsule, the exudate in bronchiectasis is largely mucopurulent and contained within the remnants of the dilated bronchial wall. **B,** These distended bronchi are filled with mucopurulent exudate (gray-white material) that exudes from airways when they are cut. (**A** courtesy Ontario Veterinary College. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

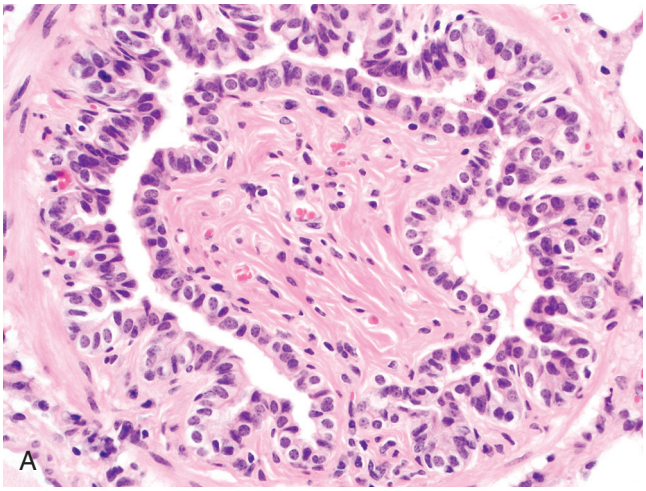
proliferation of lymphocytes (BALT hyperplasia) is also a common microscopic lesion seen in chronic bronchiolitis.

Airway Hyperresponsiveness

Airway hyperresponsiveness, or hyperreactive airway disease, is another sequela of bronchiolar injury arising from gene-environment interactions. It develops in human beings and animals (experimentally) after a transient and often innocuous viral infection of the lower respiratory tract or from exposure to certain allergens. Experimental work has shown that airway hyperreactivity in postviral bronchiolitis is associated with increased expression of TLRs and unusual susceptibility to inhaled endotoxin. Hyperreactive animals typically have an increased number of mast cells, eosinophils, and T lymphocytes in the airway mucosa. Clinically, airway hyperresponsiveness is characterized by an exaggerated bronchoconstriction after natural exposure to mild stimuli, such as cold air, or after animals are experimentally exposed to aerosols of histamine or methacholine.

Exchange System (Alveoli)

Because of their extremely delicate structure, alveoli are quite vulnerable to injury once the local defense mechanisms have been overwhelmed. The alveolar wall is a thin membrane formed by a core of interstitium supporting an extensive network of alveolar capillaries. Fibroblasts (septal cells), myofibroblasts, collagen, elastic fibers, and few interstitial macrophages and mast cells constitute the alveolar interstitium. The wall of the alveolar capillaries facing the airspace is remarkably thin and has three layers composed of vascular endothelium, basal lamina, and alveolar epithelium. These three layers of the alveolar capillaries constitute what is customarily referred to as the *blood-air barrier* (see Fig. 9-7). The epithelial side of the alveolus is primarily lined by rather thin type I



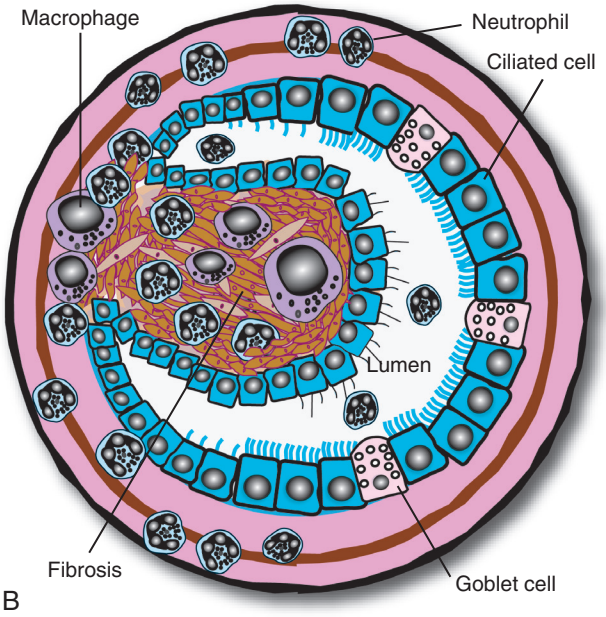
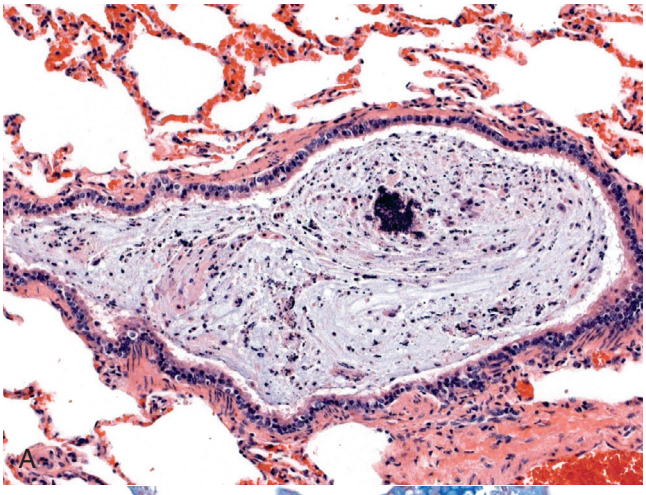
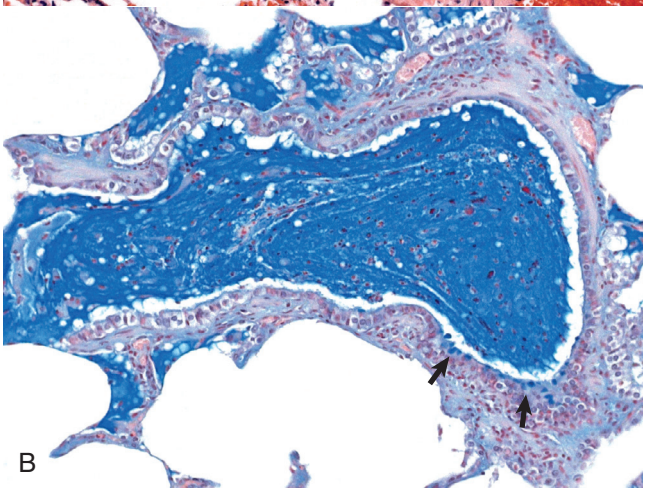


Figure 9-12 Bronchiolitis Obliterans. A, Chronic inflammation in the bronchiolar wall resulting in the formation of a nodular mass *(center)* of granulation tissue firmly attached to the airway wall, protruding into the bronchiolar lumen and lined by bronchial epithelium. H&E stain. **B,** Diagram illustrating organized exudate, formed by connective tissue, macrophages, lymphocytes, and neutrophils, that is attached to the bronchiolar wall and covered by respiratory ciliated cells. (Courtesy Dr. A. López, Atlantic Veterinary College.)





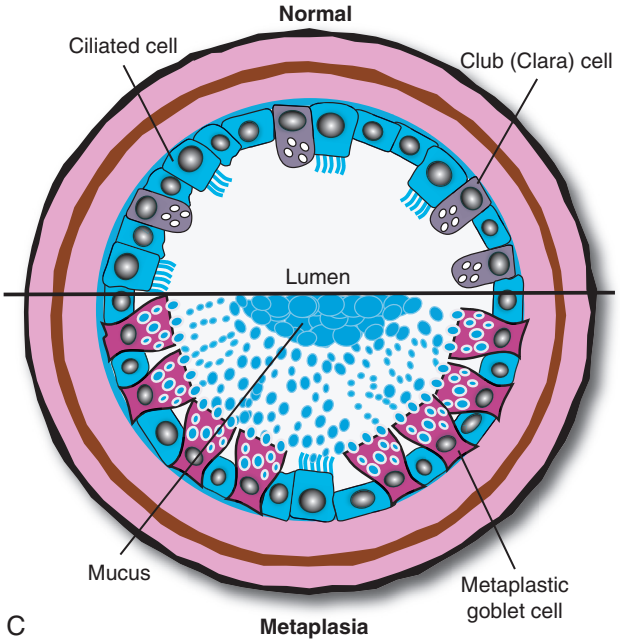


Figure 9-13 Chronic Obstructive Pulmonary Disease (Heaves), Recurrent Airway Obstruction (RAO), Bronchiole, Lung, Horse. A, This 15-year-old horse had a history of recurrent and progressive dyspnea unresponsive to treatment. Note how the bronchiole is plugged with mucus admixed with cell debris and a few neutrophils. H&E stain. **B,** The bronchiole is filled with mucus, and several goblet cells *(arrows)* are present in the mucosa. Healthy bronchioles do not have goblet cells or mucus. Alcian blue stain. **C,** Schematic diagram of a normal bronchiole *(top half of the diagram)* lined with Club cells and some ciliated cells. Bronchiole with severe goblet cell metaplasia *(bottom half of the diagram)* showing abundant metaplastic goblet cells *(purple cells)* and mucus accumulation in the lumen causing chronic obstructive pulmonary disease. (**A** and **B** courtesy Dr. A. López and Dr. C. Legge, Atlantic Veterinary College. **C** courtesy Dr. A. López, Atlantic Veterinary College.)

pneumonocytes, which are arranged as a very delicate continuous membrane extending along the alveolar surface (see Fig. 9-7). Type I pneumonocytes are particularly susceptible to noxious agents that reach the alveolar region either aerogenously or hematogenously. Injury to type I pneumonocytes rapidly causes swelling and vacuolation of these cells (Fig. 9-14). When cellular damage has become irreversible, type I cells detach, resulting in denudation of the basement membrane, increased alveolar permeability, and alveolar edema. Alveolar repair is possible as long as the basement membrane remains intact and lesions are not complicated by further injury or infection. Within 3 days, cuboidal type II (granular) pneumonocytes, which are the precursor cells and more resistant to injury, undergo mitosis and provide a large pool of new undifferentiated cells (Fig. 9-15 and see Fig. 9-14). These new cells repave the denuded alveolar basement membrane and finally differentiate into type I pneumonocytes. When alveolar injury is diffuse, proliferation

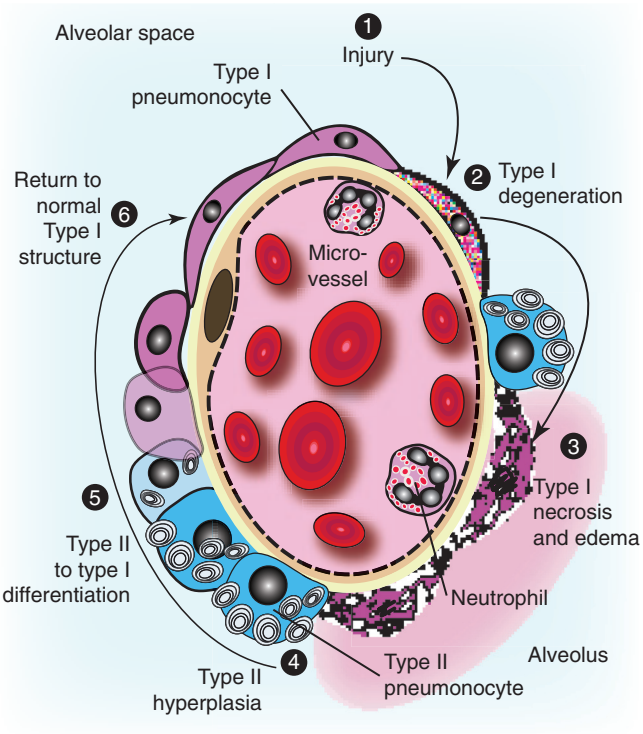


Figure 9-14 Cellular Events during Injury and Necrosis of Type I Pneumonocytes. Severe injury *(1)* can cause degeneration and necrosis of type I pneumonocytes *(2)*. Necrosis of these cells leads to transient alveolar edema *(area that is pink) (3)*, which is followed by hyperplasia of type II pneumonocytes *(4)*, stem cells that differentiate *(5)* into type I pneumonocytes as part of alveolar repair and healing *(6)*. (Courtesy Dr. A. López, Atlantic Veterinary College.)

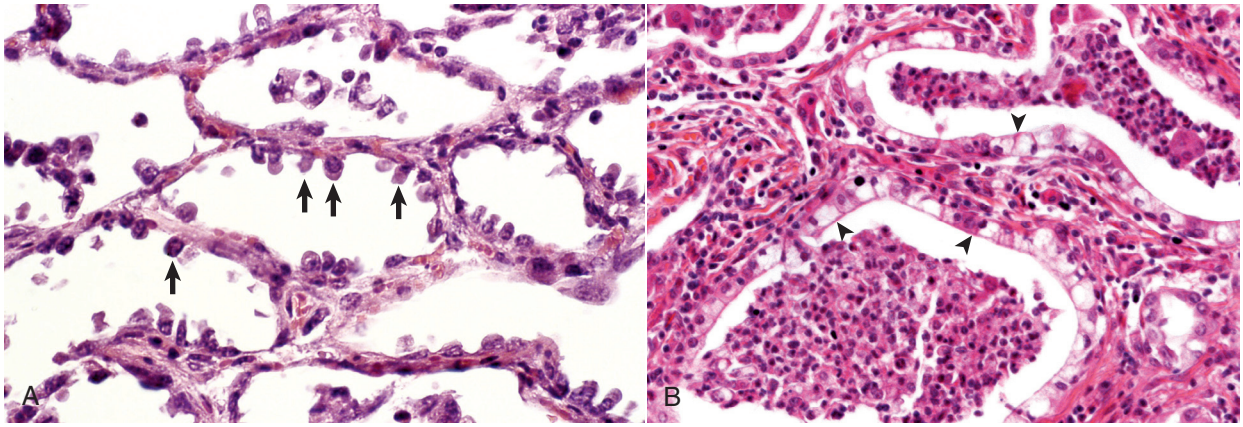


Figure 9-15 Hyperplasia of Type II Pneumonocytes. A, Acute alveolar injury, crude oil aspiration, cow. Note proliferation of cuboidal epithelial cells (type II pneumonocytes) *(arrows)* along the luminal surface of the alveolar wall. During alveolar repair, type II pneumonocytes are the precursor cell for necrotic and lost type I pneumonocytes. H&E stain. **B,** Chronic alveolar injury, interstitial pneumonia, horse. Note entire alveolar membrane lined with cuboidal type II pneumonocytes *(arrowheads)*. The alveolar interstitium is expanded with inflammatory cells, and the alveolar lumens contain cell debris mixed with leukocytes. H&E stain. (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** courtesy Dr. G. Hines, Provincial Veterinary Laboratory, New Brunswick, and Dr. A. López, Atlantic Veterinary College.)

of type II pneumonocytes becomes so spectacular that the microscopic appearance of the alveolus resembles that of a gland or fetal lung; this lesion has been termed *epithelialization* or *fetalization*. Although it is part of the normal alveolar repair, hyperplasia of type II pneumonocytes can interfere in gas exchange and cause hypoxemia. In uncomplicated cases, type II pneumonocytes eventually differentiate into type I pneumonocytes, thus completing the last stage of alveolar repair (see Fig. 9-14). In some forms of chronic interstitial lung injury, the surface of the alveolar basement membrane could become populated with migrating bronchiolar cells, a process known as alveolar *bronchiolization* or *lambertosis*. In severe cases, lambertosis, a metaplastic change, can be mistaken microscopically with alveolar adenomas.

Type I pneumonocytes are one of the three structural components of the blood-air barrier, so when these epithelial cells are damaged, there is an increase in alveolar capillary permeability and transient leakage of plasma fluid, proteins, and fibrin into the alveolar lumen (see Fig. 9-14). Under normal circumstances, these fluids are rapidly cleared from the alveolus by alveolar and lymphatic absorption, and necrotic pneumonocytes (type I) and fibrin strands are phagocytosed and removed by pulmonary alveolar macrophages. When there is persistent and severe injury, fibroblasts and myofibroblasts may proliferate in the alveolar walls (alveolar interstitium), causing alveolar septal fibrosis, whereas in other forms of severe injury, fibroblasts and myofibroblasts actively migrate from the interstitium into the alveolar spaces, causing intraalveolar fibrosis. These two types of alveolar fibrosis are most commonly seen in toxic and allergic pulmonary diseases and have a devastating effect on lung function.

Endothelial cells are also major players in the normal and abnormal physiology of the alveolus (see Figs. 9-7 and 9-14). These cells trap and share circulating antigens with intravascular and interstitial macrophages. The junction between alveolar endothelial cells is not as tight as that of the type I pneumonocytes, allowing some movement of fluid and small-size molecular weight proteins into the alveolar interstitium. Endothelial cells maintain an intimate cell contact with erythrocytes and leukocytes passing through the lung, since the lumen of alveolar capillaries is slightly smaller (5.0 μm) than the diameter of red and white blood cells. Erythrocytes are easily deformable, so their transit time through the alveolar capillaries is shorter than that of leukocytes, which are less deformable cells. This longer transit time of leukocytes and their close cellular contact with alveolar endothelial cells have major impacts in lung inflammation and acute respiratory distress syndrome (ARDS).

On a minute-to-minute basis, the pulmonary defense mechanisms deal effectively with noxious stimuli and mild tissue injury without the need for an inflammatory response. However, if normal defense mechanisms are ineffective or insufficient (overwhelmed), the inflammatory process is rapidly turned on as a second line of defense.

Postmortem Examination of the Respiratory Tract

Postmortem examination of the respiratory tract should always be conducted in a thorough and systematic manner and include the conducting system (trachea, bronchi, and bronchioles), the lungs, and the thoracic cavity and pleura. Detailed record keeping and photographic documentation are essential elements of a thorough examination. Normal lungs typically have a homogeneous pink color (Fig. 9-16) and are slightly deflated from loss of negative intrathoracic pressure. The E-sections that follow describe a systematic approach to this process.

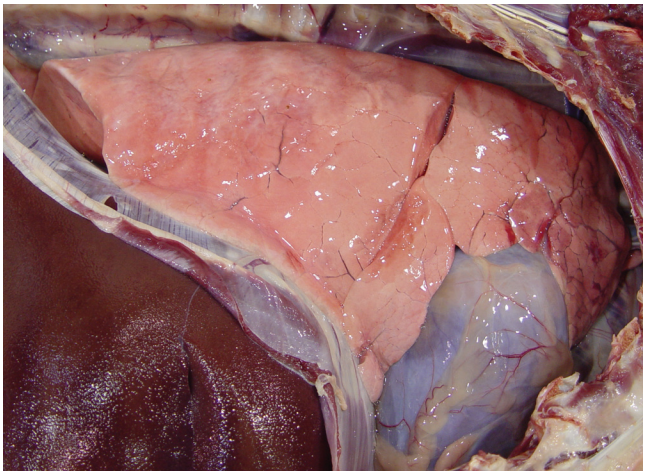


Figure 9-16 Normal Lung, Dog. The lung parenchyma appears homogeneously pink and slightly deflated from loss of negative intrathoracic pressure. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Table 9-2 Portals of Entry into the Respiratory System

Route	Agents
Aerogenous (inhalation)	Virus, bacteria, fungi, toxic gases, and pneumotoxicants
Hematogenous (blood)	Virus, bacteria, fungi, parasites, toxins, and pneumotoxicants
Direct extension	Penetrating wounds, migrating awns, bites, and ruptured esophagus or perforated diaphragm (hardware)

More information on postmortem examination of the lung can be found at www.expertconsult.com.

Histopathology and Biopsies

Information on this topic is available at www.expertconsult.com.

Bronchoalveolar Lavage and Transtracheal Wash

Information on this topic is available at www.expertconsult.com.

Portals of Entry/Pathways of Spread

Microbes, toxins, and pneumotoxicants can gain access into the respiratory system by the following routes (Table 9-2; also see Table 9-1): aerogenous, hematogenous, direct extension, and by local production of free radicals and toxic metabolites.

Aerogenous

Pathogens, such as bacteria, mycoplasmas, and viruses, along with toxic gases and foreign particles, including food, can gain access to the respiratory system via inspired air. This is the most common route in the transmission of most respiratory infections in domestic animals.

Hematogenous

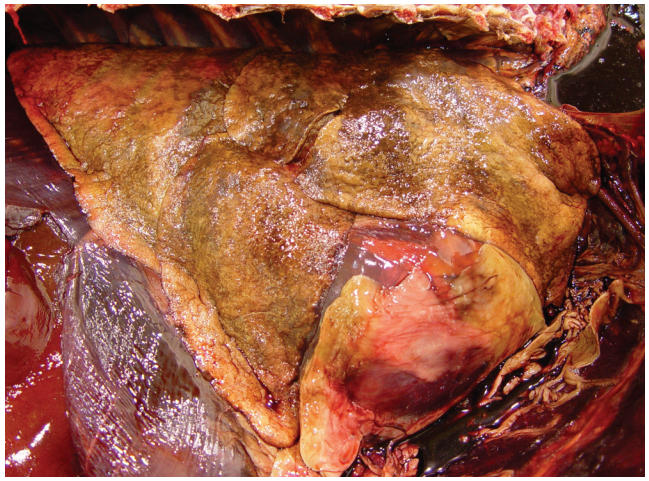
Some viruses, bacteria, parasites, and toxins can enter the respiratory system via the circulating blood. This portal of entry is commonly seen in septicemias, bacteremias, and with protozoa and viruses that target endothelial cells. Also, circulating leukocytes may release infectious organisms such as retroviruses and *Listeria monocytogenes* while traveling through the lungs.

The respiratory tract should always be examined in a systematic manner. To determine whether negative pressure is present in the thoracic cavity, the diaphragm is punctured through the abdominal cavity before the thoracic cavity has been opened. When the diaphragm is punctured in a fresh carcass, the loss of negative pressure in the thorax causes the diaphragmatic cupola to drop back caudally toward the abdominal cavity, and at the same time, there is an audible sound caused by the inrush of air into the thorax. Lack of this movement may be an indication of advanced pneumothorax, pleural effusion, or the presence of uncollapsed lungs caused by pulmonary edema, pneumonia, fibrosis, or emphysema. In carcasses that have been dead for a long time, pulmonary air and gas produced by saprophytic bacteria leak into the pleural cavity, reducing the negative thoracic pressure and collapsing the lung.

The rib cage must be removed by cutting along the costosternal joints and along the neck of the ribs (close to the costovertebral joints) in such a way that pleural adhesions and abnormal thoracic contents can be observed and grossly quantified (e.g., 200 mL of clear, yellow fluid). The tongue, pharynx, esophagus, larynx, trachea, and thoracic viscera (lungs, heart, and thymus) should be removed as a unit (often called the *pluck*) and placed on the necropsy table.

The pharynx and esophagus are opened starting at the pharynx by a single cut with scissors along the dorsal midline and are inspected for ulcers, foreign bodies, and neoplasms. The larynx and trachea must be examined by opening both along the dorsal midline from cranial to caudal ends and then extending the incision into the large bronchi of the caudal lung lobes. Normal tracheobronchial mucosa has a smooth and glistening pearl-colored surface with empty lumina in airways. The presence of foamy fluid in airways indicates pulmonary edema. Feed particles may suggest aspiration; however, careful examination of the mucosa is required because aspiration of ingesta from stomach or rumen into the lungs commonly takes place agonally or can be displaced into these areas when the carcass is moved.

The lungs should be examined before incision. Normal lungs typically have a homogeneous pink color (see Fig. 9-16). External changes include the presence of rib imprints on the pleural surface when lungs fail to collapse. In addition, the lungs should be inspected for changes in color and texture and distribution of lesions. Color changes can be various shades of red, indicating hypostatic congestion, hyperemia (acute pneumonia), and hemorrhage; dark blue collapsed lobules or areas are indicative of atelectasis; pale pink to white lungs indicate notable anemia, fibrosis, or emphysema; and uniformly or patchy yellow-brown lungs indicate chronic passive congestion and pulmonary fibrosis likely secondary to chronic heart failure. Lungs from exsanguinated animals are generally paler than the normal pink color because of reduced blood in the pulmonary tissue. Lungs with postmortem autolysis show green discoloration, a change that is also seen in other organs (E-Fig. 9-3). A covering of yellowish material on the pleural surface indicates accumulation of fibrin. Because it is impossible to describe the texture of normal lungs, experience in palpation is required to appreciate the actual texture of a normal lung. Texture is determined by gently palpating the surface and parenchyma of the lungs. Normal texture can change to firm, hard, elastic (rubbery), or crepitus (with a crackling sound or feeling). For a detailed description of lung texture, see the section on Classification of Pneumonias in Domestic Animals. Palpation of the lungs, which should be gentle, also permits detection of nonvisible nodules or abscesses in the parenchyma. Knowing the distribution of a lesion in the lungs also facilitates diagnosis because particular etiologic agents cause lesions with specific distribution. Distribution of lesions is generally described as focal, multifocal, locally extensive, or diffuse. According to their topography, pulmonary lesions can also be classified as cranioventral, dorsocaudal, and so on.



E-Figure 9-3 **Autolysis, Severe, Lung, Dog.** Lungs with autolysis have a green discoloration and often exhibit postmortem emphysema. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Necropsy reports must also contain an estimate of the extent of the pulmonary lesions, preferably expressed as a percentage of the volume of the lungs affected. For instance, a report may read "cranioventral consolidation involving 40% of the lungs." If the lungs have focal lesions, a rough estimate of the number should also be included in the report. For instance, "numerous (approximately 25), small (1 to 2 cm in diameter), hard nodules were randomly distributed in all lung lobes."

Two methods are used to examine the nasal structures. The first is making a midsagittal cut through the head and removing the nasal septum; the second is making several transverse sections of the nose at the level of the second premolar teeth. This latter method is preferred when examining pigs suspected of having atrophic rhinitis or animals suspected of having nasal neoplasms.

Microscopic examination of pulmonary tissue is routinely done in diagnostic laboratories. Samples of normal and abnormal lungs, along with other appropriate tissue, should always be submitted in 10% buffered-neutral formalin for histopathologic evaluation. A minimum of four lung samples (left cranial, left caudal, right cranial, and right caudal) should be taken for histopathologic examination in animals with a history of respiratory signs. To improve fixation, a paper towel can be placed over the samples of lung floating in fixative. When detailed evaluation of the alveolar walls is required, lungs can be fixed by a gentle intratracheal injection of fixative; however, this technique displaces transudates and exudates and can artificially cause distention of the perivascular and peribronchial spaces. Lung biopsy specimens are taken only sporadically because complications often outweigh the diagnostic value. However, the use of new techniques, such as endoscopic-directed biopsies, has notably reduced some of these complications. Biopsies of the lungs are recommended in cases of chronic persistent pulmonary disease unresponsive to treatment or intrathoracic masses of undetermined origin. Endoscopic-directed biopsies of the nasal and bronchial mucosa are routinely used in clinical practice and generally have a much better diagnostic value.

Two valuable diagnostic tools in human medicine, bronchoalveolar lavage (BAL) and transtracheal wash (TTW), have in recent years become more widely used in veterinary clinical diagnosis of

respiratory ailments, particularly in horses, dogs, and cats. The basis of BAL and TTW is sampling the lung or trachea of a living animal by infusing sterile fluid into the trachea or deep lung (respectively) and retrieving it to determine the cellular and biochemical composition of this fluid. In other words, the composition of the fluid reflects what is present in the bronchioloalveolar spaces and trachea. These procedures are performed by inserting a tube directly through the larynx into the trachea or bronchus, or transtracheally by inserting a tube through a needle percutaneously into the cervical trachea. Microscopic examination of properly collected, stored, and processed samples may reveal many erythrocytes and siderophages in pulmonary hemorrhage or left-sided heart failure; inclusion bodies or syncytial cells in viral pneumonias; increased number of leukocytes in pulmonary inflammation; abundant mucus in asthma or equine recurrent airway obstruction (RAO); the presence of pulmonary pathogens, such as parasites, fungi, and bacteria; or tumor cells in cases of pulmonary neoplasia. In the healthy animal, 80% to 95% of the BAL cells are pulmonary alveolar macrophages (see Fig. 9-19, *A*).

Direct Extension

In some instances, pathogenic organisms can also reach the pleura and lungs through penetrating injuries, such as gunshot wounds, migrating awns, or bites, or by direct extension from a ruptured esophagus or perforated diaphragm.

Local Production of Free Radicals and Toxic Metabolites

The lungs, particularly the bronchioles and alveoli, are vulnerable to endogenous injury caused by the local generation of free radicals during inflammation or by toxic metabolites generated by Club (Clara) cells (see Fig. 9-4, *B*).

Pathways of Spread from the Respiratory System (Locally, Regionally, and Systemically)

Inflammatory processes in the respiratory system, particularly those caused by infectious organisms, can spread to contiguous or distant tissues. For instance, rhinitis may spread into the sinuses causing rhinosinusitis. Similarly, laryngeal inflammation may spread into the lungs when exudate in the larynx is aspirated. Lung disease can have profound systemic effects when cytokines, produced locally during necrosis or inflammation, are released into circulation. As a result of the enormous vascular bed present in the lung, sepsis and septic shock often develop when proinflammatory molecules overwhelm the antiinflammatory response during the so-called "cytokine storm."

Defense Mechanisms/Barrier Systems

Defense Mechanisms Against Aerogenous Injury

It is axiomatic that a particle, microbe, or toxic gas must first gain entry to a vulnerable region of the respiratory system before it can induce an adaptive immune response or have a pathologic effect. The characteristics of size, shape, dispersal, and deposition of particles present in inspired air are studied in aerobiology. It is important to recognize the difference between deposition, clearance, and retention of inhaled particles. Deposition is the process by which particles of various sizes and shapes are trapped within specific regions of the respiratory tract. Clearance is the process by which deposited particles are destroyed, neutralized, or removed from the mucosal surfaces. The difference between what is deposited and what is cleared from the respiratory tract is referred to as *retention*. The main mechanisms involved in clearance are sneezing, coughing, mucociliary transport, and phagocytosis (Table 9-3). Abnormal retention of particles resulting from increased deposition, decreased clearance, or a combination of both is the underlying pathogenetic mechanism in many pulmonary diseases (Fig. 9-17).

The anatomic configuration of the nasal cavity and bronchi plays a unique role in preventing or reducing the penetration of noxious material into the lungs, especially into the alveoli, which is the most vulnerable portion of the respiratory system. The narrow nasal meatuses and the coiled arrangement of the nasal conchae generate enormous turbulence of airflow, and as a result, physical forces are created that forcefully impact particles larger than 10 µm onto the surface of the nasal mucosa (Fig. 9-18). Although particles smaller than 10 µm could escape trapping in the nasal cavity, these medium-sized particles meet a second barrier at the tracheal and bronchial

Table 9-3 Main Defense Mechanisms of the Respiratory System

Regions of the Respiratory System	Defense Mechanisms
Conducting system (nose, trachea, and bronchi)	Mucociliary clearance, antibodies, lysozyme, mucus
Transitional system (bronchioles)	Club cells, antioxidants, lysozyme, antibodies
Exchange system (alveoli)	Alveolar macrophages (inhaled pathogens), intravascular macrophages (circulating pathogens), opsonizing antibodies, surfactant, antioxidants

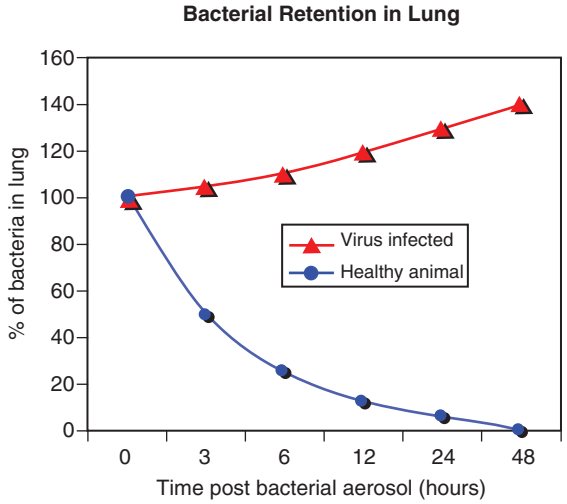


Figure 9-17 Pulmonary Clearance and Retention of Bacteria Following Inhalation of an Experimental Aerosol of Bacteria. When large numbers of bacteria are inhaled, the normal defense mechanisms promptly eliminate these microorganisms from the lungs *(blue line)*. However, when the defense mechanisms are impaired by a viral infection, lung edema, stress, and so forth, the inhaled bacteria are not eliminated but colonize and multiply in the lung *(red line)*. (Courtesy Dr. A. López, Atlantic Veterinary College.)

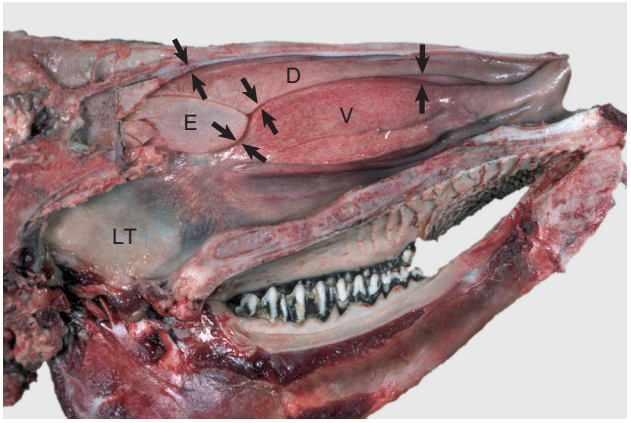


Figure 9-18 Dorsal *(D)*, Ventral *(V)*, and Ethmoidal *(E)* Conchae, Midsagittal Section of Head, Cow. These meatuses *(spaces between arrows)* are narrow, and the air turbulence produced in them by the coiled arrangement of the conchae causes suspended particles to impact on the mucus covering the surface of the nasal mucosa. These particles are then moved caudally by the mucociliary apparatus to the pharynx and finally swallowed. Note the abundant lymphoid tissue *(LT)* in the nasopharynx. (Courtesy Dr. R.G. Thomson, Ontario Veterinary College.)

bifurcations. Abrupt changes in the direction of air (inertia), which occurs at the branching of major airways, cause particles in the 2- to 10-μm size range to collide with the surface of bronchial mucosa (see Fig. 9-1). Because the velocity of inspired air at the level of the small bronchi and bronchioles has become rather slow, inertial and centrifugal forces no longer play a significant role in the trapping of inhaled particles. Here, in the transitional (bronchiolar) and exchange (alveolar) regions, particles 2 μm or smaller may come into contact with the mucosa by means of sedimentation because of gravitation or by diffusion as a result of Brownian movement. Infective aerosols containing bacteria and viruses are within the size range (0.01 to 2 μm) that can gain access to the bronchiolar and alveolar regions.

In addition to size, other factors, such as shape, length, electrical charge, and humidity, play an important role in mucosal deposition, retention, and pathogenicity of inhaled particles. For example, particles longer than 200 μm may also reach the lower respiratory tract provided their mean aerodynamic diameter is less than 1 μm. Asbestos is a good example of a large but slender fiber that can bypass the filtrating mechanisms by traveling parallel to the airstream. Once in the terminal bronchioles and alveoli, asbestos fibers cause asbestosis, a serious pulmonary disease in human beings. In summary, the anatomic features of the nasal cavity and airways provide an effective barrier, preventing the penetration of most large particles into the lungs.

Once larger particles are trapped in the mucosa of conducting airways and small particles are deposited on the surface of the nasal, tracheal, or bronchoalveolar mucosa, it is crucial that these exogenous materials be promptly removed to prevent or minimize injury to the respiratory system. For these purposes, the respiratory system is equipped with several defense mechanisms, all of which are provided by specialized cells operating in a remarkably well-coordinated manner.

Conducting System (Nose, Trachea, and Bronchi) and the Transitional System (Bronchioles)

Mucociliary clearance is the physical unidirectional movement and removal of deposited particles and gases dissolved in the mucus from the respiratory tract. Mucociliary clearance, also referred to as the *waste disposal system*, is provided by the mucociliary blanket (mucociliary escalator) and is the main defense mechanism of the conducting system (nasal cavity, trachea, and bronchi) (see Figs. 9-2 and 9-3). Mucus acts primarily as a barrier and a vehicle, and it is a complex mixture of water, glycoproteins, immunoglobulins, lipids, and electrolytes. These substances are produced by goblet (mucous) cells, serous cells, submucosal glands, and fluid from transepithelial ion and water transport. Once serous fluid and mucus are secreted onto the surface of the respiratory mucosa, a thin, double-layer film of mucus is formed on top of the cells. The outer layer of this film is in a viscous gel phase, whereas the inner layer, which is in a fluid or sol phase, is directly in contact with cilia (see Fig. 9-3 and see E-Fig. 9-1). The respiratory system of a healthy human produces approximately 100 mL of mucus per day. Each ciliated cell in the conducting system has approximately 100 to 200 motile and chemosensory cilia (6 μm long), beating metachronously (forming a wave) at a ciliary beat frequency of approximately 1000 strokes per minute, and in a horse, for example, mucus moves longitudinally at a rate of up to 20 mm per minute. Rapid and powerful movement of cilia creates a series of waves that, in a continuous and synchronized manner, propel the mucus, exfoliated cells, and entrapped particles out of the respiratory tract to the pharynx. The mucus is finally swallowed or, when present in large amounts, is coughed up out of the conducting system. If mucus flow were to move at the same rate in all levels of a conducting system, a "bottleneck" effect would be created in major airways as the minor but more numerous airways enter the bronchi. For this reason, the mucociliary transport in proximal (rostral) airways is physiologically faster than that of the distal (caudal) ones. Ciliary activity and mucus transport increase notably in response to stimuli such as in respiratory infections.

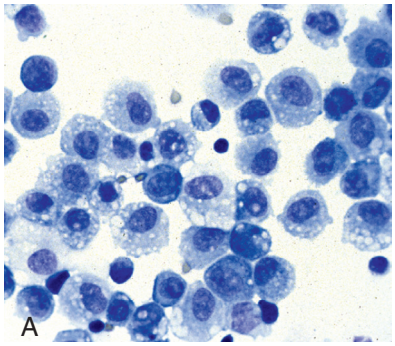
The mucociliary blanket of the nasal cavity, trachea, and bronchi also plays an important role in preventing injury from toxic gases. If a soluble gas contacts the mucociliary blanket, it mixes with the mucus, thus reducing the concentration of gas reaching deep into the alveoli. In other words, mucus acts as a "scavenger system," whereby gases are solubilized and subsequently cleared from the respiratory tract via mucociliary transport. If ciliary transport is reduced (loss of cilia) or mucus production is excessive, coughing becomes an important mechanism for clearing the airways.

In addition to the mechanical barrier and physical transport provided by the mucociliary escalator, other cells closely associated with ciliated epithelium contribute to the defense mechanism of the conducting and transitional systems. Among the most notable are the microfold (M) cells, which are modified epithelial cells covering the bronchial-associated lymphoid tissue (BALT), both of which are strategically situated at the corner of the bifurcation of bronchi and bronchioles, where inhaled particles often collide with the mucosa because of inertial forces. From here, inhaled particles and soluble antigens are phagocytosed and transported by macrophages, dendritic cells, and other professional antigen-presenting cells (APCs) into the BALT, thus providing a unique opportunity for B and T lymphocytes to enter into close contact with inhaled pathogenic substances. Pulmonary lymphocytes are not quiescent in the BALT but are in continual traffic to other organs and contribute to both cellular (cytotoxic, helper, and suppressor T lymphocytes) and humoral immune responses. Immunoglobulin A (IgA), produced by mucosal plasma cells, and, to a lesser extent, immunoglobulin G (IgG) and M (IgM) play important roles in the local immunity of the conducting and transitional systems, especially with regard to preventing attachment of pathogens to the cilia. Chronic airway diseases, especially those caused by infectious agents such as mycoplasmas or retroviruses, are often accompanied by severe hyperplasia of the BALT.

The mucociliary clearance terminates at the pharynx, where mucus, propelled caudally from the nasal cavity and cranially from the tracheobronchial tree, is eventually swallowed and thus eliminated from the conducting system of the respiratory tract. Some respiratory pathogens, such as *Rhodococcus equi*, can infect the intestines after having been removed and swallowed from the respiratory tract into the alimentary system.

Exchange System (Alveoli)

Alveoli lack ciliated and mucus-producing cells; thus the defense mechanism against inhaled particles in the alveolar region cannot be provided by mucociliary clearance. Instead, the main defense mechanisms of alveoli (exchange system) are phagocytosis provided by the pulmonary alveolar macrophages and antimicrobial molecules of the alveolar lining fluid (Fig. 9-19). Pulmonary alveolar macrophages are highly phagocytic cells, which are not to be confused with pulmonary intravascular macrophages, and are derived largely from blood monocytes and, to a much lesser extent, from a slowly dividing population of interstitial macrophages. After a temporary adaptive stage within alveolar interstitium, blood monocytes reduce their glycolytic metabolism and increase their oxidative metabolism to function in an aerobic rather than an anaerobic environment. Pulmonary alveolar macrophages contribute to the



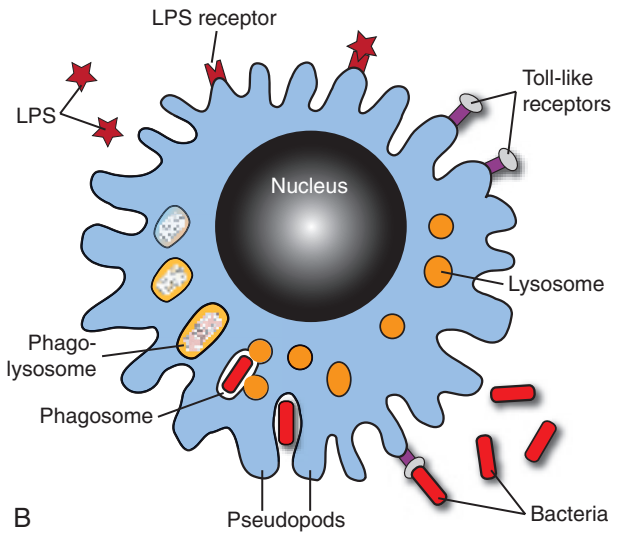


Figure 9-19 Pulmonary Alveolar Macrophages. A, Bronchoalveolar lavage, healthy pig. Alveolar macrophages characterized by abundant and vacuolated cytoplasm are the predominant cell in lavages from healthy lungs. Mayer's hematoxylin counter stain. **B,** Schematic representation of a pulmonary alveolar macrophage. Note receptors in cell membrane, attachment of bacteria to cell receptor, bacteria being engulfed by cytoplasmic projections (pseudopods), formation of cytoplasmic phagosomes, and fusion of lysosomes with phagosome (phagolysosomes), which finally kill the ingested bacteria. (**A** courtesy Dr. L.A. Rijana-Ludbit, Tübingen. **B** courtesy of Dr. A. López, Atlantic Veterinary College.)

pulmonary innate and adaptive immune response by rapidly attaching and phagocytosing bacteria and any other particles reaching the alveolar lumens. The number of free macrophages in the alveolar space is closely related to the number of inhaled particles reaching the lungs. This ability to increase, within hours, the number of available phagocytic cells is vital in protecting the distal lungs against foreign material, particularly when the inhaled particle load is high. Unlike that of tissue macrophages, the life span of alveolar macrophages in the alveoli is notably short, only a few days, and thus they are continuously being replaced by newly migrated blood monocytes.

Alveolar phagocytosis plays a prominent role in the innate defense mechanism against inhaled bacteria without the need of an inflammatory reaction. Bacteria reaching the alveoli are rapidly phagocytosed, and bactericidal enzymes present in lysosomes are discharged into the phagosome containing the bacteria (see Fig. 9-19, *B*). Except for some facultative pathogens that are resistant to intracellular killing (e.g., *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Brucella abortus*, *Rhodococcus equi*, and some *Salmonella* spp.), most bacteria reaching the lungs are rapidly destroyed by activated alveolar macrophages. Similarly, inhaled particles, such as dust, pollen, spores, carbon, or erythrocytes from intraalveolar hemorrhage, are all phagocytosed and eventually removed from alveoli by pulmonary alveolar macrophages. Most alveolar macrophages leave the alveoli by migrating toward the bronchiolar (transitional) region until the mucociliary blanket is reached. Once there, pulmonary macrophages are removed in the same way as any other particle: along the mucociliary flow to the pharynx and swallowed. In the cat, as many as 1 million macrophages per hour move out from the alveoli into the conducting system and pharynx.

Destruction and removal of inhaled microbes and particles by alveolar macrophages is a well-orchestrated mechanism that engages many cells, receptors (i.e., Toll-like receptors [TLRs]), and pulmonary secretions in the lung. The cell-to-cell interactions are complex and involve pulmonary alveolar macrophages, pneumonocytes, endothelial cells, lymphocytes, plasma cells, natural killer (NK) cells, and dendritic cells. Antibodies are also important in the protection (acquired immune response) of the respiratory tract against inhaled pathogens. IgA is the most abundant antibody in the nasal and tracheal secretions and prevents the attachment and absorption of antigens (immune exclusion). IgG and, to a lesser extent, IgE and IgM promote the uptake and destruction of inhaled pathogens by phagocytic cells (immune elimination). IgG is the most abundant antibody in the alveolar surface and acts primarily as an opsonizing antibody for alveolar macrophages and neutrophils. In addition to antibodies, there are several secretory molecules locally released into the alveoli that constitute the alveolar lining material and contribute to the pulmonary defense mechanisms. The most important of these antimicrobial products are transferrin, anionic peptides, and pulmonary surfactant (Table 9-4).

To facilitate phagocytosis and discriminate between "self" and "foreign" antigens, pulmonary alveolar macrophages are furnished with a wide variety of specific receptors on their cell surfaces. Among the most important ones are Fc receptors for antibodies; complement receptors (for C3b, C3a, and C5a); tumor necrosis factor (TNF) receptor; and CD40 receptors, which facilitate phagocytosis and destruction of opsonized particles. Toll-like receptors (TLRs) recognize microbial components, and apoptosis stimulating fragment (FAS) receptors are involved in apoptosis and in the phagocytosis of apoptotic cells in the lung. "Scavenger receptors," which are responsible for the recognition and uptake of foreign particulates, such as dust and fibers, are also present on pulmonary alveolar macrophages.

Defense Mechanisms Against Hematogenous (Blood-Borne) Injury

Lungs are also susceptible to hematogenously borne microbes, toxins, or emboli. The hepatic (Kupffer cells) and splenic macrophages are the primary phagocytic cells responsible for removing circulating bacteria and other particles from the blood of dogs, some rodents, and human beings. In contrast, the cell responsible for the removal of circulating particles, bacteria, and endotoxin from the blood of ruminants, cats, pigs, and horses is mainly the pulmonary intravascular macrophage, a distinct population of phagocytes normally residing within the pulmonary capillaries (see Fig. 9-7). In pigs, 16% of the pulmonary capillary surface is lined by pulmonary intravascular macrophages. In ruminants, 95% of intravenously injected tracer particles or bacteria are rapidly phagocytosed by these intravascular macrophages. Studies have shown that an abnormally reduced number of Kupffer cells in diseased liver results in a compensatory increase in pulmonary intravascular macrophages, even in animal species in which these phagocytic cells are normally absent from the lung. In some abnormal conditions, such as sepsis,

Table 9-4 Defense Mechanisms Provided by Some Cells and Secretory Products Present in the Respiratory System

Cells/Secretory Products	Action
Alveolar macrophage	Phagocytosis, main line of defense against inhaled particles and microbial pathogens in the alveoli
Intravascular macrophage	Phagocytosis, removal of particles, endotoxin, and microbial pathogens in the circulation
Ciliated cells	Expel mucus and inhaled particles and microbial pathogens by ciliary action
Club (Clara) cells	Detoxification of xenobiotics (mixed function oxidases) and protective secretions against oxidative stress and inflammation; production of surfactant
Mucus	Physical barrier; traps inhaled particles and microbial pathogens and neutralizes soluble gases
Surfactant	Protects alveolar walls and enhances phagocytosis
Lysozyme	Antimicrobial enzyme
Transferrin and lactoferrin	Inhibition and suppression of bacterial growth
α_1-Antitrypsin	Protects against the noxious effects of proteolytic enzymes released by phagocytic cells; also inhibits inflammation
Interferon	Antiviral agent and modulator of the immune and inflammatory responses
Interleukins	Chemotaxis, upregulation of adhesion molecules
Antibodies	Prevent microbe attachment to cell membranes, opsonization
Complement	Chemotaxis; enhances phagocytosis
Antioxidants*	Prevent injury caused by superoxide anion, hydrogen peroxide, and free radicals (ROS) generated during phagocytosis, inflammation, or by inhalation of oxidant gases (ozone, nitrogen dioxide [NO_2], sulfur dioxide [SO_2])

*Superoxide dismutase, catalase, glutathione peroxidase, and oxidant free radical scavengers (tocopherol and ascorbic acid).

excessive release of cytokines by pulmonary intravascular macrophages may result in acute lung injury.

Defense Mechanisms Against Oxidants and Free Radicals

Existing in an oxygen-rich environment and being the site of numerous metabolic reactions, the lungs also require an efficient defense mechanism against oxidant-induced cellular damage (oxidative stress). This form of damage is caused by inhaled oxidant gases (e.g., nitrogen dioxide, ozone, sulfur dioxide, or tobacco smoke), by xenobiotic toxic metabolites produced locally, by toxins reaching the lungs via the bloodstream (e.g., 3-methylindole and paraquat), or by free radicals (reactive oxygen species) released by phagocytic cells during inflammation. Free radicals and reactive oxygen species (ROS) not only induce extensive pulmonary injury but also impair the defense and repair mechanisms in the lung. Oxygen and free radical scavengers, such as catalase, superoxide dismutase, ubiquinone, and vitamins E and C, are largely responsible for protecting pulmonary cells against peroxidation. These scavengers are present in alveolar and bronchiolar epithelial cells and in the extracellular spaces of the pulmonary interstitium.

In summary, the defense mechanisms are so effective in trapping, destroying, and removing bacteria that, under normal conditions, animals can be exposed to aerosols containing massive numbers of bacteria without any ill effects. If defense mechanisms are impaired, inhaled bacteria colonize and multiply in bronchi, bronchioles, and alveoli, and they produce infection, which can result in fatal pneumonia. Similarly, when blood-borne pathogens, inhaled toxicants, or free radicals overwhelm the protective defense mechanisms, cells of the respiratory system are likely to be injured, often causing serious respiratory diseases.

Impairment of Defense Mechanisms in the Respiratory System

For many years, factors such as viral infections, toxic gases, stress, and pulmonary edema have been implicated in predisposing human beings and animals to secondary bacterial pneumonia. There are many pathways by which the defense mechanisms can be impaired; only those relevant to veterinary species are discussed.

Viral Infections

Viral agents are notorious in predisposing human beings and animals to secondary bacterial pneumonias by what is known as viral-bacterial synergism. A good example of the synergistic effect of combined virus-bacterial infections is documented from epidemics of human beings with influenza virus in which the mortality rate has been significantly increased from secondary bacterial pneumonia. The most common viruses incriminated in predisposing animals to secondary bacterial pneumonia include influenza virus in pigs and horses; bovine herpesvirus 1 (BoHV-1), bovine parainfluenza virus 3 (BPIV-3), and bovine respiratory syncytial virus (BRSV) in cattle; canine distemper virus (CDV) in dogs; and felid herpesvirus 1 (FeHV-1) and feline calicivirus (FCV) in cats. The mechanism of the synergistic effect of viral-bacterial infections was previously believed to be the destruction of the mucociliary blanket and a concurrent reduction of mucociliary clearance, but in experimental studies, viral infections did not significantly reduce the physical removal of particles or bacteria out of the lungs. Now, it is known that 5 to 7 days after a viral infection, the phagocytic function of pulmonary alveolar macrophages and, to a lesser extent, the mucociliary clearance are notably impaired (see Fig. 9-8). Other mechanisms by which viruses impair defense mechanisms are multiple and remain poorly understood (Box 9-1). Immunization against viral infections in many cases prevents or reduces the synergistic effect of viruses and thus the incidence of secondary bacterial pneumonia.

Toxic Gases

Certain gases also impair respiratory defense mechanisms, rendering animals more susceptible to secondary bacterial infections. For instance, hydrogen sulfide and ammonia, frequently encountered on farms, especially in buildings with poor ventilation, can impair pulmonary defense mechanisms and increase susceptibility to bacterial pneumonia. The effects of environmental pollutants on the defense mechanisms of human beings and animals living in crowded and polluted cities remain to be determined.

Box 9-1 Postulated Mechanisms by Which Viruses and Mycoplasma May Impair the Defense Mechanisms of the Respiratory Tract

- Reduced mucociliary clearance
- Injured epithelium enhances attachment for bacteria
- Enhanced bacterial attachment predisposes to colonization
- Decreased mucociliary clearance prolongs resident time of bacteria favoring colonization
- Injured epithelium prevents mucociliary clearance and physical removal of bacteria
- Lack of secretory products facilitates further cell injury
- Break down the antimicrobial barrier in mucus and cells (β-defensins and anionic peptides)
- Ciliostasis caused by inflammation or by some pathogenic organisms (mycoplasmas)
- Dysfunction of pulmonary alveolar macrophages and lymphocytes
- Consolidation of lung causes hypoxia resulting in decreased phagocytosis
- Infected macrophages fail to release chemotactic factors for other cells
- Infected macrophages fail to attach and ingest bacteria
- Lysosomes become disoriented and fail to fuse with phagosome-containing bacteria
- Intracellular killing or degradation is decreased because of biochemical dysfunction
- Altered cytokines and secretory products impair bacterial phagocytosis
- Viral-induced apoptosis of alveolar macrophages
- Altered CD4 and CD8 lymphocytes
- Toll-like receptors (TLRs) in virus-infected macrophages increase proinflammatory response to bacteria

Immunodeficiencies

Immunodeficiency disorders, whether acquired or congenital, are often associated with increased susceptibility to viral, bacterial, and protozoal pneumonias. For example, human beings with acquired immunodeficiency syndrome (AIDS) are notably susceptible to pneumonia caused by proliferation of *Pneumocystis* (*carinii*) *jirovecii*. A similar ubiquitous organism, which under normal circumstances is not pathogenic, is also found in the pneumonic lungs of immunosuppressed pigs, foals, dogs, and rodents. Pigs infected with the porcine reproductive and respiratory syndrome (PRRS) virus frequently develop *Pneumocystis carinii* infection (Fig. 9-20). Arabian foals born with combined immunodeficiency disease easily succumb to infectious diseases, particularly adenoviral pneumonia. Combined infections with two respiratory viruses, such as canine distemper virus (CDV) and canine adenovirus 2 (CAV-2), are sporadically reported in immunosuppressed puppies. Also, large doses of chemotherapeutic agents, such as steroids and alkylating agents, cause immunosuppression in dogs, cats, and other animals, increasing susceptibility to secondary viral and bacterial infections.

Other Conditions that Impair Defense Mechanisms

Stress, uremia, endotoxemia, dehydration, starvation, hypoxia, acidosis, pulmonary edema, anesthesia, and ciliary dyskinesia are only some of the many conditions that have been implicated in impairing respiratory defense mechanisms and consequently predisposing animals to develop secondary bacterial pneumonia. The mechanisms by which each of these factors suppresses pulmonary defenses are diverse and sometimes not well understood. For example, hypoxia and pulmonary edema decrease phagocytic function of pulmonary alveolar macrophages and alter the production of surfactant by type II pneumonocytes. Dehydration is thought to increase the viscosity of mucus, reducing or stopping mucociliary movement. Anesthesia induces ciliostasis with concurrent loss of mucociliary function. Ciliary dyskinesia, an inherited defect in cilia, causes abnormal mucus transport. Starvation, hypothermia, and stress can reduce humoral and cellular immune responses.

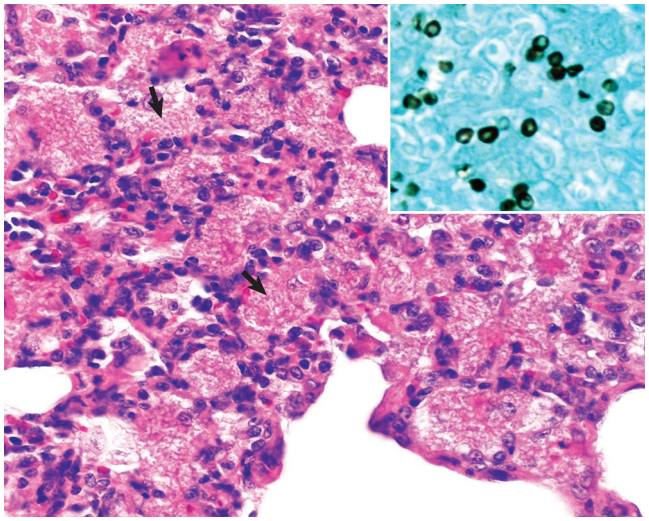


Figure 9-20 Pneumocystosis *(Pneumocystis carinii)*, Lung, Pig. Alveoli are filled with a foamy eosinophilic proteinaceous material in which numerous punctiform organisms *(arrows)* are present. H&E stain. *Inset,* Silver-stained oval bodies typical of *Pneumocystis carinii*. Pneumocystosis is generally a microscopic diagnosis because this condition does not cause remarkable gross lesions. Gomori's methenamine silver stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Disorders of the Conducting System

Disorders of the Nasal Cavity and Paranasal Sinuses in Domestic Animals

Anomalies[2]

Localized congenital anomalies of the nasal cavity are rare in domestic animals and are often merely part of a more extensive craniofacial deformity (e.g., cyclops) or a component of generalized malformation (e.g., chondrodysplasia). Congenital anomalies involving the nasal cavity and sinuses, such as choanal atresia (lack of communication between the nasal cavity and pharynx), some types of chondrodysplasia, and osteopetrosis, are incompatible with life. Examples of nonfatal congenital anomalies include cystic nasal conchae, deviation of the nasal septum, cleft upper lip (harelip and cheiloschisis), hypoplastic turbinates, and cleft palate (palatoschisis) (see Fig. 7-32). Bronchoaspiration and aspiration pneumonia are common sequelae to cleft palate. Nasal and paranasal sinus cysts are slowly growing and expansive lesions that mimic neoplasia and cause severe cranial deformation in horses. As in other organs or systems, it is extremely difficult to determine the actual cause (genetic vs. congenital) of anomalies based on pathologic evaluation.

Metabolic Disturbances

Metabolic disturbances affecting the nasal cavity and sinuses are rare in domestic animals.

[2]See E-Box 1-1 for potential, suspected, or known genetic disorders.

Nasal Amyloidosis. Amyloidosis, the deposition of amyloid protein (fibrils with a β-pleated configuration) in various tissues, has been sporadically reported as a localized lesion in the nasal cavity of horses and human beings (see Nasal Amyloidosis, in Disorders of Horses).

Circulatory Disturbances

Congestion and Hyperemia. The nasal mucosa is well vascularized and is capable of rather dramatic variation in blood flow, whether passively as a result of interference with venous return (congestion) or actively because of vasodilation (hyperemia). Congestion of the mucosal vessels is a nonspecific lesion commonly found at necropsy and presumably associated with the circulatory failure preceding death (e.g., heart failure, bloat in ruminants in which the increased intraabdominal pressure causes increased intrathoracic pressure impeding the venous return from the head and neck). Hyperemia of the nasal mucosa is seen in early stages of inflammation, whether caused by irritation (e.g., ammonia and regurgitated feed), viral infections, secondary bacterial infections, toxemia, allergy, or trauma.

Hemorrhage. *Epistaxis* is the clinical term used to denote blood flow from the nose (nosebleed) regardless of whether the blood originates from the nasal mucosa or from deep in the lungs, such as in horses with "exercise-induced pulmonary hemorrhage." Unlike blood in the digestive tract, where the approximate anatomic location of the bleeding can be estimated by the color the blood imparts to fecal material, blood in the respiratory tract is always red. This fact is due to the rapid transport of blood out of the respiratory tract by the mucociliary blanket and during breathing. Hemorrhages into the nasal cavity can be the result of local trauma, can originate from erosions of submucosal vessels by inflammation (e.g., guttural pouch mycosis), or can be caused by neoplasms. Hemoptysis refers to the presence of blood in sputum or saliva (coughing or spitting blood) and is most commonly the result of pneumonia, lung abscesses, ulcerative bronchitis, pulmonary thromboembolisms or hemorrhage, and pulmonary neoplasia.

Inflammation (Rhinitis and Sinusitis)

Inflammation of the nasal mucosa is called *rhinitis*, and inflammation of the sinuses is called *sinusitis*. These conditions usually occur together, although mild sinusitis can be undetected. Clinically, rhinosinusitis is characterized by nasal discharge.

Rhinitis. The occurrence of infectious rhinitis presupposes an upset in the balance of the normal microbial flora of the nasal cavity. Innocuous bacteria present normally protect the host through a process called *competitive exclusion*, whereby potential pathogens are kept at a harmless level. Disruption of this protective mechanism can be caused by respiratory viruses, pathogenic bacteria, fungi, irritant gases, environmental changes, immunosuppression, local trauma, stress, or prolonged antibacterial therapy.

Inflammatory processes in the nasal cavity are not life-threatening and usually resolve completely. However, some adverse sequelae in cases of infectious rhinitis include bronchoaspiration of exudate leading to bronchopneumonia. Chronic rhinitis often leads to destruction of the nasal conchae (turbinates), deviation of the septum, and, eventually, craniofacial deformation. Also, nasal inflammation may extend into the sinuses causing sinusitis; into facial bones causing osteomyelitis; through the cribriform plate causing meningitis; into the Eustachian tubes causing otitis media or guttural pouch empyema (eustachitis) in horses; and even into the inner ear causing otitis interna and vestibular syndrome (abnormal head tilt and abnormal gait), which in severe cases may lead to emaciation.

Based on the nature of exudate, rhinitis can be classified as serous, fibrinous, catarrhal, purulent, or granulomatous. These types of inflammatory reactions can progress from one to another in the course of the disease (i.e., serous to catarrhal to purulent), or in some instances exudates can be mixed, such as those seen in mucopurulent, fibrinohemorrhagic, or pyogranulomatous rhinitis. Microscopic examination of impression smears or nasal biopsy, and bacterial or fungal cultures are generally required in establishing the cause of inflammation. Common sequelae of rhinitis are hemorrhage, ulcers, and, in some cases, nasopharyngeal polyps (hyperplasia) arising from inflamed mucosa. Rhinitis also can be classified according to the age of the lesions as acute, subacute, or chronic; to the severity of the insult as mild, moderate, or severe; and to the etiologic agent as viral, allergic, bacterial, mycotic, parasitic, traumatic, or toxic.

Serous Rhinitis. Serous rhinitis is the mildest form of inflammation and is characterized by hyperemia and increased production of a clear fluid locally manufactured by serous glands present in the nasal submucosa. Serous rhinitis is of clinical interest only. It is caused by mild irritants or cold air, and it occurs during the early stages of viral infections, such as the common cold in human beings, upper respiratory tract infections in animals, or in mild allergic reactions.

Catarrhal Rhinitis. Catarrhal rhinitis is a slightly more severe process and has, in addition to serous secretions, a substantial increase in mucus production by hypersecretion of goblet cells and mucous glands. A mucous exudate is a thick, translucent, or slightly turbid viscous fluid, sometimes containing a few exfoliated cells, leukocytes, and cellular debris. In chronic cases, catarrhal rhinitis is characterized microscopically by notable hyperplasia of goblet cells. As the inflammation becomes more severe, the mucus is infiltrated with neutrophils, giving the exudate a cloudy appearance. This exudate is referred to as *mucopurulent*.

Purulent (Suppurative) Rhinitis. Purulent (suppurative) rhinitis is characterized by a neutrophilic exudate, which occurs when the nasal mucosa suffers a more severe injury that generally is accompanied by mucosal necrosis and secondary bacterial infection. Cytokines, leukotrienes, complement activation, and bacterial products cause exudation of leukocytes, especially neutrophils, which mix with nasal secretions, including mucus. Grossly, the exudate in suppurative rhinitis is thick and opaque, but it can vary from white to green to brown, depending on the types of bacteria and type of leukocytes (neutrophils or eosinophils) present in the exudate (Fig. 9-21). In severe cases, the nasal passages are completely blocked by the exudate. Microscopically, neutrophils can be seen in the submucosa and mucosa and form plaques of exudate on the mucosal surface. Neutrophils are commonly found marginated in vessels, in the lamina propria, and in between epithelial cells in their migration to the surface of the mucosa.

Fibrinous Rhinitis. Fibrinous rhinitis is a reaction that occurs when nasal injury causes a severe increase in vascular permeability, resulting in abundant exudation of plasma fibrinogen, which coagulates into fibrin. Grossly, fibrin appears as a yellow, tan, or gray rubbery mat on nasal mucosa. Fibrin accumulates on the surface and forms a distinct film of exudate sometimes referred to as *pseudomembrane* (Fig. 9-22). If this fibrinous exudate can be removed, leaving an intact underlying mucosa, it is termed a *croupous* or *pseudodiphtheritic rhinitis*. Conversely, if the pseudomembrane is difficult to remove and leaves an ulcerated mucosa, it is referred to as *diphtheritic* or *fibrinonecrotic rhinitis*. The term *diphtheritic* was derived from human diphtheria, which causes a severe and destructive inflammatory process of the nasal, tonsillar, pharyngeal, and laryngeal mucosa.

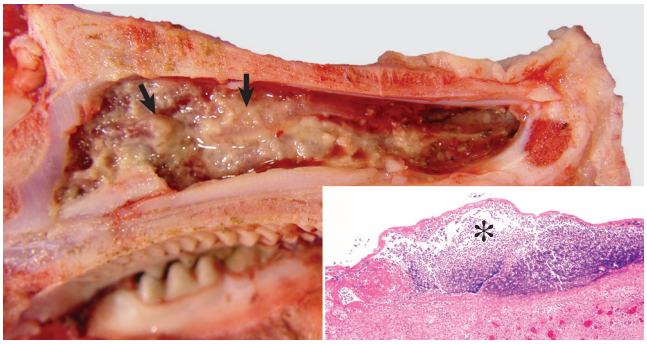


Figure 9-21 Suppurative Rhinitis, Midsagittal Section of Head, Pig. The nasal septum has been removed to expose nasal conchae. The nasal mucosa is hyperemic and covered by yellow-white purulent exudate *(arrows)*. *Inset,* Histological section showing submucosal congestion and edema and also large aggregates of neutrophils on the superficial mucosa *(asterisk)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

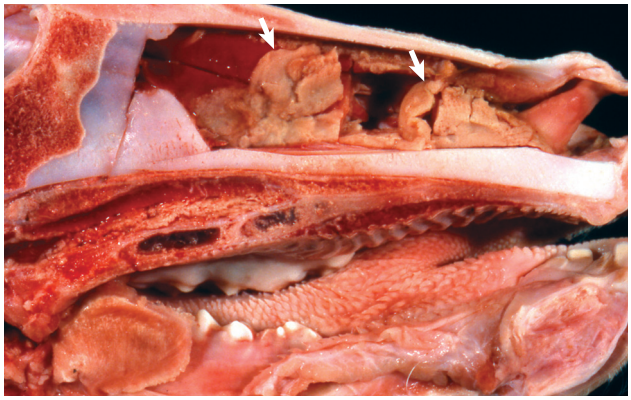


Figure 9-22 Fibrinous Rhinitis, Midsagittal Section of Head, Calf. Infectious bovine rhinotracheitis (IBR; bovine herpesvirus 1). The nasal septum has been removed to expose nasal conchae. The nasal mucosa is covered by diphtheritic yellow membranes consisting of fibrinonecrotic exudate *(arrows)*. Removal of these fibrinous membranes reveals focal ulcers in the underlying mucosa. (Courtesy Dr. Scott McBurney, Atlantic Veterinary College.)

Microscopically, the lesions include a perivascular edema with fibrin, a few neutrophils infiltrating the mucosa, and superficial plaques of exudate consisting of fibrin strands mixed with leukocytes and cellular debris covering a necrotic and ulcerated epithelium. Fungal infections, such as aspergillosis, can cause a severe fibrinonecrotizing rhinitis.

Granulomatous Rhinitis. Granulomatous rhinitis is a reaction in the nasal mucosa and submucosa that is characterized by infiltration of numerous activated macrophages mixed with a few lymphocytes and plasma cells (Figs. 9-23 and 9-24). In some cases, chronic inflammation leads to the formation of polypoid nodules that in severe cases are large enough to cause obstruction of the nasal passages (Fig. 9-25). Granulomatous rhinitis is generally associated with chronic allergic inflammation or infection with specific organisms, such as fungi (see Fig. 9-24), tuberculosis, systemic mycosis (see section on Granulomatous Pneumonia), and rhinosporidiosis (Fig. 9-26; also see Fig. 9-25). In some cases, the cause of granulomatous rhinitis cannot be determined.

Sinusitis. Sinusitis occurs sporadically in domestic animals and is frequently combined with rhinitis (rhinosinusitis), or it occurs as

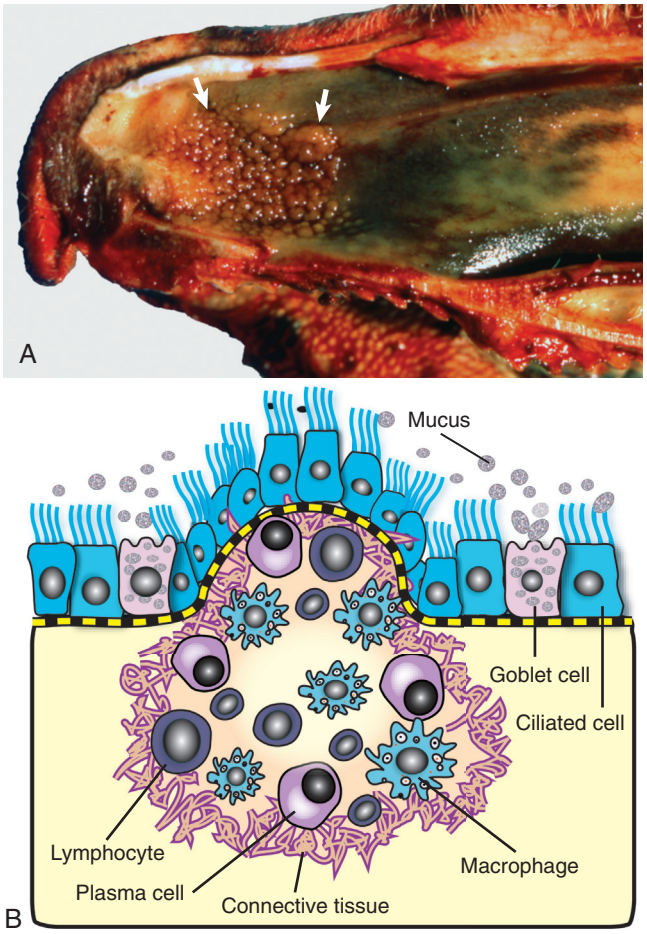


Figure 9-23 Granulomatous Rhinitis, Midsagittal Section of Head, Cow. A, Note multiple and often confluent granulomas *(arrows)* arising from the nasal mucosa. **B,** Schematic representation of a nasal granuloma showing the outer wall of the granuloma composed of connective tissue enclosing the center, which has been infiltrated with lymphocytes, plasma cells, and macrophages. (**A** courtesy Ontario Veterinary College. **B** courtesy of Dr. A. López, Atlantic Veterinary College.)

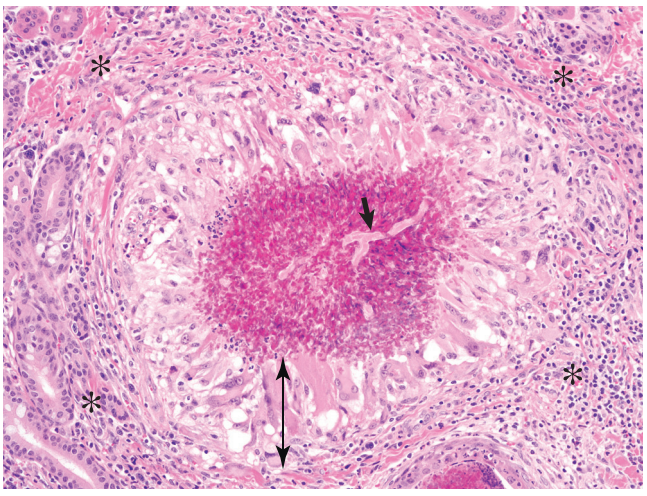


Figure 9-24 Nasal Mucosa, Granulomatous Rhinitis, Mycotic Infection, Ewe. The granuloma is composed of three distinct layers: an outer layer of fibroblasts, lymphocytes, and plasma cells *(asterisks)*; a middle thick layer of epithelioid macrophages *(double-headed arrow)*; and a necrotic center of cellular debris containing a fungal hypha *(arrow)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

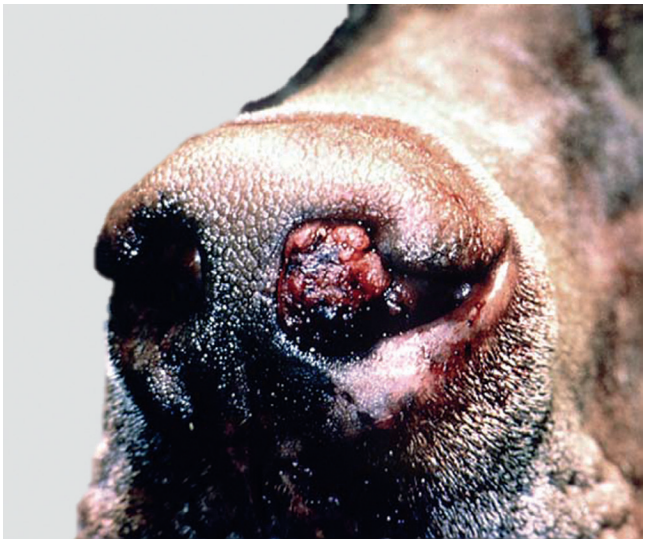


Figure 9-25 Granulomatous Rhinitis (*Rhinosporidium seeberi*), Nasal Cavity and Nostril, Dog. A polypoid granulomatous mass fills the rostral part of the left nasal cavity. (Courtesy Dr. C. Bridges, College of Veterinary Medicine, Texas A&M University, and Dr. J.M. King, College of Veterinary Medicine, Cornell University.)

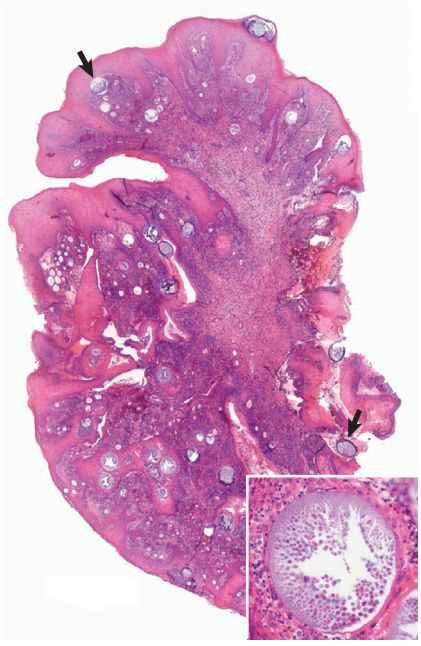


Figure 9-26 Exophytic Granulomatous Mass Surgically Removed From the Nasal Mucosa (*Rhinosporidium seeberi*), Mule. Large pedunculated mass of granulomatous tissue containing numerous sporangia *(arrows)*. *Inset,* Sporangium. Note a large encapsulated cyst filled with a myriad of *Rhinosporidium seeberi* endospores. H&E stain. (From Berrocal A, López A: *Can Vet J* 48:305-306, 2007.)

a sequela to penetrating or septic wounds of the nasal, frontal, maxillary, or palatine bones; improper dehorning in young cattle, which exposes the frontal sinus; or maxillary tooth infection in horses and dogs (maxillary sinus). Based on the type of exudate, sinusitis is classified as serous, catarrhal, fibrinous (rare), purulent, or granulomatous. Paranasal sinuses have poor drainage; therefore exudate tends to accumulate, causing mucocele (accumulation of mucus) or empyema (accumulation of pus) (Fig. 9-27). Chronic sinusitis may

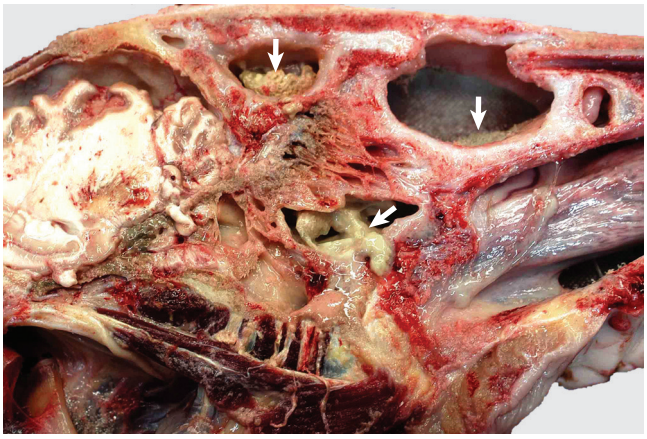


Figure 9-27 Fibrinosuppurative Sinusitis, Midsagittal Section of Head, Donkey. Note that the paranasal sinuses are filled with fibrinopurulent exudate *(arrows)*. (Courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México.)

extend into the adjacent bone (osteomyelitis) or through the ethmoidal conchae into the meninges and brain (meningitis and encephalitis).

Species-Specific Diseases of the Nasal Cavity and Paranasal Sinuses

Disorders of Horses

Metabolic Disturbances

Nasal Amyloidosis. Amyloidosis, the deposition of amyloid protein (fibrils with a β-pleated configuration) in various tissues, has been sporadically reported as a localized lesion in the nasal cavity of horses. Unlike amyloidoses in other organs of domestic animals where amyloid is generally of the reactive type (amyloid AA), equine nasal amyloidosis appears to be of the immunocytic type (amyloid AL). Affected horses with large amyloid masses have difficulty breathing because of nasal obstruction and may exhibit epistaxis and reduced athletic performance; on clinical examination, large, firm nodules resembling neoplasms (amyloidoma) can be observed in the alar folds, rostral nasal septum, and floor of nasal cavity. Microscopic lesions are similar to those seen in other organs and consist of a deposition of hyaline amyloid material in nasal mucosa that is confirmed by a histochemical stain, such as Congo red.

Circulatory Disturbances

Progressive Ethmoidal Hematoma. Progressive ethmoidal hematoma (PEH) is important in older horses and is characterized clinically by chronic, progressive, often unilateral nasal bleeding. Grossly or endoscopically, an ethmoidal hematoma appears as a single, soft, tumor-like, pedunculated, expansive, dark red mass arising from the mucosa of the ethmoidal conchae (Fig. 9-28). Microscopic examination reveals a capsule lined by epithelium and hemorrhagic stromal tissue infiltrated with abundant macrophages, most of which are siderophages.

Viral Infections. Viruses, such as equine viral rhinopneumonitis virus, influenza virus, adenovirus, and equine picornavirus, cause mild and generally transient respiratory infections in horses. The route of infection for these respiratory viruses is typically aerogenous. All of these infections are indistinguishable clinically; signs consist mainly of malaise, fever, coughing, conjunctivitis, and nasal

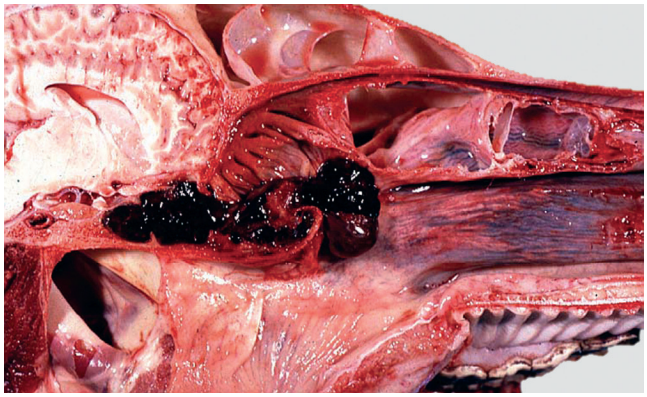


Figure 9-28 Ethmoidal Hematoma, Midsagittal Section of Head, Horse. A large amount of dark-red hemorrhage *(left center of image)* overlying the ethmoid conchae conceals an underlying hematoma in these conchae. (Courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University.)

discharge varying from serous to purulent. Viral respiratory infections are common medical problems in adult horses.

Equine Viral Rhinopneumonitis. Equine viral rhinopneumonitis (EVR) is caused by two ubiquitous equine herpesviruses (EHV-1 and EHV-4) and may be manifested as a mild respiratory disease in weanling foals and young racehorses, as a neurologic disease (myeloencephalopathy), or as abortion in mares. The portal of entry for the respiratory form is typically aerogenous, and the disease is generally transient; thus the primary viral-induced lesions in the nasal mucosa and lungs are rarely seen at necropsy unless complicated by secondary bacterial rhinitis, pharyngitis, or bronchopneumonia. Studies with polymerase chain reaction (PCR) techniques have demonstrated that, like other herpesviruses, EHV-1 and EHV-4 persist in the trigeminal ganglia for long periods of time (latency). Reactivation because of stress or immunosuppression and subsequent shedding of the virus are the typical source of infection for susceptible animals on the farm.

Equine Influenza. Equine influenza is a common, highly contagious, and self-limiting upper respiratory infection of horses caused by aerogenous exposure to type A strains of influenza virus (H7N7 [A/equi-1] and H3N8 [A/equi-2]). Equine influenza has high morbidity (outbreaks) but low mortality, and it is clinically characterized by fever, conjunctivitis, and serous nasal discharge. It occurs mainly in 2- to 3-year-old horses at the racetrack. As with human influenza, equine influenza is usually a mild disease, but occasionally it can cause severe bronchointerstitial pneumonia with pulmonary edema. In some horses, impaired defense mechanisms caused by the viral infection are complicated by a secondary bacterial bronchopneumonia caused by opportunistic organisms (*Streptococcus zooepidemicus*, *Staphylococcus aureus*, or *Bacteroides* sp.) found in the normal flora of the upper respiratory tract. Uncomplicated cases of equine influenza are rarely seen in the postmortem room. Equine influenza virus (H3N8) recently did an equine to canine "host-jump" causing extensive outbreaks of respiratory disease in dogs (see Pneumonias of Dogs).

Other Equine Respiratory Viruses. Equine picornavirus, adenovirus, and parainfluenza virus produce mild and transient upper respiratory infections (nasopharynx and trachea) in horses, unless complicated by secondary pathogens. In addition to reduced athletic performance, infected horses may have a temporary suppression of cell-mediated immunity leading to opportunistic infections such as *Pneumocystis carinii* pneumonia. Fatal adenoviral infections with severe pneumonia or enteritis occur commonly in immunocompromised horses, particularly in Arabian foals with inherited combined immunodeficiency disease.

Bacterial Infections. Strangles, glanders, and melioidosis of horses are all systemic bacterial diseases that cause purulent rhinitis and suppuration in various organs. These diseases are grouped as upper respiratory diseases because nasal discharge is often the most notable clinical sign.

Strangles. Strangles is an infectious and highly contagious disease of Equidae that is caused by *Streptococcus equi* ssp. *equi* (*Streptococcus equi*). It is characterized by suppurative rhinitis and lymphadenitis (mandibular and retropharyngeal lymph nodes) with occasional hematogenous dissemination to internal organs. Unlike *Streptococcus equi* ssp. *zooepidemicus* (*Streptococcus zooepidemicus*) and *Streptococcus dysgalactiae* ssp. *equisimilis* (*Streptococcus equisimilis*), *Streptococcus equi* is not part of the normal nasal flora. Infection occurs when susceptible horses come into contact with feed, exudate, or air droplets containing the bacterium. After penetrating through the nasopharyngeal mucosa, *Streptococcus equi* drains to the regional lymph nodes—mandibular and retropharyngeal lymph nodes—via lymphatic vessels. The gross lesions in horses with strangles (mucopurulent rhinitis) correlate with clinical findings and consist of copious amounts of mucopurulent exudate in the nasal passages with notable hyperemia of the nasal mucosa. Affected lymph nodes are enlarged and may contain abscesses filled with thick purulent exudate (purulent lymphadenitis). The term *bastard strangles* is used in cases in which hematogenous dissemination of *Streptococcus equi* results in metastatic abscesses in such organs as the lungs, liver, spleen, kidneys, or brain or in the joints. This form of strangles is often fatal.

Common sequelae to strangles include bronchopneumonia caused by aspiration of nasopharyngeal exudate; laryngeal hemiplegia ("roaring"), resulting from compression of the recurrent laryngeal nerves by enlarged retropharyngeal lymph nodes; facial paralysis and Horner syndrome caused by compression of sympathetic nerves that run dorsal to the medial retropharyngeal lymph node; and purpura hemorrhagica as a result of vasculitis caused by deposition of *Streptococcus equi* antigen-antibody complexes in arterioles, venules, and capillaries of the skin and mucosal membranes. In severe cases, nasal infection extends directly into the paranasal sinuses or to the guttural pouches via the Eustachian tubes, causing inflammation and accumulation of pus (guttural pouch empyema). Rupture of abscesses in the mandibular and retropharyngeal lymph nodes leads to suppurative inflammation of adjacent subcutaneous tissue (cellulitis), and in severe cases the exudate escapes through cutaneous fistulas.

Strangles can affect horses of all ages, but it is most commonly seen in foals and young horses. It is clinically characterized by cough, nasal discharge, conjunctivitis, and painful swelling of regional lymph nodes. Some horses become carriers and a source of infection to other horses.

Glanders. Glanders is an infectious World Organization for Animal Health (OIE)-notifiable disease of Equidae caused by *Burkholderia mallei* (*Pseudomonas mallei*) that can be transmitted to carnivores by consumption of infected horsemeat. Human beings are also susceptible, and untreated infection is often fatal. This Gram-negative bacterium has been listed as a potential agent for biologic warfare and bioterrorism. In the past, *Burkholderia mallei* was found throughout the world, but today, glanders has been eradicated from most countries, except for some areas in North Africa, Asia, and eastern Europe. There also have been sporadic outbreaks reported in Brazil. The pathogenesis of glanders is not fully understood. Results from experimental infections suggest that infection occurs

via the ingestion of contaminated feed and water and, very rarely, via inhalation of infectious droplets. The portals of entry are presumed to be the oropharynx or intestine, in which bacteria penetrate the mucosa and spread via lymph vessels to regional lymph nodes, then to the bloodstream, and thus hematogenously to the internal organs, particularly the lungs.

Lesions in the nasal cavity start as pyogranulomatous nodules in the submucosa; these lesions subsequently ulcerate, releasing copious amounts of *Burkholderia mallei*–containing exudate into the nasal cavity (see Fig. 4-25, *A*). Finally, ulcerative lesions in conchal mucosa heal and are replaced by typical stellate (star-shaped), fibrous scars. In some cases, the lungs also contain numerous gray, hard, small (2 to 10 mm), miliary nodules (resembling millet seeds) randomly distributed in one or more pulmonary lobes because of the hematogenous route. Microscopically, these nodules are typical chronic granulomas composed of a necrotic center, with or without calcification, surrounded by a layer of macrophages enclosed by a thick band of connective tissue infiltrated with macrophages, fewer giant cells, lymphocytes, and plasma cells. Cutaneous lesions, often referred to as equine farcy, are the result of severe suppurative lymphangitis characterized by nodular thickening of extended segments of lymph vessels in the subcutaneous tissue of the legs and ventral abdomen (see Fig. 4-25, *C*). Eventually, affected lymph vessels rupture and release large amounts of purulent exudate through sinuses to the surface of the skin.

Melioidosis (Pseudoglanders). Melioidosis (pseudoglanders) is an important, life-threatening disease of human beings, horses, cattle, sheep, goats, pigs, dogs, cats, and rodents caused by *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*). This disease in horses is clinically and pathologically similar to glanders, hence the name *pseudoglanders*. In human beings, this infection can cause severe sepsis and septic shock and has also been considered to have potential for biologic welfare. Melioidosis is currently present in Southeast Asia and, to a much lesser extent, in northern Australia and some European countries where the causative organism is frequently found in rodents, feces, soil, and water. Ingestion of contaminated feed and water appears to be the main route of infection; direct transmission between infected animals and insect bites has also been postulated as a possible mechanism of infection. After gaining entrance to the animal, *Burkholderia pseudomallei* is disseminated by the bloodstream and causes suppuration and abscesses in most internal organs, such as nasal mucosa, joints, brain and spinal cord, lungs, liver, kidneys, spleen, and lymph nodes. The exudate is creamy or caseous and yellow to green. The pulmonary lesions in melioidosis are those of an embolic bacterial infection with the formation of pulmonary abscesses, which can become confluent. Focal adhesive pleuritis develops where abscesses rupture through the pleura and heal.

Parasitic Infections

Rhinosporidiosis. The protistan parasite, *Rhinosporidium seeberi*, causes nasal infection in human beings, horses, mules, cattle, dogs, and cats. Gross lesions vary from barely visible granulomas to large expansive polypoid nodules that may be mistaken as tumors. These granulomatous nodules are detected by direct observation when present in the nasal mucosa close to the nares or by rhinoscopy when located in the deep nasal cavity. The offending organism, *Rhinosporidium seeberi*, is readily visible in histologic preparations and in impression smears, appearing as a large (400 μm), oval sporangium containing thousands of endospores (see Fig. 9-26). *Rhinosporidium seeberi* was once considered a mycotic agent, but recent phylogenetic investigations suggest that it is an aquatic protistan parasite of the class Mesomycetozoea.

Disorders of Ruminants (Cattle, Sheep, and Goats)

Disorders of Cattle

Viral Infections

Infectious Bovine Rhinotracheitis. Infectious bovine rhinotracheitis (IBR), or "rednose," occurs worldwide and is a disease of great importance to the cattle industry because of the synergism of the IBR virus with *Mannheimia haemolytica* in producing pneumonia. The causative agent, bovine herpesvirus 1 (BoHV-1), has probably existed as a mild venereal disease in cattle in Europe since at least the mid-1800s, but the respiratory form was not reported until intensive management feedlot systems were first introduced in North America around the 1950s. Typically, the disease is manifested as a transient, acute, febrile illness, which results in inspiratory dyspnea caused by obstruction of the airways by exudate only in very severe cases. Other forms of BoHV-1 infection include ulcerative rumenitis; enteritis; multifocal hepatitis in neonatal calves; nonsuppurative meningoencephalitis; infertility; and in experimental infections, mastitis, mammillitis, and ovarian necrosis. Except for the encephalitic form, the type of disease caused by BoHV-1 depends more on the site of entry than the viral strain. Like other herpesviruses, BoHV-1 also can remain latent in nerve ganglia, with recrudescence after stress or immunosuppression. This virus also causes bovine abortion, systemic infections of calves, and genital infections such as infectious pustular vulvovaginitis (IPV) and infectious balanoposthitis (IBP).

The respiratory form of IBR is characterized by severe hyperemia and multifocal necrosis of nasal, pharyngeal, laryngeal, tracheal, and sometimes bronchial mucosa (Fig. 9-29 and see Fig. 9-22). As in other respiratory viral infections, IBR lesions are microscopically characterized by necrosis and exfoliation of ciliated cells followed by repair. Secondary bacterial infections of these areas of necrosis result in the formation of a thick layer of fibrinonecrotic material (diphtheritic) in the nasal, tracheal, and bronchial mucosa (see Fig. 9-22). Intranuclear inclusion bodies, commonly seen in herpesvirus infections, are rarely seen in field cases because inclusion bodies occur only during the early stages of the disease.

The most important sequela to IBR is bronchopneumonia, which is caused either by direct aspiration of exudate from airways or as a result of an impairment in pulmonary defense mechanisms, thus predisposing the animal to secondary bacterial infection, most frequently *Mannheimia haemolytica* (see pneumonic mannheimiosis discussion). Postmortem diagnosis of IBR is confirmed by isolation of the virus or its identification by immunohistochemistry or PCR in affected tissues.

Other Causes of Rhinitis. Nasal granulomas occur in cattle presumably as a result of repeated exposure to an unidentified inhaled antigen. Nasal granulomas (atopic rhinitis) are reported mainly in cattle in Australia, South Africa, and the United Kingdom, where affected cattle develop multiple, small, pink or red, polypoid nodules, starting in the nasal vestibule that in time extend into the caudal aspect of the nasal septum (see Fig. 9-23). These nodules are composed of fibrovascular tissue mixed with lymphocytes (granulation tissue) superficially lined by hyperplastic epithelium with abundant mast cells and eosinophils in the lamina propria (nasal eosinophilia). The microscopic features suggest that hypersensitivity type I (immediate), type III (immune complex), and type IV (delayed) may be involved in nasal granulomas of cattle. Bovine (idiopathic) nasal granuloma must be differentiated from nasal mycetomas, nasal rhinosporidiosis, and nasal schistosomiasis, which also cause the formation of nodules in the nasal mucosa of cattle. An eosinophilic material consistent with the Splendore-Hoeppli phenomenon is occasionally observed in bovine mycotic granulomas. This phenomenon seen in some mycotic or bacterial infections is microscopically

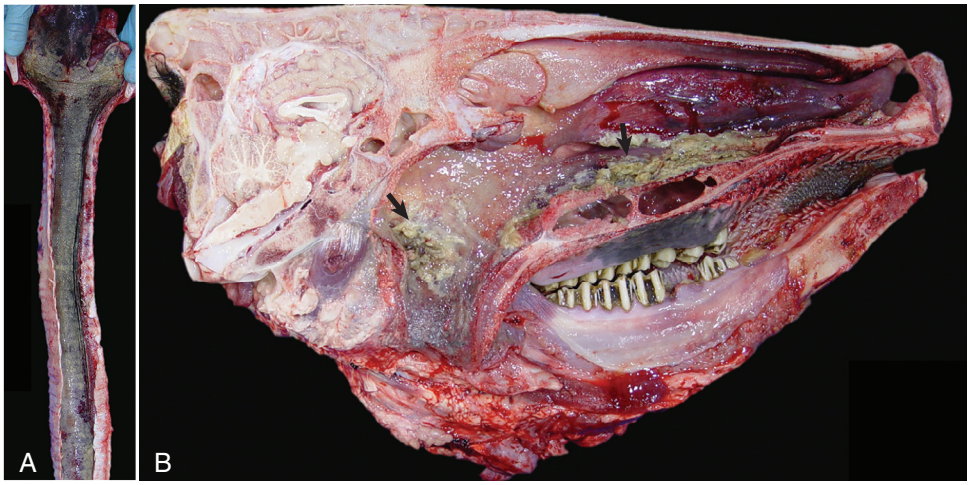


Figure 9-29 Fibrinonecrotic Rhinitis, Pharyngitis, Laryngitis, and Tracheitis, Infectious Bovine Rhinotracheitis (IBR; Bovine Herpesvirus 1), Longitudinal (Dorsal) Section of Larynx and Trachea (A) and Midsagittal Section of Head (B), Calf. Thick plaques of fibrinonecrotic exudate cover the nasal *(right arrow)*, pharyngeal *(left arrow)*, laryngeal, and tracheal mucosae. (Courtesy Dr. A. López, Atlantic Veterinary College.)

characterized by a deeply eosinophilic homogeneous material surrounded by bacteria or mycelia. It is thought to result from a localized antigen-antibody response in tissue.

Disorders of Sheep and Goats

Parasitic Infections

Oestrus ovis. *Oestrus ovis* (Diptera: Oestridae; nasal bot) is a brownish fly about the size of a honeybee that deposits its first-stage larvae in the nostrils of sheep in most areas of the world. Microscopic larvae mature into large bots (maggots), which spend most of their larval stages in nasal passages and sinuses, causing irritation, inflammation, and obstruction of airways. Mature larvae drop to the ground and pupate into flies. This type of parasitism in which living tissues are invaded by larvae of flies is known as *myiasis* (Fig. 9-30). Although *Oestrus ovis* is a nasal myiasis primarily of sheep, it sporadically affects goats, dogs, and sometimes human beings (shepherds). The presence of the larvae in nasal passages and sinuses causes chronic irritation and erosive mucopurulent rhinitis and sinusitis; bots of *Oestrus ovis* can be found easily if the head is cut to expose the nasal passages and paranasal sinuses. Rarely, larvae of *Oestrus ovis* penetrate the cranial vault through the ethmoidal plate, causing direct or secondary bacterial meningitis.

Other Causes of Rhinitis. Infectious rhinitis is only sporadically reported in goats, and most of these cases are caused by *Pasteurella multocida* or *Mannheimia haemolytica*. The lesions range from a mild serous to catarrhal or mucopurulent inflammation. Foreign body rhinitis caused by plant material is sporadically seen cattle, sheep, and goats (Fig. 9-31).

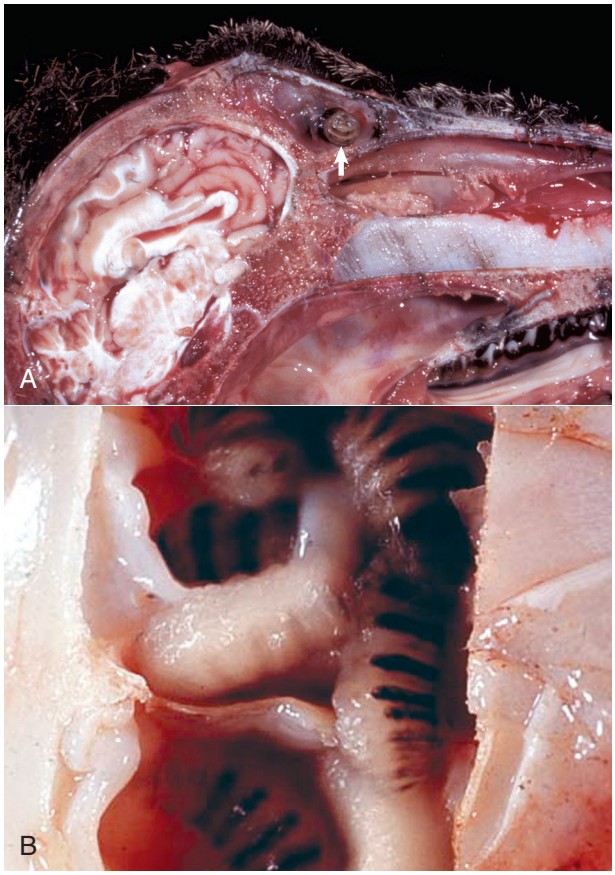


Figure 9-30 *Oestrus ovis*, Sheep. A, Frontal sinus. Note the parasitic (fly) larvae in the frontal sinus *(arrow)*. **B,** Nasal cavity. Higher magnification view of larvae of *Oestrus ovis* in a nasal cavity. (**A** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **B** courtesy Dr. M. Sierra and Dr. J. King, College of Veterinary Medicine, Cornell University.)

Disorders of Pigs

Viral Infections

Inclusion Body Rhinitis. Inclusion body rhinitis is a disease of young pigs with high morbidity and low mortality caused by a porcine cytomegalovirus (suid herpesvirus-2) and characterized by a mild rhinitis. This virus commonly infects the nasal epithelium of piglets younger than 5 weeks and causes a transient viremia. Because this disease is seldom fatal, lesions are seen only incidentally or in euthanized animals. In uncomplicated cases, the gross lesion is hyperemia of the nasal mucosa, but with secondary bacterial infections, mucopurulent exudate can be abundant. Microscopic lesions are typical and consist of a necrotizing, nonsuppurative rhinitis with giant, basophilic, intranuclear inclusion bodies in the nasal epithelium, particularly in the nasal glands (Fig. 9-32). Immunosuppressed piglets can develop a systemic cytomegalovirus infection characterized by necrosis of the liver, lungs, adrenal glands, and brain with intralesional inclusion bodies. Inclusion body rhinitis is clinically

Figure 9-31 Foreign Body Rhinitis, Midsagittal Section of Head, Nasal Cavity, Timothy Grass, Sheep. Locally extensive ulceration and inflammation of maxillary concha *(asterisk)*. Note a spikelet of Timothy grass (*Phleum pratense*) covered by mucopurulent exudate in the ventral meatus *(arrow)*. A fresh spikelet of Timothy grass is shown at the *top right*. (Courtesy Dr. A. López, Atlantic Veterinary College.)

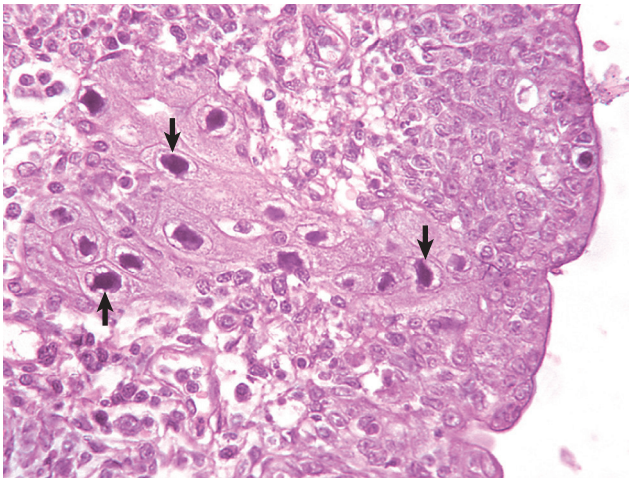


Figure 9-32 Inclusion Body Rhinitis Caused by Cytomegalovirus Infection, Nasal Conchae, 3-Week-Old Pig. Epithelial cells of mucosal glands contain large basophilic intranuclear inclusion bodies *(arrows)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

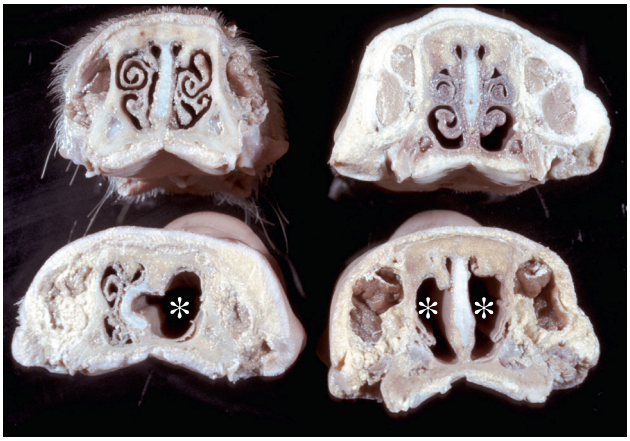


Figure 9-33 Atrophic Rhinitis, Transverse Sections of Nasal Passages and Sinuses, Caudal Surfaces, Level of the First or Second Premolar Teeth, Pigs. *Top left,* Normal nasal cavity showing complete conchae (turbinates) that fill most of the nasal cavity and form narrow air passages (meatuses). *Top right,* Mild, symmetric atrophy of nasal conchae. *Bottom left,* Severe, unilateral atrophy of the right ventral nasal concha *(asterisk)* with deviation of the nasal septum to the left and widening of the ventral meatus. *Bottom right,* Severe, bilateral atrophy with complete loss of nasal conchae and extensive widening of the meatuses *(asterisks)*. (Courtesy Dr. A. López, Atlantic Veterinary College.)

characterized by a mild and transient rhinitis, causing sneezing, nasal discharge, and excessive lacrimation.

Bacterial Infections

Atrophic Rhinitis. A common worldwide disease of pigs, atrophic rhinitis (progressive atrophic rhinitis) is characterized by inflammation and atrophy of nasal conchae (turbinates). In severe cases, atrophy of the conchae may cause a striking facial deformity in growing pigs because of deviation of the nasal septum and nasal bones. The etiopathogenesis of atrophic rhinitis is complex and has been a matter of controversy for many years. Pathogens historically associated with atrophic rhinitis include *Bordetella bronchiseptica*, *Pasteurella multocida*, *Haemophilus parasuis*, and viral infections such as porcine cytomegalovirus (inclusion body rhinitis). In addition, predisposing factors have included genetic makeup, environment, and nutritional deficiencies. The cause of atrophic rhinitis is currently believed to be a combined infection by specific strains of *Bordetella bronchiseptica* producing dermonecrotic toxin and toxigenic strains of *Pasteurella multocida*. The only lesion associated with infection with *Bordetella bronchiseptica* alone is a mild to moderate turbinate atrophy (nonprogressive atrophic rhinitis), but this bacterium actively promotes the colonization of the nasal cavity by *Pasteurella multocida*. The toxigenic strains of *Pasteurella multocida* produce potent cytotoxins that inhibit osteoblastic activity and promote osteoclastic reabsorption in nasal bones, particularly in the ventral nasal conchae, where abnormal bone remodeling results in progressive atrophy of conchae.

The degree of conchal atrophy in pigs with atrophic rhinitis varies considerably, and in most pigs, the severity of the lesions does not correspond to the severity of the clinical signs. The best diagnostic method of evaluating this disease at necropsy is to make a transverse section of the snout between the first and second premolar teeth. In normal pigs, conchae are symmetric and fill most of the cavity, leaving only narrow airspaces (meatuses) between coiled conchae. The normal nasal septum is straight and divides the cavity into two mirror-image cavities. In contrast, the septum in pigs with atrophic rhinitis is generally deviated and the conchae appear smaller and asymmetric (Fig. 9-33). Conchal atrophy causes dorsal and ventral meatuses to appear rather enlarged, and in the most advanced cases, the entire nasal conchae may be missing, leaving a large, empty space.

It may seem logical to assume that after loss of conchae in an obligate nasal breather, such as the pig, the filtration defense mechanism of the nasal cavity would be impaired, thus enhancing the chances of aerogenous infections in the lung. However, the relationship between atrophic rhinitis, pneumonia, and growth rates in pigs is still controversial.

Osteoclastic hyperplasia and osteopenia of the conchae are the key microscopic lesions in atrophic rhinitis. Depending on the stage of the disease, mucopurulent exudate may be found on the surface of the conchae. Hyperplastic or metaplastic changes can occur in the nasal epithelium and glands, and infiltrates of lymphoplasmacytic cells can be present in the lamina propria. In summary, atrophic rhinitis is an important disease in pigs worldwide; morphologic

diagnosis is simple, but additional understanding of the pathogenesis will be necessary before effective preventive measures can be established.

Atrophic rhinitis is clinically characterized by sneezing, coughing, and nasal discharge. Obstruction of the nasolacrimal duct is common and results in accumulation of dust and dried lacrimal secretions on the skin inferior to the medial canthus of the eye.

Disorders of Dogs

Viral Infections. Dogs have no specific viral infections affecting exclusively the nasal cavity or sinuses. Acute rhinitis and sinusitis occurs as part of the canine infectious respiratory disease (CIRD) group caused by several distinct viruses, such as canine distemper virus, CAV-1 and -2, canine parainfluenza virus, reovirus, and canine herpesvirus. The viral lesions in the respiratory tract are generally transient, but the effect of the virus on other tissues and cells can be fatal, as in distemper encephalitis in dogs.

Bacterial Infections. As in other species, secondary bacterial rhinitis, sinusitis, and pneumonia are possible sequelae of respiratory viral infections; *Bordetella bronchiseptica*, *Escherichia coli*, and *Pasteurella multocida* are the most common isolates in dogs with bacterial rhinitis.

Mycotic Infections. *Aspergillus* spp. and *Penicillium* spp. cause mycotic rhinitis and sinusitis in dogs (canine nasal aspergillosis) (Fig. 9-34). Nasal biopsies reveal extensive necrosis of the nasal epithelium and thick plaques of fibrinopurulent exudate mixed with many fungal hyphae. *Cryptococcus neoformans* and *Blastomyces dermatitides* infections of the nasal cavity occur sporadically in dogs (Fig. 9-35). Lesions are characterized by mucosal granulomas containing periodic acid–Schiff (PAS)-positive fungal organisms, and the infection is clinically characterized by mucopurulent nasal discharge.

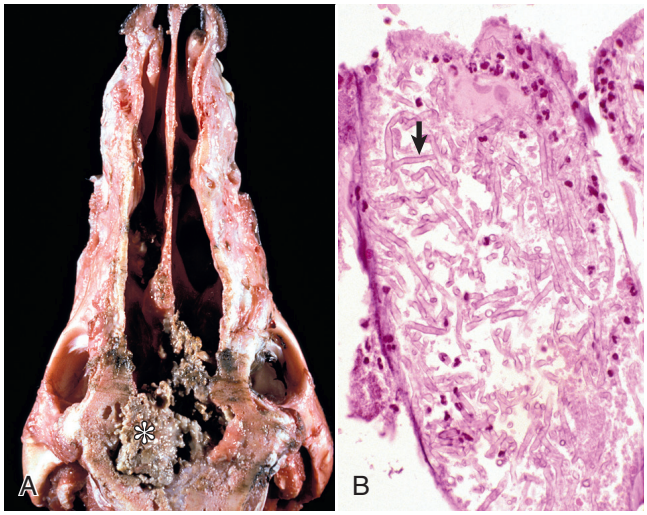


Figure 9-34 Granulomatous Rhinitis, Aspergillosis, Dorsal View of Nasal Cavities, Nasal and Frontal Bones Removed, Dog. A, The nasal conchae have been destroyed by chronic granulomatous inflammation. Mycotic exudate *(asterisk)* remaining in the caudal aspect of the nasal cavity is yellow-green and granular. **B,** Hyphae *(arrow)* of *Aspergillus* spp. were isolated from the granulomatous inflammatory exudate. Note the neutrophils at the periphery of the fungal mat. PAS stain. (**A** courtesy College of Veterinary Medicine, University of Illinois. **B** courtesy Dr. M.A. Wallig, College of Veterinary Medicine, University of Illinois.)

Parasitic Infections

Linguatula serrata. *Linguatula serrata* is a rare but highly specialized pentastomid parasite that shares some morphologic features with arthropods and annelids and causes infection when dogs consume uncooked ruminant meat containing infective larvae. It occurs primarily in carnivores, although sheep and goats may become aberrant hosts. Human beings can also acquire the infection by ingesting raw ovine or caprine meat. The adult parasite is found throughout the nasal passages and sometimes can reach the sinuses and middle ear by moving through the exudate in the Eustachian tubes. In common with other nasal parasites, *Linguatula serrata* acts as an irritant, causing sneezing, catarrhal inflammation, and epistaxis. The eggs of this parasite leave the host in the exudate, which is coughed up or swallowed and eliminated in the feces.

The nasal cavity and paranasal sinuses of dogs can occasionally be infested with other parasites, including mites (*Pneumonyssus caninum*) and *Rhinosporidium seeberi* (see Figs. 9-25 and 9-26).

Allergic Rhinitis. Allergic rhinitis (hay fever; nasolacrimal urticaria), which is so common in human beings sensitized and reexposed to inhaled pollens or allergens, has been reported only sporadically in dogs and cats. Hay fever in human beings and animals is a type I hypersensitivity reaction in which an IgE-mediated degranulation of mast cells results in an acute rhinitis and conjunctivitis. Microscopically, the nasal mucosa is edematous and infiltrated with numerous eosinophils, neutrophils, and some macrophages. Clinically, allergic rhinitis is characterized by profuse serous nasal discharge and lacrimation.

Other Causes of Rhinitis. A nonspecific (idiopathic) chronic lymphoplasmacytic rhinitis is occasionally seen in dogs. Immotile cilia syndrome (ciliary dyskinesia), a congenital disease, reduces mucociliary clearance and is an important factor in recurrent canine rhinosinusitis, bronchitis, bronchiectasis, and pneumonia.

Disorders of Cats

Viral Infections

Feline Viral Rhinotracheitis. Feline viral rhinotracheitis (FVR) is a common, worldwide respiratory disease of cats caused by felid herpesvirus 1 (FeHV-1). The disease causes an impairment of pulmonary defense mechanisms predisposing cats to secondary bacterial pneumonia or to a coinfection with feline calicivirus. The virus also can remain latent in ganglia. The vast majority of cats that recover from FVR become carriers and shed FeHV-1, either spontaneously or following stress. Susceptible animals, particularly kittens with low maternal immunity, become infected after exposure to a diseased or carrier cat. Replication of FeHV-1 in the nasal, conjunctival, pharyngeal, and, to a lesser extent, tracheal epithelium causes degeneration and exfoliation of cells.

Lesions caused by FeHV-1 are fully reversible, but secondary infections with bacteria, such as *Pasteurella multocida*, *Bordetella bronchiseptica*, *Streptococcus* spp., and *Mycoplasma felis*, can cause a chronic, severe suppurative rhinitis and also conjunctivitis. Intranuclear inclusion bodies are rarely seen in cats with FVR because inclusions are only present during the early stages of infection and have already disappeared by the time the cat is presented for diagnosis.

Respiratory sequelae to FVR can include chronic bacterial rhinitis and sinusitis with persistent purulent discharge; lysis of nasal bones, which can lead to conchal atrophy; permanent damage to the olfactory epithelium; and secondary bacterial pneumonia. In addition to rhinitis and interstitial pneumonia, FVR also causes ulcerative keratitis, hepatic necrosis, emaciation, abortion, and

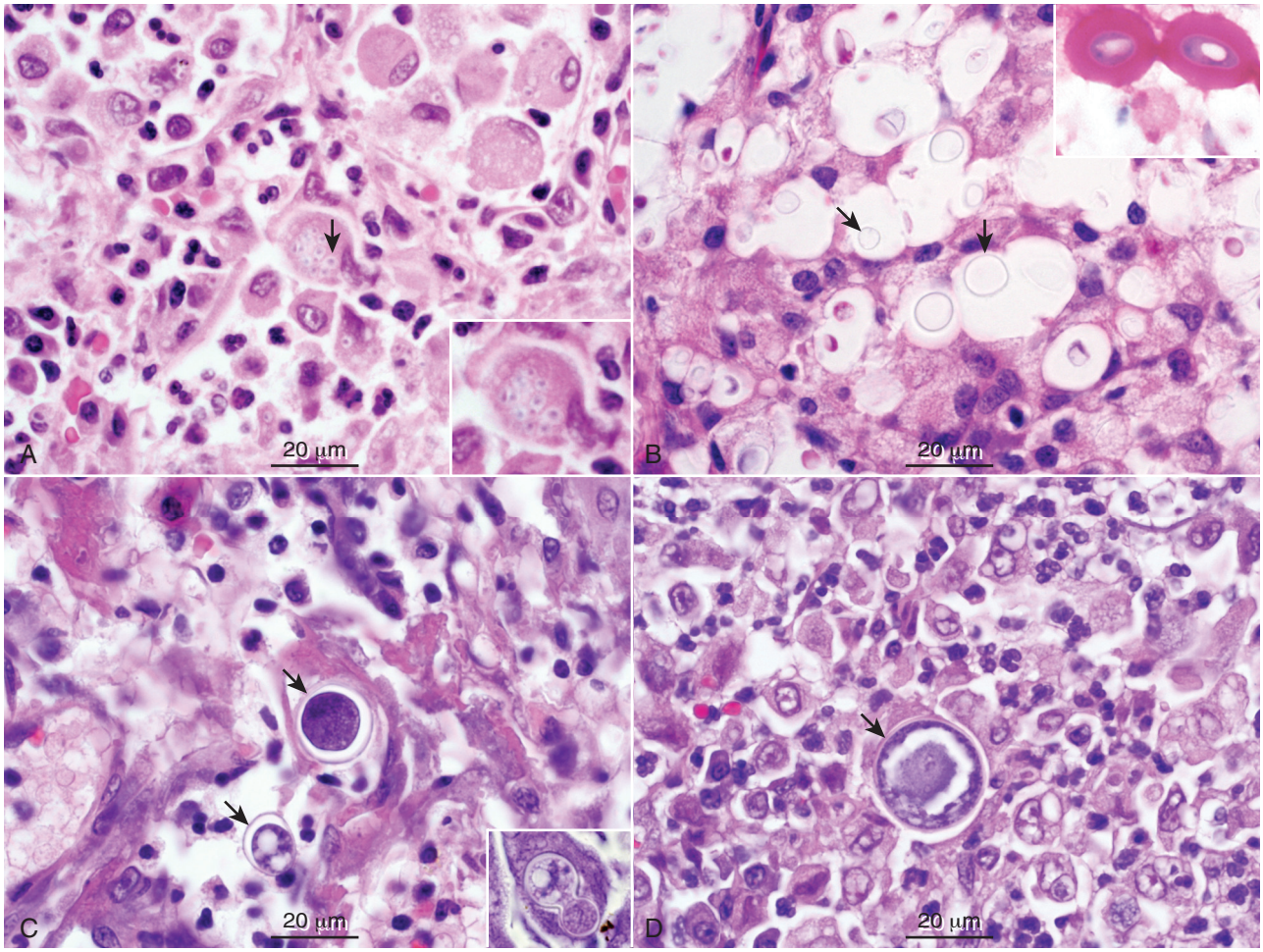


Figure 9-35 Systemic (Deep) Mycoses. *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Coccidioides immitis* Photographed All at the Same Magnification for Comparative Purposes. A, *Histoplasma capsulatum*, located intracellularly, is spherical to slightly elongated, 5 to 6 µm in diameter *(arrow)*. H&E stain. **B,** *Cryptococcus neoformans*, spherical, 2 to 10 µm in diameter *(arrows)*, usually surrounded by a thick mucus capsule, which can increase the overall diameter up to 30 µm, intracellular or extracellular location. H&E stain. *Inset,* The mucus capsule does not stain with H&E but becomes visible with mucicarmine stain. **C,** *Blastomyces dermatitidis*, 8 to 25 µm in diameter, broad-based budding spherical yeast-like organisms *(arrows)*, intracellular or extracellular location. *Inset,* Budding yeast typical of this fungus. H&E stain. **D,** *Coccidioides immitis*, spherules, 20 to 30 µm in diameter, containing endospores (<5 µm in diameter) *(arrow)*, intracellular or extracellular location. H&E stain. (**A, B, C,** and **D** courtesy Dr. A. López and Dr. M. Forzán, Atlantic Veterinary College. Inset **B** courtesy of Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

stillbirths. Clinical signs of FVR infection are characterized by lethargy, oculonasal discharge, severe rhinitis, and conjunctivitis.

Feline Calicivirus. Feline rhinitis can be caused by different strains of feline calicivirus (FCV). It is an important infection of the respiratory tract of cats, and depending on the virulence of the strain, lesions vary from a mild oculonasal discharge to severe rhinitis, mucopurulent conjunctivitis, and ulcerative gingivitis and stomatitis. The lesions, in addition to rhinitis and conjunctivitis, include acute, diffuse interstitial pneumonia with necrotizing bronchiolitis (see Pneumonias of Cats) and in some cases prominent ulcers of the tongue and hard palate. Primary viral lesions are generally transient, but secondary bacterial infections (*Bordetella bronchiseptica*, *Pasteurella multocida*, or *Escherichia coli*) are a common complication. Some kittens develop lameness after infection or vaccination with calicivirus because of an acute and self-limiting arthritis ("limping kitten syndrome"). Carrier state and virus shedding from oronasal secretions and feces are natural sequelae after recovery from the acute phase of the disease. Clinical and pathologic features of FCV disease are strikingly similar but not identical to those of FVR; these two viral infections account for 80% of all cases of feline respiratory diseases. A febrile systemic hemorrhagic syndrome with high mortality (up to 50%) has been reported in cats infected with virulent strains of FCV.

Bacterial Infections

Feline Chlamydiosis. Feline chlamydiosis is a persistent respiratory infection of cats caused by *Chlamydophila felis*. Infection results in a conjunctivitis (similar to the conjunctivitis seen in human trachoma caused by *Chlamydia trachomatis*) and serous or mucopurulent rhinitis. In the past, *Chlamydophila felis* was incriminated as the agent responsible for "feline pneumonitis," but its role in causing bronchointerstitial pneumonia in cats has been seriously challenged in recent years (see Pneumonias of Cats).

Mycotic Infections. The most common mycotic infection in the feline nasal cavity is caused by *Cryptococcus neoformans* and *Cryptococcus gatti*, but not all animals exposed to these fungi necessarily develop cryptococcosis unless they are immunosuppressed.

The lesions vary from discrete nasal granulomas to large confluent masses of mucopurulent exudate filling the entire nasal cavity and paranasal sinuses. Microscopic examination of the exudate reveals the typical thick-walled PAS-positive organisms (see Fig. 9-35).

Other Causes of Rhinitis and Sinusitis. *Mycoplasma felis* can also cause mucopurulent conjunctivitis and a mild upper respiratory infection, with clinical signs and lesions overlapping those seen with chlamydiosis, FVR, and FCR infections. Respiratory infections and bronchopneumonia in cats may also be associated with the immunosuppressive effects of feline retroviruses such as feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV). Nasal aspergillosis and allergic rhinosinusitis are sporadically reported in cats (see Disorders of the Conducting System: Species-Specific Diseases of the Nasal Cavity and Paranasal Sinuses: Disorders of Dogs: Mycotic Infections).

Neoplasia of the Nasal Cavity and Paranasal Sinuses

Neoplasms of the nasal cavity and paranasal sinuses may arise from any of the tissues forming these structures, including bone (osteoma or osteosarcoma), cartilage (chondroma or chondrosarcoma), connective tissue (fibroma or fibrosarcoma, myxoma or myxosarcoma), and blood vessels (hemangioma or hemangiosarcoma), and from all the different types of cells of glands and lining epithelium (adenoma, carcinoma, or adenocarcinoma). Nasal tumors originating from stromal tissues, such as bone, cartilage, and connective tissue, are morphologically indistinguishable from those seen in other sites. In general, nasal neoplasms are rare in domestic animals, except for enzootic ethmoidal tumor (retroviral) in sheep and goats, which can occur in several animals in a herd (see the next section).

In companion animals, nasal neoplasms are most common in dogs, particularly in medium to large breed dogs such as the collie, Airedale terrier, basset hound, and German shepherd. The cat and the horse are less frequently affected. The main sites in order of frequency are the nasal passages and sinuses for dogs, the tip of the nose and nasal passages for cats, and the maxillary sinus and nasal passages for horses.

The majority of neoplasms in the nasal cavity are malignant. Benign nasal neoplasms (papilloma and adenoma) are rare and generally are either solitary or multiple, well-delineated nodules. In contrast, nasal carcinomas and nasal sarcomas are generally larger but vary in size and are often pale and multilobulated masses composed of fleshy to friable tissue (Figs. 9-36 and 9-37). Malignant neoplasms are locally invasive and tend to infiltrate sinuses, meninges, frontal brain, olfactory nerves, and vessels resulting in epistaxis. Carcinomas vary from anaplastic (poorly differentiated) to well differentiated, in which cell and tissue morphology retains some glandular (adenocarcinoma) or squamous cell patterns. Because nasal tumors in dogs and cats are usually large and invasive at the time of diagnosis, prognosis is usually poor and survival times are short. Sarcomas originating in the nasal cavity and paranasal sinuses are less common than carcinomas. Mesenchymal tumors can arise from bone (osteoma or osteosarcoma), cartilage (chondroma or chondrosarcoma), blood vessels (hemangioma or hemangiosarcoma), and connective tissue (fibroma or fibrosarcoma). Overall, benign epithelial and mesenchymal tumors are less common than their malignant counterparts. Secondary tumors in the nasal cavity are rare, with lymphoma being the most common secondary tumor in the nasal cavity of domestic animals (Fig. 9-38).

Nasal neoplasms become secondarily infected by bacteria, and clinical signs often overlap with those of infectious rhinitis and include catarrhal or mucopurulent nasal discharge, periodic hemorrhage, increased lacrimation as a result of obstruction of nasolacrimal ducts, and sneezing. In some instances, it is not possible to clinically or grossly differentiate neoplasms from hyperplastic nodules or granulomatous rhinitis. Some neoplasms may infiltrate adjacent bone structures and produce notable facial deformities, loss of teeth, exophthalmus, and nervous signs. Large neoplasms also project into the meatuses, narrow the lumen, and interfere with airflow, causing stertorous breathing (see Figs. 9-36, 9-37, and 9-38). Biopsies, as well as brush and imprint cytology, have proven effective in the antemortem diagnosis of nasal neoplasms, particularly in those of epithelial lineage.

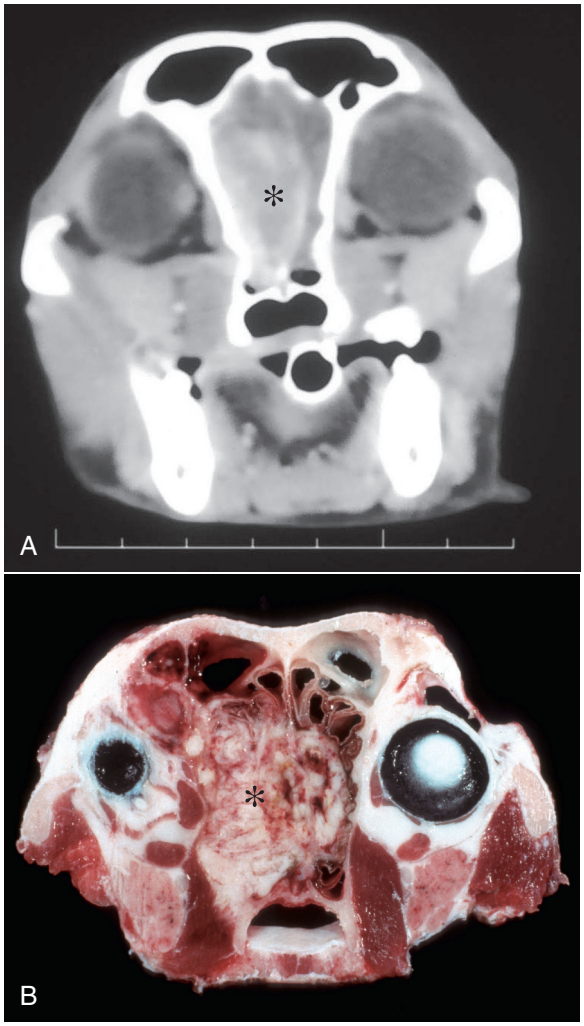


Figure 9-36 Nasal Carcinoma, Transverse Section of Nasal Passages and Sinuses, 10-Year-Old Dog. A, Computerized tomography shows a large neoplastic mass *(asterisk)* infiltrating the nasal cavity and displacing the nasal septum laterally. Scale bar units in centimeters. **B,** Transverse section of head showing tumor diffusely infiltrating the nasal conchae and obliterating the meatuses *(asterisk)*. (**A,** courtesy Atlantic Veterinary College. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

Enzootic Nasal (Ethmoidal) Tumors

A unique group of nasal carcinomas (enzootic nasal tumors, enzootic intranasal tumors, and enzootic nasal carcinoma) of sheep and goats arise from the surface epithelium and glands of the ethmoidal conchae. These types of carcinomas are caused by betaretroviruses in sheep (ENTV-1) and goats (ENTV-2). The enzootic nasal tumor has been successfully transmitted to susceptible animals by

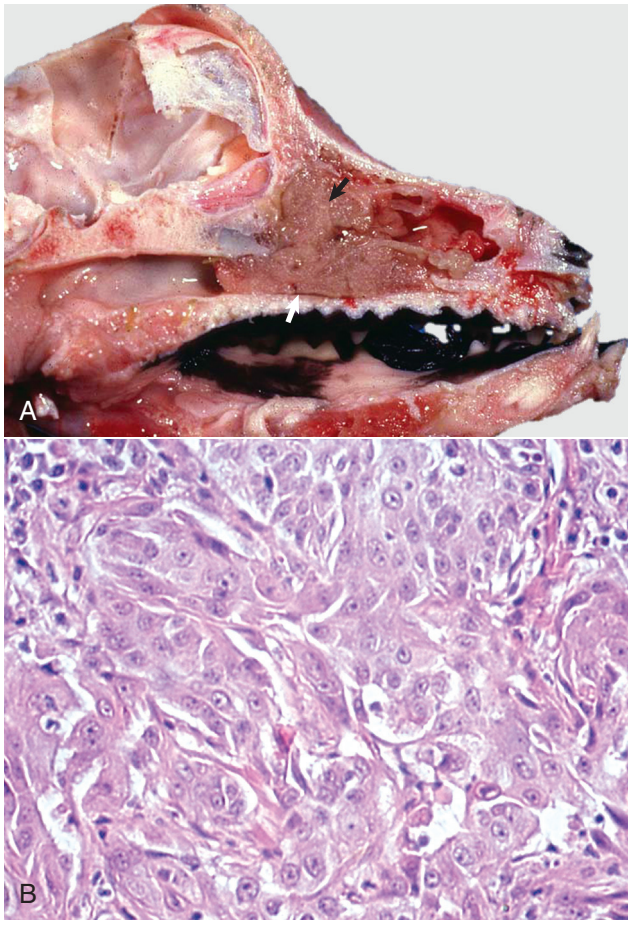


Figure 9-37 Nasal Adenocarcinoma, Midsagittal Section, Head, Adult Dog. A, A large neoplastic mass *(arrows)* has arisen from the ethmoidal concha and has infiltrated along the nasal passages. **B,** Multiple clusters of neoplastic epithelial cells with abundant eosinophilic cytoplasm and prominent nucleoli. H&E stain. (**A** courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

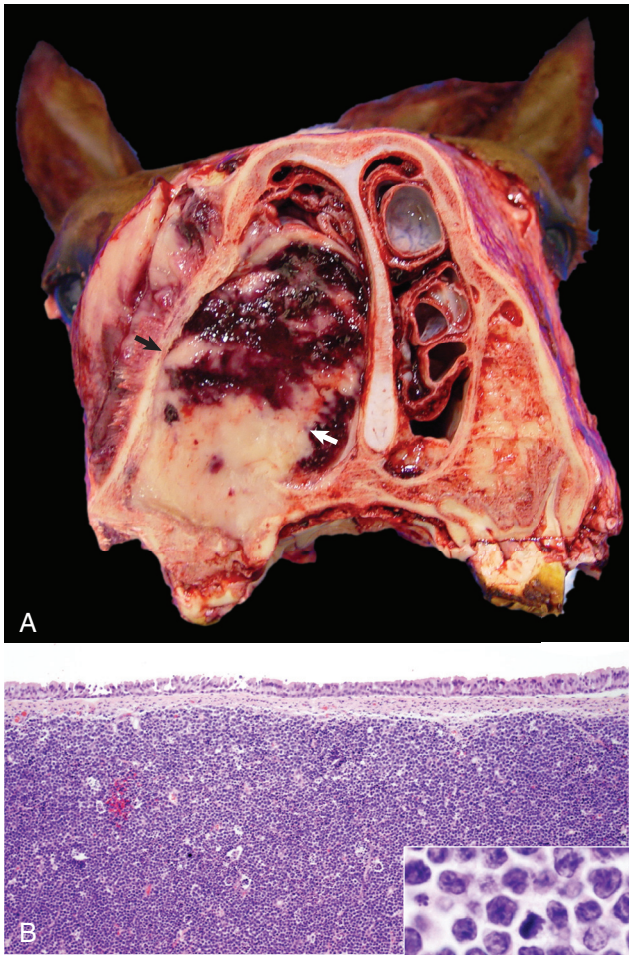


Figure 9-38 Lymphoma *(Arrows)*, Right Nasal Cavity, Horse. A, Tumoral mass occludes the right nasal cavity and invades the conchae and maxillary bone. **B,** Note diffuse infiltration of the nasal submucosa with neoplastic lymphocytes. H&E stain. *Inset,* Close-up of neoplastic lymphocytes. H&E stain. (Courtesy Dr. S. Martinson and Dr. C. Lopez-Mendez, Atlantic Veterinary College.)

inoculation of cell-free tumor filtrates. Enzootic nasal tumors are typically invasive but do not metastasize (Fig. 9-39). In some regions of the world, ethmoid tumors have been reported in horses and pigs, particularly in those farms where the endemic nasal tumors of ruminants are known to occur.

Nasal Polyps and Nasal Cysts Resembling Neoplasms

Nonneoplastic exophytic masses that resemble neoplasms are commonly found in horses, cats, and, to a lesser extent, other species. In horses, polyps tend to form in the ethmoidal region, whereas in cats, polyps are most frequently found in the nasopharynx and Eustachian tubes. The pathogenesis of these benign growths is uncertain, although in many cases they follow chronic rhinitis or sinusitis. Most recently, lymphatic obstruction secondary to inflammation has been postulated as the main culprit. Grossly, polyps appear as firm, pedunculated nodules of various sizes protruding from the nasal mucosa into the nasal passages or nasopharynx (Fig. 9-40); the surface may be smooth, ulcerated, secondarily infected, and hemorrhagic. Microscopically, polyps are characterized by a core of well-vascularized stromal tissue that contains inflammatory cells and are covered by pseudostratified or squamous epithelium (see Fig. 9-40).

Nasal and paranasal sinus cysts are common idiopathic lesions in horses and are medically important because they clinically mimic neoplasms or infections. Although not considered a neoplastic growth, cysts are expansive and cause deformation or destruction of the surrounding bone. These cysts are typically composed of an epithelial cell capsule filled with yellow or hemorrhagic fluid and do not recur after surgical removal. Ethmoidal hematomas also resemble nasal tumors in horses.

Disorders of the Pharynx, Guttural Pouches, Larynx, and Trachea in Domestic Animals

Anomalies[3]

Congenital anomalies of the pharynx, guttural pouches, larynx, and trachea are rare in all species. Depending on their location and severity, they may be inconsistent with postnatal life, pose little or no problem, interfere with quality of life, or manifest themselves in later life. If clinical signs of respiratory distress, such as stridor, coughing, dyspnea, or gagging, do occur, they are usually exacerbated by excitement, heat, stress, or exercise.

Brachycephalic Airway Syndrome. See Disorders of the Conducting System: Species-Specific Diseases of the Pharynx, Guttural

[3]See E-Table 1-1 for potential, suspected, or known genetic disorders.

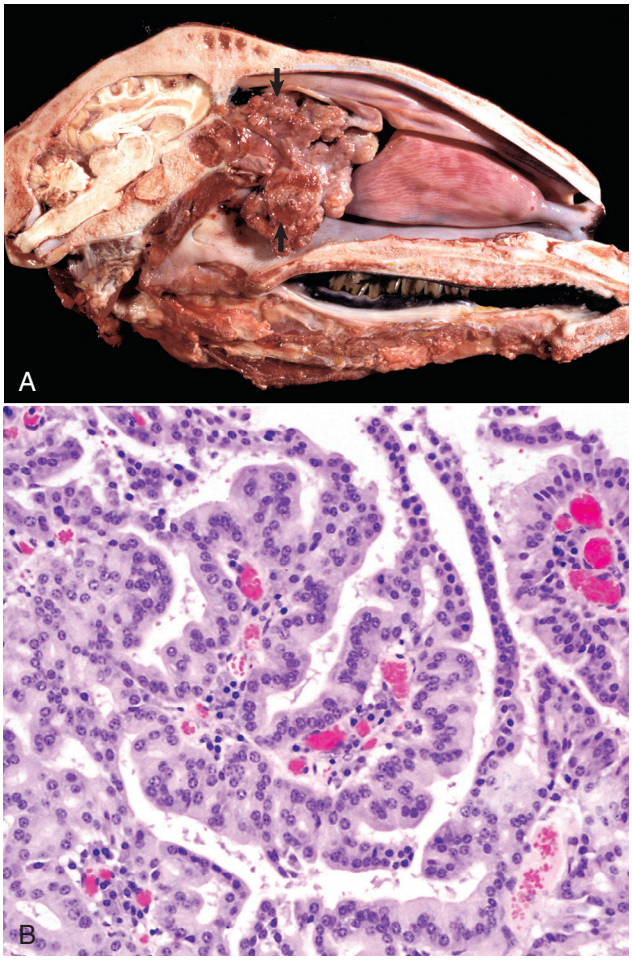


Figure 9-39 Nasal Adenocarcinoma *(Arrows)*, Midsagittal Section of the Head, Sheep. A, The tumor has occluded the right nasal passage and choanae. The location (ethmoturbinates) and type of tumor (carcinoma) are typical of retrovirus-induced "enzootic nasal carcinoma." **B,** Neoplastic cells forming conspicuous papillary growths *(center of image)*. (**A** courtesy Dr. L.E. Craig, College of Veterinary Medicine, University of Tennessee. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

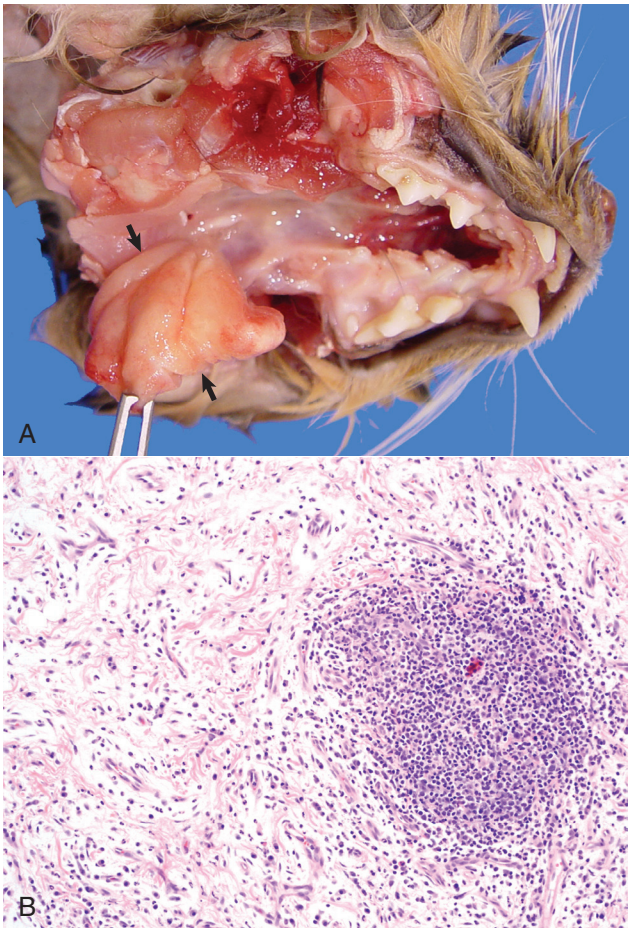


Figure 9-40 Nasopharyngeal Polyp, Oral Cavity, Cat. A, Large polypoid mass arising from the nasopharyngeal mucosa *(arrows)*. **B,** Loose connective tissue infiltrated with lymphocytes and plasma cells forms the core of the mass *(right side of figure)*. H&E stain. (Courtesy Dr. F. Marrón and Dr. A. López, Atlantic Veterinary College.)

Pouches, Larynx, and Trachea in Domestic Animals: Disorders of Dogs: Anomalies: Brachycephalic Airway Syndrome.

Hypoplastic Epiglottis, Epiglottic Entrapment, and Dorsal Displacement of the Soft Palate. See Disorders of the Conducting System: Species-Specific Diseases of the Pharynx, Guttural Pouches, Larynx, and Trachea: Disorders of Horses: Anomalies: Hypoplastic Epiglottis, Epiglottic Entrapment, and Dorsal Displacement of the Soft Palate.

Tracheal Collapse and Tracheal Stenosis. Tracheal collapse with reduction in tracheal patency occurs in toy, miniature, and brachycephalic breeds of dogs, in which the condition is also called *tracheobronchial collapse* or *central airway collapse*. The defect also occurs in horses, cattle, and goats. By radiographic, endoscopic, or gross examination, there is dorsoventral flattening of the trachea with concomitant widening of the dorsal tracheal membrane, which may then prolapse ventrally into the lumen (Fig. 9-41). Most commonly, the defect extends the entire length of the trachea and only rarely affects the cervical portion alone. Affected segments with a reduced lumen contain froth and even are covered by a diphtheritic membrane. In horses, the so-called scabbard trachea is characterized

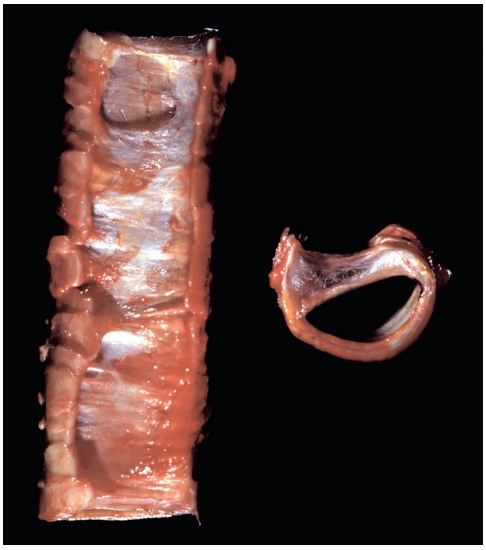


Figure 9-41 Tracheal Collapse, Trachea, Pony. *Left specimen*, The dorsal surface of the trachea is flattened dorsoventrally, the dorsal ends of the C-shaped tracheal rings are widely separated, and the dorsal ligament between the two ends is lengthened and thinned. *Right specimen* (transverse section), The ends of the tracheal rings are widely separated, and the dorsal wall of the trachea is formed by the lengthened and thinned dorsal ligament. (Courtesy Dr. C.S. Patton, College of Veterinary Medicine, University of Tennessee.)

by lateral flattening so that the tracheal lumen is reduced to a narrow vertical slit.

Segmental tracheal collapse causing stenosis has been associated with congenital and acquired abnormalities. In severe cases, abnormal cartilaginous glycoproteins and loss of elasticity of tracheal rings causes the trachea to collapse. In some other cases, it is an acquired tracheal lesion that follows trauma, compression caused by extraluminal masses, peritracheal inflammation, and flawed tracheotomy or transtracheal aspirate techniques.

Other tracheal anomalies include tracheoesophageal fistula, which is most commonly found in human beings and sporadically in dogs and cattle. Congenital fistulas can occur at any site of the cervical or thoracic segments of the trachea. Acquired tracheoesophageal fistula can be a complication of improper intubation, tracheotomy, or esophageal foreign body.

Degenerative Diseases

Laryngeal Hemiplegia. Laryngeal hemiplegia (paralysis), sometimes called *roaring* in horses, is a common but obscure disease characterized by atrophy of the dorsal and lateral cricoarytenoid muscles (abductor and adductor of the arytenoid cartilage), particularly on the left side. Muscular atrophy is most commonly caused by a primary denervation (recurrent laryngeal neuropathy) of unknown cause (idiopathic axonopathy) and, to a much lesser extent, secondary nerve damage (see the section on Denervation Atrophy in Chapters 14 and 15). Idiopathic laryngeal hemiplegia is an incurable axonal disease (axonopathy) of the cranial laryngeal nerve that affects mostly larger horses. Secondary laryngeal hemiplegia is rare and occurs after nerve damage caused by other pathologic processes such as compression or inflammation of the left recurrent laryngeal nerve. The medial retropharyngeal lymph nodes are located immediately ventral to the floor of the guttural pouches. As a result of this close anatomic relationship, swelling or inflammation of the guttural pouches or retropharyngeal lymph nodes often results in secondary damage to the laryngeal nerve. Common causes of secondary nerve damage (Wallerian degeneration) include guttural pouch mycosis, retropharyngeal abscesses, inflammation because of iatrogenic injection into the nerves, neck injury, and metastatic neoplasms involving the retropharyngeal lymph nodes (e.g., lymphosarcoma).

Grossly, the affected laryngeal muscle in a horse with laryngeal hemiplegia is pale and smaller than normal (muscle atrophy) (Fig. 9-42). Microscopically, muscle fibers have lesions of denervation atrophy (see Chapters 14 and 15). Atrophy of laryngeal muscles also occurs in dogs as an inherited condition (Siberian husky and Bouvier des Flanders), as a degenerative neuropathy in older dogs, secondary to laryngeal trauma in all species (e.g., choke chain damage), or secondary to hepatic encephalopathy in horses.

The abnormal inspiratory sounds (roaring) during exercise in horses with laryngeal hemiplegia are caused by paralysis of the left dorsal and lateral cricoarytenoid muscles, which cause incomplete dilation of the larynx, obstruction of airflow, and vibration of vocal cords.

Circulatory Disturbances

Laryngeal Edema. Laryngeal edema is a common feature of acute inflammation, but it is particularly important because swelling of the epiglottis and vocal cords can obstruct the laryngeal orifice, resulting in asphyxiation. Laryngeal edema occurs in pigs with edema disease; in horses with purpura hemorrhagica; in cattle with acute interstitial pneumonia; in cats with systemic anaphylaxis; and in all species as a result of trauma, improper endotracheal tubing, inhalation of irritant gases (e.g., smoke), local inflammation, and allergic reactions. Grossly, the mucosa of the epiglottis and vocal cords is thickened and swollen, often protrudes dorsally onto the epiglottic orifice, and has a gelatinous appearance (Fig. 9-43).

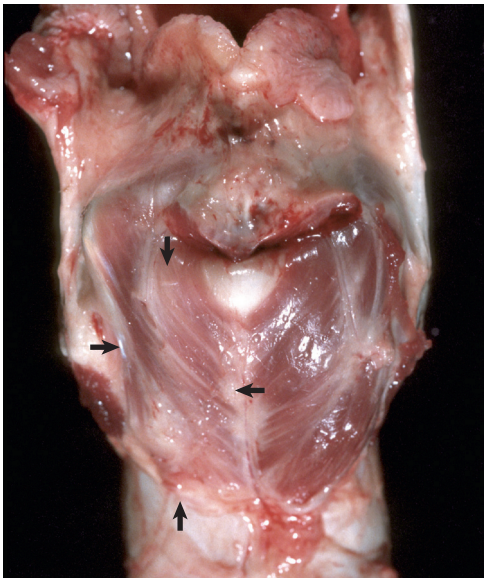


Figure 9-42 Laryngeal Hemiplegia, Larynx, Dorsal Surface, 2-Year-Old Horse. The left cricoarytenoideus dorsalis muscle is pale and atrophic *(arrows)*, whereas the right cricoarytenoideus dorsalis muscle is normal. (Courtesy Dr. A. López, Atlantic Veterinary College.)

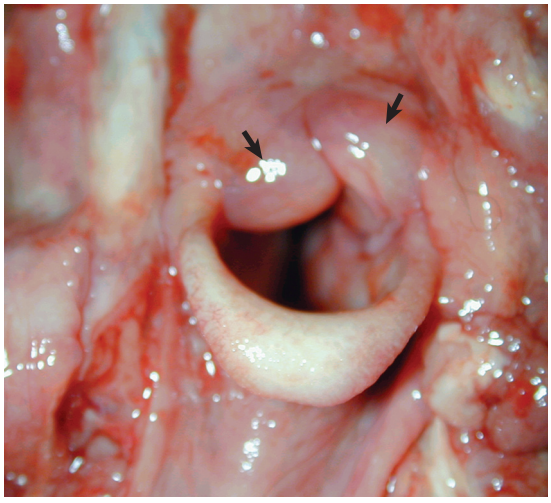


Figure 9-43 Laryngeal Edema, Larynx, Mature Cow. Note the edematous thickening of the laryngeal mucosa of the vocal cords *(arrows)*, which can cause respiratory distress due to the narrowing of the laryngeal lumen (rima glottidis). (Courtesy Dr. J. Andrews, College of Veterinary Medicine, University of Illinois.)

Laryngeal and Tracheal Hemorrhage. Hemorrhages in these sites occur as mucosal petechiae and are most commonly seen in coagulopathies; inflammation; septicemia and sepsis, particularly in pigs with classical swine fever (hog cholera); African swine fever or salmonellosis; and horses with equine infectious anemia. Severe dyspnea and asphyxia before death can cause congestion, ecchymosis, and petechiae in the laryngeal and tracheal mucosa; this lesion must be differentiated from postmortem imbibition of hemoglobin in autolyzed carcasses (see Chapter 1).

Tracheal Edema and Hemorrhage Syndrome of Feeder Cattle. See Disorders of Cattle.

Inflammation (Pharyngitis, Laryngitis, and Tracheitis)

Inflammation of the pharynx, larynx, and trachea are important because of their potential to obstruct airflow and to lead to aspiration pneumonia. The pharynx is commonly affected by infectious diseases of the upper respiratory and upper digestive tracts, and the trachea can be involved by extension from both the lungs and larynx.

Inflammation and Trauma of the Pharynx (Pharyngitis)

Pharyngeal Obstruction and Perforation. Intraluminal foreign bodies in the pharynx, such as medicament boluses, apples, or potatoes, can move down and obstruct the larynx and trachea. Also, pharyngeal obstruction can be caused by masses in the surrounding tissue, such as neoplasms of the thyroid gland, thymus, and parathyroid glands.

A number of nonspecific insults can cause lesions and clinical signs. Trauma may take the form of penetrating wounds in any species: perforation of the caudodorsal wall of the pharynx from the improper use of drenching or balling guns in sheep, cattle, and pigs; choking injury because of the use of collars in dogs and cats; and the shearing forces of bite wounds. The results of the trauma may be minimal (local edema and inflammation) or as serious as complete luminal obstruction by exudate. Foreign bodies may be lodged anywhere in the pharyngeal region; the location and size determine the occurrence of dysphagia, regurgitation, dyspnea, or asphyxiation. Pigs have a unique structure known as the *pharyngeal diverticulum* (4 cm long in adult pigs), which is located in the pharyngeal wall rostral and dorsal to the esophageal entrance. It is important because barley awns may lodge in the diverticulum, causing an inflammatory swelling that affects swallowing. The diverticular wall may be perforated by awns or drenching syringes, which results in an exudate that can extend down the tissue planes between muscles of the neck and even into the mediastinum. The pharynx of the dog may also be damaged by trauma from chicken bones, sticks, and needles, resulting in the formation of a pharyngeal abscess.

Equine Pharyngeal Lymphoid Hyperplasia. See Disorders of the Conducting System: Species-Specific Diseases of the Pharynx, Guttural Pouches, Larynx, and Trachea: Disorders of Horses: Inflammation: Equine Pharyngeal Lymphoid Hyperplasia.

Inflammation of Guttural Pouches. See Disorders of the Conducting System: Species-Specific Diseases of the Pharynx, Guttural Pouches, Larynx, and Trachea: Disorders of Horses: Inflammation: Inflammation of Guttural Pouches.

Inflammation of the Larynx (Laryngitis)

Necrotic Laryngitis. See Disorders of the Conducting System: Species-Specific Diseases of the Pharynx, Guttural Pouches, Larynx, and Trachea: Disorders of Ruminants (Cattle, Sheep, and Goats): Inflammation: Necrotic Laryngitis.

Laryngeal Contact Ulcers. See Disorders of the Conducting System: Species-Specific Diseases of the Pharynx, Guttural Pouches, Larynx, and Trachea: Disorders of Ruminants (Cattle, Sheep, and Goats): Inflammation: Laryngeal Contact Ulcers.

Inflammation of the Trachea (Tracheitis). The types of injury and host inflammatory responses in the trachea are essentially the same as those described for the nasal mucosa. Although tracheal mucosa is prone to aerogenous injury and necrosis, it has a remarkable capacity for repair. According to the exudate, tracheitis in all animal species is classified as fibrinous, catarrhal, purulent, or granulomatous (Figs. 9-44 and 9-45). Chronic polypoid tracheitis occurs in dogs and cats, probably secondary to chronic infection.

The most common causes of tracheitis are viral infections, such as those causing infectious bovine rhinotracheitis (see Fig. 9-29), equine viral rhinopneumonitis, canine distemper, and feline rhinotracheitis. Viral lesions are generally mild and transient but often become complicated with secondary bacterial infections. At the early stages, the mucosa is notably hyperemic and can show white foci of necrosis. In the most severe cases, the affected mucosa detaches from the underlying basement membrane, causing extensive tracheal ulceration.

Chemical tracheitis is also commonly seen after aspiration (see Fig. 9-45). Also, inhalation of fumes during barn fires can cause extensive injury and necrosis of the tracheal mucosa. In forensic cases, the presence of carbon pigment in the mucosal surface of trachea, bronchi, and bronchioles indicates that the burned animal was alive during the fire.

Parasitic Diseases of the Larynx and Trachea. Parasitic infections of the larynx and trachea can cause obstruction with dramatic consequences, but burdens sufficient to cause such effects are not commonly seen in veterinary practice.

Besnoitiosis (Besnoitia Spp.). Besnoitiosis (*Besnoitia* spp.) is caused by several species of this apicomplexan coccidian parasite, whose life cycle is still unknown. This parasite can cause pedunculated lesions on the skin, sclera, mucosa of the nasal cavity, and larynx of horses and donkeys, cattle, goats, and wild animals. Besnoitiosis has been reported from Africa, Central and South America, North America, and Europe. Grossly, pale, round, exophytic nodules up to 2 cm in diameter can be observed protruding from mucosal surfaces. Microscopically, these nodules consist of finger-like projections covered by hyperplastic and sometimes ulcerated epithelium containing numerous thick-walled parasitic cysts with little inflammatory response.

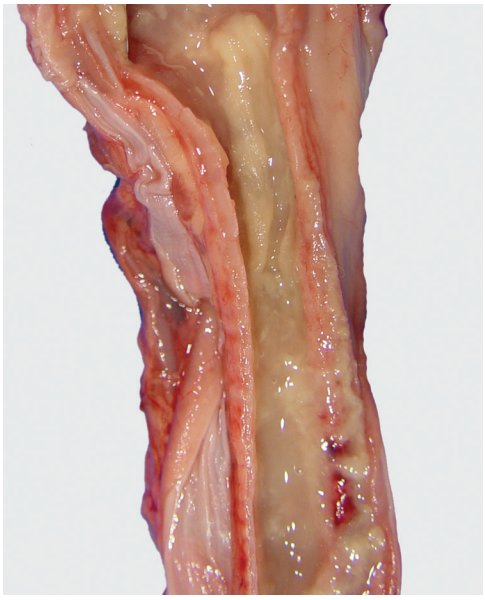


Figure 9-44 Fibrinopurulent Tracheitis, Cat. Note uniform plaque of yellow-gray fibrinopurulent exudate covering the entire tracheal mucosa. This cat also had suppurative bronchopneumonia, and *Pasteurella multocida* was isolated from the trachea and lung. (Courtesy Dr. L. Miller and Dr. A. López, Atlantic Veterinary College.)

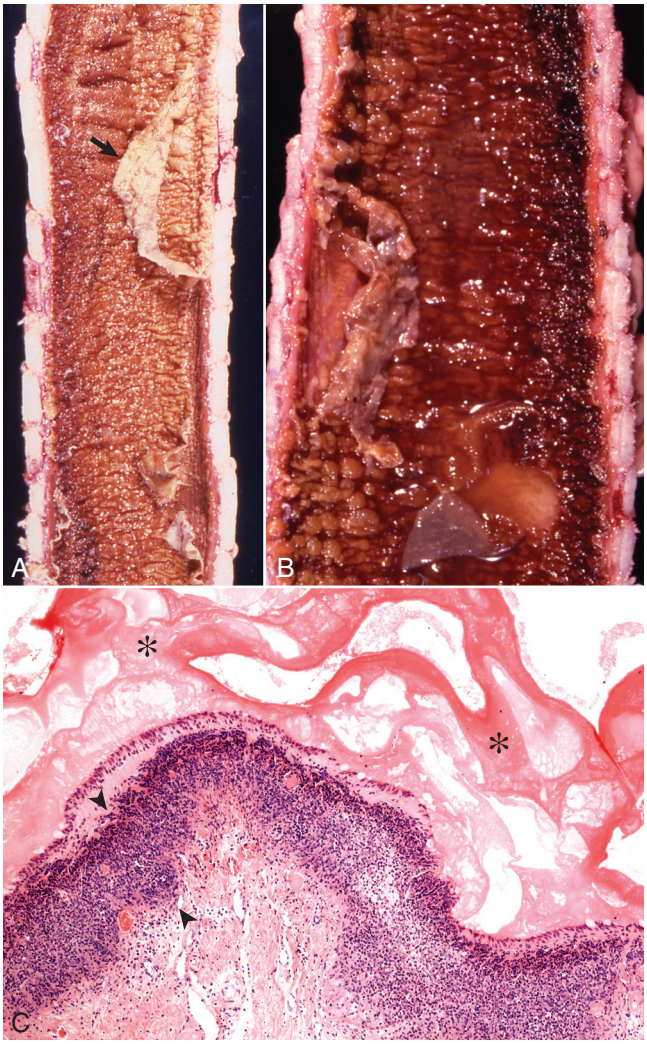


Figure 9-45 Chemical Tracheitis, Accidental Drenching with Disinfectant, Cow. A, Tracheal mucosa is diffusely covered with fibrinonecrotic exudate. Note a diphtheritic membrane peeling from the mucosa *(arrow)*. **B**, Close-up of the fibrinonecrotic exudate in a location of the trachea different from that shown in A. **C**, Section of mucosa showing a dark rim of neutrophils *(arrowheads)* and a thick layer of fibrin *(asterisks)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Mammomonogamus (Syngamus) Spp. *Mammomonogamus* (*Syngamus*) *laryngeus* is a nematode that is seen attached to the laryngeal mucosa of cattle in tropical Asia and South America, and cats (gapeworm: *Mammomonogamus ierei*) in the Caribbean and southern United States. Occasionally, human beings with a persistent cough or asthma-like symptoms have the parasite in the larynx or bronchi.

Oslerus (Filaroides) osleri. See Disorders of Dogs.

Species-Specific Diseases of the Pharynx, Guttural Pouches, Larynx, and Trachea

Disorders of Horses

Anomalies[4]

Hypoplastic Epiglottis, Epiglottic Entrapment, and Dorsal Displacement of the Soft Palate. Anomalies, such as hypoplastic epiglottis, epiglottic entrapment, and dorsal displacement of the soft palate, are important causes of respiratory problems and reduced athletic performance in horses. An undersized epiglottis is prone to being entrapped below the arytenoepiglottic fold, causing an equine syndrome known as *epiglottic entrapment*. This syndrome also occurs in horses with lateral deviation and deformity of epiglottis, epiglottic cysts, or necrosis of the tip of the epiglottis. Hypoplastic epiglottis also occurs in pigs. Dorsal displacement of the soft palate, particularly during exercise, narrows the lumen of the nasopharynx and creates abnormal air turbulence in the conducting system of horses. Epiglottic entrapment is clinically characterized by airway obstruction, exercise intolerance, respiratory noise, and cough.

Subepiglottic and Pharyngeal Cysts. Anomalous lesions, such as subepiglottic and pharyngeal cysts, are occasionally seen in horses, particularly in Standardbred and Thoroughbred racehorses. These cysts vary in size (1 to 9 cm) and occur most commonly in the subepiglottic area and to a lesser extent in the dorsal pharynx, larynx, and soft palate. Cysts are lined by squamous or pseudostratified epithelium and contain thick mucus. Large cysts cause airway obstruction, reduced exercise tolerance, or dysphagia and predispose to bronchoaspiration of food.

Inflammation

Equine Pharyngeal Lymphoid Hyperplasia. Equine pharyngeal lymphoid hyperplasia, or pharyngitis with lymphoid follicular hyperplasia, is a common cause of partial upper airway obstruction in horses, particularly in 2- and 3-year-old racehorses. Lymphoid hyperplasia is also seen in healthy horses as part of a response to mild chronic pharyngitis, which in many instances tends to regress with age in older animals. The cause is undetermined, but chronic bacterial infection combined with environmental factors may cause excessive antigenic stimulation and lymphoid hyperplasia. The gross lesions, visible endoscopically or at necropsy, consist of variably sized (1 to 5 mm) white foci located on the dorsolateral walls of the pharynx and extending into the openings of the guttural pouches and onto the soft palate. In severe cases, lesions may appear as pharyngeal polyps. Microscopically, the lesions consist of large aggregates of lymphocytes and plasma cells in the pharyngeal mucosa. Clinical signs consist of stertorous inspiration, expiration, or both.

Inflammation of Guttural Pouches. The guttural pouches of horses are large diverticula (300 to 500 mL) of the ventral portion of the auditory (Eustachian) tubes. These diverticula are therefore exposed to the same pathogens as the pharynx and have drainage problems similar to the sinuses. Although it is probable that various pathogens, including viruses, can infect them, the most common pathogens are fungi, which cause guttural pouch mycosis and guttural pouch empyema in the horse. Eustachitis is the term used for inflammatory processes involving the Eustachian (pharyngotympanic) tube. Because of the close anatomic proximity of guttural pouches to the internal carotid arteries, cranial nerves (VII, IX, X, XI, and XII), and atlantooccipital joint, disease of these diverticula may involve these structures and cause a variety of clinical signs in horses.

Guttural pouch mycosis occurs primarily in stabled horses and is caused by *Aspergillus fumigatus* and other *Aspergillus* spp. Infection is usually unilateral and presumably starts with the inhalation of spores from moldy hay. Grossly, the mucosal surfaces of the dorsal and lateral walls of the guttural pouch mucosa are first covered by focal, rounded, raised plaques of diphtheritic (fibrinonecrotic) exudate, which with time can become confluent and grow into a large fibrinonecrotic mass (Fig. 9-46). Microscopically, the lesions are severe necrotic inflammation of the mucosa and submucosa with widespread vasculitis and intralesional fungal hyphae. Necrosis of the

[4]See E-Box 1-1 for potential, suspected, or known genetic disorders.

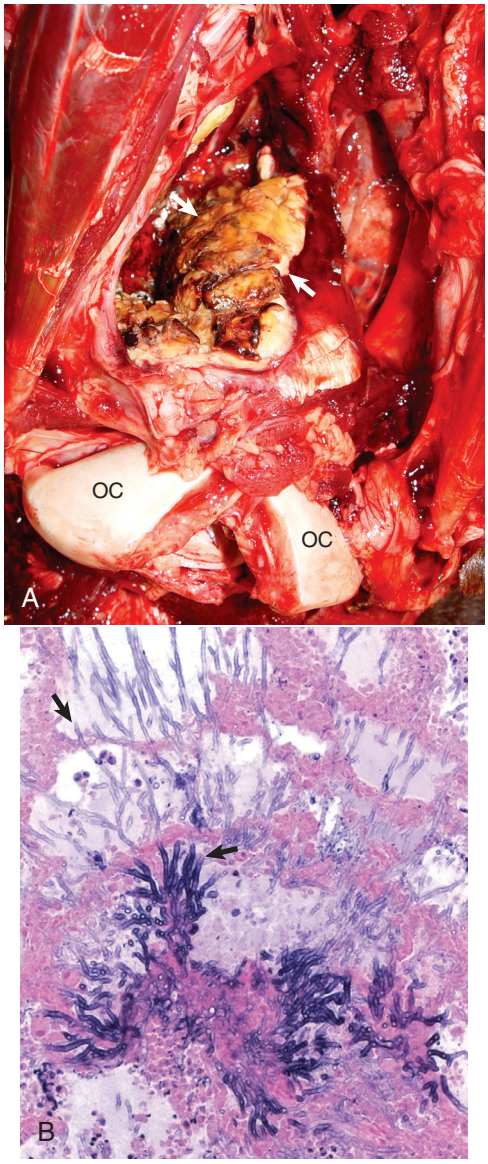


Figure 9-46 Guttural Pouch Mycosis, Ventral View of the Head, Horse. A, Note the large mass filling the right guttural pouch *(arrows)*. It is firmly attached to the wall and composed of fibrinonecrotic exudate and surrounded by clotted blood. OC, Occipital condyles. **B,** Fungal hyphae *(arrows)* are admixed with necrotic exudate. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

wall of the guttural pouches can extend into the wall of the adjacent internal carotid artery causing hemorrhage into the lumen of the guttural pouch and recurrent epistaxis. Invasion of the internal carotid artery causes arteritis, which can also lead to formation of an aneurysm and fatal bleeding into the guttural pouches. In other cases, the fungi may be angioinvasive, leading to the release of mycotic emboli into the internal carotid artery, generally resulting in multiple cerebral infarcts. Dysphagia, another clinical sign seen in guttural pouch mycosis, is associated with damage to the pharyngeal branches of the vagus and glossopharyngeal nerves, which lie on the ventral aspect of the pouches. Horner's syndrome results from damage to the cranial cervical ganglion and sympathetic fibers located in the caudodorsal aspect of the pouches. Finally, equine laryngeal paralysis (hemiplegia) can result from damage to the laryngeal nerves as previously described in the section on Laryngeal Hemiplegia.

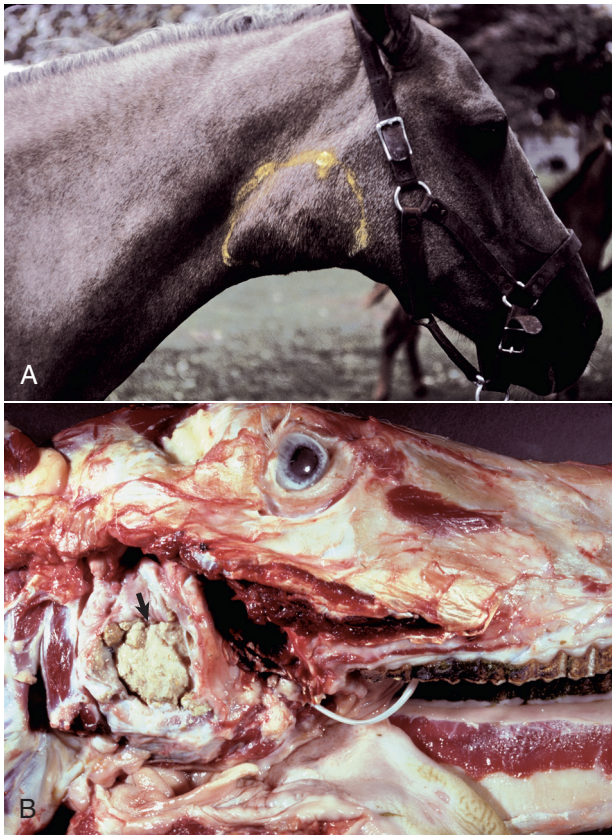


Figure 9-47 Guttural Pouch Empyema, Guttural Pouch, Horse. A, Note the swollen right neck *(outlined in yellow)* in this horse with guttural pouch empyema. **B,** The guttural pouch is filled with masses of inspissated purulent exudate *(arrow)*. (**A** courtesy College of Veterinary Medicine, University of Illinois. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Empyema of guttural pouches is a sequela to suppurative inflammation of the nasal cavities, most commonly from *Streptococcus equi* infection (strangles). In severe cases, the entire guttural pouch can be filled with purulent exudate (Fig. 9-47). The sequelae are similar to those of guttural pouch mycosis except that there is no erosion of the internal carotid artery. It is clinically characterized by nasal discharge, enlarged retropharyngeal lymph nodes, painful swelling of the parotid region, dysphagia, and respiratory distress.

Guttural pouch tympany develops sporadically in young horses when excessive air accumulates in the pouch from the one-way valve effect caused by inflammation or malformation of the Eustachian tube. Arabian and German warm-blooded horses are particularly susceptible to develop guttural pouch tympany. It is generally unilateral and characterized by nonpainful swelling of the parotid region.

Disorders of Ruminants (Cattle, Sheep, and Goats)

Circulatory Disturbances

Tracheal Edema and Hemorrhage Syndrome of Feeder Cattle. Tracheal edema and hemorrhage syndrome of feeder cattle, also known as the *honker syndrome* or *tracheal stenosis of feedlot cattle*, is a poorly documented acute disease of unknown cause, most often seen during the summer months. Severe edema and a few hemorrhages are present in the mucosa and submucosa of the dorsal surface of the trachea, extending caudally from the midcervical area as far as the tracheal bifurcation. On section, the tracheal mucosa is diffusely thickened and gelatinous. Clinical signs include inspiratory

dyspnea that can progress to oral breathing, recumbency, and death by asphyxiation in less than 24 hours.

Inflammation

Necrotic Laryngitis. Necrotic laryngitis (calf diphtheria, laryngeal necrobacillosis) is a common disease of feedlot cattle and cattle affected with other diseases, with nutritional deficiencies, or housed under unsanitary conditions. It also occurs sporadically in sheep and pigs. Necrotic laryngitis, caused by *Fusobacterium necrophorum*, is part of the syndrome termed *necrotic stomatitis* or *laryngeal necrobacillosis*, which can include lesions of the tongue, cheeks, palate, and pharynx. An opportunistic pathogen, *Fusobacterium necrophorum* produces potent exotoxins and endotoxins after gaining entry either through lesions of viral infections, such as IBR and vesicular stomatitis in cattle, or after traumatic injury produced by feed or careless use of specula or balling guns.

The gross lesions, regardless of location in the mouth or larynx (most common in the mucosa overlying the laryngeal cartilages), consist of well-demarcated, dry, yellow-gray, thick-crusted, and fibrinonecrotic exudate (Fig. 9-48) that in the early stages is bounded by a zone of active hyperemia. Deep ulceration develops, and if the lesion does not result in death, healing is by granulation tissue formation. Microscopically, the necrotic foci are first surrounded by congested borders, then by a band of leukocytes, and finally the ulcers heal by granulation tissue and collagen (fibrosis). The lesions can extend deep into the submucosal tissue. Numerous bacteria are evident at the advancing edge.

There are numerous and important sequelae to calf diphtheria; the most serious is death from severe toxemia or overwhelming fusobacteremia. Sometimes, the exudate may be copious enough to cause laryngeal obstruction and asphyxiation or be aspirated and cause bronchopneumonia. The clinical signs of necrotic laryngitis are fever, anorexia, depression, halitosis, moist painful cough, dysphagia, and inspiratory dyspnea and ventilatory failure because of fatigue of the respiratory muscles (diaphragmatic and intercostal).

Laryngeal Contact Ulcers. Ulcerative lesions in the larynx are commonly found in feedlot cattle. Grossly, the laryngeal mucosa reveals circular ulcers (up to 1 cm in diameter), which may be unilateral or bilateral and sometimes deep enough to expose the underlying arytenoid cartilages. The cause has not been established, but causal agents, such as viral, bacterial, and traumatic, have been proposed, along with increased frequency and rate of closure of the larynx (excessive swallowing and vocalization) when cattle are exposed to market and feedlot stresses such as dust, pathogens, and interruption of feeding. Contact ulcers predispose a calf to diphtheria (*Fusobacterium necrophorum*) and laryngeal papillomas. Ulceration of the mucosa and necrosis of the laryngeal cartilages have also been described in calves, sheep, and horses under the term *laryngeal chondritis*. Laryngeal abscesses involving the mucosa and underlying cartilage occur as a herd or flock problem in calves and sheep, presumably caused by a secondary infection with *Trueperella* (*Arcanobacterium*) *pyogenes*.

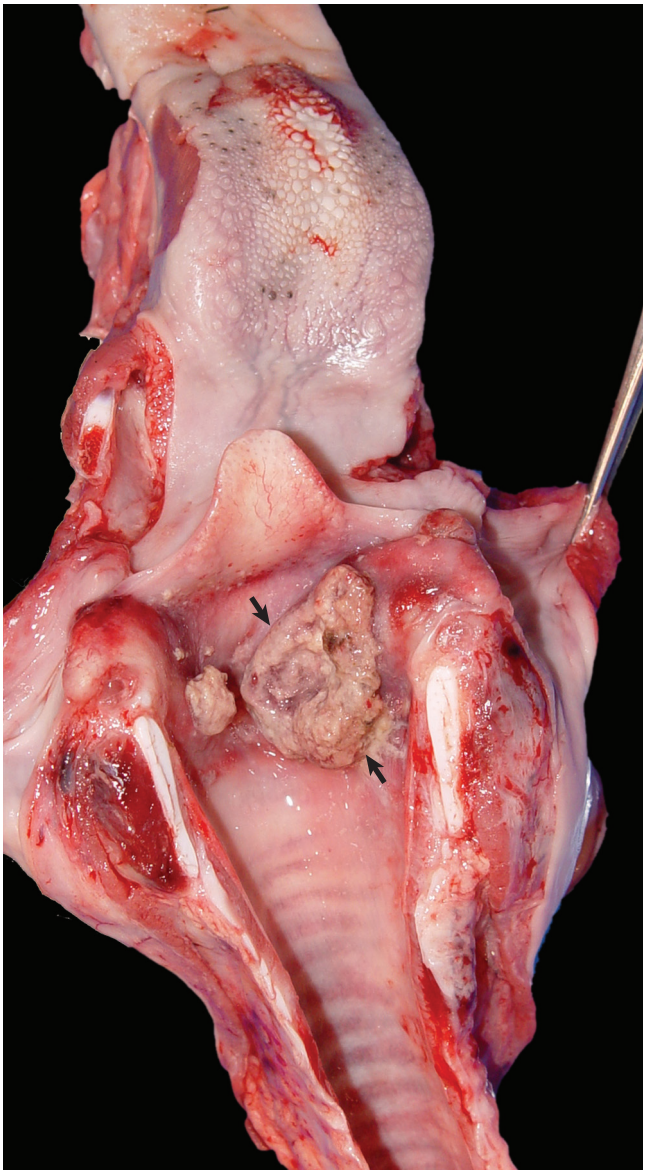


Figure 9-48 Necrotic Laryngitis, Calf Diphtheria *(Fusobacterium necrophorum)*, Larynx, Calf. Plaques of fibrinopurulent exudate are present on the mucosa of the arytenoid cartilages *(arrows)*. Pieces of the exudate can be aspirated into the lungs and cause bronchopneumonia. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Disorders of Dogs

Anomalies[5]

Brachycephalic Airway Syndrome. Brachycephalic airway syndrome is a clinical term that refers to increased airflow resistance caused by stenotic nostrils and nasal meatuses and an excessively long soft palate. These abnormalities are present in brachycephalic canine breeds such as bulldogs, boxers, Boston terriers, pugs, Pekingese, and others. The defects are a result of a mismatch of the ratio of soft tissue to cranial bone and the obstruction of airflow by excessive length of the palatine soft tissue. Secondary changes, such as nasal and laryngeal edema caused by forceful inspiration, eventually lead to severe upper airway obstruction, respiratory distress, and exercise intolerance.

Tracheal Hypoplasia. Tracheal hypoplasia occurs most often in English bulldogs and Boston terriers; the tracheal lumen is decreased in diameter throughout its length.

Inflammation

Canine Infectious Respiratory Disease. Canine infectious respiratory disease (CIRD), formerly called canine tracheobronchitis or kennel cough, is a highly contagious group of infectious diseases characterized clinically by an acute onset of coughing notably exacerbated by exercise. The term is nonspecific, much like the

[5]See E-Box 1-1 for potential, suspected, or known genetic disorders.

"common cold" in human beings or bovine respiratory disease complex (BRDC) in cattle. The infection occurs commonly as a result of mixing dogs from different origins such as occurs at commercial kennels, animal shelters, and veterinary clinics. Between bouts of coughing, most animals appear normal, although some have rhinitis, pharyngitis, tonsillitis, or conjunctivitis; some with secondary pneumonia become quite ill.

The pathogenesis of CIRD is complex, and many pathogens and environmental factors have been incriminated. *Bordetella bronchiseptica*, canine adenovirus-2 (CAV-2), and canine parainfluenza virus-2 (CPIV-2) are most commonly implicated. The severity of the disease is increased when more than one agent is involved or if there are extreme environmental conditions (e.g., poor ventilation). For example, dogs asymptomatically infected with *Bordetella bronchiseptica* are more severely affected by superinfection with CAV-2 than those not carrying the bacterium. Other agents are sometimes isolated but of lesser significance and include canine adenovirus-1 (CAV-1: infectious canine hepatitis virus), reovirus type 1, canid herpesvirus-1 (CaHV-1), canine respiratory coronavirus (CRCoV), and *Mycoplasma* species.

Depending on the agents involved, gross and microscopic lesions are completely absent or they vary from catarrhal to mucopurulent tracheobronchitis, with enlargement of the tonsils and retropharyngeal and tracheobronchial lymph nodes. In dogs with *Bordetella bronchiseptica* infection, the lesions are suppurative or mucopurulent rhinitis and tracheobronchitis, and suppurative bronchiolitis. In contrast, when lesions are purely viral, microscopic changes are focal necrosis of the tracheobronchial epithelium. Sequelae can include spread either proximally or distally in the respiratory tract, the latter sometimes inducing chronic bronchitis and bronchopneumonia.

Oslerus (Filaroides) osleri. *Oslerus* (*Filaroides*) *osleri* is a nematode parasite of dogs and other Canidae that causes characteristic protruding nodules into the lumen at the tracheal bifurcation. They are readily seen on endoscopic examination or at necropsy. In severe cases, these nodules can extend 5 cm cranially or caudally from the tracheal bifurcation and even into primary and secondary bronchi. The disease occurs worldwide, and *Oslerus osleri* is considered the most common respiratory nematode of dogs.

The gross lesions are variably sized, up to 1 cm, submucosal nodules that extend up to 1 cm into the tracheal lumen (Fig. 9-49, A). Microscopically, nodules contain adult parasites with a mild mononuclear cell reaction; with the death of the parasite, an intense foreign body reaction develops with neutrophils and giant cells (Fig. 9-49, B). Clinically, it can be asymptomatic, although it most often causes a chronic cough that can be exacerbated by exercise or excitement. Severe infestations can result in dyspnea, exercise intolerance, cyanosis, emaciation, and even death in young dogs.

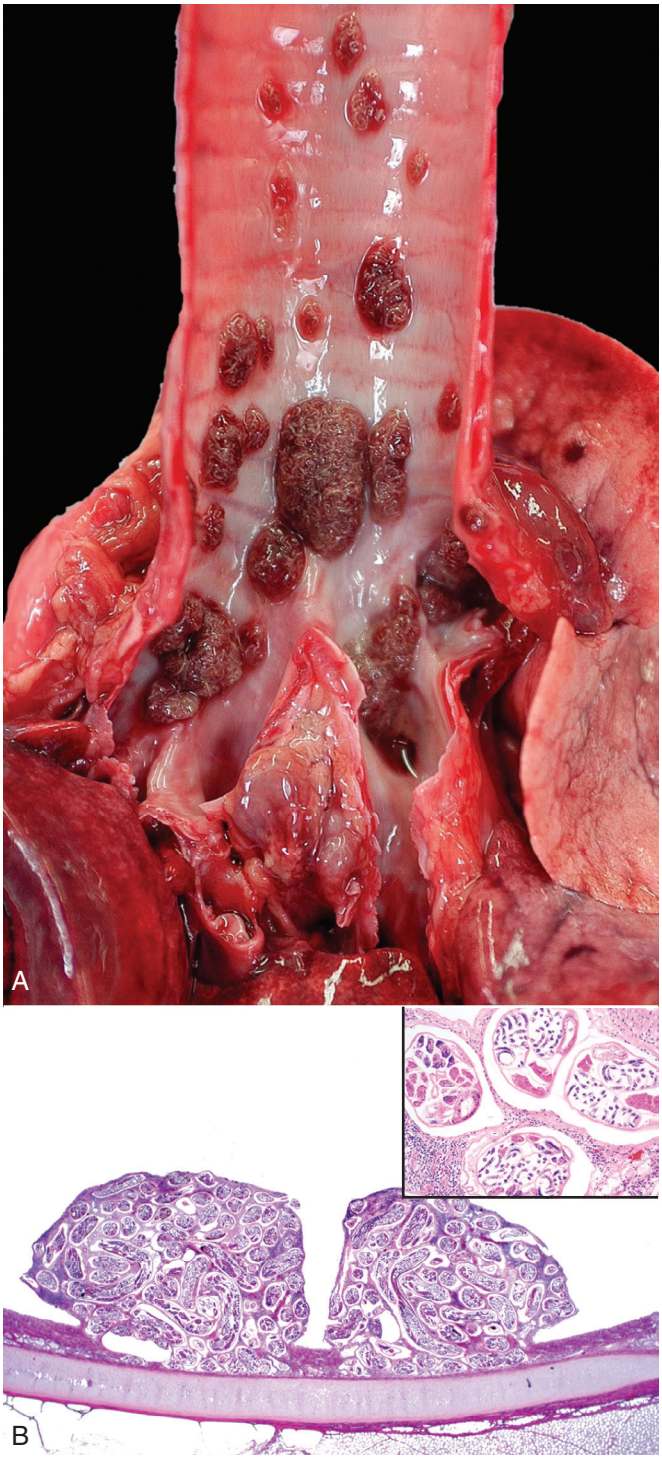


Figure 9-49 **Parasitic Tracheobronchitis (*Oslerus osleri*), Trachea and Main Bronchi, Dog. A,** Note the numerous large red-brown parasitic nodules on the mucosal surface of the distal trachea and main bronchi. These nodules cause clinical signs only in severe infections. **B,** Two parasitic nodules in the tracheal mucosa. *Inset*, Filarial forms of *Oslerus osleri* can be seen in the lamina propria of the tracheal mucosa. Numerous chronic inflammatory cells are also present. H&E stain. (**A** courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. **B** courtesy Dr. P.-Y. Daoust and Dr. A. López, Atlantic Veterinary College.)

Neoplasms of the Guttural Pouches, Larynx, and Trachea

Neoplasms of the Guttural Pouches

Neoplasms of the guttural pouches occur rarely in horses and are usually squamous cell carcinomas.

Neoplasms of the Larynx and Trachea

Laryngeal neoplasms are rare in dogs and extremely so in other species, although they have been reported in cats and horses.

The most common laryngeal neoplasms in dogs are papillomas and squamous cell carcinomas. Other less common tumors are laryngeal rhabdomyoma, previously referred to as *laryngeal oncocytoma*, and chondromas and osteochondromas. Lymphoma involving the laryngeal tissue is sporadically seen in cats.

When large enough to be obstructive, neoplasms may cause a change or loss of voice, cough, or respiratory distress with cyanosis, collapse, and syncope. Other signs include dysphagia, anorexia, and exercise intolerance. The neoplasm is sometimes visible from the oral cavity and causes swelling of the neck. The prognosis is poor because most lesions recur after excision.

Tracheal neoplasms are even more uncommon than those of the larynx. The tracheal cartilage or mucosa can be the site of an osteochondroma, leiomyoma, osteosarcoma, mast cell tumor, and carcinoma. Lymphoma in cats can extend from the mediastinum to involve the trachea.

Disorders of the Lungs

Species Differences

Each lung is subdivided into various numbers of pulmonary lobes (see Fig. 9-16). In the past, these were defined by anatomic fissures. However, in current anatomy, lobes are defined by the ramification of the bronchial tree. Following this criterion, the left lung of all domestic species is composed of cranial and caudal lobes, whereas the right lung, depending on species, is composed of cranial, middle (absent in horse), caudal, and accessory lobes. Each pulmonary lobe is further subdivided by connective tissue into pulmonary lobules, which in some species (cattle and pigs) are rather prominent and in others are much less conspicuous. From a practical standpoint, identification of the lungs among different species could be achieved by carefully observing the degree of lobation (external fissures) and the degree of lobulation (connective tissue between lobules). Cattle and pigs have well-lobated and well-lobulated lungs; sheep and goats have well-lobated but poorly lobulated lungs; horses have both poorly lobated and poorly lobulated lungs and resemble human lungs; finally, dogs and cats have well-lobated but not well-lobulated lungs. The degree of lobulation determines the degree of air movement between the lobules. In pigs and cattle, movement of air between lobules is practically absent because of the thick connective tissue of the interlobular septa separating individual lobules. This movement of air between lobules and between adjacent alveoli (via the pores of Kohn) constitutes what is referred to as collateral ventilation. This collateral ventilation is poor in cattle and pigs and good in dogs. The functional implications of collateral ventilation are discussed in the section on Pulmonary Emphysema.

The lungs have an interconnecting network of interstitial stromal tissue supporting the blood and lymphatic vessels, nerves, bronchi, bronchioles, and alveoli. For purposes of simplicity, the pulmonary interstitium can be anatomically divided into three contiguous compartments: (1) bronchovascular interstitium, where main bronchi and pulmonary vessels are situated; (2) interlobular interstitium separating pulmonary lobules and supporting small blood and lymph vessels; and (3) alveolar interstitium supporting the alveolar walls that contain pulmonary capillaries and alveolar epithelial cells (no lymphatic vessels here) (see discussion on the blood-air barrier in the section on Alveoli). Pulmonary changes, such as edema, emphysema, and inflammation, may affect one or more of these interstitial compartments.

Disorders of the Lung (Bronchioles, Bronchi, and Alveoli) in Domestic Animals

Anomalies[6]

Congenital anomalies of the lungs are rare in all species but are most commonly reported in cattle and sheep. Compatibility with life largely depends on the type of structures involved and the proportion of functional tissue present at birth. Accessory lungs are one of the most common anomalies and consist of distinctively lobulated masses of incompletely differentiated pulmonary tissue present in the thorax, abdominal cavity, or subcutaneous tissue virtually anywhere in the trunk. Large accessory lungs can cause dystocia. Ciliary dyskinesia (immotile cilia syndrome, Kartagener's syndrome) is characterized by defective ciliary movement, which results in reduced mucociliary clearance because of a defect in the microtubules of all ciliated cells and, most important, in the ciliated respiratory epithelium and spermatozoa. Primary ciliary dyskinesia often associated with situs inversus has been reported in dogs, which as a result usually have chronic recurrent rhinosinusitis, pneumonia, and infertility. Pulmonary agenesis, pulmonary hypoplasia, abnormal lobulation, congenital emphysema, lung hamartoma, and congenital bronchiectasis are occasionally seen in domestic animals. Congenital melanosis is a common incidental finding in pigs and ruminants and is usually seen at slaughter (Fig. 9-50). It is characterized by black spots, often a few centimeters in diameter, in various organs, mainly the lungs, meninges, intima of the aorta, and caruncles of the uterus. Melanosis has no clinical significance, and the texture of pigmented lungs remains unchanged. Congenital emphysema is sporadically seen in dogs (E-Fig. 9-4).

Metabolic Disturbances

Pulmonary Calcification ("Calcinosis"). Calcification of the lungs occurs in some hypercalcemic states, generally secondary to hypervitaminosis D or from ingestion of toxic (hypercalcemic) plants, such as *Solanum malacoxylon* (Manchester wasting disease), that contain vitamin D analogs. It is also a common sequela to uremia and hyperadrenocorticism in dogs and to pulmonary necrosis (dystrophic calcification) in most species. Calcified lungs may fail to collapse when the thoracic cavity is opened and have a characteristic "gritty" texture (Fig. 9-51). Microscopically, lesions vary from calcification of the alveolar basement membranes (see

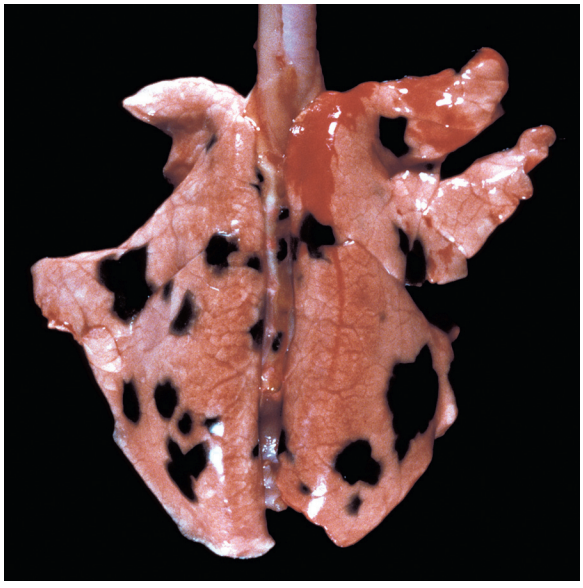
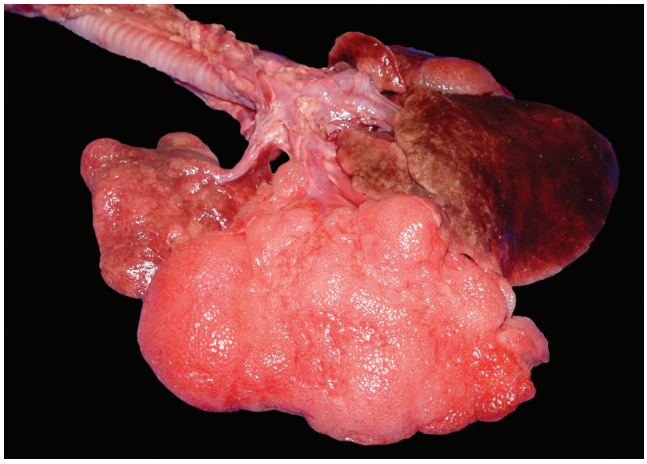


Figure 9-50 Pulmonary Melanosis, Lungs, Pig. Note the areas of black (melanin pigment) discoloration of the pleural surface. This pigmentation extends into the lungs and is an incidental finding that has no clinical or pathologic significance. It is most common in "black-face" breeds of animals, especially sheep. (Courtesy College of Veterinary Medicine, University of Illinois.)

[6]See E-Box 1-1 for potential, suspected, or known genetic disorders.



E-Figure 9-4 **Pulmonary Emphysema, Congenital, Dog.** The left cranial lobe shows severe emphysematous distention of the pulmonary parenchyma. On palpation, affected lung is notably crepitus. (Courtesy Dr. A. Bourque, Atlantic Veterinary College.)

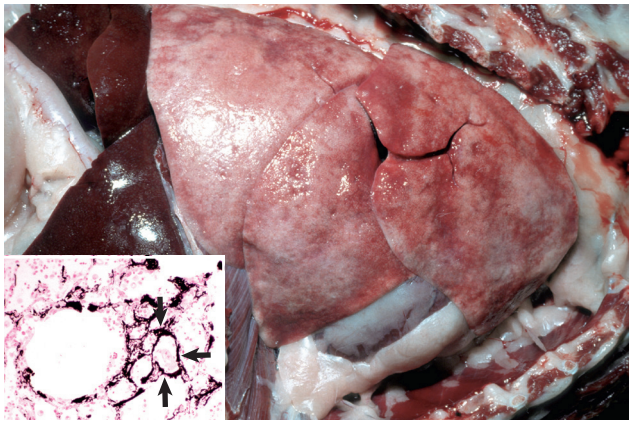


Figure 9-51 Uremic Pneumopathy From Chronic Renal Failure, Lung, 4-Year-Old Dog. The lungs have failed to collapse when the thorax was opened because of extensive mineralization of alveolar walls. *Inset*, Calcification *(black)* of alveolar septa. Note the linear deposits of mineral in the alveolar septa *(arrows)*. von Kossa stain with nuclear fast red counterstain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Fig. 9-51) to heterotopic ossification of the lungs (E-Fig. 9-5). In most cases, pulmonary calcification in itself has little clinical significance, although its cause (e.g., uremia or vitamin D toxicosis) may be very important.

Alveolar Filling Disorders

Alveolar filling disorders are a heterogeneous group of lung diseases characterized by accumulation of various chemical compounds in the alveolar lumens. The most common are *alveolar proteinosis*, in which the alveoli are filled with finely granular eosinophilic material; *pulmonary lipidosis*, in which alveoli are filled with macrophages containing endogenous or exogenous lipid; and *alveolar microlithiasis*, in which the alveoli contain numerous concentric calcified "microliths" or "calcospherites." A similar but distinct concretion is known as *corpora amylacea*, which is an accumulation of laminated bodies composed of cellular debris, lipids, proteins, and possibly amyloid. For most alveolar filling disorders, there is little host response, and in many cases, it is an incidental finding. Most of the alveolar filling disorders originate from inherited metabolic defects in which alveolar cells (epithelial or macrophages) cannot properly metabolize or remove lipids or proteins, whereas others result from an excessive synthesis of these substances in the lung.

Endogenous Lipid (Lipoid) Pneumonia. Endogenous lipid pneumonia is an obscure, subclinical pulmonary disease of cats and occasionally of dogs, which is unrelated to aspiration of foreign material. Although the pathogenesis is not understood, it is presumed that lipids from pulmonary surfactant and from degenerated cells accumulate within alveolar macrophages. Accumulation of surfactant lipids can occur in metabolic abnormalities of alveolar macrophages or in bronchial obstruction where surfactant-laden macrophages cannot exit the lungs via the mucociliary escalator. The gross lesions are multifocal, white, firm nodules scattered throughout the lungs (E-Fig. 9-6). Microscopically, the alveoli are filled with foamy lipid-laden macrophages accompanied by interstitial infiltration of lymphocytes and plasma cells, fibrosis, alveolar epithelialization, and, in some cases, cholesterol clefts and lipid granulomas.

Lipid (lipoid) pneumonia occurs frequently in the vicinity of cancerous lung lesions in human beings, cats, and dogs. The reason for this association remains unknown and frequently unrecognized by pathologists. Recent investigations suggest that excessive lipid originates from the breakdown products of neoplastic cells. Bronchial and bronchiolar obstructions such as those caused by lungworms can also cause alveolar lipidosis. The pathogenesis relates to the inability of alveolar macrophages that normally remove part of the surfactant lipids to exit the lung via the mucociliary escalator.

Exogenous Lipid Pneumonia. Another form of lipid pneumonia occurs accidentally in cats or horses given mineral oil by their owners in an attempt to remove hairballs or treat colic (aspiration pneumonia).

Inflation Disturbances of the Lung

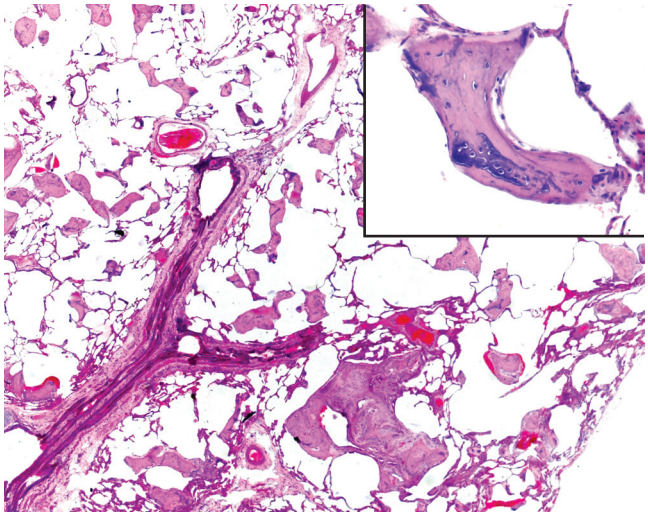
To achieve gaseous exchange, a balanced ratio of the volumes of air to capillary blood must be present in the lungs (ventilation/perfusion ratio), and the air and capillary blood must be in close proximity across the alveolar wall. A ventilation-perfusion mismatch occurs if pulmonary tissue is either collapsed (atelectasis) or overinflated (hyperinflation and emphysema).

Atelectasis (Congenital and Acquired). The term *atelectasis* means incomplete distention of alveoli and is used to describe lungs that have failed to expand with air at the time of birth (congenital or neonatal atelectasis) or lungs that have collapsed after inflation has taken place (acquired atelectasis or alveolar collapse) (Figs. 9-52 and 9-53).

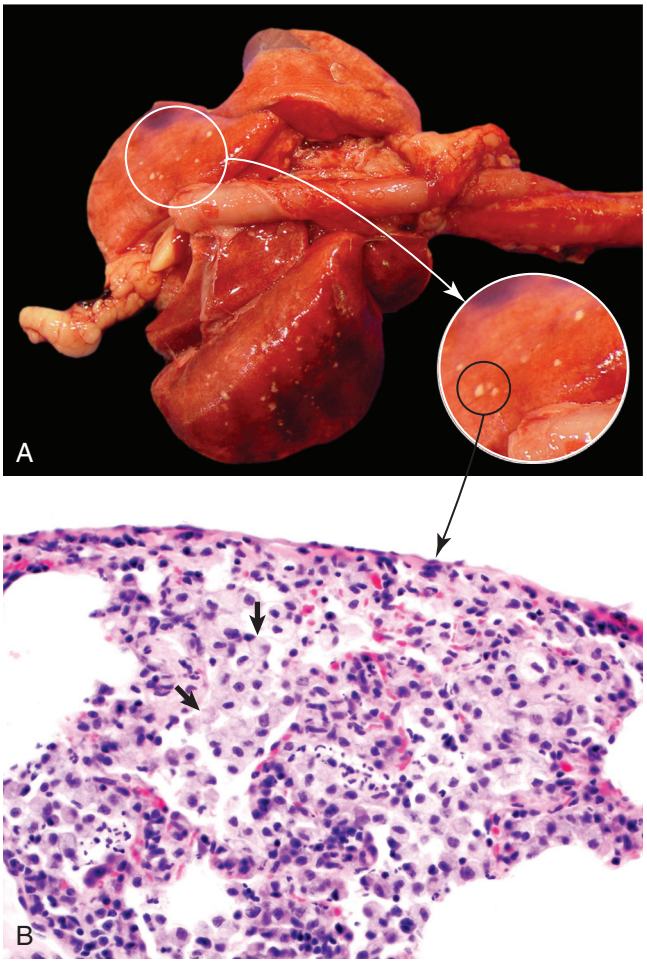
During fetal life, lungs are not fully distended, contain no air, and are partially filled with a locally produced fluid known as fetal lung fluid. Not surprisingly, lungs of aborted and stillborn fetuses sink when placed in water, whereas those from animals that have breathed float. At the time of birth, fetal lung fluid is rapidly reabsorbed and replaced by inspired air, leading to the normal distention of alveoli. Congenital atelectasis occurs in newborns that fail to inflate their lungs after taking their first few breaths of air; it is caused by obstruction of airways, often as a result of aspiration of amniotic fluid and meconium (described in the section on Meconium Aspiration Syndrome) (see Fig. 9-52). Congenital atelectasis also develops when alveoli cannot remain distended after initial aeration because of an alteration in quality and quantity of pulmonary surfactant produced by type II pneumonocytes and Club (Clara) cells. This infant form of congenital atelectasis is referred to in human neonatology as infant respiratory distress syndrome (IRDS) or as hyaline membrane disease because of the clinical and microscopic features of the disease. It commonly occurs in babies who are premature or born to diabetic or alcoholic mothers and is occasionally found in animals, particularly foals and piglets. The pathetic, gasping attempts of affected foals and pigs to breathe have prompted the use of the name "barkers"; foals that survive may have brain damage from cerebral hypoxia (see Chapter 14) and are referred to as "wanderers" due to their aimless behavior and lack of a normal sense of fear.

Acquired atelectasis is much more common and occurs in two main forms: compressive and obstructive (see Fig. 9-53). Compressive atelectasis has two main causes: space-occupying masses in the pleural cavity, such as abscesses and tumors, or transferred pressures, such as that caused by bloat, hydrothorax, hemothorax, chylothorax, and empyema (Fig. 9-54). Another form of compressive atelectasis occurs when the negative pressure in the thoracic cavity is lost because of pneumothorax. This form generally has massive atelectasis and thus is also referred to as lung collapse.

Obstructive (absorption) atelectasis occurs when there is a reduction in the diameter of the airways caused by mucosal edema and inflammation, or when the lumen of the airway is blocked by



E-Figure 9-5 **Pulmonary Ossification, Lung, Dog.** Numerous spicules of bone are replacing and destroying the alveolar walls. *Inset,* Bone spicule showing osteocytes and chondrocytes. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-6 **Pulmonary Lipidosis, Lung, Cat. A,** Numerous small (0.2 to 0.4 cm) white foci containing lipid are scattered throughout all pulmonary lobes. Pulmonary lipidosis is often an incidental finding. *White circle,* Closeup of these nodules. **B,** Aggregates of lipid-laden macrophages *(arrows)* in alveoli and bronchioles. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

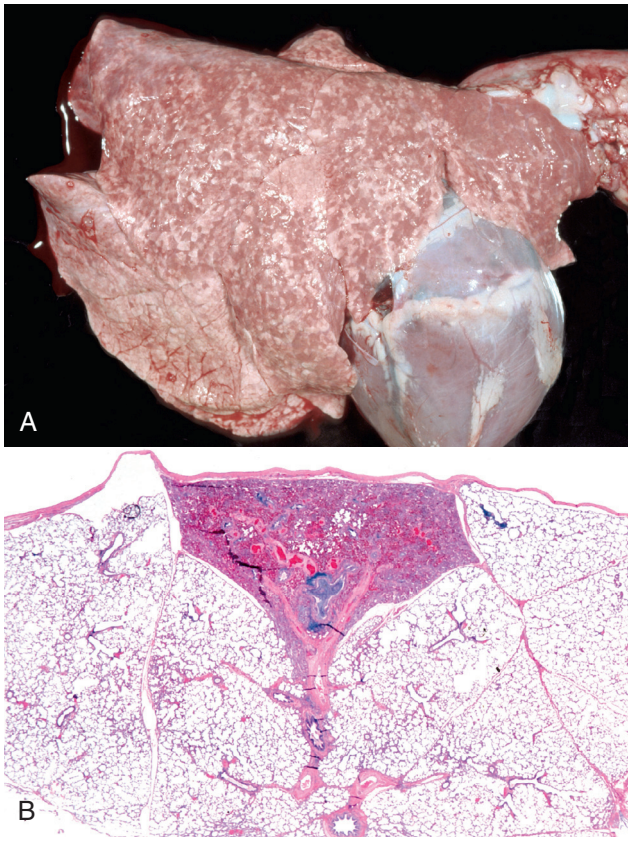


Figure 9-52 Pulmonary Atelectasis. A, Multifocal neonatal atelectasis of the lung from 1-day-old calf. Note the prominent mosaic pattern of normally inflated *(lighter)* and atelectatic, uninflated *(darker)* lobules. Neonatal atelectasis is caused by aspiration of amniotic fluid, meconium, and squamous epithelial cells, causing obstruction of small bronchi and bronchioles at the time of birth. All pulmonary lobes are involved. Although focal lobular atelectasis is commonly seen in neonates, this lesion suggests that the fetus was acidotic and aspirated amniotic fluid. **B,** Atelectasis of a superficial pulmonary lobule *(upper center of image)* in a cow. Note the absence of air in alveoli of this lobule that has resulted in its collapse and thus its darker color as shown in **A.** H&E stain. (**A** from López A, Bildfell R: *Vet Pathol* 29:104-111, 1992. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

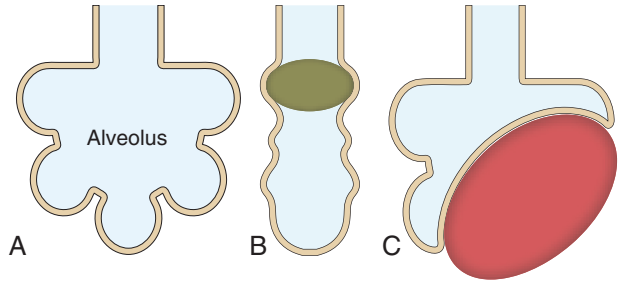


Figure 9-53 Types of Atelectasis. A, Normal alveolar distention. **B,** Obstructive atelectasis; obstruction of airways (i.e., exudate or parasite) affecting airflow and causing alveolar collapse. **C,** Compressive atelectasis; mass (i.e., abscess or tumor) compressing the lung parenchyma and causing alveolar collapse. (Redrawn from Dr. A. López, Atlantic Veterinary College.)

mucus plugs, exudate, aspirated foreign material, or lungworms (see Fig. 9-53). When the obstruction is complete, trapped air in the lung eventually becomes reabsorbed. Unlike the compression type, obstructive atelectasis often has a lobular pattern as a result of blockage of the airway supplying that lobule. This lobular

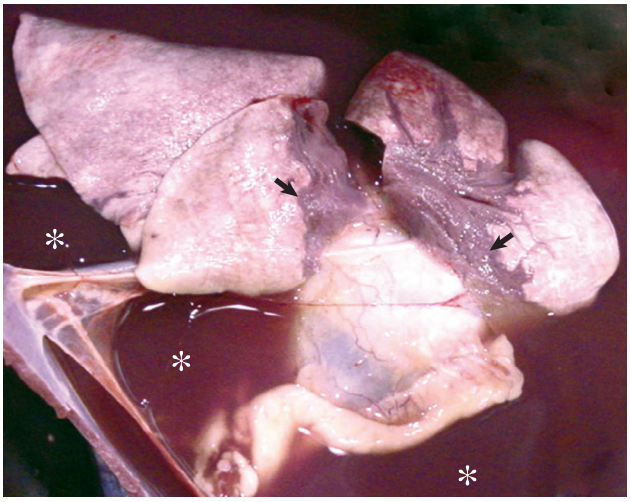


Figure 9-54 Compressive Atelectasis and Hydrothorax, Lungs, Dog. Atelectatic lung appears as dark depressed pulmonary tissues *(arrows)*. Also note a large volume of transudate in the ventral pleural cavity *(asterisks)*. (Courtesy Atlantic Veterinary College.)

appearance of atelectasis is more common in species with poor collateral ventilation, such as cattle and pigs. The extent and location of obstructive atelectasis depends largely on the size of the affected airway (large vs. small) and on the degree of obstruction (partial vs. complete).

Atelectasis also occurs when large animals are kept recumbent for prolonged periods, such as during anesthesia (hypostatic atelectasis). The factors contributing to hypostatic atelectasis are a combination of blood-air imbalance, shallow breathing, airway obstruction because of mucus and fluid that has not been drained from bronchioles and alveoli, and from inadequate local production of surfactant. Atelectasis can also be a sequel to paralysis of respiratory muscles and prolonged use of mechanical ventilation or general anesthesia in intensive care.

In general, the lungs with atelectasis appear depressed below the surface of the normally inflated lung. The color is generally dark blue, and the texture is flabby or firm; they are firm if there is concurrent edema or other processes, such as can occur in ARDS or "shock" lungs (see the section on Pulmonary Edema). Distribution and extent vary with the process, being patchy (multifocal) in congenital atelectasis, lobular in the obstructive type, and of various degrees in between in the compressive type. Microscopically, the alveoli are collapsed or slitlike and the alveolar walls appear parallel and close together, giving prominence to the interstitial tissue even without any superimposed inflammation.

Pulmonary Emphysema. Pulmonary emphysema, often simply referred to as *emphysema*, is an extremely important primary disease in human beings, whereas in animals, it is always a secondary condition resulting from a variety of pulmonary lesions. In human medicine, emphysema is strictly defined as an abnormal permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls (alveolar emphysema). This definition separates it from simple airspace enlargement or hyperinflation, in which there is no destruction of alveolar walls and which can occur congenitally (Down syndrome) or be acquired with age (aging lung, sometimes misnamed "senile emphysema"). The pathogenesis of emphysema in human beings is still controversial, but current thinking overwhelmingly suggests that destruction of

alveolar walls is largely the result of an imbalance between proteases released by phagocytes and antiproteases produced in the lung as a defense mechanism (the protease-antiprotease theory). The destructive process in human beings is markedly accelerated by defects in the synthesis of antiproteases or any factor, such as cigarette smoking or pollution, that increases the recruitment of macrophages and leukocytes in the lungs. This theory originated when it was found that human beings with homozygous α_1-antitrypsin deficiency were remarkably susceptible to emphysema and that proteases (elastase) inoculated intratracheally into the lungs of laboratory animals produced lesions similar to those found in the disease. More than 90% of the problem relates to cigarette smoking, and airway obstruction is no longer considered to play a major role in the pathogenesis of emphysema in human beings.

Primary emphysema does not occur in animals, and thus no animal disease should be called simply emphysema. In animals, this lesion is always secondary to obstruction of outflow of air or is agonal at slaughter. Secondary pulmonary emphysema occurs frequently in animals with bronchopneumonia, in which exudate plugging bronchi and bronchioles causes an airflow imbalance where the volume of air entering exceeds the volume leaving the lung. This airflow imbalance is often promoted by the so-called one-way valve effect caused by the exudate, which allows air into the lung during inspiration but prevents movement of air out of the lung during expiration.

Depending on the localization in the lung, emphysema can be classified as alveolar or interstitial. Alveolar emphysema characterized by distention and rupture of the alveolar walls, forming variably sized air bubbles in pulmonary parenchyma, occurs in all species. Interstitial emphysema occurs mainly in cattle, presumably because of their wide interlobular septa, and lack of collateral ventilation in these species does not permit air to move freely into adjacent pulmonary lobules. As a result, accumulated air penetrates the alveolar and bronchiolar walls and forces its way into the interlobular connective tissue, causing notable distention of the interlobular septa. It is also suspected that forced respiratory movements predispose to interstitial emphysema when air at high pressure breaks into the loose connective tissue of the interlobular septa (Fig. 9-55). Sometimes these bubbles of trapped air in alveolar or interstitial emphysema become confluent, forming large (several centimeters in diameter) pockets of air that are referred to as *bullae* (singular: bulla) (see E-Fig. 9-4); the lesion is then called *bullous emphysema*. This lesion is not a specific type of emphysema and does not indicate a different disease process but, rather, is a larger accumulation of air at one focus. In the most severe cases, air moves from the interlobular septa into the connective tissue surrounding the main stem bronchi and major vessels (bronchovascular bundles), and from here it leaks into the mediastinum, causing pneumomediastinum first, and eventually exits via the thoracic inlet into the cervical and thoracic subcutaneous tissue causing subcutaneous emphysema.

Note that mild and even moderate alveolar emphysema is difficult to judge at necropsy and by light microscopy unless special techniques are used to prevent collapse of the lung when the thorax is opened. These techniques include plugging of the trachea or intratracheal perfusion of fixative (10% neutral-buffered formalin) before the thorax is opened to prevent collapse of the lungs. Important diseases that cause secondary pulmonary emphysema in animals include small airway obstruction (e.g., heaves) in horses and pulmonary edema and emphysema (fog fever) in cattle (see Fig. 9-55) and exudates in bronchopneumonia. Congenital emphysema occurring secondary to bronchial cartilage hypoplasia with subsequent bronchial collapse is occasionally reported in dogs.

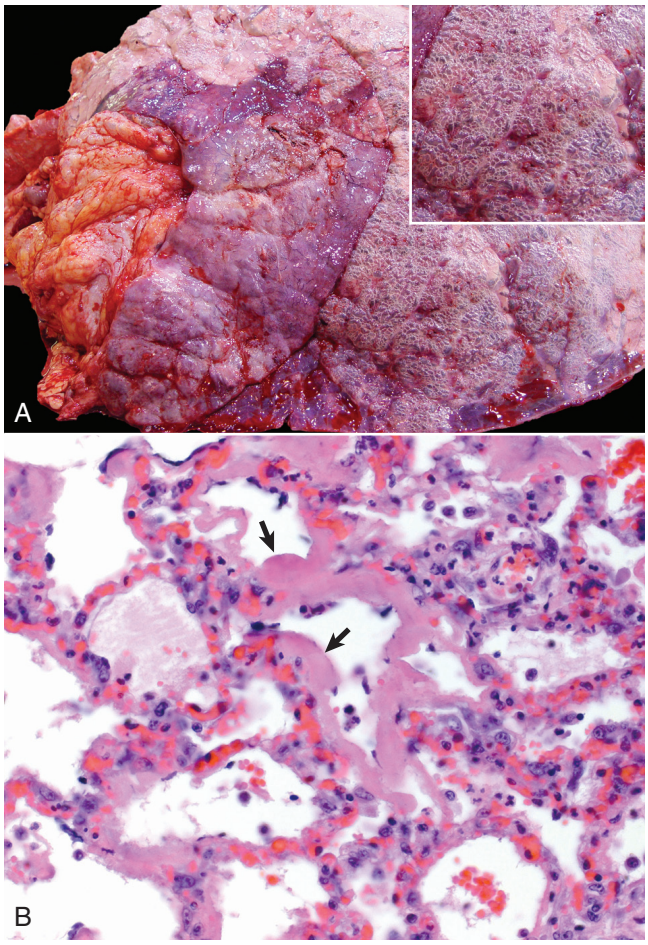


Figure 9-55 Bovine Pulmonary Edema and Emphysema (Fog Fever), Lung, Cow. A, Emphysema, edema, and interstitial pneumonia involving all pulmonary lobes. Note the variably sized air bubbles in the interlobular septa and pulmonary parenchyma. The texture of these lungs would be notably crepitus as a result of the accumulation of air in pulmonary parenchyma. *Inset,* Closer view of air bubbles in the parenchyma. **B,** Note the thick eosinophilic hyaline membranes *(arrows)* lining the alveoli. The alveoli are dilated and also contain some edema fluid, occasional pulmonary macrophages, and necrotic alveolar cells. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Circulatory Disturbances of the Lungs

Lungs are extremely well-vascularized organs with a dual circulation provided by pulmonary and bronchial arteries. Disturbances in pulmonary circulation have a notable effect on gaseous exchange, which may result in life-threatening hypoxemia and acidosis. In addition, circulatory disturbances in the lungs can have an impact on other organs, such as the heart and liver. For example, impeded blood flow in the lungs because of chronic pulmonary disease results in cor pulmonale, which is caused by unremitting pulmonary hypertension followed by cardiac dilation, right heart failure, chronic passive congestion of the liver (nutmeg liver), and generalized edema (anasarca).

Hyperemia and Congestion. Hyperemia is an active process that is part of acute inflammation, whereas congestion is the passive process resulting from decreased outflow of venous blood, as occurs in congestive heart failure (Fig. 9-56). In the early acute stages of pneumonia, the lungs appear notably red, and microscopically, blood vessels and alveolar capillaries are engorged with blood from

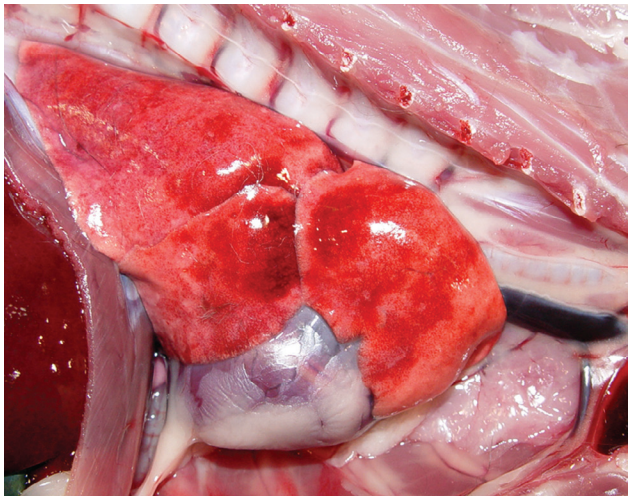


Figure 9-56 Acute Pulmonary Congestion, Lungs, Dog. The lung parenchyma is red because of congestion of pulmonary vasculature and alveolar capillaries. (Courtesy Dr. A. López, Atlantic Veterinary College.)

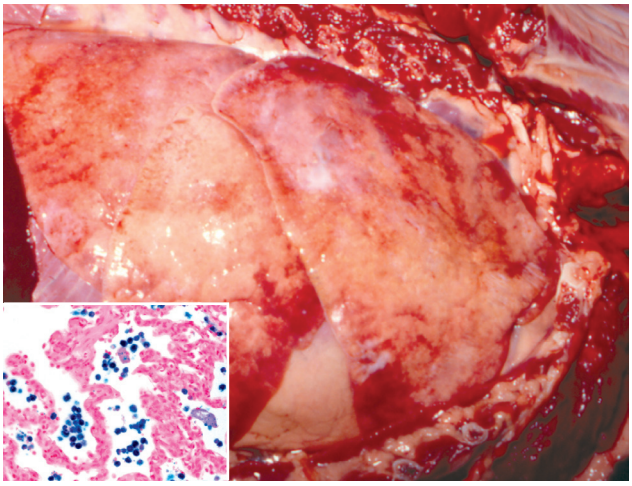


Figure 9-57 Chronic Pulmonary Congestion and Edema Because of Chronic Heart Failure (Dilative Cardiomyopathy), Lungs, 5-Year-Old Dog. The lungs have failed to collapse (fibrosis) and have a mottled and yellow-brown appearance (hemosiderosis). *Inset,* Microscopic view of alveoli. Large numbers of macrophages containing hemosiderin (heart failure cells *[blue color]*) are present in alveoli. During heart failure, red blood cells gain access to alveoli where they are rapidly phagocytosed by pulmonary macrophages and the iron of the hemoglobin molecule is converted to hemosiderin. Hemosiderin gives a positive reaction for iron with the Prussian blue reaction. Prussian blue (iron) reaction with nuclear fast red counterstain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

hyperemia. Pulmonary congestion is most frequently caused by heart failure, which results in stagnation of blood in pulmonary vessels, leading to edema and egression of erythrocytes into the alveolar spaces. As with any other foreign particle, erythrocytes in alveolar spaces are rapidly phagocytosed (erythrophagocytosis) by pulmonary alveolar macrophages. When extravasation of erythrocytes is severe, large numbers of macrophages with brown cytoplasm may accumulate in the bronchoalveolar spaces. The brown cytoplasm is the result of accumulation of considerable amounts of hemosiderin; these macrophages filled with iron pigment (siderophages) are generally referred to as *heart failure cells* (Fig. 9-57). The lungs of animals with chronic heart failure usually have a patchy red appearance with foci of brown discoloration because of accumulated hemosiderin. In severe and persistent cases of heart failure, the lungs fail to collapse because of edema and pulmonary fibrosis. Terminal pulmonary congestion (acute) is frequently seen in animals euthanized with barbiturates and should not be mistaken for an antemortem lesion.

Hypostatic congestion is another form of pulmonary congestion that results from the effects of gravity and poor circulation on a highly vascularized tissue, such as the lung. This type of gravitational congestion is characterized by the increase of blood in the lower side of the lung, particularly the lower lung of animals in lateral recumbency, and is most notable in horses and cattle. The affected portions of the lung appear dark red and can have a firmer texture. In animals and human beings who have been prostrated for extended periods of time, hypostatic congestion may be followed by hypostatic edema, and hypostatic pneumonia as edema interferes locally with the bacterial defense mechanisms.

Pulmonary Hemorrhage. Pulmonary hemorrhages can occur as a result of trauma, coagulopathies, and disseminated intravascular coagulation (DIC), vasculitis, sepsis, and pulmonary thromboembolism from jugular thrombosis or from embolism of exudate from a hepatic abscess that has eroded the wall and ruptured into the caudal vena cava (cattle). A gross finding often confused with intravital pulmonary hemorrhage is the result of severing both the trachea and the carotid arteries simultaneously at slaughter. Blood is aspirated from the transected trachea into the lungs, forming a random pattern of irregular red foci (1 to 10 mm) in one or more lobes. These red foci are readily visible on both the pleural and the cut surfaces of the lung, and free blood is visible in the lumens of bronchi and bronchioles.

Rupture of a major pulmonary vessel with resulting massive hemorrhage occurs occasionally in cattle when a growing abscess in a lung invades and disrupts the wall of a major pulmonary artery or vein (Fig. 9-58). In most cases, animals die rapidly, often with spectacular hemoptysis, and on postmortem examination, bronchi are filled with blood (see Fig. 9-58).

Pulmonary Edema. In normal lungs, fluid from the vascular space slowly but continuously passes into the interstitial tissue, where it is rapidly drained by the pulmonary and pleural lymphatic vessels. Clearance of alveolar fluid across the alveolar epithelium is also a major mechanism of fluid removal from the lung. Edema develops when the rate of fluid transudation from pulmonary vessels into the interstitium or alveoli exceeds that of lymphatic and alveolar removal (Fig. 9-59). Pulmonary edema can be physiologically classified as cardiogenic (hydrostatic; hemodynamic) and noncardiogenic (permeability) types.

Hydrostatic (cardiogenic) pulmonary edema develops when there is an elevated rate of fluid transudation because of increased hydrostatic pressure in the vascular compartment or decreased osmotic pressure in the blood. Once the lymph drainage has been overwhelmed, fluid accumulates in the perivascular spaces, causing distention of the bronchovascular bundles and alveolar interstitium, and eventually leaks into the alveolar spaces. Causes of hemodynamic pulmonary edema include congestive heart failure (increased hydrostatic pressure); iatrogenic fluid overload; and disorders in which blood osmotic pressure is reduced, such as with hypoalbuminemia seen in some hepatic diseases, nephrotic syndrome, and protein-losing enteropathy. Hemodynamic pulmonary edema also occurs when lymph drainage is impaired, generally secondary to neoplastic invasion of lymphatic vessels.

Permeability edema (inflammatory) occurs when there is excessive opening of endothelial gaps or damage to the cells that constitute the blood-air barrier (endothelial cells or type I pneumonocytes).

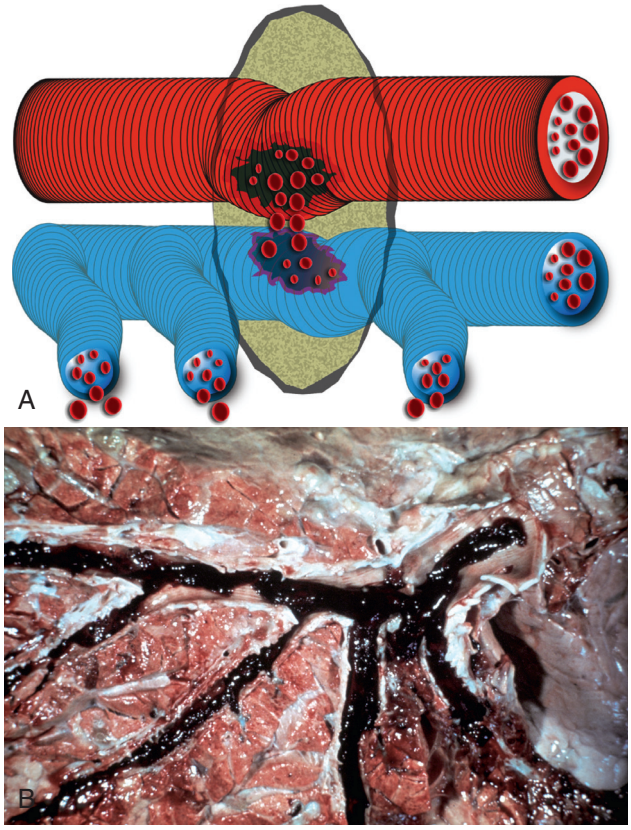


Figure 9-58 Fatal Pulmonary Hemorrhage. A, Schematic of an abscess *(green)* eroding the wall of a major pulmonary artery *(red)* and causing bleeding into the airways *(blue)*. **B,** Cut surface of lung, cow. Major bronchi and the trachea are filled with clotted dark red blood. This cow died unexpectedly, with severe respiratory distress and blood coming from the nose and mouth. A large abscess in the lung had eroded through the wall of a major pulmonary vessel. (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** courtesy Dr. R. Curtis, Atlantic Veterinary College.)

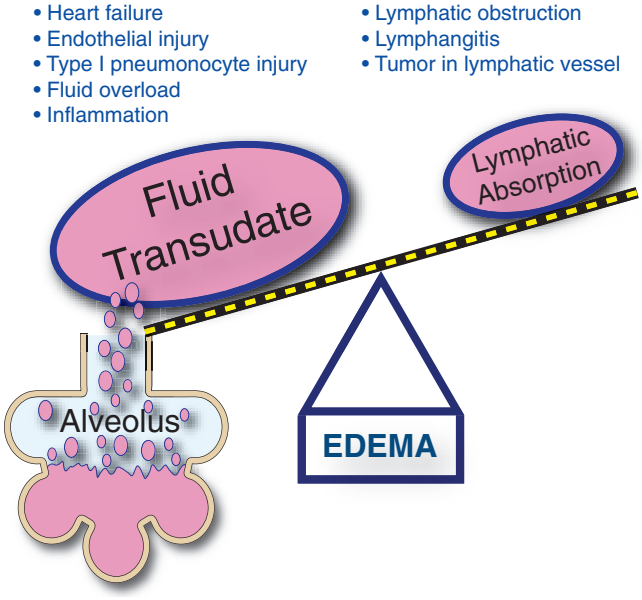


Figure 9-59 Pathogenesis of Pulmonary Edema. (Courtesy Dr. A. López, Atlantic Veterinary College.)

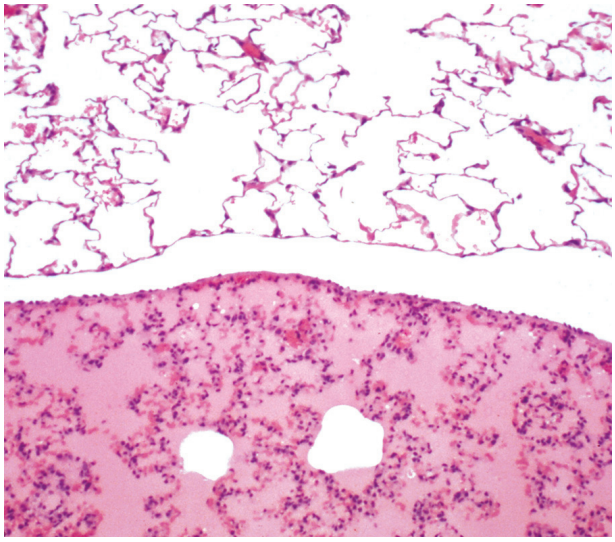
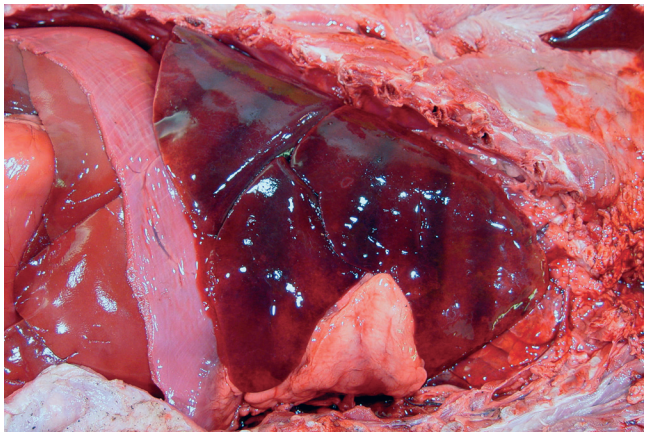


Figure 9-60 Pulmonary Edema, Lung, Rat. Normal lung with alveoli filled with air *(top)* and lung with severe pulmonary edema characterized by transudation of protein-rich fluid (deeply eosinophilic *[pink-red]*) filling the alveoli and congested alveolar septa *(bottom)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

This type of edema is an integral and early part of the inflammatory response, primarily because of the effect of inflammatory mediators, such as leukotrienes, platelet-activating factor (PAF), cytokines, and vasoactive amines released by neutrophils, macrophages, mast cells, lymphocytes, endothelial cells, and type II pneumonocytes. These inflammatory mediators increase the permeability of the blood-air barrier. In other cases, permeability edema results from direct damage to the endothelium or type I pneumonocytes, allowing plasma fluids to move freely from the vascular space into the alveolar lumen (Fig. 9-60 and see Fig. 9-14). Because type I pneumonocytes are highly vulnerable to some pneumotropic viruses (influenza and BRSV), toxicants (nitrogen dioxide [NO_2], sulfur dioxide [SO_2], hydrogen sulfide [H_2S], and 3-methylindole), and particularly to free radicals, it is not surprising that permeability edema commonly accompanies many viral or toxic pulmonary diseases. A permeability edema also occurs when endothelial cells in the lung are injured by bacterial toxins, sepsis, ARDS, DIC, anaphylactic shock, milk allergy, paraquat toxicity, adverse drug reactions, and smoke inhalation (E-Fig. 9-7).

The concentration of protein in edematous fluid is greater in permeability edema (exudate) than in hemodynamic edema (transudate); this difference has been used clinically in human medicine to differentiate one type of pulmonary edema from another. Microscopically, because of the higher concentration of protein, edema fluid in lungs with inflammation or damage to the blood-air barrier tends to stain more intensely eosinophilic than that of the hydrostatic edema from heart failure.

Grossly, the edematous lungs—independent of the cause—are wet and heavy. The color varies, depending on the degree of congestion or hemorrhage, and fluid may be present in the pleural cavity. If edema is severe, the bronchi and trachea contain considerable amounts of foamy fluid, which originates from the mixing of edema fluid and air (Fig. 9-61). On cut surfaces, the lung parenchyma oozes fluid like a wet sponge. In cattle and pigs that have distinct lobules, the lobular pattern becomes rather accentuated because of edematous distention of lymphatic vessels in the interlobular septa and the edematous interlobular septum itself (Fig. 9-62). Severe pulmonary edema may be impossible to differentiate from peracute pneumonia;



E-Figure 9-7 Smoke Inhalation, Lung, Dog. Lungs from a dog that died during a house fire. The lungs fail to collapse, show purple costal imprints on the pleura, and have diffuse congestion/hemorrhage and edema. Carbon particles were identified in the airways with histologic examination. (Courtesy Dr. S. Martinson, Atlantic Veterinary College.)

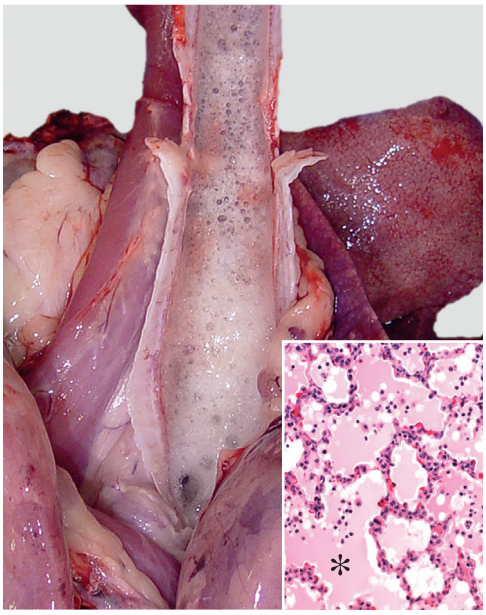


Figure 9-61 **Pulmonary Edema, Lungs and Trachea, Sepsis, Sheep.** Note large amounts of foamy fluid in the trachea and uncollapsed lungs with wet appearance. *Inset,* Alveoli filled with protein-rich edematous fluid *(light pink color [asterisk])* admixed with few inflammatory cells. H&E stain. (Courtesy Dr. C. Legge and Dr. A. López, Atlantic Veterinary College.)

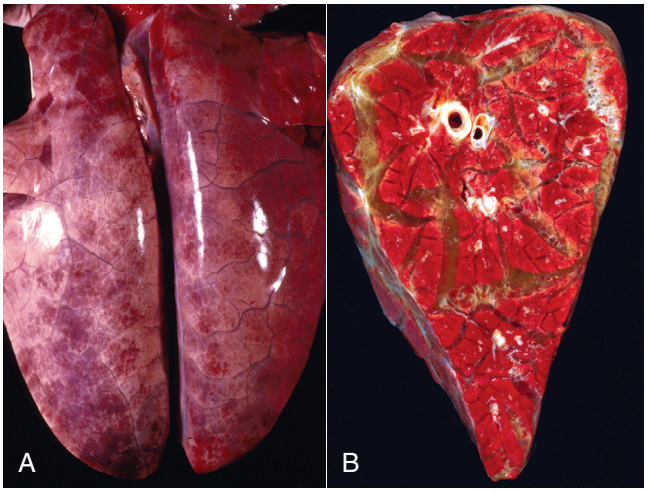


Figure 9-62 **Pulmonary Edema, Lungs, Pig. A,** The lungs are distended by edema fluid, which has resulted in rounded edges and edematous distention of the interlobular septa. **B,** The cut surface is wet and the interlobular septa are markedly distended with edema fluid. Lung lobules are also congested. (**A** and **B** courtesy College of Veterinary Medicine, University of Illinois.)

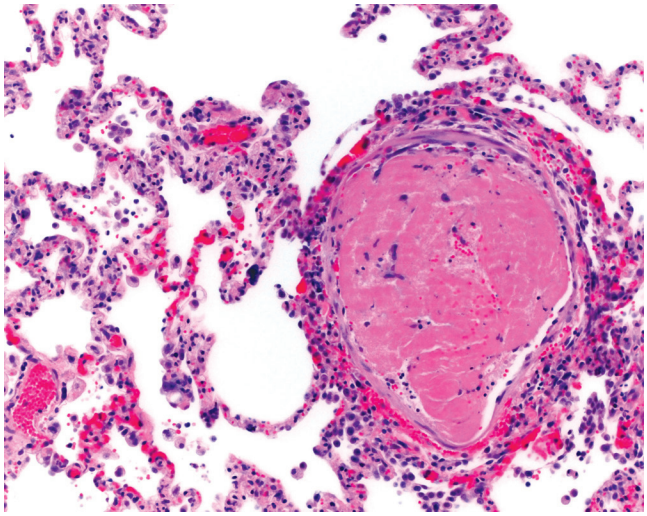
this fact is not surprising because pulmonary edema occurs in the very early stages of inflammation (see E-Fig. 9-7). Careful observation of the lungs at the time of necropsy is critical because diagnosis of pulmonary edema cannot be reliably performed microscopically. This is due in part to the loss of the edema fluid from the lungs during fixation with 10% neutral-buffered formalin and in part to the fact that the fluid itself stains very poorly or not at all with eosin because of its low protein content (hemodynamic edema). A protein-rich (permeability) edema is easier to visualize microscopically because it is deeply eosinophilic in hematoxylin and eosin (H&E)-stained sections (see Fig. 9-60), particularly if a fixative such as Zenker's solution, which precipitates protein, is used.

Acute Respiratory Distress Syndrome. Acute (adult) respiratory distress syndrome (ARDS; shock lung) is an important condition in human beings and animals characterized by pulmonary hypertension, intravascular aggregation of neutrophils in the lungs, acute lung injury, diffuse alveolar damage, permeability edema, and formation of hyaline membranes (Fig. 9-63). These membranes are a mixture of plasma proteins, fibrin, surfactant, and cellular debris from necrotic pneumonocytes (see Fig. 9-55, *B*). The pathogenesis of ARDS is complex and multifactorial but in general terms can be defined as diffuse alveolar damage that results from lesions in distant organs, from generalized systemic diseases, or from direct injury to the lung. Sepsis, major trauma, aspiration of gastric contents, extensive burns, and pancreatitis are some of the disease entities known to trigger ARDS. All these conditions provoke "hyperreactive macrophages" to directly or indirectly generate overwhelming amounts of cytokines causing what is known as a "cytokine storm." The main cytokines that trigger ARDS are TNF-α, interleukin (IL)-1, IL-6, and IL-8, which prime neutrophils previously recruited in the lung capillaries and alveoli to release cytotoxic enzymes and free radicals. These substances cause severe and diffuse endothelial and alveolar damage that culminates in a fulminating pulmonary edema (see Fig. 9-63). ARDS occurs in domestic animals and explains why pulmonary edema is one of the most common lesions found in many animals dying of sepsis, toxemia, aspiration of gastric contents, and pancreatitis, for example. A familial form of ARDS has been reported in Dalmatians. The pulmonary lesions in this syndrome are further discussed in the sections on Interstitial Pneumonia and Aspiration Pneumonia in Dogs.

Neurogenic pulmonary edema is another distinctive but poorly understood form of life-threatening lung edema in human beings that follows CNS injury and increased intracranial pressure (i.e., head injury, brain edema, brain tumors, or cerebral hemorrhage). This type of pulmonary edema can be experimentally reproduced in laboratory animals by injecting fibrin into the fourth ventricle. It involves both hemodynamic and permeability pathways presumably from massive sympathetic stimulation and overwhelming release of catecholamines. Neurogenic pulmonary edema has sporadically been reported in animals with brain injury or severe seizures or after severe stress and excitement.

Pulmonary Embolism. With its vast vascular bed and position in the circulation, the lung acts as a safety net to catch emboli before they reach the brain and other tissues. However, this positioning is often to its own detriment. The most common pulmonary emboli in domestic animals are thromboemboli, septic (bacterial) emboli, fat emboli, and tumor cell emboli.

Pulmonary thromboembolism (PTE) refers to both local thrombus formation and translocation of a thrombus present elsewhere in the venous circulation (Fig. 9-64). Fragments released inevitably reach the lungs and become trapped in the pulmonary vasculature (Fig. 9-65 and see Fig. 9-64). Small sterile thromboemboli are generally of little clinical or pathologic significance because they can be rapidly degraded and disposed of by the fibrinolytic system. Larger thromboemboli may cause small airway constriction, reduced surfactant production, pulmonary edema, and atelectasis resulting in hypoxemia, hyperventilation, and dyspnea. Parasites (e.g., *Dirofilaria immitis* and *Angiostrongylus vasorum*), endocrinopathies (e.g., hyperadrenocorticism and hypothyroidism), glomerulopathies, and hypercoagulable states can be responsible for pulmonary arterial thrombosis and pulmonary thromboembolism in dogs (E-Fig. 9-8). Pieces of



E-Figure 9-8 Thrombosis, Lung, Dog. Large, partially organized thrombus filling the entire lumen of a pulmonary artery *(right half of the figure)*. Also, there are macrophages and some neutrophils in the alveolar walls and alveolar spaces. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

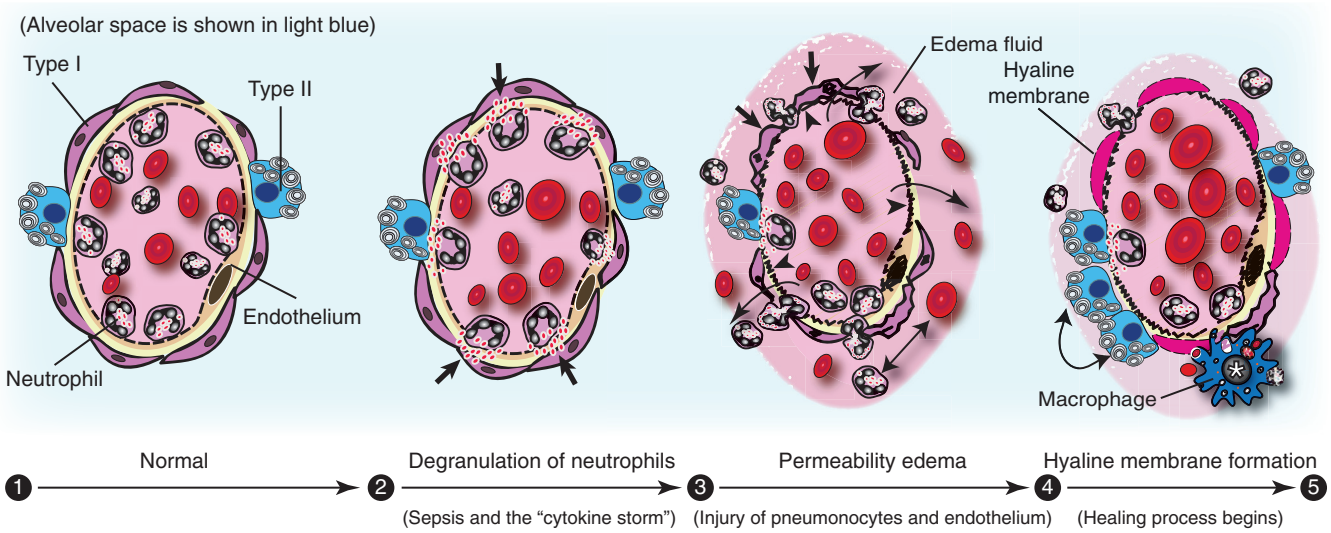


Figure 9-63 Cellular Events Leading to Acute Respiratory Distress Syndrome (ARDS) (Also See Fig. 9-104). *1,* Normal alveolar capillary externally covered by type I and type II pneumonocytes and internally by vascular endothelium (see Fig. 9-14 for more detail). *2,* At the early stages of sepsis, proinflammatory cytokines (interleukin 1 [IL-1] and tumor necrosis factor [TNF]) cause circulating neutrophils to adhere to the endothelial surface. Following a "cytokine storm," the marginated neutrophils further activated by inflammatory mediators suddenly release their cytoplasmic granules (proteolytic enzymes and elastases myeloperoxidase) into the surrounding milieu *(arrows). 3,* Enzymes released by these neutrophils cause injury to type I pneumonocytes *(arrows)* and endothelial cells *(arrowheads)*, disrupting the blood-air barrier and causing permeability edema *(curved arrows)*, alveolar hemorrhage *(double-headed arrow)*, and exocytosis of neutrophils into the alveolar space *(double-headed arrow). 4,* Extravasated plasma proteins admixed with surfactant and cell debris form thick hyaline membranes along the alveolar wall. *5,* In the unlikely event that the animal survives, the healing process starts with alveolar macrophages removing cellular debris, reabsorption of edema, and hyperplasia of type II pneumonocytes *(double-headed curved arrow)* that subsequently differentiate into type I pneumonocytes (see Fig. 9-14). (Courtesy Dr. A. López, Atlantic Veterinary College.)

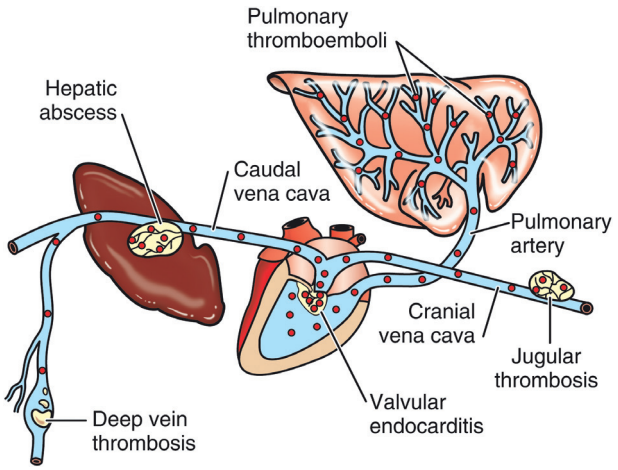


Figure 9-64 Sources of Pulmonary Emboli. Schematic diagram of pulmonary emboli *(red dots)* arising from (1) rupture of a hepatic abscess into the caudal vena cava, (2) vegetative valvular endocarditis (tricuspid valve), (3) jugular thrombosis, and (4) deep vein thrombosis. Pulmonary infarcts are rare and often of little clinical significance because of the lung's dual arterial circulation (i.e., pulmonary and bronchial arteries). (Redrawn with permission from Dr. A. López, Atlantic Veterinary College.)

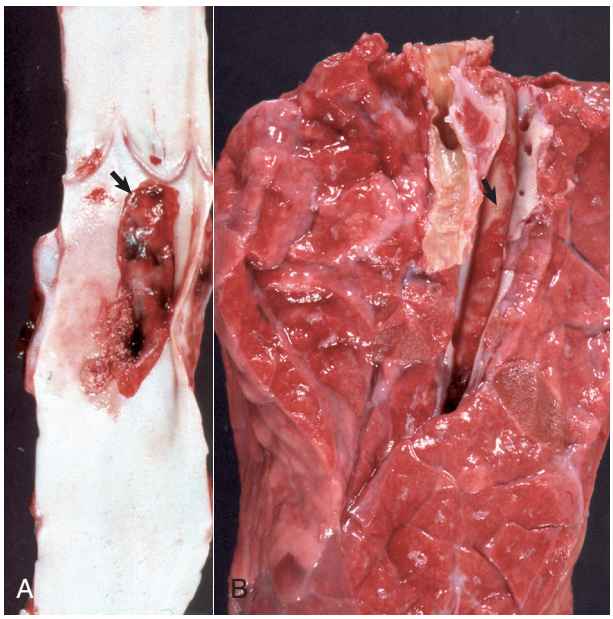


Figure 9-65 Jugular Thrombophlebitis and Pulmonary Thromboembolism, Jugular Vein and Lung, Cut Surface, Cow. A, The jugular vein has a large thrombus *(arrow)* attached to the wall at the site of prolonged catheterization. **B,** The pulmonary artery contains a large thrombus *(arrow)*, presumably a thromboembolus that has broken off the jugular mural thrombus. Note that the pulmonary thromboembolus is not attached to the wall of the pulmonary artery. (Courtesy Dr. A. López, Atlantic Veterinary College.)

thrombi breaking free from a jugular, femoral, or uterine vein can cause pulmonary thromboembolism. Pulmonary thromboembolisms occur in heavy horses after prolonged anesthesia (deep vein thrombosis), recumbent cows ("downer cow syndrome"), or in any animal undergoing long-term intravenous catheterization in which thrombi build up in the catheter and then break off (see Fig. 9-65).

Septic emboli, pieces of thrombi contaminated with bacteria or fungi and broken free from infected mural or valvular thrombi in the heart and vessels, eventually become entrapped in the pulmonary circulation. Pulmonary emboli originate most commonly from bacterial endocarditis (right side) and jugular thrombophlebitis in all species, hepatic abscesses that have eroded and discharged their contents into the caudal vena cava in cattle, and septic arthritis and omphalitis in farm animals (see Fig. 9-64). When present in large numbers, septic emboli may cause unexpected death because of massive pulmonary edema; survivors generally develop pulmonary arteritis and thrombosis and embolic (suppurative) pneumonia, which may lead to pulmonary abscesses.

Bone marrow and bone emboli can form after bone fractures or surgical interventions of bone. These are not as significant a problem in domestic animals as they are in human beings. Brain emboli (i.e., pieces of brain tissue) in the pulmonary vasculature reported in severe cases of head injury in human beings have recently been recognized in the bovine lung after strong pneumatic stunning at slaughter (captive bolt) (Fig. 9-66, *A*). Although obviously not important as an antemortem pulmonary lesion, brain emboli are intriguing as a potential risk for public health control of bovine spongiform encephalopathy (BSE). Fragments of hair can also embolize to the lung following intravenous injections (see Fig. 9-66, *B*). Hepatic emboli formed by circulating pieces of fragmented liver occasionally become trapped in the pulmonary vasculature after severe abdominal trauma and hepatic rupture (see Fig. 9-66, *C*). Megakaryocytes trapped in alveolar capillaries are a common but incidental microscopic finding in the lungs of all species, particularly dogs (see Fig. 9-66, *D*). Tumor emboli (e.g., osteosarcoma and hemangiosarcoma in dogs and uterine carcinoma in cattle) can be numerous and striking and the ultimate cause of death in malignant neoplasia. In experimental studies, cytokines released during pulmonary inflammation are chemotactic for tumor cells and promote pulmonary metastasis.

Pulmonary Infarcts. Because of a dual arterial supply to the lung, pulmonary infarction is rare and generally asymptomatic. However, pulmonary infarcts can be readily caused when pulmonary thrombosis and embolism are superimposed on an already compromised pulmonary circulation such as occurs in congestive heart

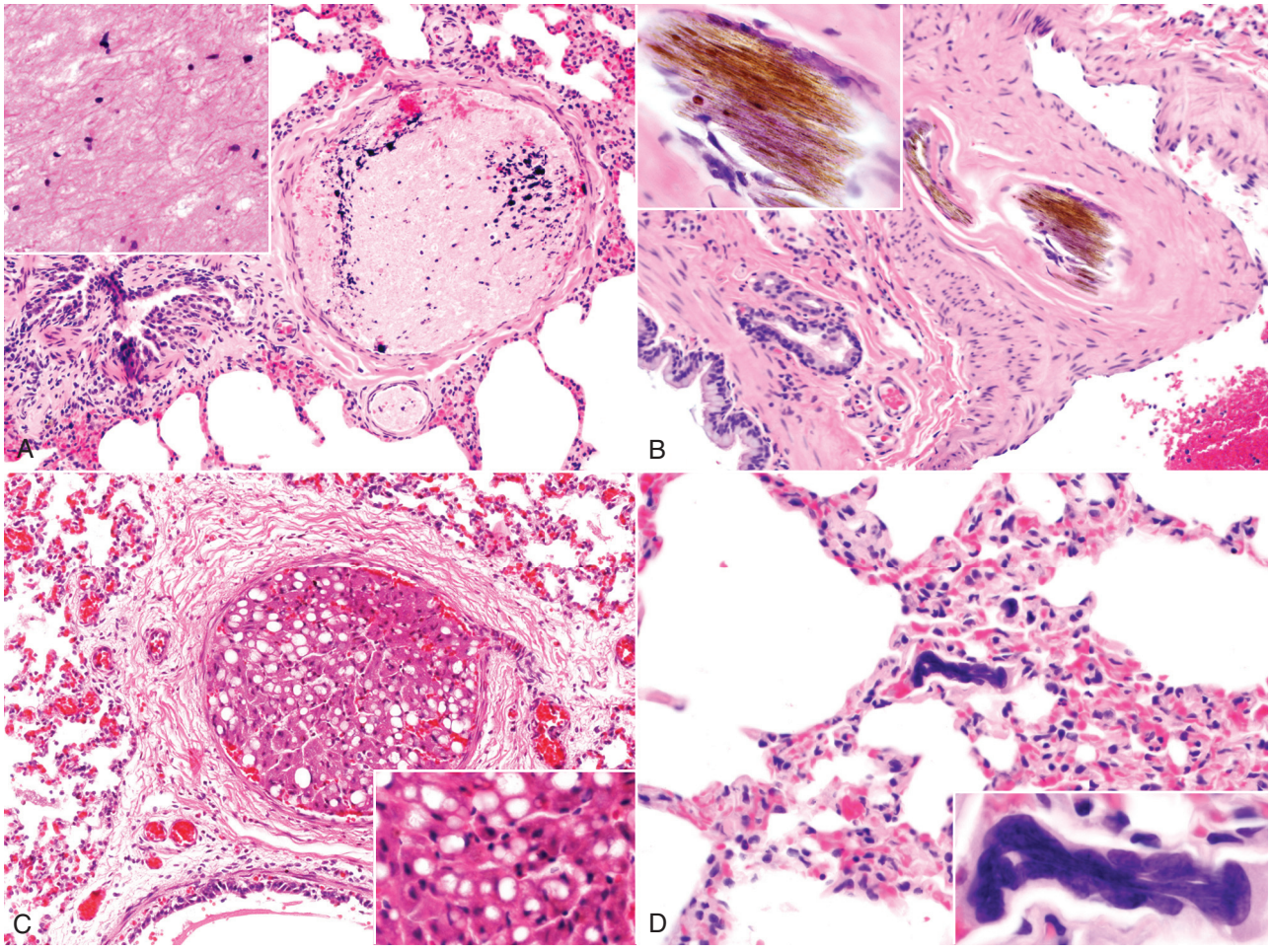


Figure 9-66 Types of Pulmonary Emboli, Microscopic Appearance, Lung. A, Brain embolism to the lung that resulted from severe head trauma. *Inset,* Note brain neuropil. H&E stain. **B,** Hair embolism to the lung (incidental finding) that resulted from an intravenous injection. *Inset,* Note pigmented hair shaft lodged in pulmonary vessel. H&E stain. **C,** Liver embolism to the lung that resulted from severe abdominal trauma caused by forced obstetric extraction of a foal. *Inset,* Vacuolated hepatocytes. H&E stain. **D,** Megakaryocyte lodged in alveolar capillary. *Inset*, Higher magnification of the megakaryocyte. This is a common incidental finding in the lungs of animals, particularly dogs. H&E stain. (Courtesy of Dr. A. López, Atlantic Veterinary College.)

failure. It also occurs in dogs with torsion of a lung lobe (Fig. 9-67). The gross features of infarcts vary considerably, depending on the stage, and they can be red to black, swollen, firm, and cone or wedge shaped, particularly at the lung margins. In the early acute stage, microscopic lesions are severely hemorrhagic, and this is followed by necrosis. In 1 or 2 days, a border of inflammatory cells develops, and a few days later, a large number of siderophages are present in the necrotic lung. If sterile, pulmonary infarcts heal as fibrotic scars; if septic, an abscess may form surrounded by a thick fibrous capsule.

General Aspects of Lung Inflammation

In the past three decades, an information explosion has increased the overall understanding of pulmonary inflammation, with so many proinflammatory and antiinflammatory mediators described to date that it would be impossible to review them all here (see Chapters 3 and 5).

Pulmonary inflammation is a highly regulated process that involves a complex interaction between cells imported from the blood (platelets, neutrophils, eosinophils, mast cells, and lymphocytes) and pulmonary cells (type I and II pneumonocytes; endothelial and Club [Clara] cells; alveolar and intravascular macrophages; and stromal interstitial cells, such as mast cells, interstitial macrophages, fibroblasts, and myofibroblasts). Blood-borne leukocytes, platelets, and plasma proteins are brought into the areas of inflammation by an elaborate network of chemical signals emitted by pulmonary cells and resident leukocytes. Long-distance communication between pulmonary cells and blood cells is largely done by soluble cytokines; once in the lung, imported leukocytes communicate with pulmonary and vascular cells through adhesion and other inflammatory molecules. The best known inflammatory mediators are the complement system (C3a, C3b, and C5a), coagulation factors (factors V and VII), arachidonic acid metabolites (leukotrienes and prostaglandins), cytokines (interleukins, monokines, and chemokines), adhesion molecules (ICAM and VCAM), neuropeptides (substance P, tachykinins, and neurokinins), enzymes and enzyme inhibitors (elastase and antitrypsin), oxygen metabolites ($O_2\bullet$, $OH\bullet$, and H_2O_2), antioxidants (glutathione), and nitric oxide (E-Table 9-1). Acting in concert, these and many other molecules send positive or negative signals to initiate, maintain, and, it is hoped, resolve the inflammatory process without causing injury to the lung.

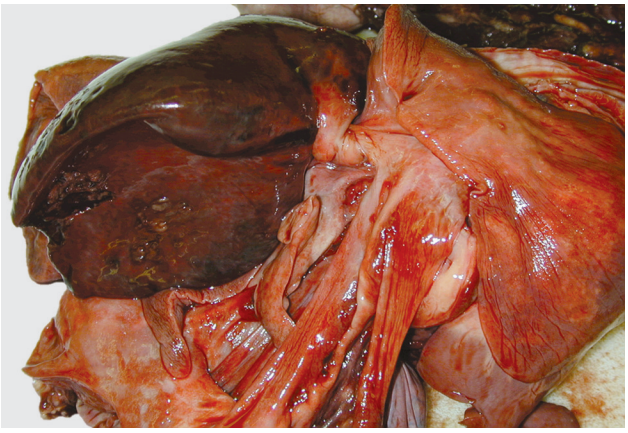


Figure 9-67 Lobe Torsion, Middle Lobe, Lung, Dog. The right middle lung lobe *(dark red)* is markedly congested and hemorrhagic from complete torsion. Although the right middle lobe is most frequently affected, other lobes can also rotate and undergo torsion. (Courtesy Dr. R. Fredrickson, College of Veterinary Medicine, University of Illinois.)

Pulmonary macrophages (alveolar, intravascular, and interstitial), which have an immense biologic armamentarium, are the single most important effector cell and source of cytokines for all stages of pulmonary inflammation. These all-purpose phagocytic cells modulate the recruitment and trafficking of blood-borne leukocytes in the lung through the secretion of chemokines (see E-Table 9-1).

Before reviewing how inflammatory cells are recruited in the lungs, three significant features in pulmonary injury must be remembered: (1) Leukocytes can exit the vascular system through the alveolar capillaries, unlike in other tissues, where postcapillary venules are the sites of leukocytic diapedesis (extravasation); (2) the intact lung contains within alveolar capillaries a large pool of resident leukocytes (marginated pool); and (3) additional neutrophils are sequestered within alveolar capillaries within minutes of a local or systemic inflammatory response. These three pulmonary idiosyncrasies, along with the enormous length of the capillary network in the lung, explain why recruitment and migration of leukocytes into alveolar spaces develops so rapidly. Experimental studies with aerosols of endotoxin or Gram-negative bacteria have shown that within minutes of exposure, there is a significant increase in capillary leukocytes, and by 4 hours the alveolar lumen is filled with neutrophils. Not surprisingly, the BAL fluid collected from patients with acute pneumonia contains large amounts of inflammatory mediators such as TNF-α, IL-1, and IL-8. Also, the capillary endothelium of patients with acute pneumonia has increased "expression" of adhesion molecules, which facilitate the migration of leukocytes from capillaries into the alveolar interstitium and from there into the alveolar lumen. In allergic pulmonary diseases, eotaxin and IL-5 are primarily responsible for recruitment and trafficking of eosinophils in the lung.

Movement of plasma proteins into the pulmonary interstitium and alveolar lumen is a common but poorly understood phenomenon in pulmonary inflammation. Leakage of fibrinogen and plasma proteins into the alveolar space occurs when there is structural damage to the blood-air barrier. This leakage is also promoted by some types of cytokines that enhance procoagulant activity, whereas others reduce fibrinolytic activity. Excessive exudation of fibrin into the alveoli is particularly common in ruminants and pigs. The fibrinolytic system plays a major role in the resolution of pulmonary inflammatory diseases. In some cases, excessive plasma proteins leaked into alveoli mix with necrotic type I pneumonocytes and pulmonary surfactant, forming microscopic eosinophilic bands (membranes) along the lining of alveolar septa. These membranes, known as *hyaline membranes*, are found in specific types of pulmonary diseases, particularly in ARDS, and in cattle with acute interstitial pneumonias such as bovine pulmonary edema and emphysema and extrinsic allergic alveolitis (see Pneumonias of Cattle).

In the past few years, nitric oxide has been identified as a major regulatory molecule of inflammation in a variety of tissues, including the lung. Produced locally by macrophages, pulmonary endothelium, and pneumonocytes, nitric oxide regulates the vascular and bronchial tone, modulates the production of cytokines, controls the recruitment and trafficking of neutrophils in the lung, and switches on/off genes involved in inflammation and immunity. Experimental work has also shown that pulmonary surfactant upregulates the production of nitric oxide in the lung, supporting the current view that pneumonocytes are also pivotal in amplifying and downregulating the inflammatory and immune responses in the lung (see E-Table 9-1).

As the inflammatory process becomes chronic, the types of cells making up cellular infiltrates in the lung change from mainly neutrophils to largely mononuclear cells. This shift in cellular composition is accompanied by an increase in specific cytokines, such as

E-Table 9-1 Main Chemical Mediators Involved in Pulmonary Inflammation

Name	Source	Function in the Lung
Histamine	Mast cells, basophils, monocytes	Increase vascular permeability, pain
Prostaglandins and leukotrienes	Cell membranes	Increase permeability, platelet aggregation, vasoconstriction or vasodilation, lung edema, pain
L-selectin	Neutrophils, monocytes	Leukocyte attachment and migration, homing to areas of pulmonary inflammation
P-selectin, E-selectin; ICAM-1, ELAM-1	Venules and capillary endothelium	Leukocyte attachment and migration to areas of pulmonary inflammation
IL-1	Alveolar macrophages	ELAMs, leukocyte chemotaxis
IL-6	Macrophages	Lymphocyte and fibroblast activation in the lung; downregulates TNF and reduces inflammation
IL-8	Macrophages, fibroblasts	Leukocyte and lymphocyte chemotaxis
IL-9	Macrophages, alveolar cells	Decreases cytokine production in pulmonary alveolar macrophages
TNF-α	Alveolar macrophages	ELAMs, endothelial adhesion, vascular permeability, lung edema; fever and acute-phase proteins, apoptosis
Eotaxin and IL-5	Lymphocytes	Eosinophil chemotaxis, airway eosinophilia, asthma, pulmonary allergies
Epithelial secretory proteins	Type I and II pneumonocytes, Club (Clara) cells	Modulation of lung inflammation; regulation of fibroblasts-fibrosis and NO
Surfactant A, B (collectins)	Type II pneumonocytes, Club cells	Chemotaxis, phagocytosis, immunomodulation, regulation of NO
NO	Pneumonocytes, macrophages, endothelium	Decreases cytokine production in pulmonary alveolar macrophages, modulation of apoptosis
TGF-α and TGF-β	Pneumonocytes, macrophages	Lung remodeling, deposition of connective tissue, fibrosis
Neuropeptides (tachykinins: substance P, neurokinins	Macrophages	Lung permeability, lung edema, bronchoconstriction, bronchial secretions, inflammation

ELAM, Endothelial adhesion molecule; *ICAM,* intercellular adhesion molecule; *IL,* interleukin; *NO,* nitric oxide; *TGF,* transforming growth factor; *TNF,* tumor necrosis factor.

IL-4, interferon-γ (IFN-γ), and interferon-inducible protein (IP-10), which are chemotactic for lymphocytes and macrophages. Under appropriate conditions, these cytokines activate T lymphocytes, regulate granulomatous inflammation, and induce the formation of multinucleated giant cells such as in mycobacterial infections.

Inflammatory mediators locally released from inflamed lungs also have a biologic effect in other tissue. For example, pulmonary hypertension and right-sided heart failure (cor pulmonale) often follows chronic alveolar inflammation, not only as a result of increased pulmonary blood pressure but also from the effect of inflammatory mediators on the contractibility of smooth muscle of the pulmonary and systemic vasculature. Cytokines, particularly TNF-α, that are released during inflammation are associated, both as cause and as effect, with the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis with multiple organ dysfunction, and septic shock (cardiopulmonary collapse).

As it occurs in any other sentinel system where many biologic promoters and inhibitors are involved (coagulation, the complement and immune systems), the inflammatory cascade could go into an "out-of-control" state, causing severe damage to the lungs. Acute lung injury (ALI), extrinsic allergic alveolitis, ARDS, pulmonary fibrosis, and asthma are archetypical diseases that ensue from an uncontrolled production and release of cytokines (cytokine storm).

As long as acute alveolar injury is transient and there is no interference with the normal host response, the entire process of injury, degeneration, necrosis, inflammation, and repair can occur in less than 10 days. On the other hand, when acute alveolar injury becomes persistent or when the capacity of the host for repair is impaired, lesions can progress to an irreversible stage in which restoration of alveolar structure is no longer possible. In diseases, such as extrinsic allergic alveolitis, the constant release of proteolytic enzymes and free radicals by phagocytic cells perpetuates alveolar damage in a vicious circle. In other cases, such as in paraquat toxicity, the magnitude of alveolar injury can be so severe that type II pneumonocytes, basement membranes, and alveolar interstitium are so disrupted that the capacity for alveolar repair is lost. Fibronectins and transforming growth factors (TGFs) released from macrophages and other mononuclear cells at the site of chronic inflammation regulate the recruitment, attachment, and proliferation of fibroblasts. In turn, these cells synthesize and release considerable amounts of ECM (collagen, elastic fibers, or proteoglycans), eventually leading to fibrosis and total obliteration of normal alveolar architecture. In summary, in diseases in which there is chronic and irreversible alveolar damage, lesions invariably progress to a stage of terminal alveolar and interstitial fibrosis.

Species-Specific Disorders of the Lung (Bronchi, Bronchioles, and Alveoli) in Domestic Animals

For pneumonia, see section Species-Specific Pneumonia of Domestic Animals.

Disorders of Horses

Circulatory Disturbances

Exercise-Induced Pulmonary Hemorrhage. *Exercise-induced pulmonary hemorrhage (EIPH)* is a specific form of pulmonary hemorrhage in racehorses that occurs after exercise and clinically is characterized by epistaxis. Because only a small percentage of horses with bronchoscopic evidence of hemorrhage have clinical epistaxis, it is likely that EIPH goes undetected in many cases. The pathogenesis is still controversial, but current literature suggests laryngeal paralysis, bronchiolitis, and extremely high pulmonary vascular and alveolar pressures during exercise, alveolar hypoxia, and preexisting pulmonary injury as possible causes. EIPH is seldom fatal; postmortem lesions in the lungs of horses that have been affected with several episodes of hemorrhage are characterized by large areas of dark brown discoloration, largely in the caudal lung lobes. Microscopically, lesions are alveolar hemorrhages, abundant alveolar macrophages containing hemosiderin (siderophages), mild alveolar fibrosis, and occlusive remodeling of pulmonary veins.

Inflammation with Mucosal Injury in the Lung

Recurrent Airway Obstruction. Recurrent airway obstruction (RAO) of horses, also referred to as COPD, heaves, chronic bronchiolitis-emphysema complex, chronic small airway disease, alveolar emphysema, and "broken wind," is a common clinically asthma-like syndrome of horses and ponies. RAO is characterized by recurrent respiratory distress, chronic cough, poor athletic performance, airway neutrophilia, bronchoconstriction, mucus hypersecretion, and airway obstruction. The pathogenesis is still obscure, but genetic predisposition, T_H2 (allergic) immune response, and the exceptional sensitivity of airways to environmental allergens (hyperreactive airway disease) have been postulated as the basic underlying mechanisms. What makes small airways hyperreactive to allergens is still a matter of controversy. Epidemiologic and experimental studies suggest that it could be the result of preceding bronchiolar damage caused by viral infections; ingestion of pneumotoxicants (3-methylindole); or prolonged exposure to organic dust, endotoxin, and environmental allergens (molds). It has been postulated that sustained inhalation of dust particles, whether antigenic or not, upregulates the production of cytokines (TNF-α, IL-8, and monokine-inducible protein [MIP-2]) and neuropeptides (neurokinin A [NKA], neurokinin B [NKB], and substance P), attracting neutrophils into the bronchioloalveolar region and promoting leukocyte-induced bronchiolar injury. Summer pasture-associated obstructive pulmonary disease (SPAOPD) is a seasonal airway disease also reported in horses with similar clinical and pathologic findings. More recently, the term *inflammatory airway disease (IAD)* has been introduced in equine medicine to describe RAO-like syndrome in young horses 2 to 4 years old.

The lungs of horses with heaves are grossly unremarkable, except for extreme cases in which alveolar emphysema may be present. Microscopically, the lesions are often remarkable and include goblet cell metaplasia in bronchioles; plugging of bronchioles with mucus mixed with few eosinophils and neutrophils (see Fig. 9-13); peribronchiolar infiltration with lymphocytes, plasma cells, and variable numbers of eosinophils; and hypertrophy of smooth muscle in bronchi and bronchioles. In severe cases, accumulation of mucus leads to the complete obstruction of bronchioles and alveoli and resultant alveolar emphysema characterized by enlarged "alveoli" from the destruction of alveolar walls.

Disorders of Cats

Inflammation with Mucosal Injury in the Lung

Feline Asthma Syndrome. Feline asthma syndrome, also known as *feline allergic bronchitis*, is a clinical syndrome in cats of any age characterized by recurrent episodes of bronchoconstriction, cough, or dyspnea. The pathogenesis is not well understood but is presumed to originate, as in human asthma, as a type I hypersensitivity (IgE–mast cell reaction) to inhaled allergens. Dust, cigarette smoke, plant and household materials, and parasitic proteins have been incriminated as possible allergens. This self-limited allergic disease responds well to steroid therapy; thus it is rarely implicated as a primary cause of death except when suppressed defense mechanisms allow a secondary bacterial pneumonia. Bronchial biopsies from affected cats at the early stages reveal mild to moderate inflammation characterized by mucosal edema and infiltration of leukocytes, particularly eosinophils. Increased numbers of circulating eosinophils (blood eosinophilia) are present in some but not all cats with feline asthma.

In the most advanced cases, chronic bronchoconstriction and excess mucus production may result in smooth muscle hyperplasia and obstruction of the bronchi and bronchioles and infiltration of the airway mucosa by eosinophils. A syndrome known as *canine asthma* has been reported in dogs but is not as well characterized as the feline counterpart.

Classification of Pneumonias in Domestic Animals

Few subjects in veterinary pathology have caused so much debate as the classification of pneumonias. Historically, pneumonias in animals have been classified or named based on the following:

1. Presumed cause, with names such as viral pneumonia, Pasteurella pneumonia, distemper pneumonia, verminous pneumonia, chemical pneumonia, and hypersensitivity pneumonitis
2. Type of exudation, with names such as suppurative pneumonia, fibrinous pneumonia, and pyogranulomatous pneumonia
3. Morphologic features, with names such as gangrenous pneumonia, proliferative pneumonia, and embolic pneumonia
4. Distribution of lesions, with names such as focal pneumonia, cranioventral pneumonia, diffuse pneumonia, and lobar pneumonia
5. Epidemiologic attributes, with names such as enzootic pneumonia, contagious bovine pleuropneumonia, and "shipping fever"
6. Geographic regions, with names such as Montana progressive pneumonia
7. Miscellaneous attributes, with names such as atypical pneumonia, cuffing pneumonia, progressive pneumonia, aspiration pneumonia, pneumonitis, farmer's lung, and extrinsic allergic alveolitis

Until a universal and systematic nomenclature for animal pneumonias is established, veterinarians should be acquainted with this heterogeneous list of names and should be well aware that one disease may be known by different names. In pigs, for instance, enzootic pneumonia and *Mycoplasma* pneumonia refer to the same disease caused by *Mycoplasma hyopneumoniae*.

The word *pneumonitis* has been used by some as a synonym for pneumonia; however, others have restricted this term to chronic proliferative inflammation generally involving the alveolar interstitium and with little or no evidence of exudate. In this chapter, the word *pneumonia* is used for any inflammatory lesion in the lungs, regardless of whether it is exudative or proliferative, alveolar, or interstitial.

On the basis of texture, distribution, appearance, and exudation, pneumonias can be grossly diagnosed into four morphologically distinct types: bronchopneumonia, interstitial pneumonia, embolic pneumonia, and granulomatous pneumonia. By using this classification, it is possible at the time of a necropsy to predict with some degree of certainty the likely cause (virus, bacteria, fungi, or parasites), routes of entry (aerogenous vs. hematogenous), and possible sequelae. These four morphologic types allow the clinician or pathologists to predict the most likely etiology and therefore facilitate the decision as to what samples need to be taken and which tests should be requested to the diagnostic laboratory (i.e., histopathology, bacteriology, virology, or toxicology). However, overlapping of these four types of pneumonias is possible, and sometimes two morphologic types may be present in the same lung.

The criteria used to classify pneumonias grossly into bronchopneumonia, interstitial pneumonia, embolic pneumonia, and granulomatous pneumonia are based on morphologic changes, including distribution, texture, color, and general appearance of the affected lungs (Table 9-5). Distribution of the inflammatory lesions in the lungs can be (1) cranioventral, as in most bronchopneumonias; (2) multifocal, as in embolic pneumonias; (3) diffuse, as in interstitial pneumonias; or (4) locally extensive, as in granulomatous

Table 9-5 Morphologic Types of Pneumonias in Domestic Animals

Type of Pneumonia	Portal of Entry (e.g., Pathogens)	Distribution of Lesions	Texture of Lung	Grossly Visible Exudate	Disease Example	Common Pulmonary Sequelae
Bronchopneumonia: Suppurative (lobular)	Aerogenous (bacteria)	Cranioventral consolidation	Firm	Purulent exudate in bronchi	Enzootic pneumonia	Cranioventral abscesses, adhesions, bronchiectasis
Bronchopneumonia: Fibrinous (lobar)	Aerogenous (bacteria)	Cranioventral consolidation*	Hard	Fibrin in lung and pleura	Pneumonic mannheimiosis	BALT hyperplasia, "sequestra," pleural adhesions, abscesses
Interstitial pneumonia	Aerogenous or hematogenous (virus, toxin, allergen, sepsis)	Diffuse	Elastic with rib imprints	Not visible, trapped in alveolar septa	Influenza, extrinsic allergic alveolitis, PRRS, ARDS	Edema, emphysema, type II pneumonocyte hyperplasia, alveolar fibrosis
Granulomatous pneumonia	Aerogenous or hematogenous (mycobacteria, systemic mycoses)	Multifocal	Nodular	Pyogranulomatous, caseous necrosis, calcified nodules	Tuberculosis, blastomycosis, cryptococcosis	Dissemination of infection to lymph nodes and distant organs
Embolic pneumonia	Hematogenous (septic emboli)	Multifocal	Nodular	Purulent foci surrounded by hyperemia	Vegetative endocarditis, ruptured liver abscess	Abscesses randomly distributed in all pulmonary lobes

ARDS, Acute respiratory distress syndrome; *BALT,* bronchial-associated lymphoid tissue; *PRRS,* porcine reproductive and respiratory syndrome.
*Porcine pleuropneumonia is an exception because it often involves the caudal lobes.

pneumonias (Fig. 9-68). Texture of pneumonic lungs can be firmer or harder (bronchopneumonias), more elastic (rubbery) than normal lungs (interstitial pneumonias), or have a nodular feeling (granulomatous pneumonias). Describing in words the palpable difference between the texture of a normal lung compared with the firm or hard texture of a consolidated lung can be a difficult undertaking. An analogy illustrating this difference based on touching the parts of the face with the tip of your finger has been advocated by some pathologists. The texture of a normal lung is comparable to the texture of the center of the cheek. Firm consolidation is comparable to the texture of the tip of the nose, and hard consolidation is comparable to the texture of the forehead. The term *consolidation* is frequently used to describe a firm or hard lung filled with exudate.

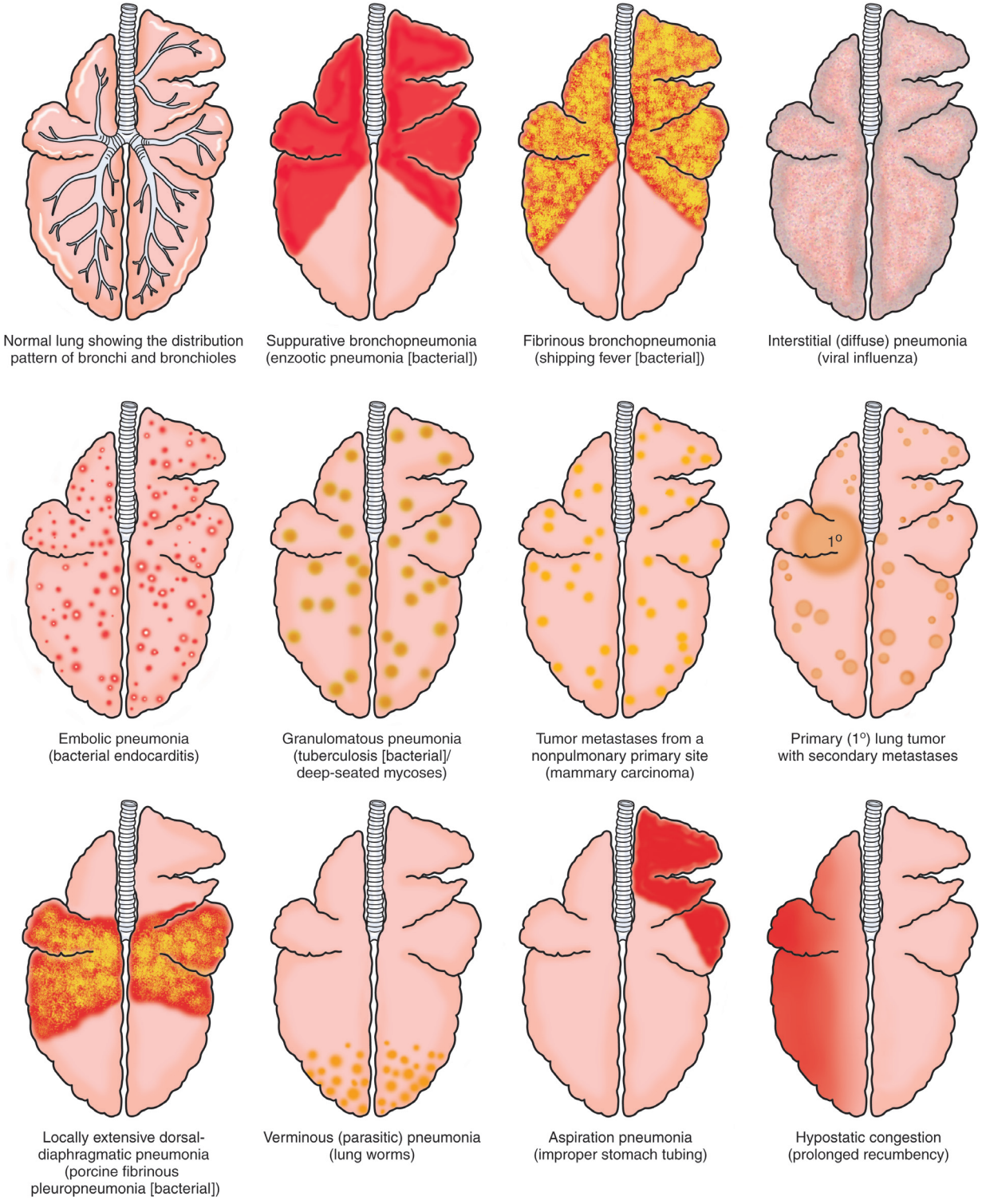


Figure 9-68 Patterns of Pneumonia and Lung Lesions. A dorsal view of the bovine lung illustrates these patterns. They can readily be extrapolated to the lungs of other domestic animal species. (Courtesy Dr. A. López, Atlantic Veterinary College and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

Changes in the gross appearance of pneumonic lungs include abnormal color, the presence of nodules or exudate, fibrinous or fibrous adhesions, and the presence of rib imprints on serosal surfaces (see Fig. 9-68). On cut surfaces, pneumonic lungs may have exudate, hemorrhage, edema, necrosis, abscesses, bronchiectasis, granulomas or pyogranulomas, and fibrosis, depending on the stage.

Palpation and careful observation of the lungs are essential in the diagnosis of pneumonia. (For details, see the section on Examination of the Respiratory Tract.)

Bronchopneumonia

Bronchopneumonia refers to a particular morphologic type of pneumonia in which injury and the inflammatory process take place primarily in the bronchial, bronchiolar, and alveolar lumens. Bronchopneumonia is undoubtedly the most common type of pneumonia seen in domestic animals and is with few exceptions characterized grossly by cranioventral consolidation of the lungs (Fig. 9-69 and see Fig. 9-68). The reason why bronchopneumonias in animals are almost always restricted to the cranioventral portions of the lungs is not well understood. Possible factors contributing to this topographic selectivity within the lungs include (1) gravitational sedimentation of the exudate, (2) greater deposition of infectious organisms, (3) inadequate defense mechanisms, (4) reduced vascular perfusion, (5) shortness and abrupt branching of airways, and (6) regional differences in ventilation.

The term *cranioventral* in veterinary anatomy is the equivalent of "anterosuperior" in human anatomy. The latter is defined as "in front (ventral) and above (cranial)." Thus, applied to the lung of animals, "cranioventral" means the ventral portion of the cranial lobe. However, by common usage in veterinary pathology, the term *cranioventral* used to describe the location of lesions in pneumonias has come to mean "cranial and ventral." Thus it includes pneumonias affecting not only the ventral portion of the cranial lobe (true cranioventral) but also those cases in which the pneumonia has involved the ventral portions of adjacent lung lobes—initially the middle and then caudal on the right and the caudal lobe on the left side.

Bronchopneumonias are generally caused by bacteria and mycoplasmas, by bronchoaspiration of feed or gastric contents, or by improper tubing. As a rule, the pathogens causing bronchopneumonias arrive in the lungs via inspired air (aerogenous), either from infected aerosols or from the nasal flora. Before establishing infection, pathogens must overwhelm or evade the pulmonary defense mechanisms. The initial injury in bronchopneumonias is centered on the mucosa of bronchioles; from there, the inflammatory process can spread downward to distal portions of the alveoli and upward to the bronchi. Typically, for bronchopneumonias, the inflammatory exudates collect in the bronchial, bronchiolar, and alveolar lumina leaving the alveolar interstitium relatively unchanged, except for hyperemia and possibly edema. Through the pores of Kohn, the exudate can spread to adjacent alveoli until most or all of the alveoli in an individual lobule are involved. If the inflammatory process cannot control the inciting cause of injury, the lesions spread rapidly from lobule to lobule through alveolar pores and destroyed alveolar walls until an entire lobe or large portion of a lung is involved. The lesion tends to spread centrifugally, with the older lesions in the center, and exudate can be coughed up and then aspirated into other lobules, where the inflammatory process starts again.

At the early stages of bronchopneumonia, the pulmonary vessels are engorged with blood (active hyperemia), and the bronchi, bronchioles, and alveoli contain some fluid (permeability edema). In cases in which pulmonary injury is mild to moderate, cytokines locally released in the lung cause rapid recruitment of neutrophils and alveolar macrophages into bronchioles and alveoli (Fig. 9-70 and see Fig. 9-69). When pulmonary injury is much more severe, proinflammatory cytokines induce more pronounced vascular changes by further opening endothelial gaps, thus increasing vascular permeability resulting in leakage of plasma fibrinogen (fibrinous exudates) and sometimes hemorrhage in the alveoli. Alterations in permeability can be further exacerbated by structural damage to pulmonary capillaries and vessels directly caused by microbial toxins. Filling of alveoli, bronchioles, and small bronchi with inflammatory exudate progressively obliterates airspaces, and as a consequence of this process, portions of severely affected (consolidated) lungs sink to the bottom of the container when placed in fixative. The replacement of air by exudate also changes the texture of the lungs, and depending on the severity of bronchopneumonia, the texture varies from firmer to harder than normal.

The term *consolidation* is used at gross examination when the texture of pneumonic lung becomes firmer or harder than normal as a result of loss of airspaces because of exudation and atelectasis. (For details, see the discussion of lung texture in the section on Classification of Pneumonias in Domestic Animals). Inflammatory consolidation of the lungs has been referred to in the past as *hepatization* because the affected lung had the appearance and texture of liver. The process was referred to as *red hepatization* in acute cases in which

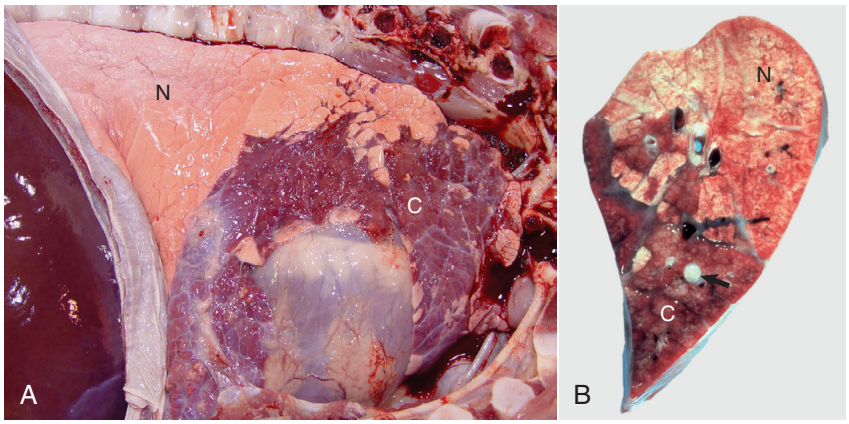


Figure 9-69 Suppurative Bronchopneumonia, Enzootic Pneumonia, Lung, Calf. A, Cranioventral consolidation *(C)* of the lung involves approximately 40% of the pulmonary parenchyma. Most of the caudal lung is normal *(N)*. **B,** Cut surface. Consolidated lung is dark red to mahogany *(C)*, and a major bronchus contains purulent exudate *(arrow)*. *N*, Normal. (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** courtesy Ontario Veterinary College.)

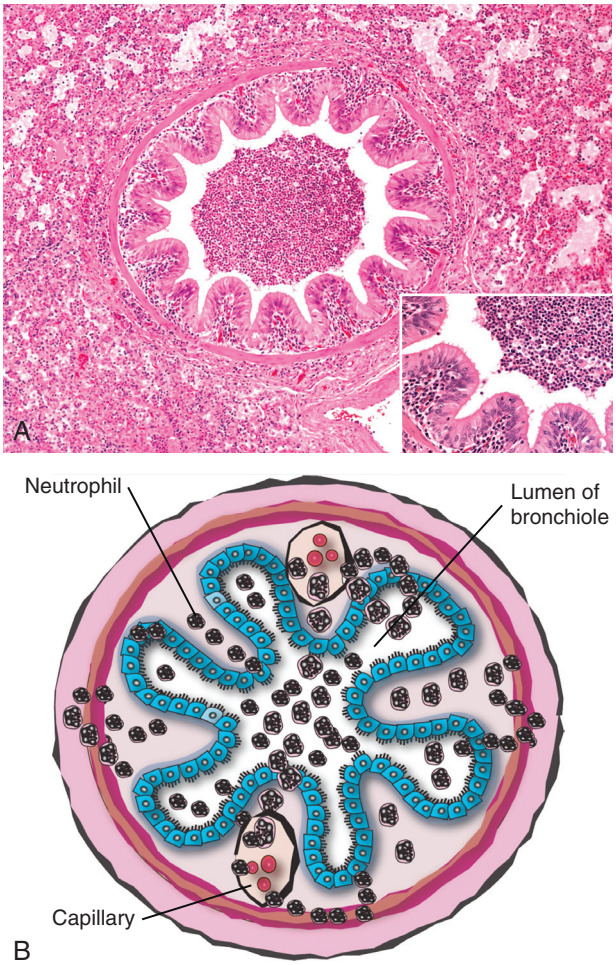


Figure 9-70 Suppurative Bronchopneumonia, Lung, Pig. A, Note the bronchiole in the center of the figure plugged with purulent exudate. The adjacent alveoli are filled with leukocytes and edema fluid. *Inset,* Higher magnification of wall of bronchiole. H&E stain. **B,** Schematic diagram of acute bronchiolitis. Note the neutrophils exiting the submucosal capillaries (leukocyte adhesion cascade; see Chapter 3) and moving into the walls of the bronchioles (blue cells = ciliated mucosal epithelium) and then into the bronchiolar lumen. (Courtesy Dr. A. López, Atlantic Veterinary College.)

there was notable active hyperemia with little exudation of neutrophils; conversely, the process was referred to as *gray hepatization* in those chronic cases in which hyperemia was no longer present, but there was abundant exudation of neutrophils and macrophages. This terminology, although used for and applicable to human pneumonias, is rarely used in veterinary medicine primarily because the evolution of pneumonic processes in animals does not necessarily follow the red-to-gray hepatization pattern.

Bronchopneumonia can be subdivided into *suppurative bronchopneumonia* if the exudates are predominantly composed of neutrophils and *fibrinous bronchopneumonia* if fibrin is the predominant component of the exudates (see Table 9-5). It is important to note that some veterinarians use the term *fibrinous pneumonia* or *lobar pneumonia* as a synonym for fibrinous bronchopneumonia, and *bronchopneumonia* or *lobular pneumonia* as a synonym for suppurative bronchopneumonia. Human pneumonias for many years have been classified based on their etiology and morphology, which explains why pneumococcal pneumonia (*Streptococcus pneumoniae*) has been synonymous with lobar pneumonia. In the old literature, four distinct stages of pneumococcal pneumonia were described as (1) congestion, (2) red hepatization (liver texture), (3) gray hepatization, and (4) resolution. Because of the use of effective antibiotics and prevention, pneumococcal pneumonia and its four classic stages are rarely seen; thus this terminology has been largely abandoned. Currently, the term *bronchopneumonia* is widely used for both suppurative and fibrinous consolidation of the lungs because both forms of inflammation have essentially the same pathogenesis in which the pathogens reach the lung by the aerogenous route, injury occurs initially in the bronchial and bronchiolar regions, and the inflammatory process extends centrifugally deep into the alveoli. It must be emphasized that it is the severity of pulmonary injury that largely determines whether bronchopneumonia becomes suppurative or fibrinous. In some instances, however, it is difficult to discriminate between suppurative and fibrinous bronchopneumonia because both types can coexist (fibrinosuppurative bronchopneumonia), and one type can progress to the other.

Suppurative Bronchopneumonia. Suppurative bronchopneumonia is characterized by cranioventral consolidation of lungs (see Figs. 9-68 and 9-69), with typically purulent or mucopurulent exudate present in the airways. This exudate can be best demonstrated by expressing intrapulmonary bronchi, thus forcing exudate out of the bronchi (see Fig. 9-69). The inflammatory process in suppurative bronchopneumonia is generally confined to individual lobules, and as a result of this distribution, the lobular pattern of the lung becomes notably emphasized. This pattern is particularly obvious in cattle and pigs because these species have prominent lobulation of the lungs. The gross appearance often resembles an irregular checkerboard because of an admixture of normal and abnormal (consolidated) lobules (see Fig. 9-69). Because of this typical lobular distribution, suppurative bronchopneumonias are also referred to as lobular pneumonias.

Different inflammatory phases occur in suppurative bronchopneumonia where the color and appearance of consolidated lungs varies considerably, depending on the virulence of offending organisms and chronicity of the lesion. The typical phases of suppurative bronchopneumonia can be summarized as follows:

1. During the first 12 hours when bacteria are rapidly multiplying, the lungs become hyperemic and edematous.
2. Soon after, neutrophils start filling the airways, and by 48 hours the parenchyma starts to consolidate and becomes firm in texture.
3. Three to 5 days later, hyperemic changes are less obvious, but the bronchial, bronchiolar, and alveolar spaces continue to fill with neutrophils and macrophages, and the affected lung sinks when placed in formalin. At this stage, the affected lung has a gray-pink color, and on cut surface, purulent exudate can be expressed from bronchi.
4. In favorable conditions where the infection is under control of the host defense mechanisms, the inflammatory processes begin to regress, a phase known as *resolution*. Complete resolution in favorable conditions could take 1 to 2 weeks.
5. In animals in which the lung infection cannot be rapidly contained, inflammatory lesions can progress into a chronic phase. Approximately 7 to 10 days after infection, the lungs become pale gray and take a "fish flesh" appearance. This appearance is the result of purulent and catarrhal inflammation, obstructive atelectasis, mononuclear cell infiltration, peribronchial and peribronchiolar lymphoid hyperplasia, and early alveolar fibrosis.

Complete resolution is unusual in chronic bronchopneumonia, and lung scars, such as pleural and pulmonary fibrosis; bronchiectasis as a consequence of chronic destructive bronchitis (see bronchiectasis [Dysfunction/Responses to Injury and Patterns of Injury]); atelectasis; pleural adhesions; and lung abscesses may remain unresolved

for a long time. "Enzootic pneumonias" of ruminants and pigs are typical examples of chronic suppurative bronchopneumonias.

Microscopically, acute suppurative bronchopneumonias are characterized by hyperemia, abundant neutrophils, macrophages, and cellular debris within the lumen of bronchi, bronchioles, and alveoli (see Fig. 9-70). Recruitment of leukocytes is promoted by cytokines, complement, and other chemotactic factors that are released in response to alveolar injury or by the chemotactic effect of bacterial toxins, particularly endotoxin. In most severe cases, purulent or mucopurulent exudates completely obliterate the entire lumen of bronchi, bronchioles, and alveoli.

If suppurative bronchopneumonia is merely the response to a transient pulmonary injury or a mild infection, lesions resolve uneventfully. Within 7 to 10 days, cellular exudate can be removed from the lungs via the mucociliary escalator, and complete resolution may take place within 4 weeks. In other cases, if injury or infection is persistent, suppurative bronchopneumonia can become chronic with goblet cell hyperplasia, an important component of the inflammatory process. Depending on the proportion of pus and mucus, the exudate in chronic suppurative bronchopneumonia varies from mucopurulent to mucoid. A mucoid exudate is found in the more chronic stages when the consolidated lung has a "fish flesh" appearance.

Hyperplasia of BALT is another change commonly seen in chronic suppurative bronchopneumonias; it appears grossly as conspicuous white nodules (cuffs) around bronchial walls (cuffing pneumonia). This hyperplastic change merely indicates a normal reaction of lymphoid tissue to infection. Further sequelae of chronic suppurative bronchopneumonia include bronchiectasis (see Figs. 9-10 and 9-11), pulmonary abscesses, pleural adhesions (from pleuritis) (Fig. 9-71), and atelectasis and emphysema from completely or partially obstructed bronchi or bronchioles (e.g., bronchiectasis).

Clinically, suppurative bronchopneumonias can be acute and fulminating but are often chronic, depending on the etiologic agent, stressors affecting the host, and immune status. The most common pathogens causing suppurative bronchopneumonia in domestic animals include *Pasteurella multocida*, *Bordetella bronchiseptica*, *Trueperella* (*Arcanobacterium*) *pyogenes*, *Streptococcus* spp., *Escherichia coli*, and several species of mycoplasmas. Most of these organisms are secondary pathogens requiring a preceding impairment of the pulmonary defense mechanisms to allow them to colonize the lungs and establish an infection. Suppurative bronchopneumonia can also result from aspiration of bland material (e.g., milk). Pulmonary gangrene may ensue when the bronchopneumonic lung is invaded by saprophytic bacteria (aspiration pneumonia).

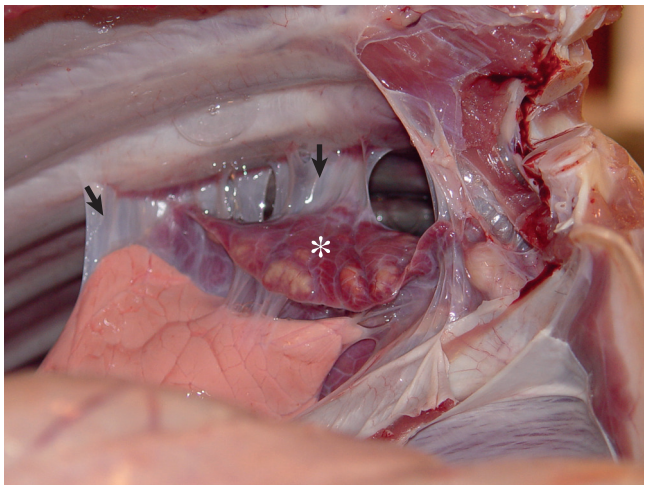


Figure 9-71 Pleural Adhesions, Chronic Bronchopneumonia, Steer. Note thick bands *(arrows)* of connective tissue between the visceral and parietal pleura. The cranial lobe *(asterisk)* appears consolidated and dark red. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Fibrinous Bronchopneumonia. Fibrinous bronchopneumonia is similar to suppurative bronchopneumonia except that the predominant exudate is fibrinous rather than neutrophilic. With only a few exceptions, fibrinous bronchopneumonias also have a cranioventral distribution (Fig. 9-72 and see Fig. 9-68). However, exudation is not restricted to the boundaries of individual pulmonary lobules, as is the case in suppurative bronchopneumonias. Instead, the inflammatory process in fibrinous pneumonias involves numerous contiguous lobules and the exudate moves quickly through pulmonary tissue until the entire pulmonary lobe is rapidly affected. Because of the involvement of the entire lobe and pleural surface, fibrinous bronchopneumonias are also referred to as lobar pneumonias or pleuropneumonias. In general terms, fibrinous bronchopneumonias are the result of more severe pulmonary injury and thus cause death earlier in the sequence of the inflammatory process than suppurative bronchopneumonias. Even in cases in which fibrinous bronchopneumonia involves 30% or less of the total area, clinical signs and death can occur as a result of severe toxemia and sepsis.

The gross appearance of fibrinous bronchopneumonia depends on the age and severity of the lesion and on whether the pleural surface or the cut surface of the lung is viewed. Externally, early stages of fibrinous bronchopneumonias are characterized by severe congestion and hemorrhage, giving the affected lungs a characteristically intense red discoloration. A few hours later, fibrin starts to permeate and accumulate on the pleural surface, giving the pleura a ground glass appearance and eventually forming plaques of fibrinous exudate over a red, dark lung (see Fig. 9-72). At this stage, a yellow fluid starts to accumulate in the thoracic cavity. The color of fibrin deposited over the pleural surface is also variable. It can be bright yellow when the exudate is formed primarily by fibrin, tan when fibrin is mixed with blood, and gray when a large number of leukocytes and fibroblasts are part of the fibrinous plaque in more chronic cases. Because of the tendency of fibrin to deposit on the pleural surface, some pathologists use the term *pleuropneumonia* as a synonym for fibrinous bronchopneumonia.

On the cut surface, early stages of fibrinous bronchopneumonia appear as simple red consolidation. In more advanced cases (24 hours), fibrinous bronchopneumonia is generally accompanied by notable dilation and thrombosis of lymph vessels and edema of interlobular septa (see Fig. 9-72, *B*). This distention of the interlobular septa gives affected lungs a typical marbled appearance. Distinct focal areas of coagulative necrosis in the pulmonary parenchyma are also common in fibrinous bronchopneumonia such as in shipping fever pneumonia and contagious bovine pleuropneumonia. In animals that survive the early stage of fibrinous bronchopneumonia, pulmonary necrosis often develops into pulmonary "sequestra," which are isolated pieces of necrotic lung encapsulated by connective tissue. Pulmonary sequestra result from extensive necrosis of lung tissue either from severe ischemia (infarct) caused by thrombosis of a major pulmonary vessel such as in contagious bovine pleuropneumonia or from the effect of necrotizing toxins released by pathogenic bacteria such as *Mannheimia haemolytica*. Sequestra in veterinary pathology should not be confused with "bronchopulmonary sequestration," a term used in human pathology to describe a congenital malformation in which whole lobes or parts of the lung develop without normal connections to the airway or vascular systems.

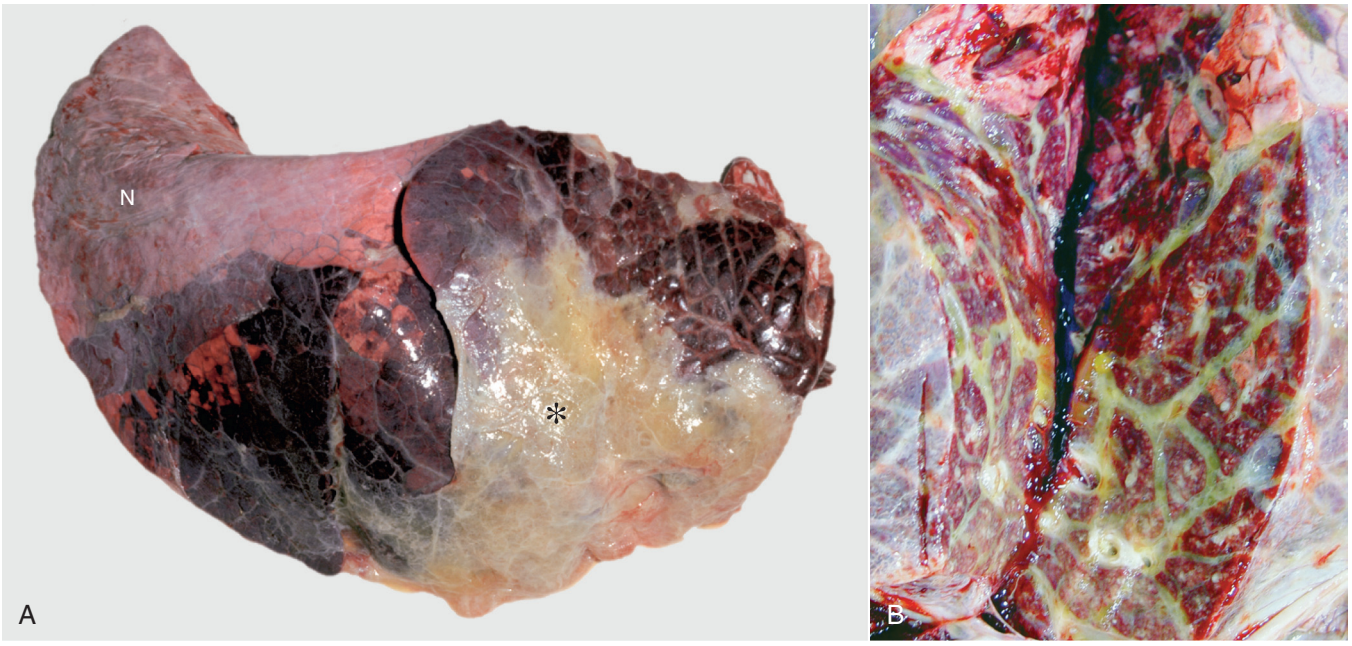


Figure 9-72 Fibrinous Bronchopneumonia (Pleuropneumonia), Right Lung, Steer. A, The pneumonia has a cranioventral distribution that extends into the middle and caudal lobes and affects approximately 80% of the lung parenchyma. The lung is firm, swollen, and covered with yellow fibrin *(asterisk)*. The dorsal portion of the caudal lung is normal *(N)*. **B,** Cut surface. Affected parenchyma appears dark and hyperemic compared with more normal lung *(top quarter of figure)*. Interlobular septa are prominent as yellow bands due to the accumulation of fibrin and edema fluid. This type of lesion is typical of *Mannheimia haemolytica* infection in cattle (shipping fever). (**A** courtesy Ontario Veterinary College. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

Microscopically, in the initial stage of fibrinous bronchopneumonia, there is massive exudation of plasma proteins into the bronchioles and alveoli, and as a result, most of the airspaces become obliterated by fluid and fibrin. Leakage of fibrin and fluid into alveolar lumina is due to extensive disruption of the integrity and increased permeability of the blood-air barrier. Fibrinous exudates can move from alveolus to alveolus through the pores of Kohn. Because fibrin is chemotactic for neutrophils, these types of leukocytes are always present a few hours after the onset of fibrinous inflammation. As inflammation progresses (3 to 5 days), fluid exudate is gradually replaced by fibrinocellular exudates composed of fibrin, neutrophils, macrophages, and necrotic debris (Fig. 9-73). In chronic cases (after 7 days), there is notable fibrosis of the interlobular septa and pleura.

In contrast to suppurative bronchopneumonia, fibrinous bronchopneumonia rarely resolves completely, thus leaving noticeable scars in the form of pulmonary fibrosis and pleural adhesions. The most common sequelae found in animals surviving an acute episode of fibrinous bronchopneumonia include alveolar fibrosis and bronchiolitis obliterans, in which organized exudate becomes attached to the bronchiolar lumen (see Fig. 9-12). These changes are collectively referred to as *bronchiolitis obliterans organizing pneumonia* (BOOP), a common microscopic finding in animals with unresolved bronchopneumonia. Other important sequelae include pulmonary gangrene, when saprophytic bacteria colonize necrotic lung; pulmonary sequestra; pulmonary fibrosis; abscesses; and chronic pleuritis with pleural adhesions. In some cases, pleuritis can be so extensive that fibrous adhesions extend onto the pericardial sac. Pathogens causing fibrinous bronchopneumonias in domestic animals include *Mannheimia* (*Pasteurella*) *haemolytica* (pneumonic mannheimiosis), *Histophilus somni* (formerly *Haemophilus somnus*), *Actinobacillus pleuropneumoniae* (porcine pleuropneumonia), *Mycoplasma bovis*, and *Mycoplasma mycoides* ssp. *mycoides* small colony type (contagious bovine pleuropneumonia). Fibrinous bronchopneumonia and pulmonary gangrene can also be the result of bronchoaspiration of irritant materials such as gastric contents.

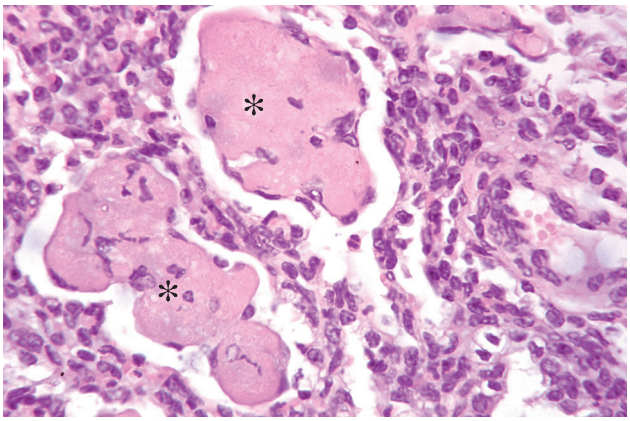


Figure 9-73 Fibrinous Bronchopneumonia, Chronic, Lung, Calf. Note large aggregates of condensed fibrin *(asterisks)* surrounded and infiltrated by phagocytic cells. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Fulminating hemorrhagic bronchopneumonia can be caused by highly pathogenic bacteria such as *Bacillus anthracis*. Although the lesions in anthrax are primarily related to a severe septicemia and sepsis, anthrax should always be suspected in animals with sudden death and exhibiting severe acute fibrinohemorrhagic pneumonia, splenomegaly, and multisystemic hemorrhages. Animals are considered good sentinels for anthrax in cases of bioterrorism.

Interstitial Pneumonia

Interstitial pneumonia refers to that type of pneumonia in which injury and the inflammatory process take place primarily in any

of the three layers of the alveolar walls (endothelium, basement membrane, and alveolar epithelium) and the contiguous bronchiolar interstitium (see Fig. 9-7). This morphologic type of pneumonia is the most difficult to diagnose at necropsy and requires microscopic confirmation because it is easily mistaken in the lung showing congestion, edema, hyperinflation, or emphysema.

In contrast to bronchopneumonias, in which distribution of lesions is generally cranioventral, in interstitial pneumonias, lesions are more diffusely distributed and generally involve all pulmonary lobes, or in some cases, they appear to be more pronounced in the dorsocaudal aspects of the lungs (see Fig. 9-68). Three important gross features of interstitial pneumonia are (1) the failure of lungs to collapse when the thoracic cavity is opened, (2) the occasional presence of rib impressions on the pleural surface of the lung indicating poor deflation, and (3) the lack of visible exudates in airways unless complicated with secondary bacterial pneumonia. The color of affected lungs varies from diffusely red in acute cases to diffusely pale gray to a mottled red, pale appearance in chronic ones. Pale lungs are caused by severe obliteration of alveolar capillaries (reduced blood-tissue ratio), especially evident when there is fibrosis of the alveolar walls. The texture of lungs with uncomplicated interstitial pneumonia is typically elastic or rubbery, but definitive diagnosis based on texture alone is difficult and requires histopathologic examination. On a cut surface, the lungs may appear and feel more "meaty" (having the texture of raw meat) and have no evidence of exudate in the bronchi or pleura (Fig. 9-74). In acute interstitial pneumonias, particularly in cattle, there is frequently pulmonary edema (exudative phase) and interstitial emphysema secondary to partial obstruction of bronchioles by edema fluid and strenuous air gasping before death. Because edema tends to gravitate into the cranioventral portions of the lungs, and emphysema is often more obvious in the dorsocaudal aspects, acute interstitial pneumonias in cattle occasionally have a gross cranioventral-like pattern that may resemble bronchopneumonia, although the texture is different. Lungs are notably heavy because of the edema and the infiltrative and proliferative changes.

The pathogenesis of interstitial pneumonia is complex and can result from aerogenous injury to the alveolar epithelium (type I and II pneumonocytes) or from hematogenous injury to the alveolar capillary endothelium or alveolar basement membrane. Aerogenous inhalation of toxic gases (i.e., ozone and NO_2) or toxic fumes (smoke inhalation) and infection with pneumotropic viruses (influenza, herpesviruses, or canine distemper virus) can damage the alveolar epithelium. Inhaled antigens, such as fungal spores, combine with circulating antibodies and form deposits of antigen-antibody complexes (type III hypersensitivity) in the alveolar wall, which initiate a cascade of inflammatory responses and injury (allergic alveolitis). Hematogenous injury to the vascular endothelium occurs in septicemias, sepsis, DIC, larva migrans (*Ascaris suum*), toxins absorbed in the alimentary tract (endotoxin) or toxic metabolites locally generated in the lungs (3-methylindole and paraquat), release of free radicals in alveolar capillaries (ARDS), and infections with endotheliotropic viruses (canine adenovirus and classical swine fever [hog cholera]).

Interstitial pneumonias in domestic animals and human beings are subdivided based on morphologic features into acute and chronic. It should be kept in mind, however, that not all acute interstitial pneumonias are fatal and that they do not necessarily progress to the chronic form.

Acute Interstitial Pneumonias. Acute interstitial pneumonias begin with injury to either type I pneumonocytes or alveolar capillary endothelium, which provokes a disruption of the blood-air barrier and a subsequent exudation of plasma proteins into the alveolar space (see Fig. 9-14). This leakage of proteinaceous fluid into the alveolar lumen constitutes the exudative phase of acute interstitial pneumonia. In some cases of diffuse alveolar damage, exuded plasma proteins mix with lipids and other components of pulmonary surfactant and form elongated membranes that become partially attached to the alveolar basement membrane and bronchiolar walls. These membranes are referred to as hyaline membranes because of their hyaline appearance (eosinophilic, homogeneous, and amorphous) microscopically (see Figs. 9-55 and 9-63). In addition to intraalveolar exudation of fluid, inflammatory edema and neutrophils accumulate in the alveolar interstitium and cause thickening of the alveolar walls. This acute exudative phase is generally followed a few days later by the proliferative phase of acute interstitial pneumonia, which is characterized by hyperplasia of type II pneumonocytes to replace the lost type I pneumonocytes (see Fig. 9-15). Type II pneumonocytes are in fact progenitor cells that differentiate and replace necrotic type I pneumonocytes (see Fig. 9-14). As a consequence, the alveolar walls become increasingly thickened. This process is in part the reason why lungs become rubbery on palpation, what prevents their normal collapse after the thorax is opened, and why the cut surface of the lung has a "meaty" appearance (see Fig. 9-74).

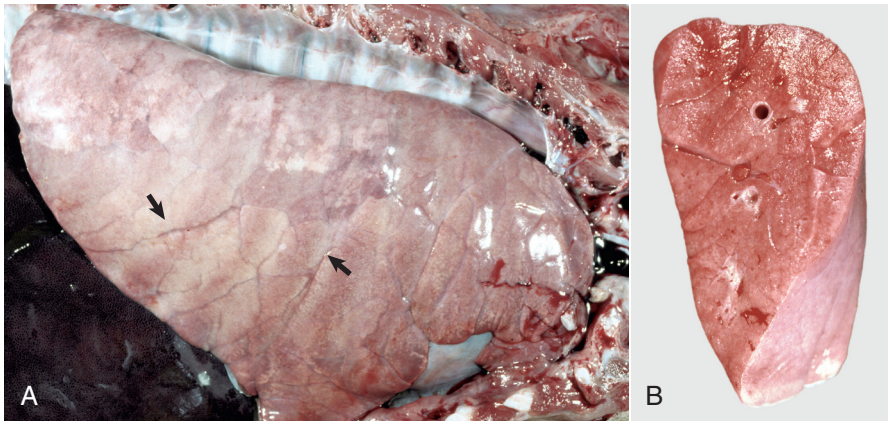


Figure 9-74 **Interstitial Pneumonia, Lung, Feeder Pig. A,** The lung is heavy, pale, and rubbery in texture. It also has prominent costal (rib) imprints *(arrows)*, a result of hypercellularity of the interstitium and the failure of the lungs to collapse when the thorax was opened. **B,** Transverse section. The pulmonary parenchyma has a "meaty" appearance and some edema, but no exudate is present in airways or on the pleural surface. This type of lung change in pigs is highly suggestive of a viral pneumonia. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Acute interstitial pneumonias are often mild and transient, especially those caused by some respiratory viruses, such as those responsible for equine and porcine influenza. These mild forms of pneumonia are rarely seen in the postmortem room because they are not fatal and do not leave significant sequelae (see the section on Defense Mechanisms/Barrier Systems). In severe cases of acute interstitial pneumonias, animals may die of respiratory failure, usually as a result of diffuse alveolar damage, a profuse exudative phase (leakage of proteinaceous fluid) leading to a fatal pulmonary edema. Examples of this type of fatal acute interstitial pneumonia are bovine pulmonary edema and emphysema, and ARDS in all species.

Chronic Interstitial Pneumonia. When the source of alveolar injury persists, the exudative and proliferative lesions of acute interstitial pneumonia can progress into a morphologic stage referred to as *chronic interstitial pneumonia*. The hallmark of chronic interstitial pneumonia is fibrosis of the alveolar walls (with or without intraalveolar fibrosis) and the presence of lymphocytes, macrophages, fibroblasts, and myofibroblasts in the alveolar interstitium (Figs. 9-75 and 9-76). In other cases, these chronic changes are accompanied by hyperplasia and persistence of type II pneumonocytes, squamous metaplasia of the alveolar epithelium, microscopic granulomas, and hyperplasia of smooth muscle in bronchioles and pulmonary arterioles. It should be emphasized that although the lesions in interstitial pneumonia are centered in the alveolar wall and its interstitium, a mixture of desquamated epithelial cells, macrophages, and mononuclear cells are usually present in the lumens of bronchioles and alveoli. Ovine progressive pneumonia, hypersensitivity pneumonitis in cattle and dogs, and silicosis in horses are good veterinary examples of chronic interstitial pneumonia. Pneumoconioses (silicosis and asbestosis), paraquat toxicity, pneumotoxic antineoplastic drugs (bleomycin), and extrinsic allergic alveolitis (farmer's lung) are well-known examples of diseases that lead to chronic interstitial pneumonias in human beings. Massive pulmonary migration of ascaris larvae in pigs also causes interstitial pneumonia (Fig. 9-77).

There is an insidious and poorly understood group of chronic idiopathic interstitial diseases, both in human beings and in animals, that eventually progress to terminal interstitial fibrosis. These were originally thought to be the result of repeated cycles of alveolar injury, inflammation, and fibroblastic/myoblastic response to an unknown agent. However, aggressive antiinflammatory therapy generally fails to prevent or reduce the severity of fibrosis. Now, it is

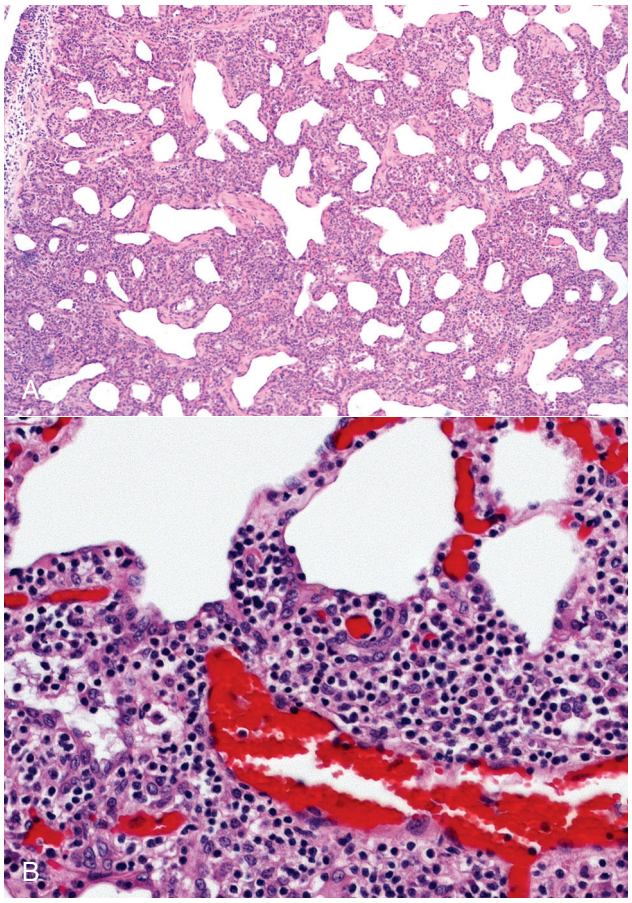


Figure 9-75 Interstitial Pneumonia, Lung, Aged Ewe. A, The alveolar septa are notably thickened by severe interstitial infiltration of inflammatory cells. H&E stain. **B,** Higher magnification of **A** showing large numbers of lymphocytes and other mononuclear cells infiltrating the alveolar septal interstitium. H&E stain. (**A** courtesy Western College of Veterinary Medicine. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

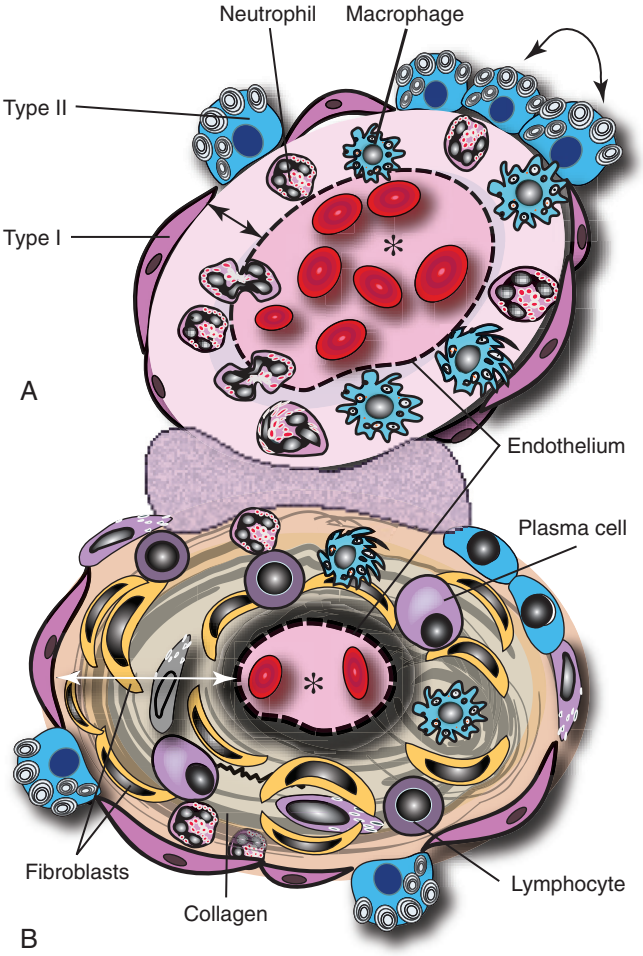


Figure 9-76 Acute and Chronic Interstitial Pneumonia. A, Acute interstitial pneumonia. Thickening of the alveolar septum caused by edema *(double-headed arrow)*, infiltration of neutrophils and macrophages, and hyperplasia of type II pneumonocytes *(double-headed curved arrow)*. Note the relative diameter of the capillary lumen *(asterisk)*. **B,** Chronic interstitial pneumonia. Thickening of the alveolar septum with notably reduced diameter of the capillary lumen *(asterisk)* caused by proliferation of connective tissue (fibroblasts, ECM, and collagen fibers) and infiltration of lymphocytes and plasma cells *(double-headed white arrow)*. In severe cases, the alveolar capillary may be totally obliterated. (Courtesy Dr. A. López, Atlantic Veterinary College.)

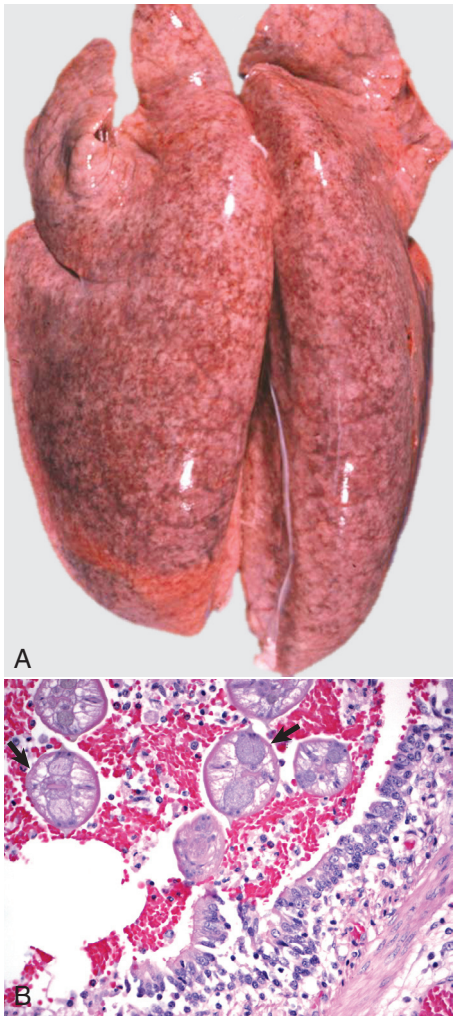


Figure 9-77 Interstitial Pneumonia, Edema, and Hemorrhages, Lungs, *Ascaris suum* Larvae, Pig. A, This pig had migrating *Ascaris suum* larvae. The lungs are heavy and wet and failed to collapse when the thorax was opened, as a result of pulmonary edema. The mottled appearance of the lungs is due to the presence of numerous petechiae scattered in the pulmonary parenchyma. Petechiae are likely alveolar hemorrhages caused by migrating larvae. Larvae leave the bloodstream to enter the alveoli by penetrating and rupturing alveolar capillaries and thus damage the air-blood barrier of alveolar septa. **B**, Multiple ascarid larvae *(arrows)*, erythrocytes, and small numbers of inflammatory cells are present within the lumen of a bronchus. H&E stain. (**A** courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University. **B** courtesy Dr. S. Martinson, Atlantic Veterinary College.)

proposed that a genetic mutation alters the cell-cell communication between epithelial and mesenchymal cells in the lung. This aberrant cellular communication leads to an overexpression of inflammatory and repair molecules (i.e., IL-4, IL-13, TGF-β1, and caveolin), leading to increased apoptosis and interstitial deposition of extracellular matrix (ECM). The chronic interstitial (restrictive) diseases in human medicine include "idiopathic pulmonary fibrosis," "nonspecific interstitial pneumonia," "unusual interstitial pneumonia," and "cryptogenic organizing pneumonia," also referred to as idiopathic *bronchiolitis obliterans organizing pneumonia* (idiopathic BOOP). Feline idiopathic pulmonary fibrosis is an example of this type of progressive interstitial disease in veterinary medicine. It has been reported that in rare cases, chronic alveolar remodeling and interstitial fibrosis can progress to lung cancer.

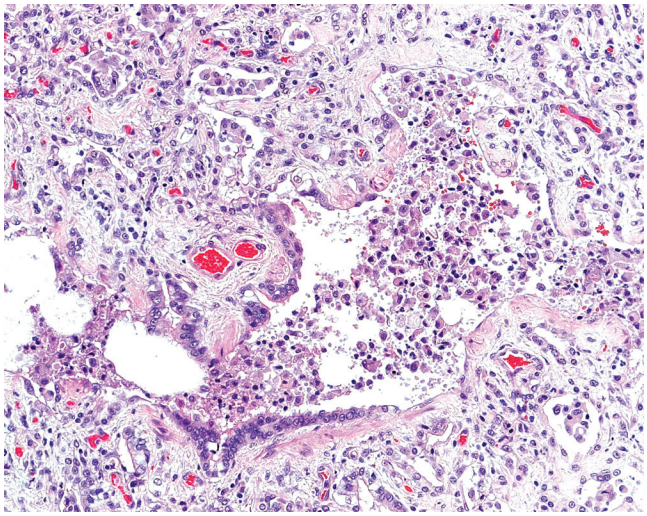
The term *bronchointerstitial pneumonia* is used in veterinary pathology to describe cases in which microscopic lesions share some histologic features of both bronchopneumonia and interstitial pneumonia (E-Fig. 9-9). This combined type of pneumonia is in fact frequently seen in many viral infections in which viruses replicate and cause necrosis in bronchial, bronchiolar, and alveolar cells. Damage to the bronchial and bronchiolar epithelium causes an influx of neutrophils similar to that in bronchopneumonias, and damage to alveolar walls causes proliferation of type II pneumonocytes, similar to that which takes place in the proliferative phase of acute interstitial pneumonias. It is important to emphasize that bronchointerstitial pneumonia is a microscopic not a gross diagnosis. Examples include uncomplicated cases of respiratory syncytial virus infections in cattle and lambs, canine distemper, and influenza in pigs and horses.

Embolic Pneumonia

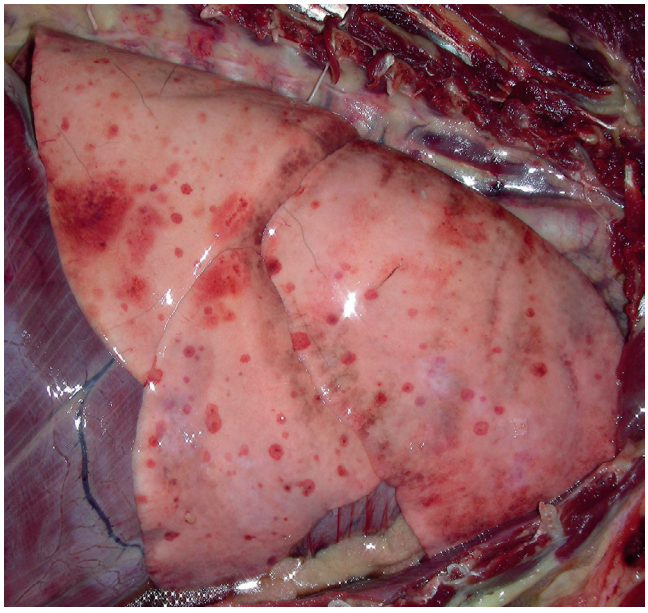
Embolic pneumonia refers to a particular type of pneumonia in which gross and microscopic lesions are multifocally distributed in all pulmonary lobes. By definition, lung injury is hematogenous, and the inflammatory response is typically centered in pulmonary arterioles and alveolar capillaries. Lungs act as a biologic filter for circulating particulate matter. Sterile thromboemboli, unless extremely large, are rapidly dissolved and removed from the pulmonary vasculature by fibrinolysis, causing little, if any, ill effects. Experimental studies have confirmed that most types of bacteria when injected intravenously (bacteremia) are phagocytosed by pulmonary intravascular macrophages, or they bypass the lungs and are finally trapped by macrophages in the liver, spleen, joints, or other organs. To cause pulmonary infection, circulating bacteria must first attach to the pulmonary endothelium with specific binding proteins or simply attach to intravascular fibrin and then evade phagocytosis by intravascular macrophages or leukocytes. Septic thrombi facilitate entrapment of bacteria in the pulmonary vessels and provide a favorable environment to escape phagocytosis. Once trapped in the pulmonary vasculature, usually in small arterioles or alveolar capillaries, offending bacteria disrupt endothelium and basement membranes, spread from the vessels to the interstitium and then to the surrounding lung, finally forming a new nidus of infection.

Embolic pneumonia is characterized by multifocal lesions randomly distributed in all pulmonary lobes (see Fig. 9-68 and E-Figs. 9-10 and 9-11). Early lesions in embolic pneumonia are characterized grossly by the presence of very small (1 to 10 mm), white foci surrounded by discrete, red, hemorrhagic halos (Fig. 9-78). Unless emboli arrive in massive numbers, causing fatal pulmonary edema, embolic pneumonia is seldom fatal; therefore these acute lesions are rarely seen at postmortem examination. In most instances, if unresolved, acute lesions rapidly progress to pulmonary abscesses. These are randomly distributed in all pulmonary lobes and are not restricted to the cranioventral aspects of the lungs, as is the case of abscesses developing from suppurative bronchopneumonia. The early microscopic lesions in embolic pneumonias are always focal or multifocal (Fig. 9-79); thus they differ from those of endotoxemia or septicemia, in which endothelial damage and interstitial reactions (interstitial pneumonia) are diffusely distributed in the lungs.

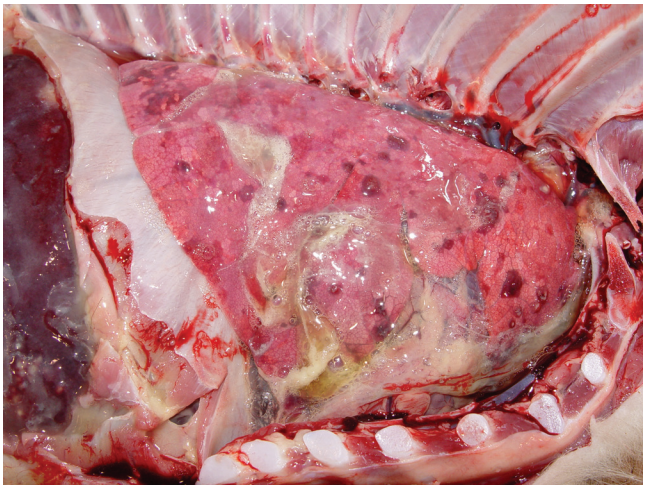
When embolic pneumonia or its sequela (abscesses) is diagnosed at necropsy, an attempt should be made to locate the source of septic emboli. The most common sources are hepatic abscesses that have ruptured into the caudal vena cava in cattle, omphalophlebitis in farm animals, chronic bacterial skin or hoof infections, and a contaminated catheter in all species (see Fig. 9-64). Valvular or mural endocarditis in the right heart is a common source of septic emboli and embolic pneumonia in all species. Most frequently, bacterial



E-Figure 9-9 **Bronchointerstitial Pneumonia, Subacute, Respiratory Syncytial Virus, Lung, Calf.** Necrotizing bronchiolitis where large numbers of epithelial cells have exfoliated into the lumen *(right center of image)*. There is also edematous distention of the bronchovascular interstitium. The alveolar walls are thickened and lined by hyperplastic type II pneumonocytes. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-10 **Acute to Subacute Embolic Pneumonia, Lung, Dog.** The lung has numerous circular areas of hemorrhage distributed randomly throughout all lung lobes (embolic pattern [see Fig. 9-68]). These foci arise from injury to the microvasculature in alveolar septa and the visceral pleura secondary to lodgment of bacterial or fungal emboli (septic emboli) from valvular or mural endocarditis in the right heart or from other bacterial or fungal diseases where the bacterium or fungus gains access to the circulatory system as occurs in many bacterial and fungal enteritides or pneumonias caused by *Salmonella* spp., *E. coli*, or *Aspergillus* spp. (Courtesy College of Veterinary Medicine, University of Illinois.)



E-Figure 9-11 **Acute to Subacute Embolic Pneumonia and Hepatitis, Lung and Liver, 15-Day-Old Lamb.** The lungs fail to collapse and show numerous hemorrhagic nodules distributed randomly throughout all lung lobes (embolic pattern [see Fig. 9-68]). Embolic nodules are also present in the liver. Septic emboli in this lamb originated from a severe septic omphalophlebitis (see Chapter 10). (Courtesy Dr. A. López, Atlantic Veterinary College.)

isolates from septic pulmonary emboli in domestic animals are *Trueperella* (*Arcanobacterium*) *pyogenes* (cattle), *Fusobacterium necrophorum* (cattle, pigs, and human beings), *Erysipelothrix rhusiopathiae* (pigs, cattle, dogs, and human beings), *Streptococcus suis* (pigs), *Staphylococcus aureus* (dogs and human beings), and *Streptococcus equi* (horses).

Granulomatous Pneumonia

Granulomatous pneumonia refers to a particular type of pneumonia in which aerogenous or hematogenous injury is caused by organisms or particles that cannot normally be eliminated by phagocytosis and that evoke a local inflammatory reaction with numerous alveolar and interstitial macrophages, lymphocytes, a few neutrophils, and sometimes giant cells. The term *granulomatous* is used here to describe an anatomic pattern of pneumonia typically characterized by the presence of granulomas.

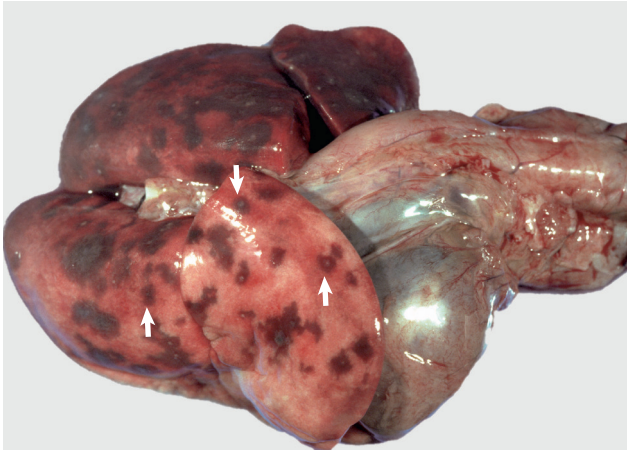


Figure 9-78 Embolic Pneumonia, Lungs, 6-Week-Old Puppy. Large hemorrhagic foci are scattered relatively uniformly throughout all pulmonary lobes *(arrows)*. These hemorrhagic foci are the sites of lodgment of *Pseudomonas aeruginosa* emboli (septic) that originated from necrotizing enteritis. Note the multifocal distribution of the inflammatory foci, which is typical of embolic pneumonia. Septic emboli were also present in the liver. (Courtesy Atlantic Veterinary College.)

The pathogenesis of granulomatous pneumonia shares some similarities with that of interstitial and embolic pneumonias. Not surprisingly, some pathologists group granulomatous pneumonias within one of these types of pneumonias (e.g., granulomatous interstitial pneumonia). What makes granulomatous pneumonia a distinctive type is not so much the portal of entry or site of initial injury in the lungs but, rather, the unique type of inflammatory response that results in the formation of granulomas, which can be easily recognized at gross and microscopic examination. As a rule, agents causing granulomatous pneumonias are resistant to intracellular killing by phagocytic cells and to the acute inflammatory response, allowing prolonged persistence of these agents in tissues.

The most common causes of granulomatous pneumonia in animals include systemic fungal diseases, such as cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gatti*), coccidioidomycosis (*Coccidioides immitis*), histoplasmosis (*Histoplasma capsulatum*), and blastomycosis (*Blastomyces dermatitidis*) (see Fig. 9-35). In most of these fungal diseases, the port of entry is aerogenous, and from the lungs the fungi disseminate systemically to other organs, particularly the lymph nodes, liver, and spleen. Filamentous fungi such as *Aspergillus* spp. or *Mucor* spp. can also reach the lung by the hematogenous route.

Granulomatous pneumonia is also seen in some bacterial diseases, such as tuberculosis (*Mycobacterium bovis*) in all species and *Rhodococcus equi* in horses. Sporadically, aberrant parasites such as *Fasciola hepatica* in cattle and aspiration of foreign bodies can also cause granulomatous pneumonia (E-Fig. 9-12). Feline infectious peritonitis (FIP) is one of a few viral infections of domestic animals that result in granulomatous pneumonia (see Pneumonias of Cats).

Granulomatous pneumonia is characterized by the presence of variable numbers of caseous or noncaseous granulomas randomly distributed in the lungs (see Fig. 9-68). On palpation, lungs have a typical nodular character given by well-circumscribed, variably sized nodules that generally have a firm texture, especially if calcification has occurred (Fig. 9-80). During postmortem examination, granulomas in the lungs occasionally can be mistaken for neoplasms. Microscopically, pulmonary granulomas are composed of a center of necrotic tissue, surrounded by a rim of macrophages (epithelioid cells) and giant cells and an outer delineated layer of connective tissue commonly infiltrated by lymphocytes and plasma cells (Fig. 9-81). Unlike other types of pneumonias, the causative agent in granulomatous pneumonia can, in many cases, be identified

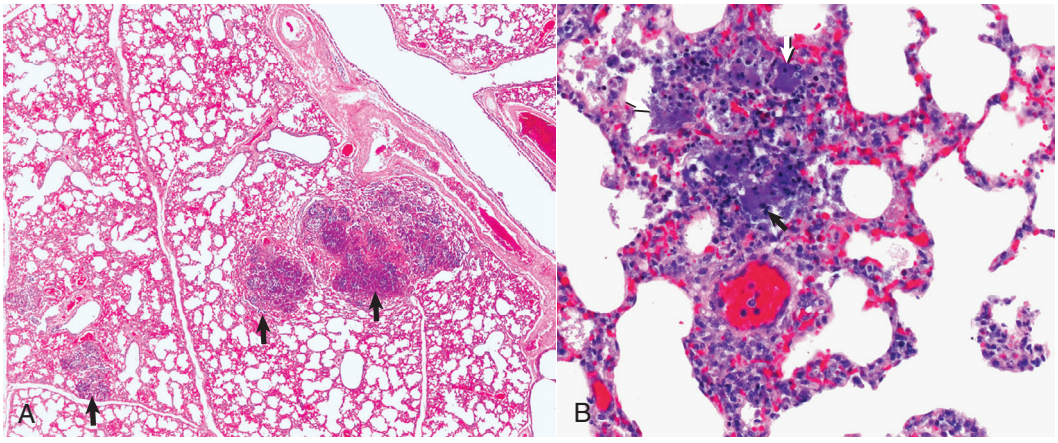
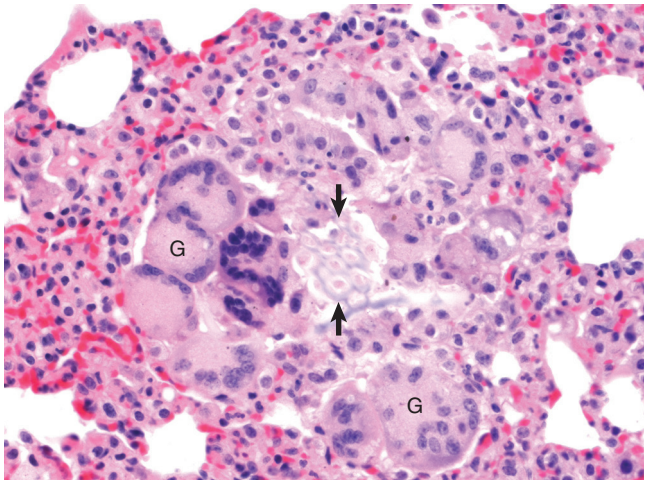


Figure 9-79 Embolic Pneumonia, Lung, Cow. A, Foci of necrosis and infiltration of neutrophils *(arrows)* resulting from septic emboli. Note the multifocal distribution of the lesion, which is typical of embolic pneumonia. Vegetative endocarditis involving the tricuspid valve was the source of septic emboli in this cow. H&E stain. **B,** Embolic focus in the lung. Note bacterial colonies *(arrows)* mixed with neutrophils and cellular debris. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-12 Granulomatous Pneumonia, Aspiration of Feed Particles, Lung, Guinea Pig. Vegetable particle *(arrows)* surrounded by multinucleated (foreign body) giant cells *(G)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

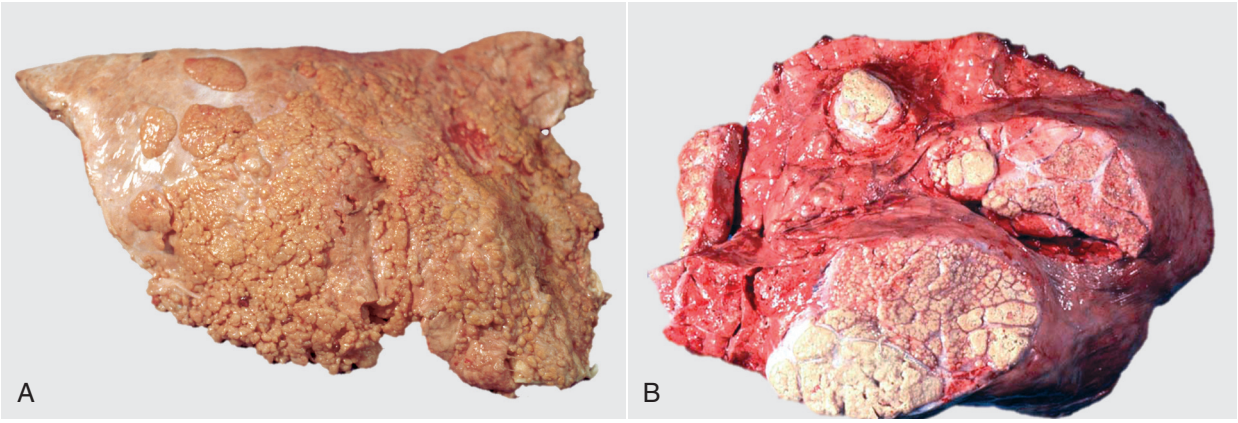


Figure 9-80 Pulmonary Tuberculosis, Lung, Aged Cow. A, Multifocal, coalescing granulomatous pneumonia involves most of the lung, except for the dorsal portion of the caudal lung lobe. **B,** Transverse section. Large multifocal to confluent caseating granulomas are present in the pulmonary parenchyma. Note the caseous ("cheesy," pale yellow-white) appearance of the granulomas, which is typical of bovine tuberculosis. (**A** courtesy Facultad de Medicina Veterinaria y Zootecnia, UNAM, México. **B** courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University.)

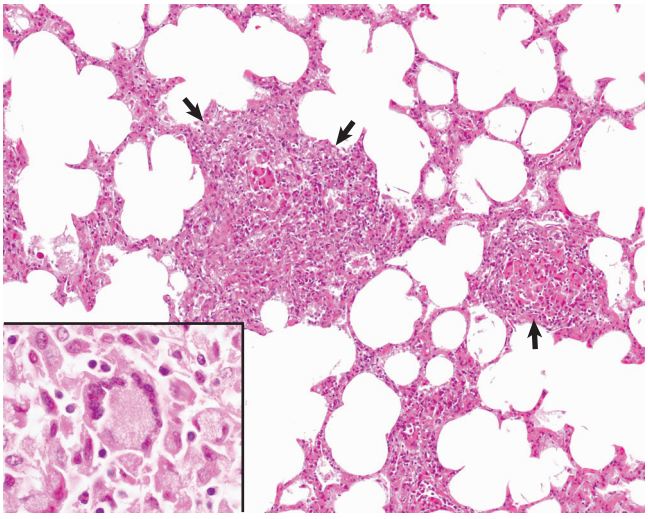


Figure 9-81 Granulomatous Pneumonia, Lung, Cow. Confluent noncaseous granulomas *(arrows)* with a small necrotic center filled with neutrophils, surrounded by histiocytes and mononuclear cells, and with an outer rim of connective tissue. H&E stain. *Inset,* Epithelioid macrophages and a large multinucleated giant cell *(in center of figure)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

microscopically in sections by PAS reaction or Grocott-Gomori's methenamine silver (GMS) stain for fungi or by an acid-fast stain for mycobacteria.

Species-Specific Pneumonias of Domestic Animals

Pneumonias of Horses

Viral infections of the respiratory tract, particularly equine viral rhinopneumonitis and equine influenza, are important diseases of horses throughout the world. The effects of these and other respiratory viruses on the horse can be manifested in three distinct ways. First, as pure viral infections, their severity may range from mild to severe, making them a frequent interfering factor in training and athletic performance. Second, superimposed infections by opportunistic bacteria, such as *Streptococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Rhodococcus equi*, and various anaerobes, can cause fibrinous or suppurative bronchopneumonias. Third, it is possible but yet unproven that viral infections may also predispose horses to airway hyperresponsiveness and recurrent airway obstruction (RAO).

Viral Pneumonias

Equine Influenza. Equine influenza is an important and highly contagious flulike respiratory disease of horses characterized by high morbidity and low mortality and explosive outbreaks in susceptible populations. It is an OIE-notifiable disease. Two antigenically unrelated subtypes of equine influenza virus have been identified (H7N7 [A/equi-1] and H3N8 [A/equi-2]). The course of the disease is generally mild and transient, and its importance is primarily because of its economic impact on horse racing. The types of injury and host response in the conducting system are described in the section on disorders of the nasal cavity and paranasal sinuses of horses. Uncomplicated lesions in the lungs are mild and self-limiting bronchointerstitial pneumonia. In fatal cases, the lungs are hyperinflated with coalescing areas of dark red discoloration. Microscopically, there is a bronchointerstitial pneumonia characterized by necrotizing bronchiolitis that is followed by hyperplastic bronchiolitis, hyperplasia of type II pneumonocytes, hyaline membranes in alveoli, and sporadic multinucleated giant cells. The microscopic changes are ARDS in severe and fatal cases. The influenza virus antigen can be readily demonstrated in ciliated cells and alveolar macrophages. Clinical signs are characterized by fever, cough, abnormal lung sounds (crackles and wheezes), anorexia, and depression. Secondary bacterial infections (*Streptococcus equi*, *Streptococcus zooepidemicus*, *Staphylococcus aureus*, and *Escherichia coli*) commonly complicate equine influenza.

Equine Viral Rhinopneumonitis. Equine viral rhinopneumonitis (EVR), or equine herpesvirus infection, is a respiratory disease of young horses that is particularly important in weanlings between 4 and 8 months of age and to a much lesser extent in young foals and adult horses. The causative agents are ubiquitous equine herpesviruses (EHV-1 and EHV-4) that in addition to respiratory disease can cause abortion in pregnant mares and neurologic disease (equine herpes myeloencephalopathy) (see the section on disorders of the nasal cavity and paranasal sinuses of horses).

The respiratory form of EVR is a mild and a transient bronchointerstitial pneumonia seen only by pathologists when complications with secondary bacterial infections cause a fatal bronchopneumonia

(*Streptococcus equi*, *Streptococcus zooepidemicus*, or *Staphylococcus aureus*). Uncomplicated lesions in EVR are seen only in aborted fetuses or in foals that die within the first few days of life. They consist of focal areas of necrosis (0.5 to 2 mm) in various organs, including liver, adrenal glands, and lungs. In some cases, intranuclear inclusion bodies are microscopically observed in these organs. Outbreaks of interstitial pneumonia in donkeys have been attributed to multiple strains of asinine herpesviruses (AHV-4 and -5). Clinically, horses and donkeys affected with the respiratory form of EVR exhibit fever, anorexia, conjunctivitis, cough, and nasal discharge.

Equine Viral Arteritis. Equine viral arteritis (EVA), a pansystemic disease of horses, donkeys, and mules caused by an arterivirus (equine arteritis virus [EAV]), occurs sporadically throughout the world, sometimes as an outbreak. This virus infects and causes severe injury to macrophages and endothelial cells. Gross lesions are hemorrhage and edema in many sites, including lungs, intestine, scrotum, and periorbital tissues and voluminous hydrothorax and hydroperitoneum. The basic lesion is fibrinoid necrosis and inflammation of the vessel walls (vasculitis), particularly the small muscular arteries (lymphocytic arteritis), which is responsible for the edema and hemorrhage that explain most of the clinical features. Pulmonary lesions are those of interstitial pneumonia with hyperplasia of type II pneumonocytes and vasculitis with abundant edema in the bronchoalveolar spaces and distended pulmonary lymphatic vessels. Viral antigen can be detected by immunoperoxidase techniques in the walls and endothelial cells of affected pulmonary vessels and in alveolar macrophages.

Clinical signs are respiratory distress, fever, abortion, diarrhea, colic, and edema of the limbs and ventral abdomen. Respiratory signs are frequent and consist of serous or mucopurulent rhinitis and conjunctivitis with palpebral edema. Like most viral respiratory infections, EVA can predispose horses to opportunistic bacterial pneumonias.

African Horse Sickness. African horse sickness (AHS) is an arthropod-borne, OIE-notifiable disease of horses, mules, donkeys, and zebras that is caused by an orbivirus (family Reoviridae) and characterized by respiratory distress or cardiovascular failure. AHS has a high mortality rate—up to 95% in the native population of horses in Africa, the Middle East, India, Pakistan, and, most recently, Spain and Portugal. Although the AHS virus is transmitted primarily by insects (*Culicoides*) to horses, other animals, such as dogs, can be infected by eating infected equine flesh. The pathogenesis of African horse sickness remains unclear, but this equine orbivirus has an obvious tropism for pulmonary and cardiac endothelial cells and, to a lesser extent, mononuclear cells. Based on clinical signs (not pathogenesis), African horse sickness is arbitrarily divided into four different forms: pulmonary, cardiac, mixed, and mild.

The pulmonary form is characterized by severe respiratory distress and rapid death because of massive pulmonary edema, presumably from viral injury to the pulmonary endothelial cells. Grossly, large amounts of froth are present in the airways, lungs fail to collapse, subpleural lymph vessels are distended, and the ventral parts of the lungs are notably edematous (see Fig. 4-40). In the cardiac form, recurrent fever is detected, and heart failure results in subcutaneous and interfascial edema, most notably in the neck and supraorbital region. The mixed form is a combination of the respiratory and cardiac forms. Finally, the mild form, rarely seen in postmortem rooms, is characterized by fever and clinical signs resembling those of equine influenza; it is in most cases transient and followed by a complete recovery. This mild form is most frequently seen in donkeys, mules, and zebras and in horses with some degree of immunity. Detection of viral antigen for diagnostic purposes can be done by immunohistochemistry in paraffin-embedded tissues.

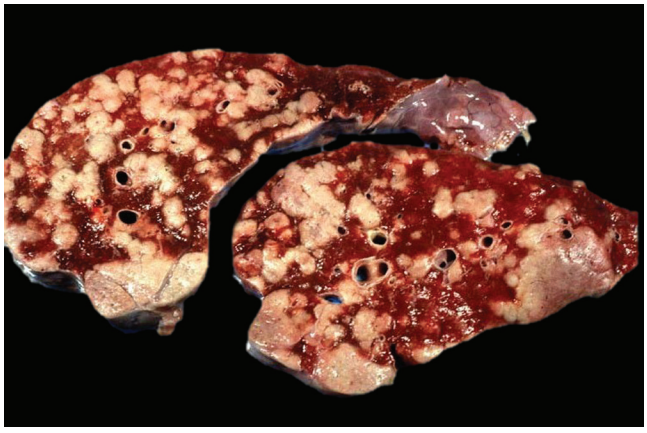
Equine Henipavirus (Hendra Virus). Fatal cases of a novel respiratory disease in horses and human beings suddenly appeared in approximately 1994 in Hendra, a suburb of Brisbane, Australia. This outbreak was attributed to a newly recognized zoonotic virus that was tentatively named equine *Morbillivirus*. Now called Hendra virus (HeV), this emerging viral pathogen is currently classified as a member of the genus *Henipavirus* (includes Hendra virus and Nipah virus), in the family Paramyxoviridae. Fruit bats (flying foxes) act as natural reservoirs and are involved in the transmission by poorly understood mechanisms. The lungs of affected horses are severely edematous with gelatinous distention of pleura and subpleural lymph vessels. Microscopically, the lungs have diffuse alveolar edema associated with vasculitis, thrombosis, and the presence of multinucleated syncytial cells in the endothelium of small pulmonary blood vessels and alveolar capillaries. The lymphatic vessels are notably distended with fluid. The characteristic inclusion bodies seen in other paramyxovirus infections are not seen in horses; however, the virus can be easily detected by immunohistochemistry in pulmonary endothelial cells and alveolar epithelial cells (pneumonocytes). Clinical signs are nonspecific and include fever, anorexia, respiratory distress, and nasal discharge.

Equine Multinodular Pulmonary Fibrosis. Equine multinodular pulmonary fibrosis is a lung disease characterized by well-demarcated fibrotic nodular lesions in the lung (E-Fig. 9-13). Until recently, the pathogenesis was unclear, but recent studies proposed equine herpesvirus 5 (EHV-5) as the putative etiology. Grossly, the lungs show multifocal to coalescing, firm tan nodules scattered in all pulmonary lobes, which resemble pulmonary neoplasia. Microscopically, alveolar walls are thickened due to collagen deposition, infiltration of lymphocytes and macrophages, and cuboidal cells lining the alveolar walls. The alveolar lumens contain neutrophils and macrophages, some of which may contain a large eosinophilic intranuclear inclusion body. Typical clinical signs include weight loss, low-grade fever, and progressive exercise intolerance. This condition has a poor prognosis.

Bacterial Pneumonias

Rhodococcus equi. *Rhodococcus equi* is an important cause of morbidity and mortality in foals throughout the world. This facultative intracellular Gram-positive bacterium causes two major forms of disease: The first involves the intestine, causing ulcerative enterocolitis, and the second severe and often fatal bronchopneumonia. Although half of foals with pneumonia have ulcerative enterocolitis, it is rare to find animals with intestinal lesions alone. Occasionally, infection disseminates to lymph nodes, joints, bones, the genital tract, and other organs. Because *Rhodococcus equi* is present in soil and feces of herbivores (particularly foals), it is common for the disease to become enzootic on farms ("hot spots") where the organism has been shed earlier by infected foals. Serologic evidence of infection in horses is widespread, yet clinical disease is sporadic and largely restricted to young foals or to adult horses with severe immunosuppression. Virulence factors encoded by plasmids (virulence-associated protein A [*vap*A gene]) are responsible for the survival and replication of *Rhodococcus equi* in macrophages, thus determining the evolution of the disease. This bacterium has also been sporadically incriminated with infections in cattle, goats, pigs, dogs, and cats, and quite often in immunocompromised human beings, for example, those infected with the AIDS virus, after organ transplantation, or undergoing chemotherapy.

It is still debatable whether natural infection starts as a bronchopneumonia (aerogenous route) from which *Rhodococcus equi* reaches the intestine via swallowed sputum or whether infection starts as an enteritis (oral route) with a subsequent bacteremia into the lungs.



E-Figure 9-13 **Multinodular Pulmonary Fibrosis, Lung, Cut Surface, Horse.** Numerous well-demarcated white-tan fibrotic nodular lesions resembling neoplasia are scattered throughout the lungs. These nodular lesions are observed in a pulmonary condition of horses known as *equine multinodular fibrosis* caused by equine herpesvirus 5 (EHV-5). (Courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University.)

The results of experimental studies suggest that natural infection likely starts from inhalation of infected dust or aerosols. Once in the lung, *Rhodococcus equi* is rapidly phagocytosed by alveolar macrophages, but because of defective phagosome-lysosome fusion and premature lysosomal degranulation, bacteria survive and multiply intracellularly, eventually leading to the destruction of the macrophage. Interestingly, *Rhodococcus equi* appears to be easily killed by neutrophils but not macrophages. Released cytokines and lysosomal enzymes and bacterial toxins are responsible for extensive caseous necrosis of the lungs and the recruitment of large numbers of neutrophils, macrophages, and giant cells containing intracellular Gram-positive organisms in their cytoplasm.

Depending on the stage of infection and the immune status and age of affected horses, pulmonary lesions induced by *Rhodococcus equi* can vary from pyogranulomatous to granulomatous pneumonia. In young foals, the infection starts as a suppurative cranioventral bronchopneumonia, which progresses within a few days into small variable-size pulmonary abscesses. These abscesses rapidly transform into pyogranulomatous nodules, some of which become confluent and form large masses of caseous exudate (Fig. 9-82). Microscopically, the early lesion starts with neutrophilic infiltration, followed by an intense influx of alveolar macrophages into the bronchoalveolar spaces. This type of histiocytic inflammation persists for a long period of time because *Rhodococcus equi* is a facultative intracellular organism that survives the bactericidal effects of equine alveolar macrophages. In the most chronic cases, the pulmonary lesions culminate with the formation of large caseonecrotic masses with extensive fibrosis of the surrounding pulmonary parenchyma. PCR analysis of tracheobronchial aspirates has successfully been used as an alternative to bacteriologic culture in the diagnosis of *Rhodococcus equi* infection in live foals.

Clinically, *Rhodococcus equi* infection can be acute, with rapid death caused by severe bronchopneumonia, or chronic, with depression, cough, weight loss, and respiratory distress. In either form, there may be diarrhea, arthritis, osteomyelitis, or subcutaneous abscess formation.

Parasitic Pneumonias

Parascaris equorum. *Parascaris equorum* is a large nematode (roundworm) of the small intestine of horses; the larval stages migrate through the lungs as ascarid larvae do in pigs. It is still unclear whether migration of *Parascaris equorum* larvae can cause significant pulmonary lesions under natural conditions. Experimentally, migration of larvae results in coughing, anorexia, weight loss, and small necrotic foci and petechial hemorrhages in the liver, hepatic and tracheobronchial lymph nodes, and lungs. Microscopically, eosinophils are prominent in the interstitium and airway mucosa during the parasitic migration and in focal granulomas caused by dead larvae in the lung.

Dictyocaulus arnfieldi. *Dictyocaulus arnfieldi* is not a very pathogenic nematode, but it should be considered if there are signs of coughing in horses that are pastured together with donkeys. Donkeys are considered the natural hosts and can tolerate large numbers of parasites without ill effects. *Dictyocaulus arnfieldi* does not usually become patent in horses, so examination of fecal samples is not useful; BAL is only occasionally diagnostic because eosinophils (but not parasites) are typically found in the lavage fluid. Mature parasites (up to 8 cm in length) cause obstructive bronchitis, edema, and atelectasis, particularly along the dorsocaudal lung. The microscopic lesion is an eosinophilic bronchitis similar to the less acute infestations seen in cattle and sheep with their *Dictyocaulus* species.

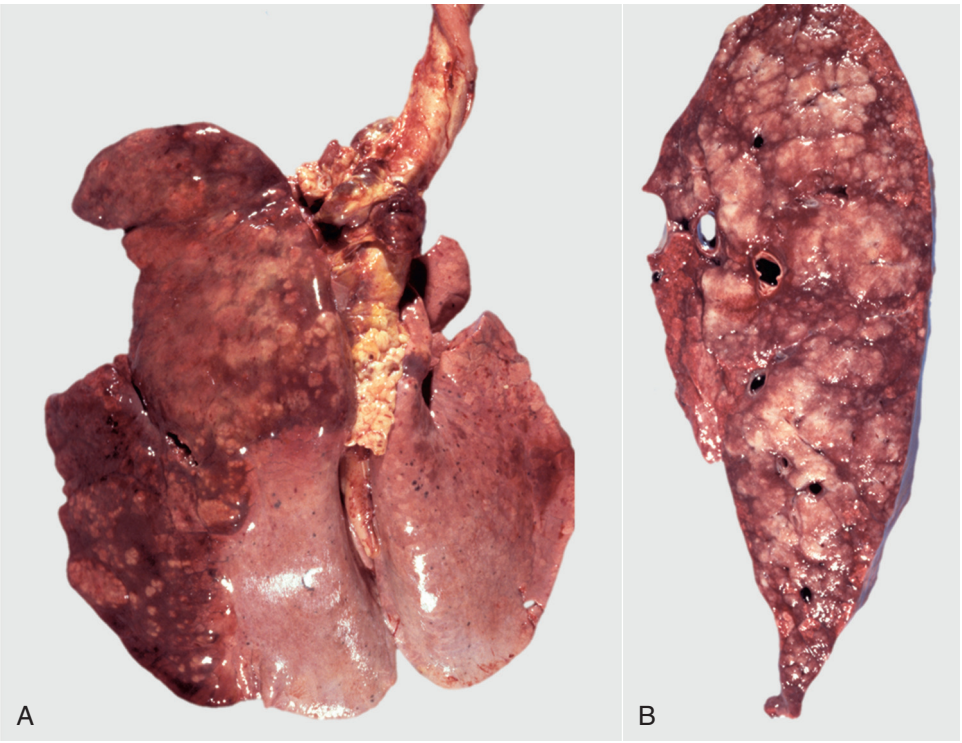


Figure 9-82 **Granulomatous Pneumonia *(Rhodococcus equi)*, Lungs, Foal. A,** Cranioventral consolidation of the lungs with subpleural granulomas. Note that the pneumonic lesions in this foal are unilateral. This was an experimental case in which a foal was intratracheally inoculated with a suspension of *Rhodococcus equi*. **B,** Cut surface. Note the numerous, large, confluent, caseated white-brown granulomas. (Courtesy Dr. J. Yager and Dr. J. Prescott, Ontario Veterinary College.)

Aspiration Pneumonia. Aspiration pneumonia is often a devastating sequela to improper gastric tubing of horses, particularly exogenous lipid pneumonia from mineral oil delivered into the trachea in treatment of colic. Gross and microscopic lesions are described in detail in the section on aspiration pneumonias of cattle.

Other Causes of Pneumonia

Opportunistic Infections. *Chlamydophila* (*Chlamydia*) spp., obligatory intracellular zoonotic pathogens, can cause systemic infection in many mammalian and avian species; in horses, they can also cause keratoconjunctivitis, rhinitis, pneumonia, abortion, polyarthritis, enteritis, hepatitis, and encephalitis. Serologic studies suggest that infection without apparent disease is common in horses. Horses experimentally infected with *Chlamydophila psittaci* develop mild and transient bronchointerstitial pneumonia. There are unconfirmed reports suggesting a possible association between these organisms and recurrent airway obstruction in horses. Detection of chlamydial organisms in affected tissue is not easy and requires special laboratory techniques such as PCR, immunohistochemistry, and fluorescent antibody tests.

Horses are only sporadically affected with mycobacteriosis (*Mycobacterium avium* complex, *Mycobacterium tuberculosis*, and *Mycobacterium bovis*). The intestinal tract and associated lymph nodes are generally affected, suggesting an oral route of infection with subsequent hematogenous dissemination to the lungs. The tubercles (granulomas) differ from those in ruminants and pigs, being smooth, gray, solid, sarcoma-like nodules without grossly visible caseous necrosis or calcification (E-Fig. 9-14). Microscopically, the tubercles are composed of macrophages, epithelioid cells, and multinucleated giant cells. Fibrosis increases with time, accounting in part for the sarcomatous appearance.

Adenovirus infections occur commonly in Arabian foals with combined immunodeficiency (CID), a hereditary lack of B and T lymphocytes. In cases of adenoviral infection, large basophilic or amphophilic inclusions are present in the nuclei of tracheal, bronchial, bronchiolar, alveolar, renal, and intestinal epithelial cells. As it occurs in other species, infection with a unique fungal pathogen known as *Pneumocystis carinii* typically occurs in immunosuppressed or immunoincompetent individuals such as Arabian foals with CID (see Fig. 9-20). Diagnosis of *Pneumocystis carinii* requires microscopic examination of lungs and special stains.

Idiopathic Interstitial Pneumonia. Interstitial and bronchointerstitial pneumonias of undetermined cause that can progress to severe pulmonary fibrosis have been reported in foals and young horses. The gross and microscopic lesions are reminiscent of those of bovine pulmonary edema and emphysema or ARDS. The lungs are notably congested and edematous and microscopically are characterized by necrosis of the bronchiolar epithelium, alveolar edema, hyperplasia of type II pneumonocytes, and hyaline membranes. The cause of this form of equine interstitial pneumonia is not known, but toxic and particularly viral causes have been proposed.

Pneumonias of Cattle

Bovine respiratory disease complex (BRDC) and acute undifferentiated respiratory disease are general terms often used by clinicians to describe acute and severe bovine respiratory illness of clinically undetermined cause. These terms do not imply any particular type of pneumonia and therefore should not be used in pathology reports. Clinically, the BRD complex includes bovine enzootic pneumonia (multifactorial etiology); pneumonic mannheimiosis (*Mannheimia haemolytica*); respiratory histophilosis (*Histophilus somni*), previously known as respiratory hemophilosis (*Haemophilus somnus*); *Mycoplasma bovis*; respiratory viral infections, such as infectious bovine rhinotracheitis (IBR)/bovine herpes virus 1 (BoHV-1), bovine parainfluenza virus 3 (BPIV-3), and bovine respiratory syncytial virus (BRSV); and noninfectious interstitial pneumonias, such as bovine pulmonary edema and emphysema, reinfection syndrome, and many others.

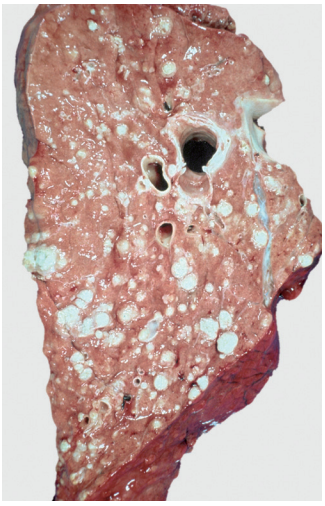
Bovine Enzootic Pneumonia. Enzootic pneumonia, sometimes simply referred to as *calf pneumonia*, is a multifactorial disease caused by a variety of etiologic agents that produces an assortment of lung lesions in young, intensively housed calves. The host-microbial-environmental triad is central in the pathogenesis of this disease. Morbidity is often high (up to 90%), but fatalities are uncommon (>5%) unless management is poor or unless new, virulent pathogens are introduced by additions to the herd. Enzootic pneumonia is also called *viral pneumonia* because it often begins with an acute respiratory infection with BPIV-3, BRSV, or possibly with one or more of several other viruses (adenovirus, BoHV-1, reovirus, bovine coronavirus [BCoV], and bovine rhinitis virus). Mycoplasmas, notably *Mycoplasma dispar*, *Mycoplasma bovis*, *Ureaplasma*, and possibly *Chlamydophila*, may also be primary agents. Following infection with any of these agents, opportunistic bacteria, such as *Pasteurella multocida*, *Trueperella* (*Arcanobacterium*) *pyogenes*, *Histophilus somni*, *Mannheimia haemolytica*, and *Escherichia coli*, can cause a secondary suppurative bronchopneumonia, the most serious stage of enzootic pneumonia. The pathogenesis of the primary invasion and how it predisposes the host to invasion by the opportunists are poorly understood, but it is likely that there is impairment of pulmonary defense mechanisms. Environmental factors, including air quality (poor ventilation), high relative humidity, and animal crowding, have been strongly incriminated. The immune status of the calf also plays an important role in the development and severity of enzootic pneumonia. Calves with bovine leukocyte adhesion deficiency (BLAD), which prevents the migration of neutrophils from the capillaries, are highly susceptible to bronchopneumonia.

Lesions are variable and depend largely on the agents involved and on the duration of the inflammatory process. In the acute phases, lesions caused by viruses are those of bronchointerstitial pneumonia, which are generally mild and transient, and therefore are seen only sporadically at necropsy. Microscopically, the lesions are necrotizing bronchiolitis, necrosis of type I pneumonocytes with hyperplasia of type II pneumonocytes, and mild interstitial and alveolar edema.

In the case of BPIV-3 and BRSV infection, intracytoplasmic inclusion bodies and the formation of large multinucleated syncytia, resulting from the fusion of infected bronchiolar and alveolar epithelial cells, can also be observed in the lungs (Fig. 9-83). Airway hyperreactivity has been described in calves after BRSV infection; however, the significance of this syndrome in relation to enzootic pneumonia of calves is still under investigation.

The mycoplasmas also can cause bronchiolitis, bronchiolar and alveolar necrosis, and an interstitial reaction, but in contrast to viral-induced pneumonias, mycoplasmal lesions tend to progress to a chronic stage characterized by striking peribronchiolar lymphoid hyperplasia (cuffing pneumonia). When complicated by secondary bacterial infections (e.g., *Pasteurella multocida* and *Trueperella pyogenes*), viral or mycoplasmal lesions change from a pure bronchointerstitial to a suppurative bronchopneumonia (Fig. 9-84). In late stages of bronchopneumonia, the lungs contain a creamy-mucoid exudate in the airways and later often have pulmonary abscesses and bronchiectasis (see Fig. 9-11).

Note that the same viruses and mycoplasmas involved in the enzootic pneumonia complex can also predispose cattle to other diseases, such as pneumonic mannheimiosis (*Mannheimia*



E-Figure 9-14 **Multifocal Granulomatous Pneumonia, Atypical Mycobacteriosis (*Mycobacterium Avium*-Complex), Lung, Cut Surface, Aged Horse.** Note the large numbers of noncaseating white granulomas scattered throughout the pulmonary parenchyma. In horses, granulomas caused by mycobacteria often resemble sarcomatous nodules. (Courtesy Western College of Veterinary Medicine.)

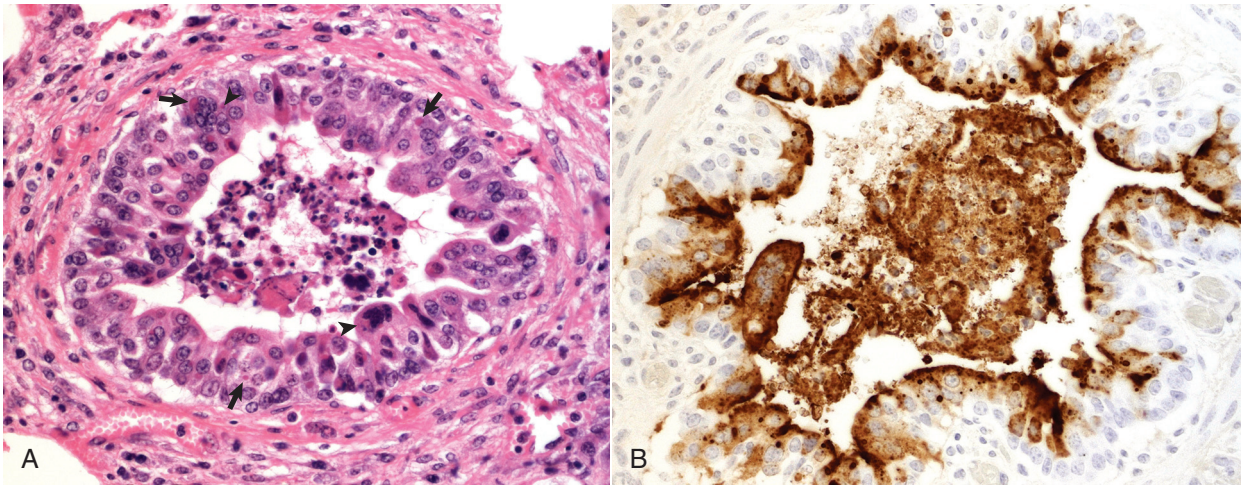


Figure 9-83 Necrotizing Bronchiolitis, Bovine Respiratory Syncytial Virus, Lung, 5-Week-Old Calf. This is the reparative stage of necrotizing bronchiolitis and is characterized by epithelial hyperplasia and exfoliation of necrotic cells into the bronchiolar lumen. **A,** Epithelial cells are swollen, some are multinucleated *(arrowheads)*, and the cytoplasm of some cells contains eosinophilic inclusion bodies surrounded by a clear halo *(arrows)*. Many of these hyperplastic bronchiolar cells eventually undergo apoptosis during the last stage of bronchiolar repair. H&E stain. **B,** Necrotizing viral bronchiolitis, immunohistochemistry. Note positive staining for bovine respiratory syncytial virus antigen in bronchiolar cells and in exfoliated necrotic material in the bronchiolar lumen. Immunoperoxidase stain. (**A** and **B** courtesy Dr. A. López, Atlantic Veterinary College.)

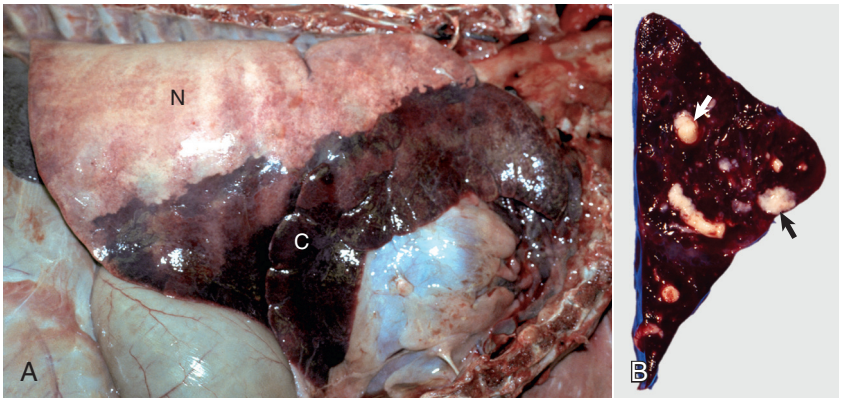


Figure 9-84 Suppurative Bronchopneumonia, Right Lung, Calf. A, Approximately 40% of the lung parenchyma is consolidated and includes most of the cranial lung lobe and the ventral portions of the middle and caudal lung lobes, a distribution often designated as cranioventral. Note the dark color of the consolidated lung (C) and the normal appearance of the dorsal portion of the caudal lung lobe *(N)*. **B,** Transverse section of the cranial lung lobe showing bronchi filled with purulent exudate *(arrows)*. (Courtesy Ontario Veterinary College.)

haemolytica). Clinically, enzootic pneumonia is usually mild, but fatal cases are occasionally seen even in farms with optimal health management.

Bacterial Pneumonias

Pneumonic Mannheimiosis (Shipping Fever). Shipping fever (transit fever) is a vague clinical term used to denote acute respiratory diseases that occur in cattle several days or weeks after shipment. The disease is characterized by a severe fibrinous bronchopneumonia, reflecting the fact that death generally occurs early or at an acute stage. Because *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*) is most frequently isolated from affected lungs, the names pneumonic mannheimiosis and pneumonic pasteurellosis have been used synonymously. It is known that pneumonic mannheimiosis can occur in animals that have not been shipped and that organisms other than *Mannheimia haemolytica* can cause similar lesions. Therefore the term *shipping fever* should be relinquished in favor of more specific names, such as pneumonic mannheimiosis or respiratory histophilosis.

Pneumonic mannheimiosis (shipping fever) is the most important respiratory disease of cattle in North America, particularly in feedlot animals that have been through the stressful marketing and assembly processes. *Mannheimia haemolytica* biotype A, serotype 1 is the etiologic agent most commonly responsible for the severe pulmonary lesions. A few investigators still consider that *Pasteurella multocida* and other serotypes of *Mannheimia haemolytica* are also causes of this disease.

Even after many years of intense investigation, from the gross lesions to the molecular aspects of the disease, the pathogenesis of pneumonic mannheimiosis remains incompletely understood. Experiments have established that *Mannheimia haemolytica* A1 alone is usually incapable of causing disease because it is rapidly cleared by pulmonary defense mechanisms. These findings may explain why *Mannheimia haemolytica*, despite being present in the nasal cavity of healthy animals, only sporadically causes disease. For *Mannheimia haemolytica* to be established as a pulmonary infection, it is first required that stressors impair the defense mechanisms and allow the bacteria to colonize the lung (see section on Impairment of Defense

Mechanisms). These stressors include weaning, transport, fatigue, crowding, mixing of cattle from various sources, inclement weather, temporary starvation, and viral infections. Horizontal transmission of viruses and *Mannheimia haemolytica* occurs during crowding and transportation of cattle.

Viruses that most commonly predispose cattle to pneumonic mannheimiosis include BoHV-1, BPIV-3, and BRSV. Once established in the lungs, *Mannheimia haemolytica* causes lesions by means of different virulence factors, which include endotoxin, lipopolysaccharide, adhesins, and outer membrane proteins; however, the most important is probably the production of a leukotoxin (exotoxin), which binds and kills bovine macrophages and neutrophils. The fact that this toxin exclusively affects ruminant leukocytes probably explains why *Mannheimia haemolytica* is a respiratory pathogen in cattle and sheep but not in other species. During *Mannheimia haemolytica* infection, alveolar macrophages, neutrophils, and mast cells release maximum amounts of proinflammatory cytokines, particularly TNF-α, IL-1, IL-8, adhesion molecules, histamine, and leukotrienes. By locally releasing enzymes and free radicals, leukocytes further contribute to the injury and necrosis of bronchiolar and alveolar cells.

The gross lesions of acute and subacute pneumonic mannheimiosis are the prototypic fibrinous bronchopneumonia, with prominent fibrinous pleuritis (Fig. 9-85 and see Fig. 9-72) and pleural effusion. Lesions are always cranioventral and usually ventral to a horizontal line through the tracheal bifurcation. The interlobular septa are distended by yellow, gelatinous edema and fibrin. The "marbling" of lobules is the result of intermixing areas of coagulation necrosis, interlobular interstitial edema, and congestion (Fig. 9-86).

Microscopically, lung lesions are evident 4 hours after experimental infection in which neutrophils fill the bronchial, bronchiolar, and alveolar spaces. Within 24 to 48 hours, the cytotoxic effect of *Mannheimia haemolytica* is manifested by necrosis of individual alveolar cells and fibrin begins to exude into the alveoli from increased permeability of the air-blood barrier. These changes are exacerbated by endothelial swelling, altered platelet function, increased procoagulant activity, and diminished profibrinolytic activity in the lungs. By 72 hours, alveolar macrophages start to appear in the bronchoalveolar space. At this time, large and irregular areas of coagulative necrosis are typically bordered by a rim of elongated cells often referred to as *oat-shaped cells* or *oat cells* that are degenerating neutrophils mixed with a few alveolar macrophages (see Fig. 9-86). In the early stages of necrosis, there is no evidence of vascular thrombosis, suggesting that necrosis is primarily caused by the cytotoxin of *Mannheimia haemolytica* and is not the result of an ischemic change. The interlobular septa become distended with protein-rich edematous fluid, and the lymphatic vessels contain fibrin thrombi. The trachea and bronchi can have considerable amounts of blood and exudate, which are transported by the mucociliary escalator or coughed up from deep within the lungs, but the walls of the trachea and major bronchi may or may not be involved. Because of the necrotizing process, sequelae to pneumonic mannheimiosis can be serious and can include abscesses, encapsulated sequestra (isolated pieces of necrotic lung), chronic pleuritis, fibrous pleural adhesions, and bronchiectasis.

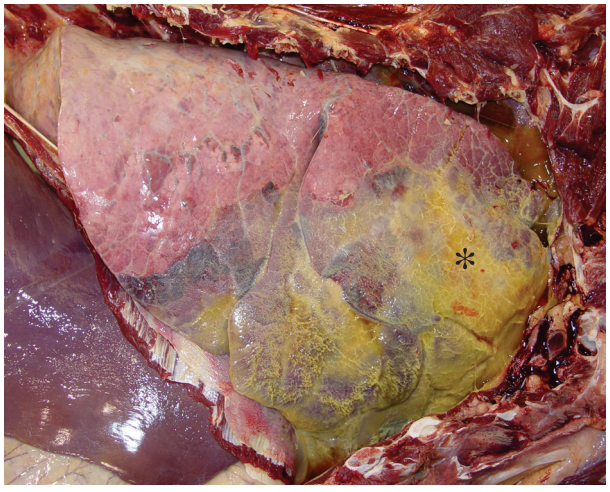


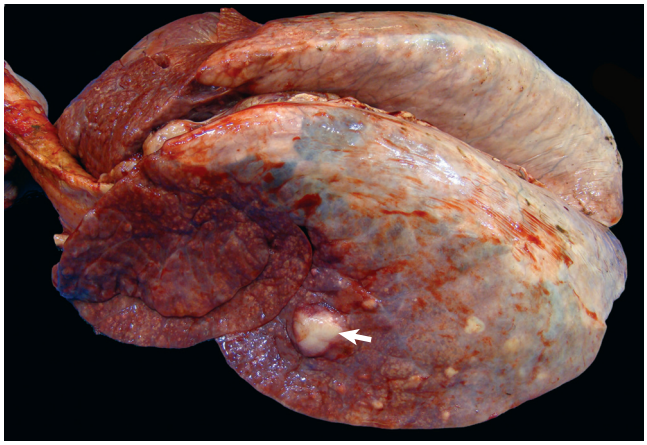
Figure 9-85 Fibrinous Bronchopneumonia (Pleuropneumonia), Pneumonic Mannheimiosis *(Mannheimia haemolytica)*, Right Lung, Steer. Note the cranioventral pneumonia involving approximately 85% of the lung parenchyma. The affected lung is firm and swollen, and the pleura is covered with a thick layer of fibrin *(asterisk)*. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Clinically, pneumonic mannheimiosis is characterized by a severe toxemia that can kill animals even when considerable parts of the lungs remain functionally and structurally normal. Cattle usually become depressed, febrile (104° to 106° F [40° to 41° C]), and anorexic and have a productive cough, encrusted nose, mucopurulent nasal exudate, shallow respiration, or an expiratory grunt.

Hemorrhagic Septicemia. Pneumonic mannheimiosis should not be confused with *hemorrhagic septicemia* (septicemic pasteurellosis) of cattle and water buffalo (*Bubalus bubalis*) caused by inhalation or ingestion of serotypes 6:B and 6:E of *Pasteurella multocida*. This OIE-notifiable disease does not occur in North America and currently is reported only from some countries in Asia, Africa, and recently in Germany. In contrast to pneumonic mannheimiosis, in which lesions are always confined to the lower respiratory tract, the bacteria of hemorrhagic septicemia always disseminates hematogenously to other organs. At necropsy, typically, generalized petechiae are present on the serosal surfaces of the intestine, heart, and lungs and in skeletal muscles. Superficial and visceral lymph nodes are swollen and hemorrhagic. Variable lesions include edematous and hemorrhagic lungs with or without consolidation; hemorrhagic enteritis; blood-tinged fluid in the thorax and abdomen; and subcutaneous edema of the head, neck, and ventral abdomen. Bacteria can be cultured from blood, and animals have high fever and die rapidly (100% case fatality).

Respiratory Histophilosis (Haemophilosis). Respiratory histophilosis is part of the *Histophilus somni* (*Haemophilus somnus*) disease complex, which has at least eight different clinicopathologic forms, each one involving different organs. This complex includes septicemia, encephalitis (known as *thrombotic meningoencephalitis* [TME]), pneumonia (respiratory histophilosis), pleuritis, myocarditis, arthritis, ophthalmitis, conjunctivitis, otitis, and abortion. The portals of entry for the different forms of histophilosis have not been properly established.

The respiratory form of bovine histophilosis is the result of the capacity of the bacterium to induce both suppurative and fibrinous bronchopneumonia (E-Fig. 9-15). The latter is in some cases indistinguishable from that of pneumonic mannheimiosis. The pathogenesis of respiratory histophilosis is still poorly understood, and the disease cannot be reproduced consistently by administration of *Histophilus somni* alone. Like *Mannheimia haemolytica*, it requires predisposing factors such as stress or a preceding viral infection. *Histophilus somni* is often isolated from the lungs of calves with enzootic pneumonia. The capacity of *Histophilus somni* to cause septicemia and localized infections in the lungs, brain, eyes, ear, heart, mammary gland, male and female genital organs, or placenta is perhaps attributable to specific virulence factors, such as immunoglobulin-binding proteins (IgBPs) and lipooligosaccharide (LOS). Also, *Histophilus*



E-Figure 9-15 **Chronic Bronchopneumonia, Pulmonary Abscesses, *Histophilus somni*, Calf.** Note the cranioventral pneumonia involving approximately 60% of the lung parenchyma. A large pulmonary abscess (*arrow*) is protruding from the surface, and several small abscesses are visible below the pleura. This calf had been treated for pneumonia a few weeks prior. (Courtesy Dr. A. López, Atlantic Veterinary College.)

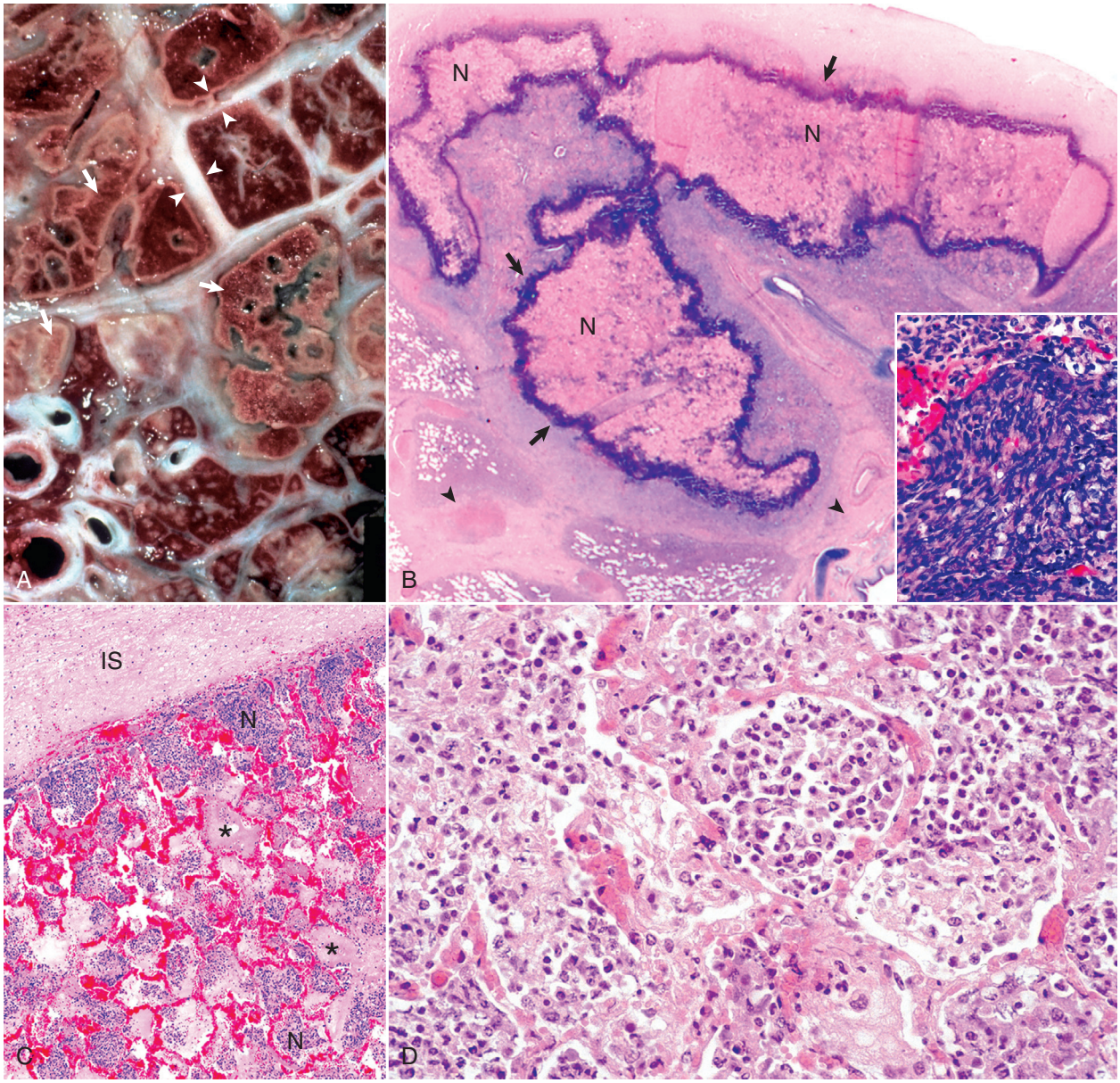
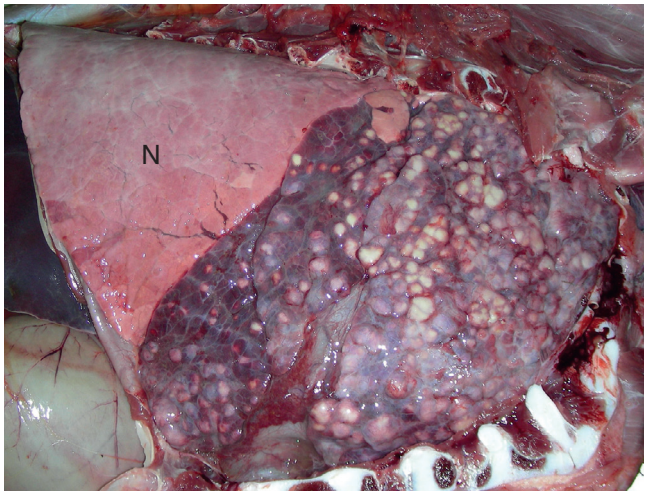


Figure 9-86 Pneumonic Mannheimiosis (*Mannheimia haemolytica*), Lung, Steer. A, Cut surface. Interlobular septa *(arrowheads)* are notably distended by edema and fibrin. In the lung parenchyma are irregular areas of coagulative necrosis *(arrows)* surrounded by a rim of inflammatory cells. **B,** Note a large irregular area of necrosis *(N)* of the pulmonary parenchyma. Typically, these necrotic areas are surrounded by an outer dense layer of inflammatory cells *(arrows)*. The interlobular septa are distended *(arrowheads)*. Inset *(bottom right corner)* shows the typical elongated and basophilic appearance of degenerated neutrophils known as oat cells. H&E stain. **C,** Note alveoli filled with fibrin *(asterisks)* and with neutrophils *(N)*. The interlobular septum *(IS)* is distended with proteinaceous fluid. H&E stain. **D,** *Mannheimia haemolytica* produces leukotoxin (cytotoxic for ruminant leukocytes) and lipopolysaccharide. Note the accumulation of cells, chiefly neutrophils, in the alveoli. Also note the active hyperemia of acute inflammation of the alveolar capillaries. H&E stain. (**A, B,** and **C** courtesy Dr. A. López, Atlantic Veterinary College. **D** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

somni has the ability to undergo structural and antigenic variation, evade phagocytosis by promoting leukocytic apoptosis, inhibit intracellular killing, reduce transferrin concentrations, and induce endothelial apoptosis in the lungs of affected calves. Mixed pulmonary infections of *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Trueperella pyogenes*, and mycoplasmas are fairly common in calves.

***Mycoplasma bovis* Pneumonia.** *Mycoplasma bovis* is the most common *Mycoplasma* sp. isolated from pneumonic lungs of cattle in Europe and North America. Pulmonary infection is exacerbated by stress or any other adverse factor (e.g., viral infection) that depresses the pulmonary defense mechanisms. Lung lesions are typically those of a chronic bronchopneumonia with numerous well-delineated caseonecrotic nodules (Fig. 9-87 and E-Fig. 9-16). Microscopically, lesions are quite characteristic and consist of distinct areas of pulmonary necrosis centered on bronchi or bronchioles. The lesion is formed by a core of fine eosinophilic granular debris surrounded by a rim of neutrophils, macrophages, and fibroblasts (see Fig. 9-87). Although the origin of the caseonecrotic lesions is under investigation, recent studies incriminate reactive oxygen species (ROS) and reactive nitrogen species (RNS) as the major contributors for cell injury in the lung. The diagnosis is confirmed by isolation or



E-Figure 9-16 Caseated Granulomas, Chronic-Active Bronchopneumonia, Cow. Note the cranioventral pneumonia and the sharp line of demarcation between normal *(N)* and pneumonic lung. The affected lung is firm and plum colored due to inflammation and contains numerous randomly distributed caseated white-tan granulomas. This cow had a dual bacterial infection with *Mycoplasma* sp. and *Mannheimia haemolytica*. (Courtesy Dr. V.E. Valli and Dr. S.J. Akare, College of Veterinary Medicine, University of Illinois.)

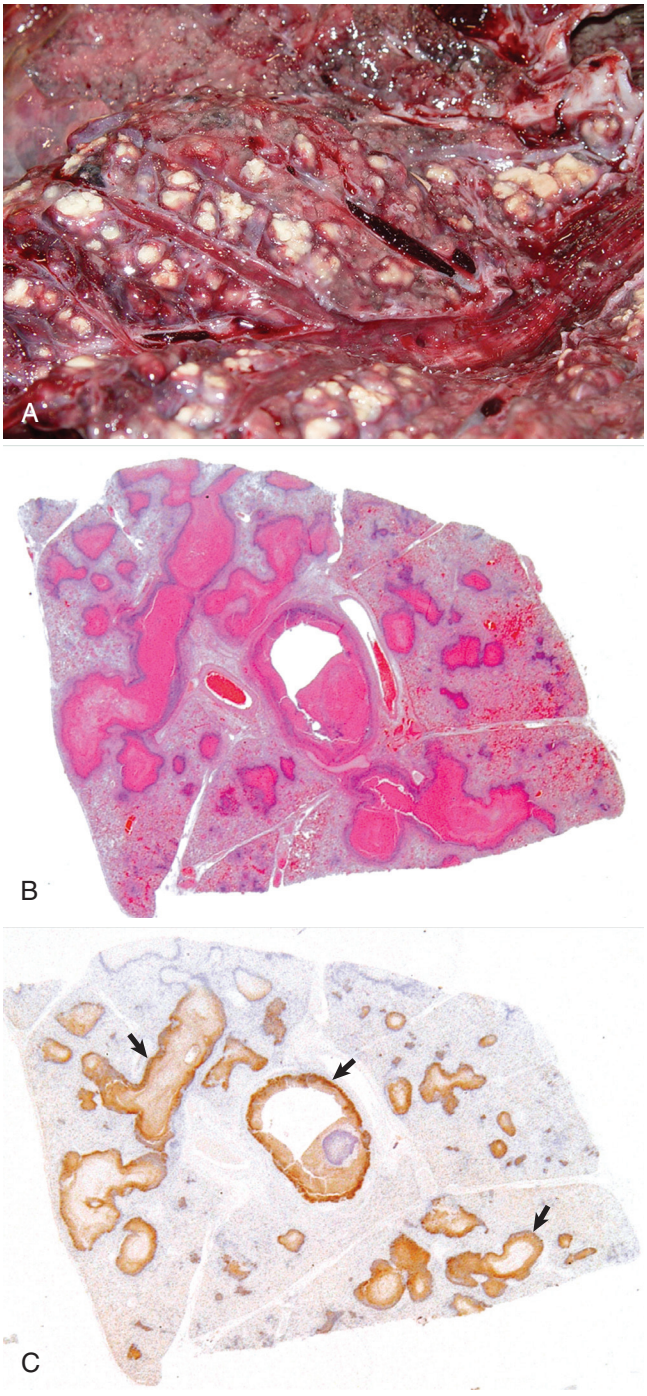


Figure 9-87 Chronic Bronchopneumonia (*Mycoplasma bovis*), Steer. **A,** Cut surface of lung showing multifocal to coalescing yellow-white caseonecrotic nodules. **B,** Section of lung showing large rounded areas of necrosis filled with hypereosinophilic *(pink-red)* granular debris. H&E stain. **C,** Necrotizing bronchopneumonia, immunohistochemistry. Note positive staining *(brown)* for *Mycoplasma bovis* antigen in the margin of the necrotic lung *(arrows)*. Immunoperoxidase stain. (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** and **C** courtesy Dr. A. López and Dr. C. Legge, Atlantic Veterinary College.)

immunohistochemical labeling of tissue sections for *Mycoplasma* antigens. *Mycoplasma bovis* is also incriminated in arthritis, otitis, mastitis, abortion, and keratoconjunctivitis.

Contagious Bovine Pleuropneumonia. Contagious bovine pleuropneumonia is an OIE-notifiable disease of historic interest in veterinary medicine because it was the object of early national control programs for infectious disease. It was eradicated from North America in 1892 and from Australia in the 1970s, but it is still enzootic in large areas of Africa, Asia, and eastern Europe. The etiologic agent, *Mycoplasma mycoides* ssp. *mycoides* small colony type, was the first *Mycoplasma* isolated and is one of the most pathogenic of those that infect domestic animals. Natural infection occurs in cattle and Asian buffalo. The portal of entry is aerogenous, and infections occur when a susceptible animal inhales infected droplets. The pathogenic mechanisms are still inadequately understood but are suspected to involve toxin and galactan production, unregulated production of TNF-α, ciliary dysfunction, immunosuppression, and immune-mediated vasculitis. Vasculitis and thrombosis of pulmonary arteries, arterioles, veins, and lymphatic vessels lead to lobular infarction.

The name of the disease is a good indication of the gross lesions. It is a severe, fibrinous bronchopneumonia (pleuropneumonia) similar to that of pneumonic mannheimiosis (see Figs. 9-72 and 9-85) but having a more pronounced "marbling" of the lobules because of extensive interlobular edema and lymphatic thrombosis. Typically, 60% to 79% of lesions are in the caudal lobes (not cranioventrally), and pulmonary sequestra (necrotic lung encapsulated by connective tissue) are more frequent and larger than pneumonic mannheimiosis. Unilateral lesions are common in this disease. Microscopically, the appearance again is like that of pneumonic mannheimiosis, except that vasculitis and thrombosis of pulmonary arteries, arterioles, and capillaries are much more obvious and are clearly the major cause of the infarction and thrombosis of lymphatic vessels in interlobular septa. *Mycoplasma mycoides* ssp. *mycoides* small colony type remains viable in the sequestra for many years, and under stress (e.g., starvation), the fibrous capsule may break down releasing mycoplasma into the airways, thus becoming a source of infection for other animals. Clinical signs are those of severe sepsis, including fever, depression, and anorexia followed by severe respiratory signs such as opened-mouth breathing, dyspnea and coughing, and crepitation and pleural friction on thoracic auscultation. Vaccination is highly effective in preventing the disease.

Bovine Tuberculosis. Tuberculosis is an ancient, communicable, worldwide, chronic disease of human beings and domestic animals. It continues to be a major problem in human beings in underdeveloped countries, and it is on the rise in some industrialized nations, largely because of the immunosuppressive effects of AIDS, immigration, and movement of infected animals across borders. The World Health Organization (WHO) estimates that more than 1 million people die of tuberculosis and 8 million new cases appear each year, mostly in developing countries. *Mycobacterium tuberculosis* is transmitted between human beings, but where unpasteurized milk is consumed, *Mycobacterium bovis* from the milk of cattle with mammary tuberculosis is also an important cause of human tuberculosis. *Mycobacterium bovis* infections have also been reported in a number of domestic and wild mammalian species; in some countries, wildlife reservoirs exist and may act as a source of infection for cattle.

Bovine tuberculosis is primarily caused by *Mycobacterium bovis*, but infection with *Mycobacterium tuberculosis*, the pathogen of human tuberculosis, and *Mycobacterium caprae* (formerly *Mycobacterium bovis* ssp. *caprae*/*Mycobacterium tuberculosis* ssp. *caprae*) can occur sporadically. Tuberculosis can be acquired by several routes, but infection of the lungs by inhalation of *Mycobacterium bovis* is the most common in adult cattle, whereas ingestion of infected milk is more predominant in young animals. Organisms belonging to the *Mycobacterium avium* complex can also infect cattle, but for infection caused by these organisms, the term *atypical mycobacteriosis* (not tuberculosis) is currently preferred.

Respiratory infection usually starts when inhaled bacilli reach the alveoli and are phagocytosed by pulmonary alveolar macrophages. If these cells are successful in destroying the bacteria, infection is averted. However, *Mycobacterium bovis*, being a facultative pathogen of the monocytic-macrophage system, may multiply intracellularly, kill the macrophage, and initiate infection. From this first nidus of infection, bacilli spread aerogenously via airways within the lungs and eventually via the lymph vessels to tracheobronchial and mediastinal lymph nodes.

The initial focus of infection at the portal of entry (lungs) plus the involvement of regional lymph nodes is termed the *primary (Ghon) complex* of tuberculosis. If the infection is not contained within this primary complex, bacilli disseminate via the lymph vessels to distant organs and other lymph nodes by the migration of infected macrophages. Hematogenous dissemination occurs sporadically when a granuloma containing mycobacteria erodes the wall of a blood vessel, causes vasculitis, and allows the granuloma to discharge mycobacteria into the alveolar circulation. If dissemination is sudden and massive, mycobacteria are widely disseminated and numerous small foci of infection develop in many tissues and organs and the process is referred to as miliary tuberculosis (like millet seeds). The host becomes hypersensitive to the mycobacterium, which enhances the cell-mediated immune defenses in early or mild infections but can result in host-tissue destruction in the form of caseous necrosis. The evolution and dissemination of the pulmonary infection are closely regulated by cytokines and TNF-α production by alveolar macrophages.

Unlike abscesses that tend to grow rather fast, granulomas evolve slowly at the site of infection. The lesion starts with few macrophages and neutrophils ingesting the offending organism, but because mycobacterium organisms are resistant to phagocytosis, infected macrophages eventually die, releasing viable bacteria, lipids, and cell debris. Cell debris accumulates in the center of the lesion, whereas viable bacteria and bacterial lipids attract additional macrophages and a few lymphocytes at the periphery of the lesion. Some of these newly recruited macrophages are activated by local lymphocytes and become large phagocytic cells with abundant cytoplasm resembling epithelial cells, thus the term *epithelioid macrophages*. Multinucleated giant cells (also macrophages) appear at the edges of the lesion, and finally the entire focus of inflammatory process becomes surrounded by fibroblasts and connective tissue (see Fig. 9-81). It may take weeks or months for a granuloma to be grossly visible.

Bovine tuberculosis, the prototype for granulomatous pneumonia, is characterized by the presence of a few or many caseated granulomas (see Fig. 9-80). The early gross changes are small foci (tubercles) most frequently seen in the dorsocaudal, subpleural areas. With progression, the lesions enlarge and become confluent with the formation of large areas of caseous necrosis. Calcification of the granulomas is a typical finding in bovine tuberculosis. Single nodules or clusters occur on the pleura and peritoneum, and this presentation has been termed *pearl disease*. Microscopically, the tubercle is composed of mononuclear cells of various types. In young tubercles, which are noncaseous, epithelioid and Langhans' giant cells are at the center, surrounded by lymphocytes, plasma cells, and macrophages. Later, caseous necrosis develops at the center, secondary to the effects of cell-mediated hypersensitivity and enclosed by fibrosis at the periphery. Acid-fast organisms may be numerous but more often are difficult to find in histologic section or smears.

Clinically, the signs of tuberculosis relate to the dysfunction of a particular organ system or to general debilitation, reduced milk production, and emaciation. In the pulmonary form, which is more than 90% of bovine cases, a chronic, moist cough can progress to dyspnea. Enlarged tracheobronchial lymph nodes can contribute to the dyspnea by impinging on airways, and the enlargement of caudal mediastinal nodes can compress the caudal thoracic esophagus and cause bloating.

Interstitial Pneumonias. Atypical interstitial pneumonia (AIP) is a vague clinical term well entrenched in veterinary literature but one that has led to enormous confusion among veterinarians. It was first used to describe acute or chronic forms of bovine pneumonia that did not fit in any of the "classic" forms because of the lack of exudate and lack of productive cough. Microscopically, the criteria for diagnosis of AIP in cattle were based on the absence of obvious exudate and the presence of edema, interstitial emphysema (see the section on Pulmonary Emphysema), hyaline membranes, hyperplasia of type II pneumonocytes, and alveolar fibrosis with interstitial cellular infiltrates. At that time, any pulmonary disease or pulmonary syndrome that had a few of the previously mentioned lesions was traditionally diagnosed as AIP, and grouping all these different syndromes together was inconsequential because their etiopathogenesis were then unknown.

Field and laboratory investigations have demonstrated that most of the bovine syndromes previously grouped under AIP have rather different causes and pathogeneses (Fig. 9-88). Furthermore, what was "atypical" in the past has become so common that it is fairly routine nowadays to find "typical cases" of AIP. For all these reasons, investigators, largely from Britain, proposed that all these syndromes previously clustered into AIP should be named according to their specific cause or pathogenesis. The most common bovine syndromes characterized by edema, emphysema, hyaline membranes, and hyperplasia of type II pneumonocytes include bovine pulmonary edema and emphysema (fog fever), "extrinsic allergic alveolitis" (hypersensitivity pneumonitis), "reinfection syndromes" (hypersensitivity to *Dictyocaulus* sp. or BRSV), milk allergy, ingestion of moldy potatoes, paraquat toxicity, toxic silo gases, mycotoxins, and others.

Acute Bovine Pulmonary Edema and Emphysema (Fog Fever). Acute bovine pulmonary edema and emphysema (ABPEE), known in Britain as fog fever (no association with atmospheric conditions), occurs in cattle usually grazing "fog" pastures (i.e., aftermath or foggage, regrowth after a hay or silage has been cut). Epidemiologically, ABPEE usually occurs in adult beef cattle in the fall when there is a change in pasture from a short, dry grass to a lush, green grass. It is generally accepted that L-tryptophan present in the pasture is metabolized in the rumen to 3-methylindole, which in turn is absorbed into the bloodstream and carried to the lungs. Mixed function oxidases present in the nonciliated bronchiolar epithelial (Club) cells metabolize 3-methylindole into a highly pneumotoxic compound that causes extensive and selective necrosis of bronchiolar cells and type I pneumonocytes (Fig. 9-89 and see Fig. 9-88) and increases alveolar permeability, leading to edema, thickening of the alveolar interstitium, and alveolar and interstitial emphysema. 3-Methylindole also interferes with the lipid metabolism of type II pneumonocytes.

The gross lesions are those of a diffuse interstitial pneumonia with severe alveolar and interstitial edema and interlobular emphysema (see Fig. 9-55, *A*). The lungs are expanded, pale, and rubbery in texture, and the lesions are most notable in the caudal lobes. Microscopically, the lesions are alveolar and interstitial edema and emphysema, formation of characteristic hyaline membranes within alveoli (see Fig. 9-55, *B*), and in those animals that survive for several days, hyperplasia of type II pneumonocytes and alveolar interstitial fibrosis.

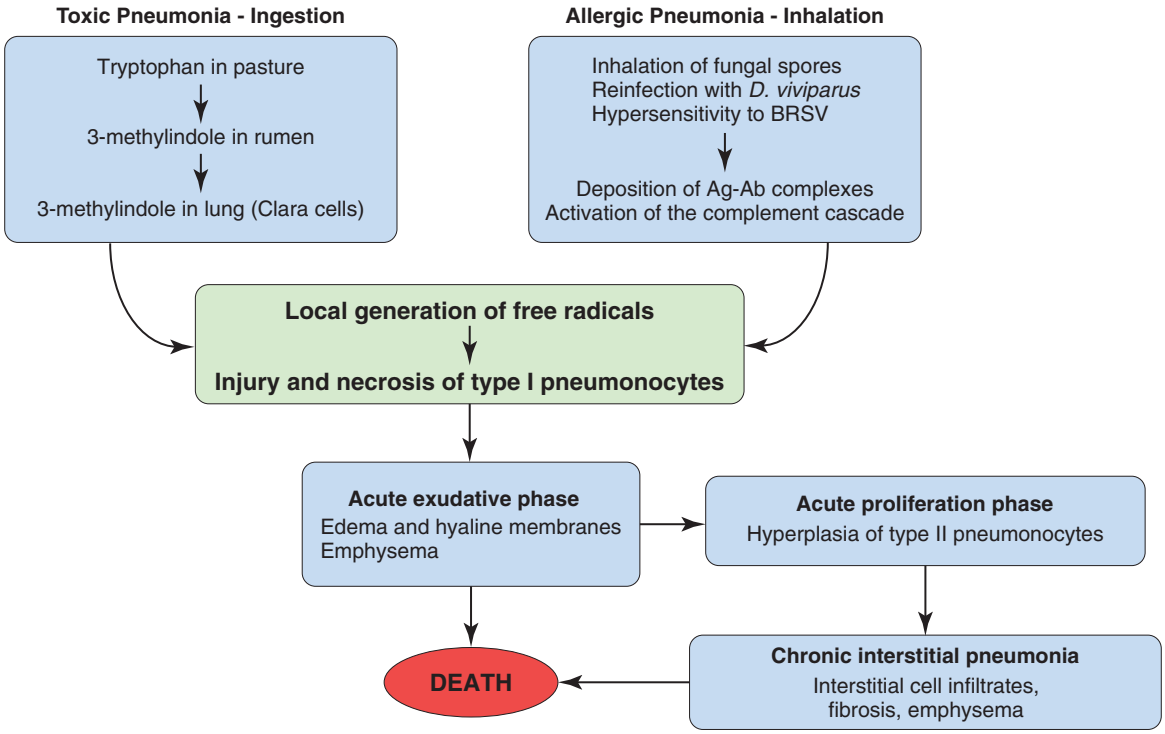


Figure 9-88 Pathogenesis of Toxic and Allergic Pneumonias ("Atypical Interstitial Pneumonias") in Cattle. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Clinically, severe respiratory distress develops within 10 days of the abrupt pasture change, and cattle develop expiratory dyspnea, oral breathing, and evidence of emphysema within the lungs and even subcutaneously along the back. Experimentally, reducing ruminal conversion of L-tryptophan to 3-methylindole prevents the development of ABPEE.

A number of other agents cause virtually the same clinical and pathologic syndrome as is seen in ABPEE. The pathogenesis is assumed to be similar, although presumably other toxic factors are specific for each syndrome. One of these pneumotoxic factors is 4-ipomeanol, which is found in moldy sweet potatoes contaminated with the fungus *Fusarium solani*. Mixed function oxidases in the lungs activate 4-ipomeanol into a potent pneumotoxicant capable of producing irreversible oxidative injury to type I pneumonocytes and bronchiolar epithelial cells, presumably through lipoperoxidation of cell membranes. Similarly, purple mint (*Perilla frutescens*), stinkwood (*Zieria arborescens*), and rapeseed and kale (*Brassica* species) also cause pulmonary edema, emphysema, and interstitial pneumonia.

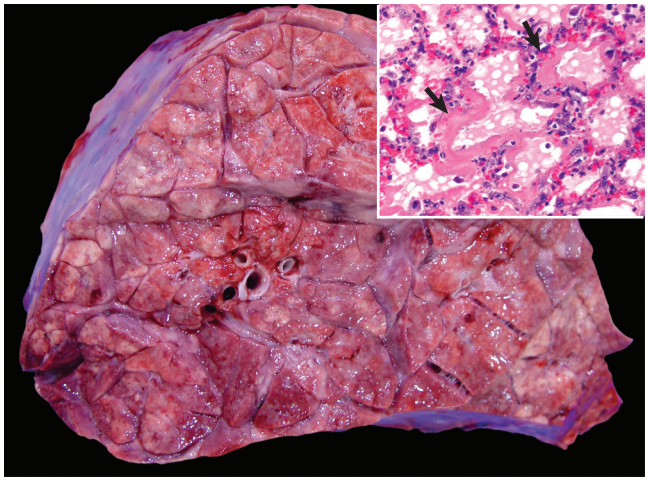
Extrinsic Allergic Alveolitis. Extrinsic allergic alveolitis (hypersensitivity pneumonitis), one of the most common allergic diseases in cattle, is seen mainly in housed adult dairy cows in the winter. This disease shares many similarities with its human counterpart known as *farmer's lung*, which results from a type III hypersensitivity reaction to inhaled organic antigens, most commonly microbial spores, mainly of the thermophilic actinomycete, *Saccharopolyspora rectivirgula* (*Micropolyspora faeni*), commonly found in moldy hay. This is followed by an antibody response to inhaled spores and local deposition of antigen-antibody complexes (Arthus reaction) in the lungs (see Fig. 9-88). Because it affects only a few animals of the herd or the sporadic person working in a farm, it is presumed that intrinsic host factors, such as dysregulation of dendritic cells, T lymphocytes, IgG, interleukins, IFN-γ, and surfactant, are involved in the pathogenesis of the disease.

Grossly, the postmortem lesions vary from subtle, gray, subpleural foci (granulomatous inflammation) to severe lesions, in which the lungs are firm and heavy and have a "meaty appearance" because of interstitial pneumonia (E-Fig. 9-17) with type II pneumonocyte hyperplasia, lymphocytic infiltration, and interstitial fibrosis. Characteristically, discrete noncaseous granulomas formed in response to the deposition of antigen-antibody complexes are scattered throughout the lungs. Chronic cases of extrinsic allergic alveolitis can eventually progress to diffuse fibrosing alveolitis. Clinically, it can be acute or chronic; the latter has a cyclical pattern of exacerbation during winter months. Weight loss, coughing, and poor exercise tolerance are clinical features. Full recovery can occur if the disease is recognized and treated early.

Reinfection Syndrome. Hypersensitivity to reinfection with larvae of *Dictyocaulus viviparus* is another allergic syndrome manifested in the lungs that causes signs and lesions indistinguishable from ABPEE, with the exception of eosinophils and possibly larvae in the alveolar exudate. The hypersensitivity reaction in the lung causes diffuse alveolar damage and edema, necrosis of type I pneumonocytes, and hyperplasia of type II pneumonocytes. In the later stages of the disease, there is formation of small granulomas with interstitial infiltrates of mononuclear cells.

It has been suggested but not confirmed that emphysema with diffuse proliferative alveolitis and formation of hyaline membranes can also occur sporadically in the late stages of BRSV infection in cattle. Presumably, this disease shares many similarities with "atypical" infections occasionally seen in children with respiratory syncytial virus (RSV human strain), in which a hypersensitivity to the virus or virus-induced augmentation of the immune response results in hypersensitivity pneumonitis (see Fig. 9-88). BRSV infection is also known to enhance hypersensitivity to environmental allergens in cattle.

Other Forms of Bovine Interstitial Pneumonia. Inhalation of manure ("pit") gases, such as nitrogen dioxide (NO_2), hydrogen



E-Figure 9-17 Interstitial Pneumonia, Adult Cow. Note meaty appearance of the pulmonary parenchyma and mild edematous distention of the interlobular septa. *Inset*, Thick hyaline membranes *(arrows)* lining hypercellular alveolar walls. Hypersensitivity pneumonia was suspected. (Courtesy Dr. A. López, Atlantic Veterinary College.)

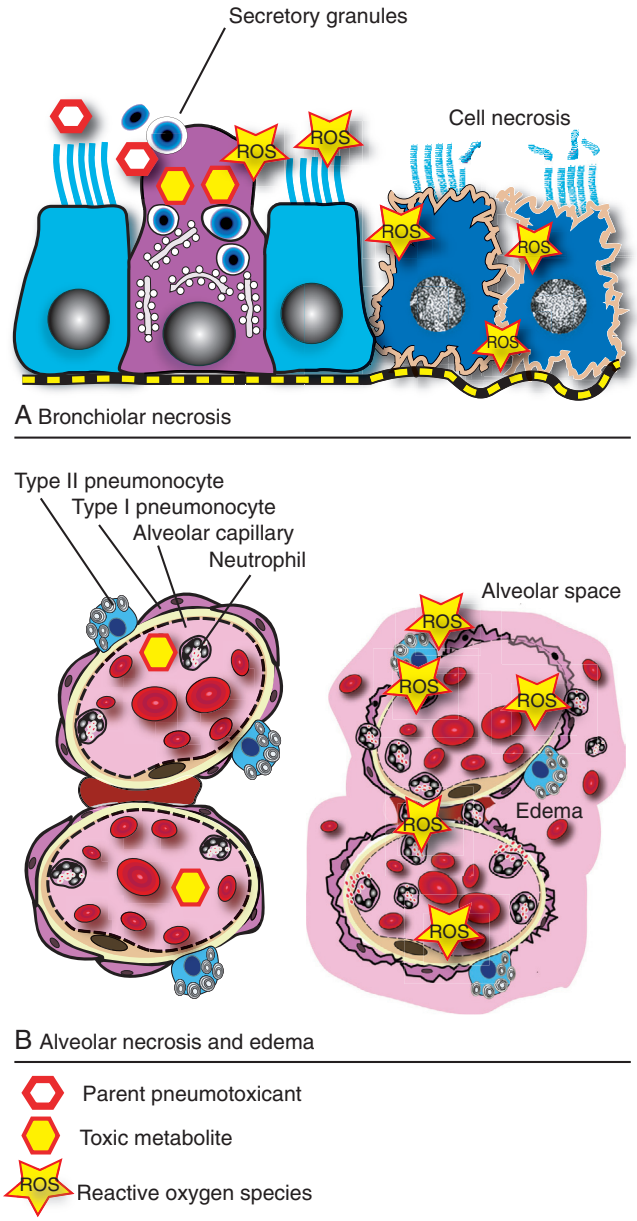


Figure 9-89 Bronchiolar and Alveolar Injury Caused by Pneumotoxicants. A, Inhaled pneumotoxicants, such as paraquat or 3-methylindole, are metabolized into toxic metabolites and reactive oxygen species *(ROS)* by bronchiolar Club cells. ROS reach adjacent bronchiolar cells *(blue)* by diffusion and cause injury and necrosis *(right two cells)*. Secretory granules released by Club cells contain several proteins, such as surfactant-like protein, antiinflammatory protein (CC10), and bronchiolar lining proteins. **B,** ROS produced by Club cells are also absorbed into capillaries within the lamina propria and are transferred by the circulatory system to pulmonary capillaries where they disrupt the air-blood barrier, causing degeneration and necrosis of type I pneumonocytes. This process leads to leakage of plasma fluid (alveolar edema *[pink color]*) and extravasation of erythrocytes (alveolar hemorrhage) and neutrophils (inflammation). Ingested pneumotoxicants can be metabolized by the liver, leading to release of ROS into the circulatory system that then disrupts the air-blood barrier in a similar manner. (Courtesy Dr. A. López, Atlantic Veterinary College.)

sulfide (H_2S), and ammonia (NH_3), from silos or sewage can be a serious hazard to animals and human beings. At toxic concentrations, these gases cause necrosis of bronchiolar cells and type I pneumonocytes and fulminating pulmonary edema that causes asphyxiation and rapid death (see Fig. 9-60). Like other oxidant gases, inhalation of NO_2 (silo gas) also causes bronchiolitis, edema, and interstitial pneumonia and, in survivors, bronchiolitis obliterans ("silo filler's disease").

Smoke inhalation resulting from barn or house fires is sporadically seen by veterinarians and pathologists. In addition to skin burns, animals involved in fire accidents suffer extensive thermal injury produced by the heat on the nasal and laryngeal mucosa, and severe chemical irritation caused by inhalation of combustion gases and particles in the lung. Animals that survive or are rescued from fires frequently develop nasal, laryngeal, and tracheal edema, and pulmonary hemorrhage and alveolar edema, which are caused by chemical injury to the blood-air barrier or by ARDS caused by the excessive production of free radicals during the pulmonary inflammatory response (see E-Fig. 9-7). Microscopic examination of the lungs often reveals carbon particles (soot) on mucosal surfaces of the conducting system.

Parasitic Pneumonias

Verminous Pneumonia (Dictyocaulus viviparus). Pulmonary lesions in parasitic pneumonias vary from interstitial pneumonia caused by migrating larvae to chronic bronchitis from intrabronchial adult parasites, to granulomatous pneumonia, which is caused by dead larvae, aberrant parasites, or eggs of parasites. In many cases, an "eosinophilic syndrome" in the lungs is characterized by infiltrates of eosinophils in the pulmonary interstitium and bronchoalveolar spaces and by blood eosinophilia. Atelectasis and emphysema secondary to the obstruction of airways by parasites and mucous secretions are also common findings in parasitic pneumonias. The severity of these lesions relates to the numbers and size of the parasites and the nature of the host reaction, which sometimes includes hypersensitivity reactions (see section on Reinfection Syndrome). A common general term for all of these diseases is *verminous pneumonia*, and the adult nematodes are often visible grossly in the airways (Fig. 9-90).

Dictyocaulus viviparus is an important pulmonary nematode (lungworm) responsible for a disease in cattle referred to as *verminous pneumonia* or *verminous bronchitis*. Adult parasites live in the bronchi of cattle, mainly in the caudal lobes, and cause severe bronchial irritation, bronchitis, and pulmonary edema, which in turn are responsible for lobular atelectasis and interstitial emphysema. Atelectasis is confined to the lobules of the lungs ventilated by the obstructed bronchi (dorsocaudal). Interstitial emphysema (interlobular) is caused by forced expiratory movements against a partially obstructed single bronchus. In addition to the inflammation of bronchial mucosa, bronchoaspiration of larvae and eggs also causes an influx of leukocytes into the bronchoalveolar space (alveolitis). Verminous pneumonia is most commonly seen in calves during their first summer grazing pastures that are repeatedly used from year to year, particularly in regions of Europe that have a moist cool climate. The parasite can overwinter in pastures, even in climates as cold as Canada's, and older animals may be carriers for a considerable length of time.

At necropsy, lesions appear as dark or gray, depressed, wedge-shaped areas of atelectasis involving few or many lobules usually along the dorsocaudal aspect of the lungs. On cut surface, edematous foam and mucus mixed with white, slender (up to 80-mm long) nematodes are visible in the bronchi (see Fig. 9-90). In the most severe cases, massive numbers of nematodes fill the bronchial tree. Microscopically, the bronchial lumens are filled with parasites admixed with mucus because of goblet cell hyperplasia, and there is squamous metaplasia of the bronchial and bronchiolar epithelium because of chronic irritation. There are also inflammatory infiltrates in the bronchial mucosa; alveolar edema; hyperplasia of BALT

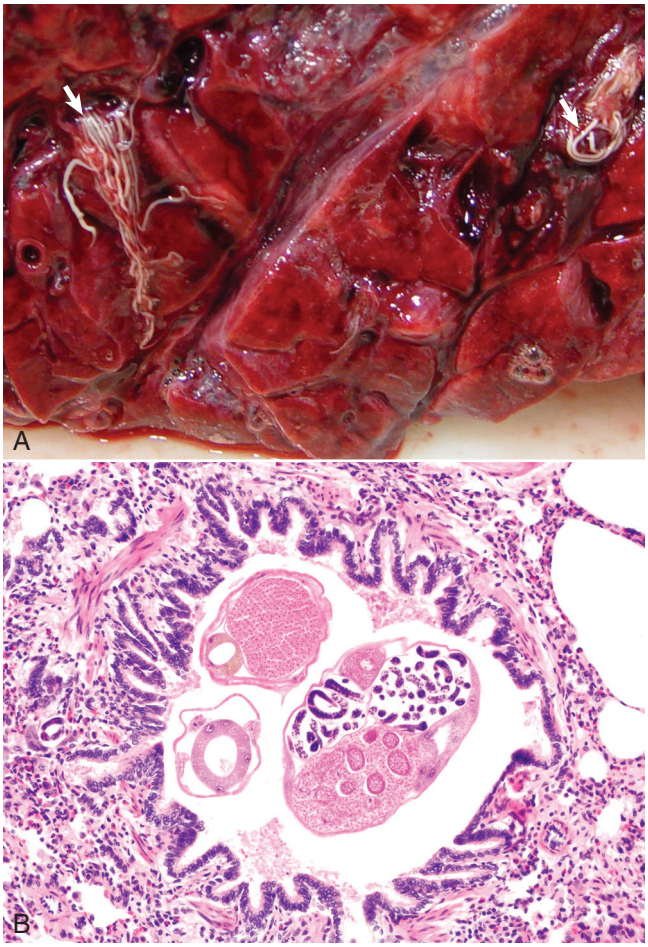


Figure 9-90 Verminous Pneumonia (*Dictyocaulus viviparus*), Bronchus, Calf. A, The bronchi contain numerous slender white lungworms *(arrows)* and large amounts of clear foamy fluid, indicative of pulmonary edema. **B,** Cross section of bronchus containing nematodes. H&E stain. (**A** courtesy Dr. A. López and Dr. L. Miller, Atlantic Veterinary College. **B** courtesy Dr. A. López, Atlantic Veterinary College.)

caused by persistent immunologic stimuli; hypertrophy and hyperplasia of bronchiolar smooth muscle because of increased contraction and decreased muscle relaxation; and a few eosinophilic granulomas around the eggs and dead larvae. These granulomas, grossly, are gray, noncaseated nodules (2 to 4 mm in diameter) and may be confused with those seen at the early stages of tuberculosis.

The clinical signs (coughing) vary with the severity of infection, and severe cases can be confused clinically with interstitial pneumonias. Expiratory dyspnea and death can occur with heavy parasitic infestations when there is massive obstruction of airways.

A different form of bovine pneumonia, an acute allergic reaction known as *reinfection syndrome*, occurs when previously sensitized adult cattle are exposed to large numbers of larvae (*Dictyocaulus viviparus*). Lesions in this syndrome are those of a hypersensitivity pneumonia as previously described.

Other Lung Parasites. *Ascaris suum* is the common intestinal roundworm of pigs; larvae cannot complete their life cycle in calves, but the larvae can migrate through the lungs and cause severe pneumonia and death of calves within 2 weeks of infection. Infection is usually acquired from the soil on which infested pigs were previously kept. The gross lesions are a diffuse interstitial pneumonia with hemorrhagic foci, atelectasis, and interlobular edema and

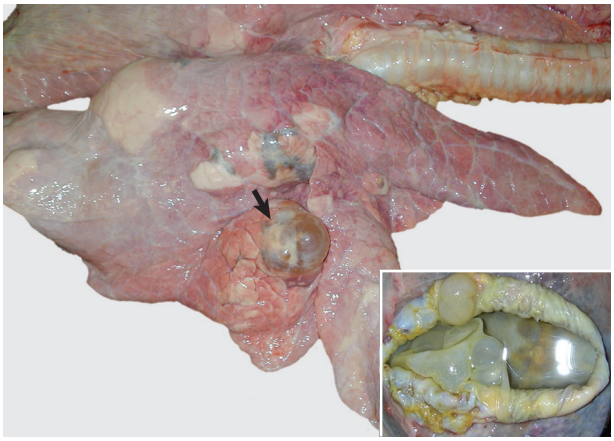


Figure 9-91 Hydatidosis (Echinococcosis), Lung, Sheep. A large hydatid cyst *(arrow)* is present in the pulmonary parenchyma. *Inset,* Hydatid cyst, cut-open section. The cyst contains fluid and larvae and is enclosed by a fibrous capsule. (Courtesy Dr. Manuel Quezada, Universidad de Concepción, Chile.)

emphysema, similar to what is seen in the lungs of pigs (see Fig. 9-77). Microscopically, there are focal intraalveolar hemorrhages caused by larvae migrating through the alveolar walls. Some larvae admixed with edematous fluid and cellular exudate (including eosinophils) may be visible in bronchioles and alveoli. The alveolar walls are thickened because of edema and a few inflammatory cells. Clinical signs include cough and expiratory dyspnea to the point of oral breathing.

Hydatid cysts, the intermediate stage of *Echinococcus granulosus*, can be found in the lungs and liver and other viscera of sheep and to a lesser extent in cattle, pigs, goats, horses, and human beings. The adult stage is a tapeworm that parasitizes the intestine of Canidae. Hydatidosis is still an important zoonosis in some countries, and perpetuation of the parasite life cycle results from animals being fed uncooked offal from infected sheep and consumption of uninspected meat. Hydatid cysts are generally 5 to 15 cm in diameter, and numerous cysts can be found in the viscera of affected animals (Fig. 9-91). Each parasitic cyst is filled with clear fluid; numerous daughter cysts attach to the wall, each containing several "brood capsules" with protoscolices inside. Hydatid cysts have little clinical significance in animals but are economically important because of carcass condemnation.

Aspiration Pneumonias. The inhalation of regurgitated ruminal contents or iatrogenic deposition of medicines or milk into the trachea can cause severe and often fatal aspiration pneumonia. Bland substances, such as mineral oil, may incite only a mild suppurative or histiocytic bronchopneumonia, whereas some "home remedies" or ruminal contents are highly irritating and cause a fibrinous, necrotizing bronchopneumonia. The right cranial lung lobe tends to be more severely affected because the right cranial bronchus is the most cranial branch and enters the ventrolateral aspect of the trachea. However, the distribution may vary when animals aspirate while in lateral recumbency. In some severe cases, pulmonary necrosis can be complicated by infection with saprophytic organisms present in ruminal contents, causing fatal gangrenous pneumonia. Aspiration pneumonia should always be considered in animals whose swallowing has been compromised—for example, those with cleft palate or hypocalcemia (milk fever). On the other hand, neurological diseases such as encephalitis (e.g., rabies) or encephalopathy (e.g., lead poisoning) should be investigated in animals in which the cause of aspiration pneumonia could not be

explained otherwise. Depending on the nature of the aspirated material, histopathologic evaluation generally reveals foreign particles such as vegetable cells, milk droplets, and large numbers of bacteria in bronchi, bronchioles, and alveoli (E-Fig. 9-18). Vegetable cells and milk typically induce an early neutrophilic response followed by a histiocytic reaction with "foreign body" multinucleated giant cells (see E-Fig. 9-12). Special stains are used for the microscopic confirmation of aspirated particles in the lung (e.g., PAS for vegetable cells and Oil Red-O for oil or milk droplets).

Pneumonias of Sheep and Goats

Viral Pneumonias

Maedi (Visna/Maedi). Maedi is an important, lifelong, and persistent viral disease of sheep and occurs in most countries, except Australia and New Zealand. Maedi means "shortness of breath" in the Icelandic language, and it is known as *Graaff-Reinet disease* in South Africa, *Zwoegerziekte* in The Netherlands, *La bouhite* in France, and *ovine progressive pneumonia* (OPP) in the United States. More recently, the disease has also been referred to as *ovine lentivirus-induced lymphoid interstitial pneumonia* or simply *lymphoid interstitial pneumonia* (LIP).

Maedi is caused by visna/maedi virus (VMV), a nononcogenic small ruminant lentivirus (SRLV) of the family Retroviridae that is antigenically related to the lentivirus causing caprine arthritis-encephalitis (CAE). Seroepidemiologic studies indicate that infection is widespread in the sheep population, yet the clinical disease seems to be rare.

The pathogenesis is incompletely understood, but it is known that transmission occurs largely vertically, through ingestion of infected colostrum, and horizontally, via inhalation of infected respiratory secretions. Once in the body, the ovine lentivirus causes lifelong infections within monocytes and macrophages, including alveolar and pulmonary intravascular macrophages; clinical signs do not develop until after a long incubation period of 2 years or more.

Pulmonary lesions at the time of death are severe interstitial pneumonia and failure of the lungs to collapse when the thorax is opened. Notable rib imprints, indicators of uncollapsed lungs, are often present on the pleural surface (Fig. 9-92). The lungs are pale, mottled, and typically heavy (two or three times normal weight), and the tracheobronchial lymph nodes are enlarged. Microscopically, the interstitial pneumonia is characterized by BALT hyperplasia and thickening of alveolar walls and peribronchial interstitial tissue by heavy infiltration of lymphocytes, largely T lymphocytes (see Fig. 9-75). Recruitment of mononuclear cells into the pulmonary interstitium is presumably the result of sustainable production of cytokines by retrovirus-infected pulmonary macrophages and lymphocytes. Hyperplasia of type II pneumonocytes is not a prominent feature of maedi, likely because in this disease there is no injury to type I pneumonocytes, but there is some alveolar fibrosis and smooth muscle hypertrophy in bronchioles. Secondary bacterial infections often cause concomitant bronchopneumonia. Enlargement of regional lymph nodes (tracheobronchial) is due to severe lymphoid hyperplasia, primarily of B lymphocytes. The virus can also infect many other tissues, causing nonsuppurative encephalitis (visna), lymphocytic arthritis, lymphofollicular mastitis, and vasculitis.

Maedi is clinically characterized by dyspnea and an insidious, slowly progressive emaciation despite good appetite. Death is inevitable once clinical signs are present, but it may take many months.

Caprine Arthritis-Encephalitis. Caprine arthritis-encephalitis (CAE) is a retroviral disease of goats (small ruminant lentivirus) that has a pathogenesis remarkably similar to that of visna/maedi in sheep. It was first described in the United States in the 1970s, but it also occurs in Canada, Europe, Australia, and probably elsewhere. This disease has two major clinicopathologic forms: One involves the central nervous system of goat kids and young goats and is characterized by a nonsuppurative leukoencephalomyelitis; the other form involves the joints of adult goats and is characterized by a chronic, nonsuppurative arthritis-synovitis. In addition, infection with CAE virus can cause chronic lymphocytic interstitial pneumonia.

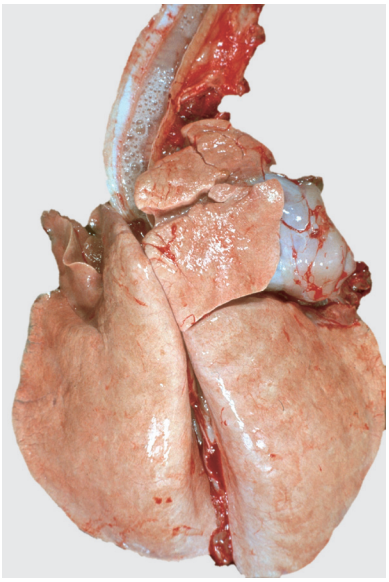
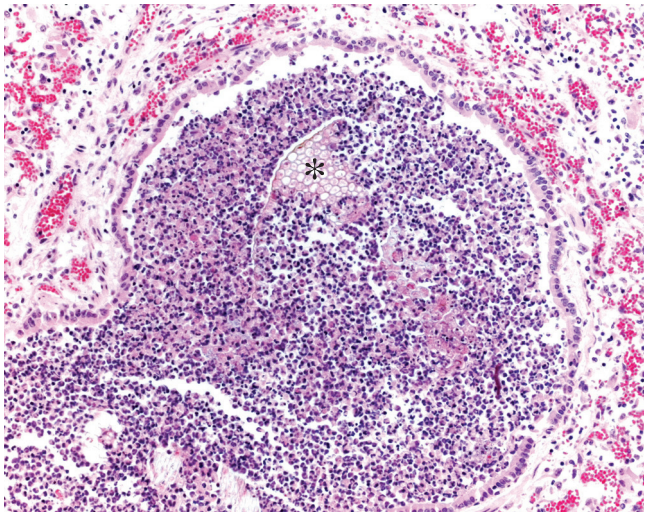


Figure 9-92 Interstitial Pneumonia (Unknown Etiology), Lung, Sheep. The lungs are heavy, rubbery, and show costal (rib) imprints on the visceral pleural surface. The diffuse distribution is typical of interstitial pneumonia. The trachea contains froth (edema fluid). (Courtesy Western College of Veterinary Medicine.)

The lentivirus of CAE, caprine arthritis and encephalitis virus (CAEV), is closely related to visna/maedi virus and, in fact, cross infection with CAE virus in sheep has been achieved experimentally. Similar to maedi, CAE infection presumably occurs during the first weeks of life when the doe transmits the virus to her offspring through infected colostrum or milk. Horizontal transmission between infected and susceptible goats via the respiratory route has also been described. After coming into contact with mucosal cells at the portal of entry, the virus is phagocytized by macrophages, which migrate to the regional lymph nodes. Infected macrophages are disseminated hematogenously to the central nervous system, joints, lungs, and mammary glands. Like maedi, there is some evidence that the recruitment of lymphocytic cells results from dysregulation of cytokine production by infected macrophages and lymphocytes in affected tissues. It can take several months before serum antibodies can be detected in infected goats.

Grossly, the interstitial pneumonia is diffuse and tends to be most severe in the caudal lobes. The lungs are gray-pink and firm in texture with numerous, 1- to 2-mm, gray-white foci on the cut surface. The tracheobronchial lymph nodes are consistently enlarged. Microscopically, the alveolar walls are thickened by lymphocytes and conspicuous hyperplasia of type II pneumonocytes (Fig. 9-93). One important difference between the pneumonias of CAE and maedi is that in CAE the alveoli are filled with proteinaceous eosinophilic material (alveolar proteinosis), which in electron micrographs has structural features of pulmonary surfactant. The pulmonary form of CAE can be mistaken for parasitic pneumonia (*Muellerius capillaris*) because these two diseases have lymphocytic interstitial pneumonia and can coexist in the same goat.



E-Figure 9-18 **Suppurative Bronchopneumonia, Aspiration of Ruminal Contents, Lung, Cow.** Note bronchiole filled with neutrophils surrounding a large piece a plant material *(asterisk)*. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

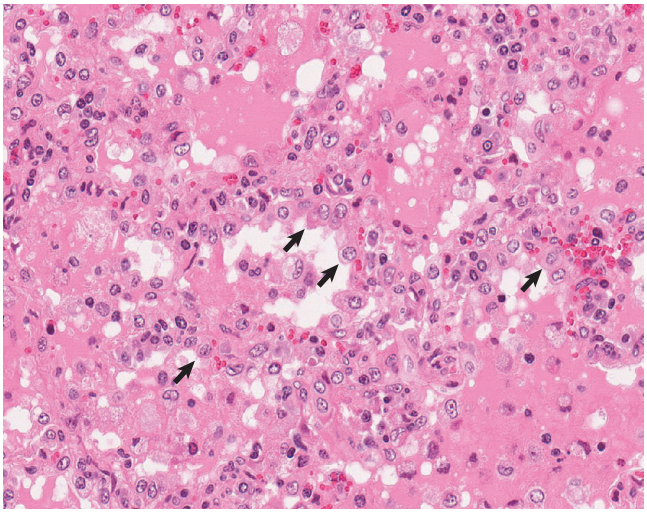


Figure 9-93 Interstitial Pneumonia, Caprine Arthritis-Encephalitis, Lung, Goat. Thickening of alveolar septa with hyperplasia of type II pneumonocytes *(arrows)*. The alveolar lumens are filled with protein-rich fluid admixed with occasional macrophages or exfoliated cells. H&E stain. (Courtesy Joint Pathology Center, Conference 201, Case 02 20222026.)

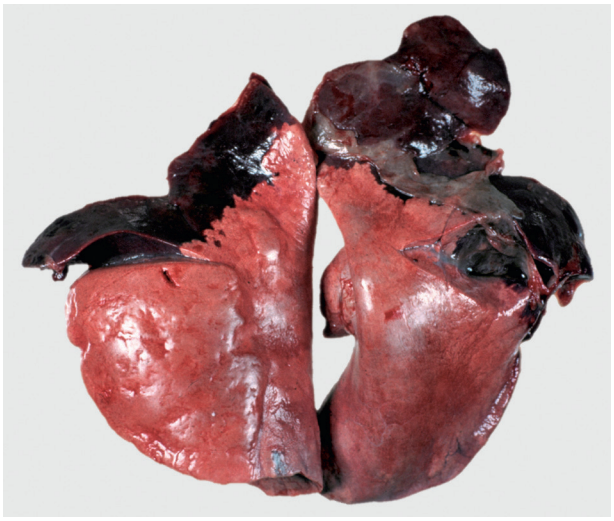


Figure 9-94 Acute Fibrinous Bronchopneumonia (Pleuropneumonia), Pneumonic Mannheimiosis *(Mannheimia haemolytica)*, Lungs, Lamb. The cranioventral aspects of the lung are red, swollen, and very firm (consolidated), with some fibrin on the pleural surface. Note that the consolidated lung resembles liver, a change that was previously referred to as "hepatization." (Courtesy Ontario Veterinary College.)

Clinically, goats are active and afebrile but progressively lose weight despite normal appetite. The encephalitic or arthritic signs tend to obscure the respiratory signs, which are only evident on exertion. Secondary bacterial bronchopneumonia is common in affected animals.

Bacterial Pneumonias. In the past, *Pasteurella haemolytica* was incriminated in four major ovine diseases known as (1) *acute ovine pneumonic pasteurellosis* (shipping fever), (2) *enzootic pneumonia* (nonprogressive chronic pneumonia), (3) *fulminating septicemia*, and (4) *mastitis*. Under the new nomenclature, *Mannheimia haemolytica* is responsible for ovine pneumonia resembling shipping fever in cattle (ovine pneumonic mannheimiosis), septicemia in young lambs (younger than 3 months of age), and ovine enzootic pneumonia and sporadic severe gangrenous mastitis in ewes. *Bibersteinia* (*Pasteurella*) *trehalosi* (formerly *Pasteurella haemolytica* biotype T) is the agent incriminated in septicemia in lambs 5 to 12 months old.

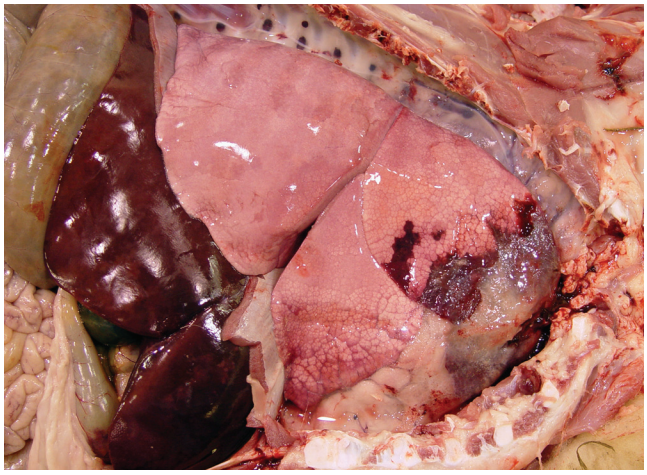
Chronic Enzootic Pneumonia. In sheep, this entity is a multifactorial disease complex that, in contrast to ovine pneumonic mannheimiosis, causes only a mild to moderate pneumonia and it is rarely fatal. It generally affects animals younger than 1 year of age. Significant costs associated with chronic enzootic pneumonia include reduction of weight gain, labor costs, veterinary fees, and slaughterhouse waste. The modifier "chronic" is used here to avoid any confusion with pneumonic mannheimiosis ("acute enzootic pneumonia"). It is also sometimes called atypical pneumonia, chronic nonprogressive pneumonia, proliferative pneumonia, or other names.

Chronic enzootic pneumonia is a clinical epidemiologic term and does not imply a single causal agent but is the result of a combination of infectious, environmental, and managerial factors. The list of infectious agents involved in ovine enzootic pneumonia includes *Mannheimia haemolytica*, *Pasteurella multocida*, parainfluenza virus 3 (PI-3), adenovirus, reovirus, respiratory syncytial virus (RSV), chlamydiae, and mycoplasmas (*Mycoplasma ovipneumoniae*).

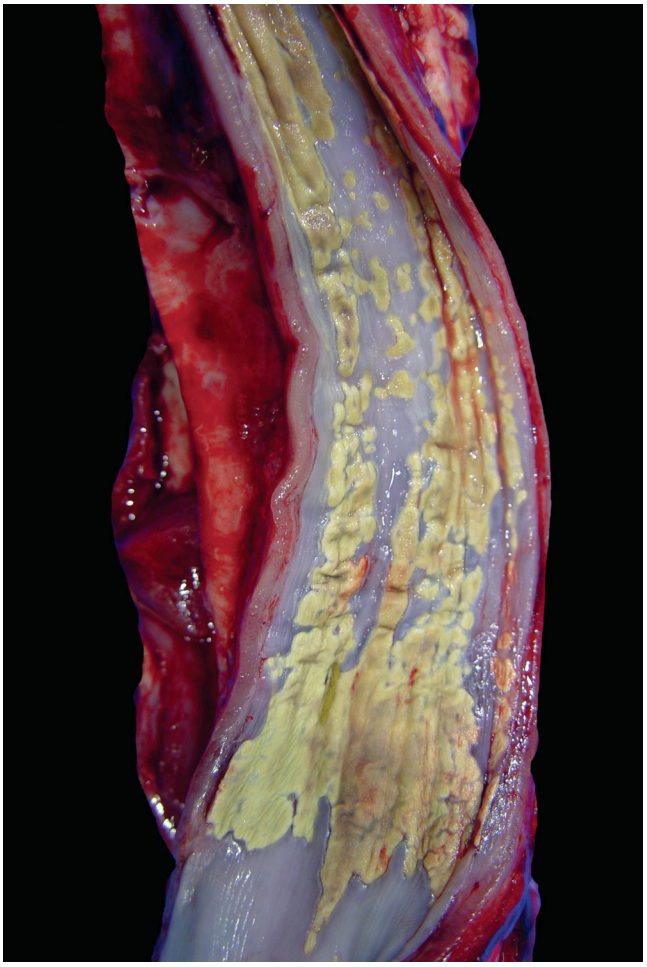
In the early stages of enzootic pneumonia, a cranioventral bronchointerstitial pneumonia is characterized by moderate thickening of alveolar walls because of hyperplasia of type II pneumonocytes. In some cases, when lungs are infected with secondary pathogens, such as *Pasteurella multocida*, pneumonia may progress to fibrinous or suppurative bronchopneumonia. One might expect some specific evidence pointing to the infectious agents (e.g., large intranuclear inclusion bodies in epithelial cells with adenoviral infection), but this is often not the case, either because examination is seldom done at the acute stage when the lesions are still present or because secondary bacterial infections mask the primary lesions. In the late stages, chronic enzootic pneumonia is characterized by hyperplastic bronchitis, atelectasis, alveolar and peribronchiolar fibrosis, and marked peribronchial lymphoid hyperplasia (cuffing pneumonia).

Ovine Pneumonic Mannheimiosis. Ovine pneumonic mannheimiosis is one of the most common and economically significant diseases in most areas where sheep are raised. It is caused by *Mannheimia haemolytica* and has a pathogenesis and lesions similar to those of pneumonic mannheimiosis of cattle. Colonization and infection of lungs are facilitated by stressors such as changes in weather; handling; deworming; dipping; viral infections such as parainfluenza virus 3 (PIV3), respiratory syncytial virus (RSV), and adenovirus; and probably chlamydiae and *Bordetella parapertussis* infections. Lesions are characterized by a severe fibrinous bronchopneumonia (cranioventral) with pleuritis (Fig. 9-94 and E-Fig. 9-19). Subacute to chronic cases progress to purulent bronchopneumonia, and sequelae include abscesses and fibrous pleural adhesions. A similar form of pneumonic mannheimiosis has been reported with increased frequency in bighorn sheep.

Septicemic Pasteurellosis. Septicemic pasteurellosis, a common ovine disease, is caused by *Bibersteinia trehalosi* (formerly *Pasteurella trehalosi or Mannheimia haemolytica* biotype T) in lambs 5 months of age or older or by *Mannheimia haemolytica* (biotype A) in lambs younger than 2 months of age. Both organisms are carried in the tonsils and oropharynx of clinically healthy sheep, and under abnormal circumstances (particularly under stress from dietary or environmental changes) bacteria can invade adjacent tissues, enter the bloodstream, and cause septicemia. Gross lesions include a distinctive necrotizing pharyngitis and tonsillitis; ulcerative esophagitis (E-Fig. 9-20); severe congestion and edema of the lungs; focal hepatic necrosis; and petechiae in the mucosa of the tongue, esophagus, and intestine and particularly in the lungs and pleura.



E-Figure 9-19 Bronchopneumonia, Acute, Severe with Fibrinous Pleuritis, *Mannheimia haemolytica*, Lung, Lamb. Note cranioventral consolidation of the lung with fibrin on the pleural surface. The non-pneumonic lung appears pink, distended, and edematous. (Courtesy Dr. S. Martinson, Atlantic Veterinary College.)



E-Figure 9-20 Esophagitis, Fibrinonecrotizing, Acute, Extensive, Severe, *Mannheimia haemolytica*, Lamb. Note the large discrete and coalescing, often elongate, plaques of beige-yellow fibrinonecrotic exudate on the surface of the esophageal mucosa. (Courtesy Dr. S. Martinson, Atlantic Veterinary College.)

Microscopically, the hallmark lesion is a disseminated intravascular thrombosis often with bacterial colonies in the capillaries of affected tissues. The alveolar capillaries contain bacteria and microthrombi, and the alveolar lumens have fibrin and red blood cells. *Mannheimia haemolytica* and *Bibersteinia trehalosi* are readily isolated from many organs. Affected animals usually die within a few hours of infection, and these animals only rarely have clinical signs such as dullness, recumbency, and dyspnea.

Contagious Caprine Pleuropneumonia. A number of *Mycoplasma* spp., often referred to as the "mycoides cluster," can produce respiratory tract infections in goats; however, only *Mycoplasma capricolum* ssp. *capripneumoniae* is considered to cause contagious caprine pleuropneumonia. This disease is the goat counterpart of contagious bovine pleuropneumonia in cattle; sheep do not have a corresponding disease. This OIE-notifiable disease is important in Africa, the Middle East, and areas of Asia, but it is also seen elsewhere.

The gross lesions caused by *Mycoplasma capricolum* ssp. *capripneumoniae* are similar to those of the bovine disease and consist of a severe, often unilateral fibrinous bronchopneumonia and pleuritis; however, distention of the interlobular septa (which are normally not as well developed in goats as in cattle) and formation of pulmonary sequestra are less obvious than in the bovine disease. Clinically, contagious caprine pleuropneumonia is similar to contagious bovine pleuropneumonia, with high morbidity and mortality, fever, cough, dyspnea, and increasing distress and weakness.

Other Small Ruminant Mycoplasmas. Pneumonia, fibrinous polyarthritis, septicemia, meningitis, mastitis, peritonitis, and abortion are possible manifestations of disease caused by *Mycoplasma mycoides* ssp. *mycoides* large colony type and *Mycoplasma mycoides* ssp. *capri*. The pathogenicity of other mycoplasmas, such as *Mycoplasma ovipneumoniae*, *Mycoplasma arginini*, and *Mycoplasma capricolum* ssp. *capricolum*, in sheep and goats is still being defined and specific description of the lesions would be premature. These organisms probably cause disease only in circumstances similar to those for enzootic pneumonia, where host, infectious, and environmental factors create a complex interaction in the pathogenesis of the disease. It has been suggested that IgG antibodies directed against ovine mycoplasmal antigens cross-react with ciliary proteins, causing inflammation and ciliary dysfunction, a condition in lambs referred to as *coughing syndrome*.

Tuberculosis. Although tuberculosis has generally been considered uncommon in sheep and goats, caprine tuberculosis has become a significant disease in areas of Spain and Europe. *Mycobacterium caprae* (formerly *Mycobacterium bovis* ssp. *caprae*/*Mycobacterium tuberculosis* ssp. *caprae*) is the most common cause, but infection with *Mycobacterium bovis* or with the *Mycobacterium avium* complex does occur when the disease is prevalent in other species in the locality. The pulmonary form, similar to that seen in cattle, is characterized by a granulomatous pneumonia with multiple, large, caseous, calcified, and well-encapsulated granulomas scattered throughout the lungs. Intralesional acid-fast organisms within macrophages are not as abundant as in bovine tuberculosis.

Staphylococcus aureus. Young sheep (2 to 12 weeks old) are susceptible to *Staphylococcus aureus* septicemia (tick pyemia). This bacterium causes disseminated inflammation and abscesses in the joints, heart, liver, kidneys, and CNS, and in the lung it can also produce bronchopneumonia and pulmonary abscesses (E-Fig. 9-21).

Parasitic Pneumonias

Dictyocaulus filaria. *Dictyocaulus filaria*, also called the *large lungworm*, is a serious, worldwide, parasitic disease of the lungs, most commonly of lambs and goat kids but occurring in adults as well. The life cycle and lesions are similar to those of *Dictyocaulus viviparus* of cattle. As seen in cattle with *Dictyocaulus viviparus*, areas of atelectasis secondary to bronchiolar obstruction are present, particularly along the dorsal caudal aspects of the caudal lung lobes. Microscopically, affected lungs are characterized by a catarrhal, eosinophilic bronchitis, with peribronchial lymphoid hyperplasia and smooth muscle hyperplasia of bronchi and bronchioles. Bronchioles and alveoli can contain edematous fluid, eosinophils, and parasitic larvae and eggs. Microscopic granulomas caused by aspirated eggs can be observed in the distal lung. The clinical signs (cough, moderate dyspnea, and loss of condition) and lesions relate mainly to obstruction of the small bronchi by adult worms and filaria. Anemia of undetermined pathogenesis and secondary bacterial pneumonia are common in small ruminants with this parasitic disease.

Muellerius capillaris. *Muellerius capillaris*, also called the *nodular lungworm*, occurs in sheep and goats in most areas of the world and is the most common lung parasite of sheep in Europe and Northern Africa. It requires slugs or snails as intermediate hosts. The lesions in sheep are typically multifocal, subpleural nodules that tend to be most numerous in the dorsal areas of the caudal lung lobes (Fig. 9-95, A). These nodules are soft and hemorrhagic in the early stages but later become gray-green and hard or even calcified. Microscopically, a focal, eosinophilic, and granulomatous reaction occurs in the

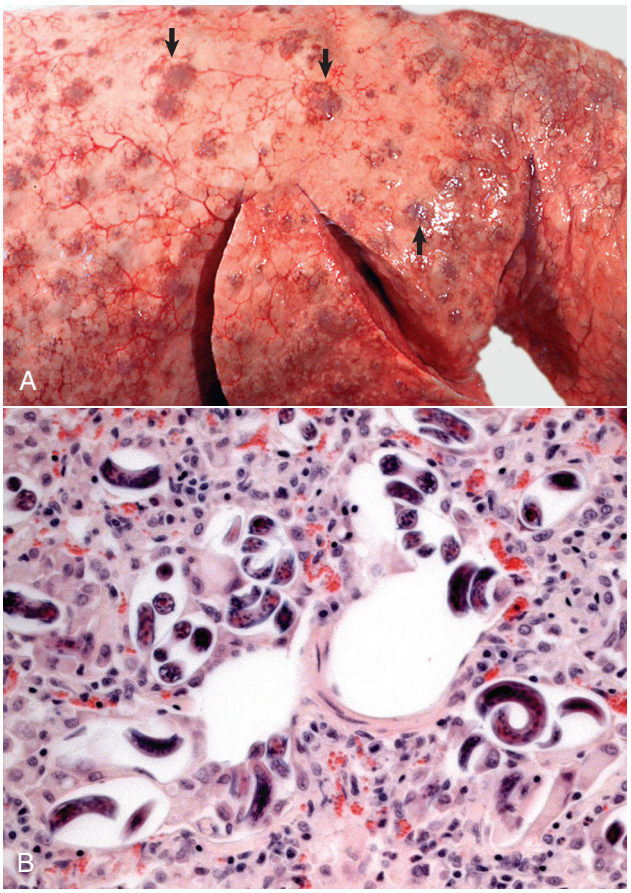
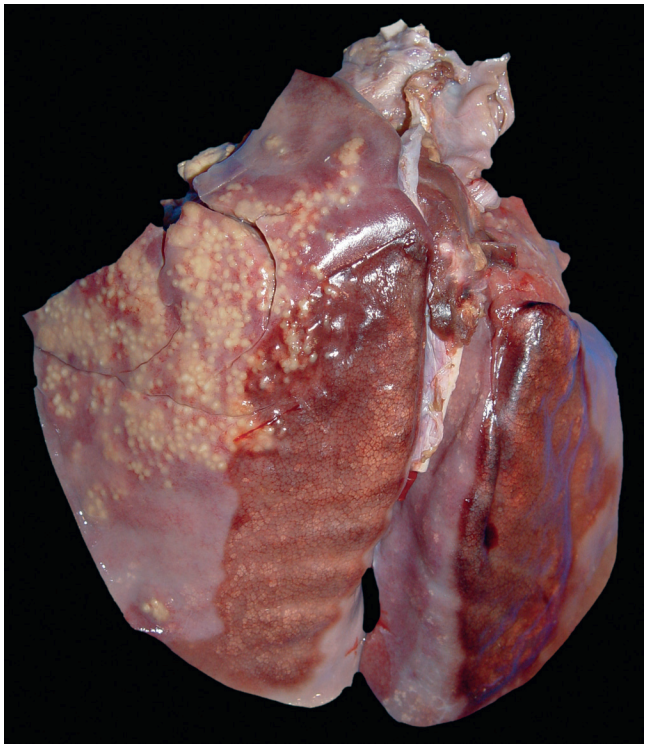


Figure 9-95 Multifocal Granulomatous Pneumonia, Lungworm (*Muellerius* spp.), Lungs, Sheep. A, Multiple gray-red nodules (granulomas) *(arrows)* are scattered throughout the pulmonary parenchyma. On palpation, the lungs have a nodular texture. **B,** Coiled larvae of *Muellerius* spp. in the lung. Note also mononuclear cells extending into the surrounding pulmonary interstitium. H&E stain. (**A** courtesy Dr. J. Edwards, Texas A&M University, Olafson Short Course, Cornell Veterinary Medicine. **B** courtesy Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-21 **Suppurative Bronchopneumonia, Lung, *Staphylococcus aureus*, 4-Day-Old Lamb.** Note cranioventral consolidation of both lungs affecting greater than 60% of the pulmonary parenchyma. Small focal to coalescing yellow-white nodules are scattered in the left lung. Microscopically, these nodules appear as necrotic foci containing bacterial colonies. The sharp "cut" edges of the left cranial lung lobes are an artifact caused by a knife blade. (Courtesy Dr. M. Forzán, Atlantic Veterinary College.)

subpleural alveoli where the adults, eggs, and coiled larvae reside (Fig. 9-95, *B*). Clinical signs are usually not apparent.

Goats differ from sheep by having diffuse interstitial rather than focal lesions, and the reaction to the parasites seen microscopically varies from almost no lesions to a severe interstitial pneumonia with heavy infiltrates of mononuclear cells in alveolar walls resembling CAE or mycoplasmal infections. Secondary effects of *Muellerius capillaris* infection in sheep and goats include decreased weight gain and possibly secondary bacterial infections.

Protostrongylus rufescens. *Protostrongylus rufescens* is a worldwide parasite of sheep, goats, and wild ruminants. It requires an intermediate snail as a host. Infection is usually subclinical, but *Protostrongylus rufescens* can be pathogenic for lambs and goat kids and can cause anorexia, diarrhea, weight loss, and mucopurulent nasal discharge. The adult parasite lives in bronchioles as *Dictyocaulus* spp., but it causes pulmonary nodules similar to those of *Muellerius capillaris*.

Pneumonias of Pigs

Porcine pneumonias are unequivocally a major obstacle for the contemporary swine industry. The incidence, prevalence, and mortality rates of pneumonias in pigs depend on a series of complex, multifactorial interactions. Among the most commonly recognized elements linked to porcine pneumonias are the following:

- Host (age, genetic makeup, immune status)
- Infectious agents (viruses, bacteria)
- Environmental determinants (humidity, temperature, ammonia concentrations)
- Management practices (crowding, mixing of animals, air quality, nutrition, stress)

Because of the nature of these multifactorial interactions, it will become obvious in the following paragraphs that more often than not a specific type of pneumonia frequently progresses to or coexists with another. The term *porcine respiratory disease complex* (PRDC) has been introduced in clinical practice to describe pigs with signs of respiratory infection involving combined bacterial and viral infections. Commonly implicated microbes include porcine reproductive and respiratory syndrome virus (PRRSV), swine influenza virus (SIV), porcine circovirus 2 (PCV2), porcine respiratory coronavirus (PRCoV), *Mycoplasma hyopneumoniae*, and *Pasteurella multocida*.

Viral Pneumonias

Swine Influenza (Swine Flu). Swine influenza is a highly contagious acute respiratory viral disease of swine that is caused by swine influenza virus (SIV), a type A influenza virus of the family Orthomyxoviridae. It is generally accepted that swine influenza resulted from adaptation of the type A influenza virus that caused the human influenza pandemic during World War I. The most common subtypes of SIV currently circulating in pigs are H1N1, H1N2, and H3N2. Swine influenza is enzootic worldwide and is known to infect human beings who are in close contact with sick pigs. In 2009, an outbreak of swine-human influenza (H1N1), presumably transmitted from pigs to human beings, emerged in Mexico and rapidly spread to many countries throughout the world. This new "pandemic" was attributed to a triple-reassortant of influenza A virus containing gene segments of swine, Eurasian avian, and human strains. Human infection with this novel strain affected mainly children and young adults, as well as individuals of any age with an underlying debilitating condition.

Transmission between influenza-infected and susceptible pigs occurs mainly by aerosol or oral route. SIV attaches to and replicates within epithelial cells of the upper respiratory tract; the infection of epithelial cells spreads rapidly throughout the nasal, tracheal, and bronchial mucosa, with the more severe outbreaks reflecting more involvement of intrapulmonary airways and secondary infection with *Pasteurella multocida*, *Trueperella* (*Arcanobacterium*) *pyogenes*, or *Haemophilus* spp. Although uncommon, human beings infected with swine influenza (H1N1) can transmit the virus to pigs; therefore it is important that veterinarians or workers with influenza-like illness stay away from pig farms. Natural transmission of H1N1 and H5N1 from human beings to ferrets (*Mustela putorius furo*) and from human beings to cats and dogs has also been reported.

Pulmonary lesions caused by influenza virus alone are rarely seen in the postmortem room because this disease has a very low mortality rate unless complicated with secondary bacterial infections. Grossly, a copious catarrhal to mucopurulent inflammation extends from the nasal passages to the bronchioles, with the volume of mucus being sufficient to plug small airways and cause a lobular or multilobular atelectasis in the cranioventral regions of the lungs. The appearance can be similar grossly, although not microscopically, to that of *Mycoplasma hyopneumoniae*. Fatal cases have severe alveolar and interstitial pulmonary edema. Microscopically, the lesions in uncomplicated cases are typical of a virus-induced, necrotizing bronchitis-bronchiolitis, which in severe cases extends into the alveoli as bronchointerstitial pneumonia. It is characterized by necrosis of the bronchial/bronchiolar epithelium, thickening and infiltration of the alveolar wall with mononuclear cells and aggregates of macrophages, neutrophils, mucus, and some necrotic cells within the alveolar lumen. If these changes are extensive enough, the lumen of bronchioles can be occluded by exudate, causing lobular atelectasis. Viral antigen can be demonstrated in infected epithelial cells by immunoperoxidase techniques. In the later stages of alveolar inflammation, neutrophils are progressively replaced by intraalveolar macrophages, unless the pneumonia is complicated by secondary bacterial infections. Recent serologic surveys indicate that infection is also prevalent in wild pigs.

Clinically, a sudden onset of fever, nasal discharge, stiffness, labored breathing, weakness or even prostration, followed by painful and often paroxysmal coughing, is seen in animals of all age groups and may affect most of the herd. The outbreak subsides virtually without mortality within 1 or 2 weeks; the clinical appearance is much more alarming than the pathologic changes, unless the pigs have secondary infection with bacteria. Infection can be confirmed using PCR in secretions collected with nasal swabs. The most important effect of most outbreaks of influenza is severe weight loss, but pregnant sows may abort or give birth to weak piglets.

Porcine Reproductive and Respiratory Syndrome. A disease originally named *mystery swine disease* was first recognized in the United States in 1987. In 1990, it was seen in Europe, and the disease now occurs worldwide in most major pig-raising countries. In 1991, Dutch investigators isolated a virus as the etiologic agent; porcine reproductive and respiratory syndrome virus (PRRSV) is currently classified in the genus *Arterivirus* of the family Arteriviridae.

As its name implies, PRRS is characterized by late-term abortions and stillbirths and respiratory problems. The respiratory form is generally seen in nursery and grow/finish pigs. The pathogenesis has not been completely elucidated, but it is presumed that there is a mucosal portal of entry with virus replication in macrophages of the lymphoid tissue, followed by viremia and finally dissemination of infected macrophages to the lungs and other organs, such as the thymus, liver (Kupffer cells), spleen, lymph nodes, and intestine. The pulmonary alveolar and intravascular macrophages are the major targets for PRRS virus, which induces apoptosis of these cells. The virus also downregulates the innate immune response by

inhibiting interferons and deregulates the adaptive immune response, thus interfering with the normal defense mechanisms predisposing pigs to septicemia and bacterial pneumonia. The most common opportunistic organisms are *Streptococcus suis*, *Salmonella* Choleraesuis, *Mycoplasma hyopneumoniae*, *Haemophilus parasuis*, *Bordetella bronchiseptica*, *Pasteurella multocida*, and *Pneumocystis carinii*. Dual viral infections with PRRSV and porcine circovirus 2 (PCV2), SIV, and porcine respiratory coronavirus (PRCoV) are commonly found in pigs, and such coinfections increase the severity of disease.

On postmortem examination, pulmonary lesions vary from very mild changes characterized by failure of the lung to collapse when the thorax is opened and the presence of rib imprints (see Fig. 9-74) to severe changes manifested by consolidation of the lung in cases that have been complicated with bacterial pneumonia. Tracheobronchial and mediastinal lymph nodes are typically enlarged. Microscopically, pulmonary changes are those of interstitial pneumonia characterized by thickening of alveolar walls by infiltrating macrophages and lymphocytes and mild hyperplasia of type II pneumonocytes. Necrotic cells are scattered in the alveolar lumens. Unlike some other viral infections, bronchiolar epithelium does not appear to be affected. Diagnosis of PRRS in tissue collected at necropsy can be confirmed by immunohistochemistry and PCR techniques. Infected pigs may become carriers and transmit the infection through body fluids and semen. Clinically, PRRS in nursery and young growing animals is characterized by sneezing, fever, anorexia, dyspnea, cough, and occasional death. Some piglets develop severe cyanosis of the abdomen and ears, which explains why this syndrome was named *blue ear disease* when first described in Europe.

Porcine Circovirus-Associated Disease. Another emerging porcine syndrome, characterized clinically by progressive emaciation in weaned pigs, was originally described in the 1990s in Canada, the United States, and Europe. Since then, it has disseminated to many countries, causing economic devastation in pig farms worldwide. Because of the clinical signs and lesions in many organs, this syndrome was named *postweaning multisystemic wasting syndrome* (PMWS). Porcine circovirus 2 (PCV2) has been incriminated as the etiologic agent and is a member of the Circoviridae family. PCV2 has been associated with a number of syndromes in pigs, including systemic PCV2 infection (the preferred term for PMWS because it may also affect mature pigs), PCV2-associated pneumonia, PCV2-associated enteritis, porcine dermatitis and nephropathy syndrome (PDNS), PCV2-associated reproductive failure, and, most recently, PCV2-associated cerebellar vasculitis. The diseases caused by PCV2 are now collectively known as porcine circovirus-associated disease (PCVAD); the most common manifestations are systemic PCV2 infection (PMWS) and PCV2-associated pneumonia as part of the porcine respiratory disease complex. All of these manifestations affect more than one organ, and there is substantial overlap between the syndromes.

At necropsy, pigs with systemic PCV2 infection (PMWS) and PCV2-associated pneumonia are often in poor body condition, and the most remarkable changes, not considering other possible secondary infections, are enlargement of the superficial and visceral lymph nodes and a mild interstitial pneumonia characterized by failure of the lungs to collapse when the thorax is opened. Jaundice is occasionally observed. Microscopically, the lymphoid tissues show lymphoid depletion, histiocytic replacement of follicles, and notable proliferation of parafollicular histiocytes, some of which fuse and form syncytial cells (granulomatous lymphadenitis); necrosis of the lymphoid follicles is seen less often. In some cases, large basophilic inclusion bodies are present singly or as grapelike clusters (botryoid inclusions) within the cytoplasm of macrophages, particularly in Peyer's patches, spleen, and lymph nodes (E-Fig. 9-22). Similar inclusions are occasionally seen in bronchial glandular and renal epithelial cells. The lungs show thickening of the alveolar walls because of hyperplasia of type II pneumonocytes and interstitial infiltrates of mononuclear cells, peribronchiolar fibrous hyperplasia, and necrotizing bronchitis/bronchiolitis. Circovirus can be confirmed in affected tissue by immunohistochemical or PCR techniques.

Dual infections with PCV2 and PRRSV frequently occur in pigs, and secondary infections with *Pneumocystis carinii* are commonly seen in pigs with this coinfection. Characteristically, alveoli are filled with a distinctive foamy exudate that contains the organism, which is not visible in H&E-stained sections but is easily demonstrated with Gomori's methenamine silver stain (see Fig. 9-20). In human beings, *Pneumocystis* (*carinii*) *jirovecii* pneumonia (pneumocystosis) is one of the most common and often fatal complications in AIDS patients. As in AIDS patients, abnormal populations of $CD4^+$ and $CD8^+$ T lymphocytes have been incriminated as the underlying mechanism leading to pneumocystosis in foals and pigs.

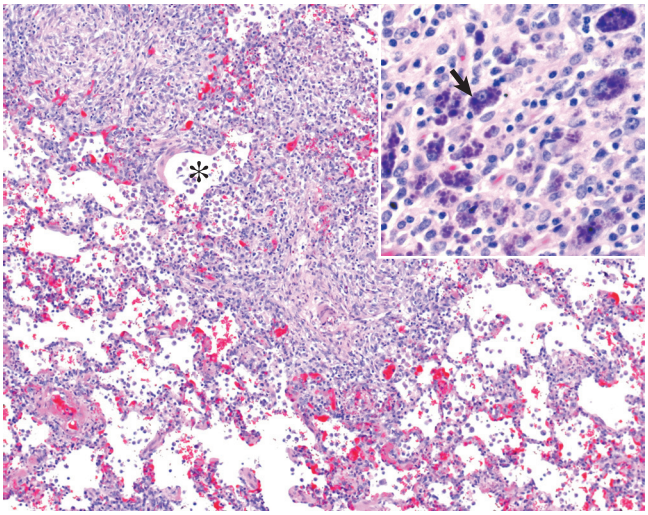
Nipah Virus. Nipah virus belongs to the Paramyxoviridae family and shares a genus (*Henipavirus*) with the closely related Hendra virus (see section on Pneumonias of Horses). Another emerging zoonotic disease, Nipah virus caused a major epidemic with significant human mortality in Southeast Asia in 1998 and 1999. People handling pigs were primarily affected. Similar to Hendra virus, fruit bats (flying foxes) act as natural reservoir and are involved in the transmission to pigs by poorly understood mechanisms. In pigs, this virus infects the respiratory system resulting in pneumonia with syncytial cells occurring in the vascular endothelium and in the respiratory epithelium at all levels of the lung. Disease is spread to human beings via the respiratory route. Human-to-human transmission of this virus has been reported in more recent outbreaks.

Other Viral Pneumonias of Pigs. Porcine respiratory coronavirus (PRCoV) is sporadically incriminated in pneumonia in pigs. This viral pneumonia is generally mild, and most pigs fully recover if the pneumonia is not complicated with other infections. Lesions in the lung are those of bronchointerstitial pneumonia with necrotizing bronchiolitis. Interestingly, infections with porcine and other respiratory coronaviruses have been used to investigate the pathogenesis of severe acute respiratory syndrome (SARS), an emerging and highly contagious condition in human beings that is attributed to a novel human coronavirus (SARS-CoV). The relationship between SARS-CoV and animal coronavirus is still under investigation.

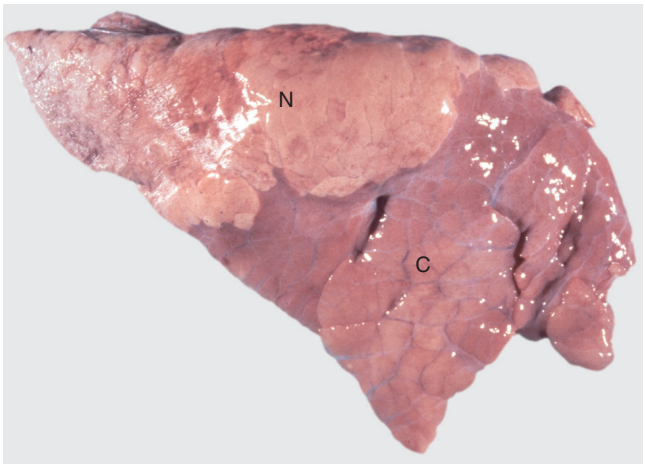
Other viruses rarely incriminated in porcine respiratory disease complex (PRDC) include paramyxovirus, encephalomyocarditis virus, hemagglutinating encephalomyocarditis virus, and adenovirus. Petechial hemorrhages in the lung and pulmonary edema may be seen with African swine fever, classical swine fever, and pseudorabies virus infections.

Bacterial Pneumonias

Porcine Enzootic Pneumonia. Porcine enzootic pneumonia, a highly contagious disease of pigs caused by *Mycoplasma hyopneumoniae*, is grossly characterized by suppurative or catarrhal bronchopneumonia (Fig. 9-96 and E-Fig. 9-23). When its worldwide prevalence and deleterious effect on feed conversion are taken into account, this disease is probably the most economically significant respiratory disease of pigs. Although an infectious disease, it is very much influenced by immune status and management factors, such as crowding (airspace and floor space), ventilation (air exchange rate), concentrations of noxious gases in the air (ammonia and hydrogen sulfide), relative humidity, temperature fluctuations, and mixing of stock from various sources. It has been demonstrated with



E-Figure 9-22 Interstitial Pneumonia, Lymphohistiocytic, Chronic with Fibrosis, Lung, Porcine Circovirus 2, Pig. Note extensive loss of airspaces *(asterisk)* due to fibrosis and infiltrates of macrophages and lymphocytes. Alveoli of less affected areas have thickened walls, and the lumens contain macrophages and exfoliated cells. *Inset,* Macrophages containing large basophilic (botryoid) cytoplasmic inclusion bodies *(arrow)* typical of circovirus. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-23 Suppurative Bronchopneumonia, Chronic, Porcine Enzootic Pneumonia, *Mycoplasma hyopneumoniae*, Lung, Pig. Cranioventral consolidation of 40% to 50% of pulmonary parenchyma. Consolidated lung (C) is firm, and the outlines of the lobules are accentuated by edema of the interlobular septa. *N*, Normal lung. (Courtesy Ontario Veterinary College.)

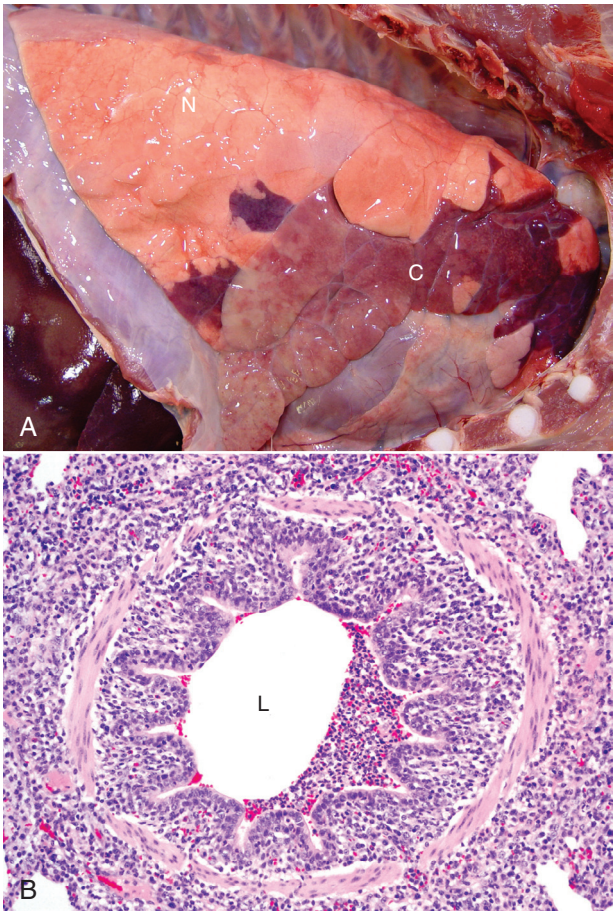


Figure 9-96 Chronic-Active (Suppurative) Bronchopneumonia (Enzootic Pneumonia), *Mycoplasma hyopneumoniae*, Lung, Pig. A, Cranioventral consolidation of 40% to 50% of the pulmonary parenchyma. Consolidated lung (*C*) is firm, and the outlines of the lobules are accentuated by edema of the interlobular septa. *N,* Normal lung. **B,** Lymphocytes and histiocytes infiltrate the bronchiolar lamina propria and peribronchiolar and alveolar interstitium. The bronchiolar lumen also contains neutrophils and erythrocytes. *L,* lumen of the affected bronchiole. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

PCR that *Mycoplasma hyopneumoniae* is present in the air of infected farms.

The causative agent, *Mycoplasma hyopneumoniae*, is a fastidious organism and very difficult to grow; thus the final diagnosis is frequently based on interpretation of lesions alone or supported by ancillary tests to detect this mycoplasma in affected lungs by immunohistochemistry, immunofluorescence, or PCR. The bronchopneumonic lesions of porcine enzootic pneumonia are in most cases mild to moderate, and thus mortality is low unless complicated with secondary pathogens, such as *Pasteurella multocida*, *Trueperella* (*Arcanobacterium*) *pyogenes*, *Bordetella bronchiseptica*, *Haemophilus* spp., *Mycoplasma hyorhinis*, and other mycoplasmas and ureaplasmas. Although the pathogenesis of porcine enzootic pneumonia is not completely elucidated, it is known that *Mycoplasma hyopneumoniae* first adheres to the cilia of the bronchi by means of a unique adhesive protein, produces ciliostasis, and finally colonizes the respiratory system by firmly attaching to the ciliated epithelial cells of the trachea and the bronchi of the cranioventral regions of the lungs. Once attached to the respiratory epithelium, it provokes an influx of neutrophils into the tracheobronchial mucosa; causes extensive loss of cilia (deciliation); stimulates an intense hyperplasia of lymphocytes in the BALT; and attracts mononuclear cells into the peribronchial, bronchiolar, and alveolar interstitium. Additional virulence factors include the ability of *Mycoplasma hyopneumoniae* to cause immunosuppression, reduce the phagocytic activity of neutrophils in the lung, and change the chemical composition of mucus. All of these functional alterations can predispose the lung to secondary bacterial infections.

The lesions caused by *Mycoplasma hyopneumoniae* start as a bronchointerstitial pneumonia and progress to a suppurative or mucopurulent bronchopneumonia once secondary pathogens are involved (commonly seen at necropsy). In most pigs, gross lesions affect only portions of the cranial lobes, but in more severely affected pigs, lesions involve 50% or more of the cranioventral portions of the lungs (see Fig. 9-96). The affected lungs are dark red in the early stages but have a homogeneous pale-gray ("fish flesh") appearance in the more chronic stages of the disease. On cut surface, exudate can easily be expressed from airways, and depending on the stage of the lesions and secondary infections, the exudate varies from purulent to mucopurulent to mucoid. Microscopic lesions are characterized by an influx of macrophages and neutrophils into the bronchi, bronchioles, and alveoli, and with time there is also notable BALT hyperplasia (see Fig. 9-96, *B*). In some cases, accumulation of exudate can be severe enough to cause occlusion of bronchioles and atelectasis of the corresponding lobules. The suppurative bronchopneumonia may be accompanied by a mild fibrinous pleuritis, which is often more severe if other organisms, such as *Mycoplasma hyorhinis*, *Pasteurella multocida*, or *Actinobacillus pleuropneumoniae*, are also involved. Abscesses and fibrous pleural adhesions are sequelae of chronic complicated infections.

Clinically, enzootic pneumonia occurs as a herd problem in two disease forms. A newly acquired infection of a previously clean herd causes disease in all age groups, resulting in acute respiratory distress and low mortality. In a chronically infected herd, the mature animals are immune and clinical signs are usually apparent only in growing pigs at times of particular stress such as at weaning. In such herds, coughing and reduced rate of weight gain are the most notable signs.

Porcine Pasteurellosis. Porcine pasteurellosis is an infectious disease complex with unclear pathogenesis that includes primary infections by *Pasteurella multocida* alone (primary pasteurellosis) or, more frequently, after the defense mechanisms are impaired and a secondary bacterium colonizes the lung (porcine pneumonic pasteurellosis). In rare cases, *Pasteurella multocida* causes acutely fatal septicemias in pigs (primary septicemic pasteurellosis). It is important to remember that *Pasteurella multocida* serotypes A and D are both part of the normal nasal flora and are also causative agents of bronchopneumonia, pleuritis, and atrophic rhinitis in pigs.

Pasteurella multocida is one of the most common secondary pathogens isolated from the lungs of pigs with swine influenza virus (SIV), porcine reproductive and respiratory syndrome virus (PRRSV), porcine circovirus 2 (PCV2), pseudorabies (SuHV-1), classical swine fever (hog cholera), enzootic pneumonia, and porcine pleuropneumonia. Secondary infections with *Pasteurella multocida* notably change the early and mild bronchointerstitial reaction of enzootic and viral pneumonias into a severe suppurative bronchopneumonia with multiple abscesses and sometimes pleuritis. The other important role of *Pasteurella multocida* in porcine pneumonias is as a cause of a fulminating, cranioventral, fibrinous bronchopneumonia (pleuropneumonia) after influenza virus infection or stress from inadequate ventilation resulting in high levels of ammonia in the air. The nature of the lesion and the predisposing factors of poor management or coexisting viral infections suggest that fulminating porcine pasteurellosis has a pathogenesis similar to that of pneumonic mannheimiosis of cattle. Pharyngitis with subcutaneous cervical edema, fibrinohemorrhagic polyarthritis, and focal lymphocytic

interstitial nephritis are also present in porcine pneumonic pasteurellosis. Sequelae of porcine pneumonic pasteurellosis include fibrous pleuritis and pericarditis, pulmonary abscesses, so-called sequestra, and usually death. In contrast to ruminants, *Mannheimia haemolytica* is not a respiratory pathogen for pigs, but in some instances, it can cause abortion in sows.

Porcine Pleuropneumonia. Porcine pleuropneumonia is a highly contagious, worldwide disease of pigs caused by *Actinobacillus* (*Haemophilus*) *pleuropneumoniae* (APP), which is characterized by a severe, often fatal, fibrinous bronchopneumonia with extensive pleuritis (pleuropneumonia). Survivors generally develop notable residual lesions and become carriers of the organisms. Porcine pleuropneumonia is an increasingly important cause of acute and chronic pneumonias, particularly in intensively raised pigs (2 to 5 months old). Transmission of *Actinobacillus pleuropneumoniae* occurs by the respiratory route, and the disease can be reproduced experimentally by intranasal inoculation of the bacterium. Considered a primary pathogen, *Actinobacillus pleuropneumoniae* can sporadically produce septicemia in young pigs and otitis media and otitis interna with vestibular syndrome in weaned pigs. Two biovars and 15 serotypes of the organism have been identified; all serotypes can cause the disease, but differences in virulence exist. The pathogenesis is not yet well understood, but specific virulence factors, such as RTX toxins (hemolytic/cytolytic toxins Apx I to Apx IV), capsular factors, fimbriae and adhesins, lipopolysaccharide, and permeability factors have been identified. These factors allow *Actinobacillus pleuropneumoniae* to attach to cells; produce pores in cell membranes; damage capillaries and alveolar walls, resulting in vascular leakage and thrombosis; impair phagocytic function; and elicit failure of clearance mechanisms.

The gross lesions in the acute form consist of a fibrinous bronchopneumonia characterized by severe consolidation and a fibrinous exudate on the pleural surface. Although all lobes can be affected, a common site is the dorsal area of the caudal lobes. In fact, a large area of fibrinous pleuropneumonia involving the caudal lobe of a pig's lung is considered almost diagnostic for this disease (Fig. 9-97). On cut surface, consolidated lungs have notably dilated interlobular septa and irregular but well-circumscribed areas of necrosis caused by potent cytotoxins produced by *Actinobacillus pleuropneumoniae*. Except for the distribution, pulmonary lesions of porcine pleuropneumonia are identical to those of pneumonic mannheimiosis of cattle. The microscopic lesions are also very similar and include areas of coagulative necrosis surrounded by a thick cluster of "streaming (oat-shaped/oat cell) leukocytes" and notable distention of the interlobular septa because of severe edema and lymphatic thrombosis. Bronchioles and alveoli are filled with edematous fluid, fibrin, neutrophils, and few macrophages (see Fig. 9-97). Pigs with the chronic form have multiple pulmonary abscesses and large (2 to 10 cm) pieces of necrotic lung encapsulated by connective tissue (sequestra)—changes frequently seen in slaughterhouses.

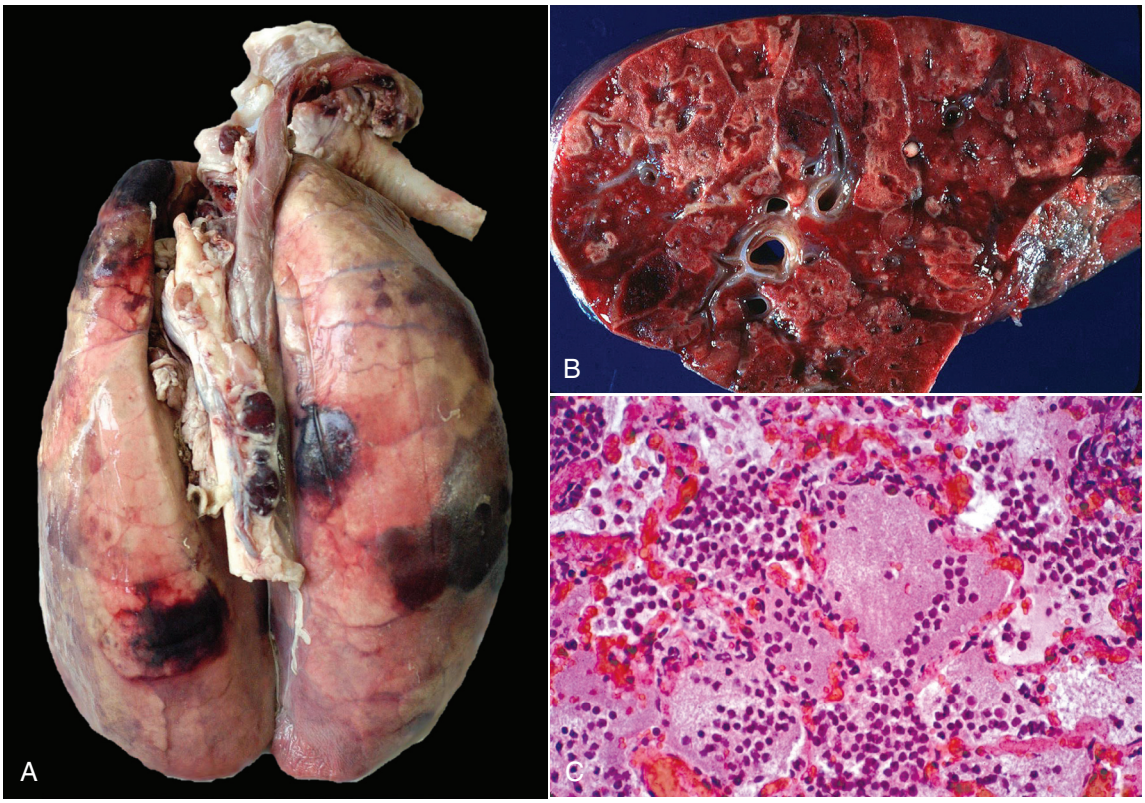


Figure 9-97 Porcine Pleuropneumonia (*Actinobacillus pleuropneumoniae*), Lung, Pig. A, In peracute porcine pleuropneumonia, the red to dark red pneumonic lesions are locally extensive in the dorsal aspects of the caudal lung lobes. There is lobular congestion, consolidation, and interlobular edema. As the disease progresses and becomes acute to subacute, the lesions expand in size and severity. **B,** The cut surface has numerous discrete and coalescing zones of lobular inflammation and necrosis *(upper left)*, which are pale pink to white and often surrounded by a white margin (inflammation). There is extensive congestion (active hyperemia) and hemorrhage throughout the section. **C,** Alveoli are filled with fibrin, edema fluid, and neutrophils. Capillaries in alveolar septa are congested (active hyperemia), and in many cases, there is necrosis of alveolar septa (not visible at this magnification). (**A** courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. **B** and **C** courtesy Dr. A.R. Doster, University of Nebraska; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

Clinically, porcine pleuropneumonia can vary from an acute form with unexpected death and blood-stained froth at the nostrils and mouth to a subacute form characterized by coughing and dyspnea accompanied by clinical signs of sepsis such as high fever, hypoxemia, anorexia, and lethargy (E-Fig. 9-24). A chronic form is characterized by decreased growth rate and persistent cough. Animals that survive often carry the organism in the tonsils, shed the organism, and infect susceptible pigs.

Haemophilus Pneumonia. In addition to Glasser's disease characterized by polyserositis (pericarditis, pleuritis, peritonitis, polyarthritis, and meningitis) (E-Fig. 9-25), some serotypes of *Haemophilus parasuis* (originally *Haemophilus influenzae suis*) can also cause suppurative bronchopneumonia that in severe cases can be fatal. The causal organism, *Haemophilus parasuis*, is usually carried in the nasopharynx of normal pigs and requires abnormal circumstances such as those following stress (weaning and cold weather) or viral infections (swine influenza or PCV2). Specific pathogen-free (SPF) pigs seem to be particularly susceptible to Glasser's disease (arthritis and serositis) but not to pulmonary infection (bronchopneumonia).

Streptococcal Pneumonia. *Streptococcus suis* is a common cause of porcine disease worldwide and a serious zoonosis capable of causing death by septic shock or meningitis and residual deafness in butchers, veterinarians, and pig farmers. Typically, *Streptococcus suis* gains entrance to the susceptible young pig through the oropharyngeal mucosa and is carried in the tonsils, nasal mucosa, and mandibular lymph nodes of healthy animals, particularly in survivors of an outbreak. Infected sows can abort or vertically transmit the infection to their offspring. Some serotypes of *Streptococcus suis* cause neonatal septicemia, and this can result in suppurative meningitis, otitis, arthritis, polyserositis, myocarditis, valvular endocarditis, and embolic pneumonia (Fig. 9-98). Other serotypes of *Streptococcus suis* can reach the lung by the aerogenous route and cause a suppurative bronchopneumonia, in combination with *Pasteurella multocida*, *Escherichia coli*, or *Mycoplasma hyopneumoniae*, or in combination with *Actinobacillus pleuropneumoniae*, which causes a fibrinous bronchopneumonia. Coinfections of *Streptococcus suis* with PCV2 and PRRSV are also frequently seen in some farms.

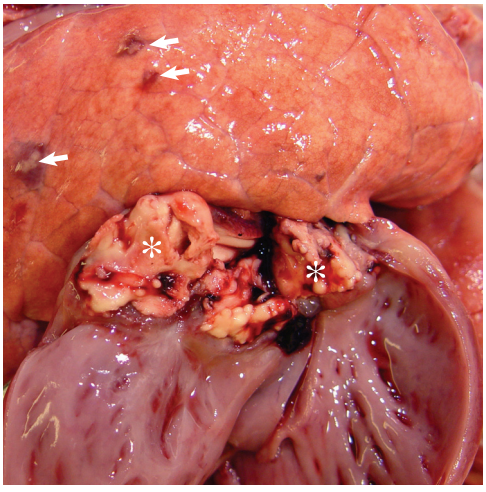


Figure 9-98 Vegetative Endocarditis, Heart and Multiple Embolic Lesions, Lung, Pig. Note the large vegetative (cauliflower-like) mass attached to the tricuspid valve *(asterisks)*. The lung *(top half of figure)* shows multifocal well-circumscribed nodules *(arrows)*, the result of emboli being released from the tricuspid valve. (Courtesy Dr. A. López, Atlantic Veterinary College.)

Tuberculosis. Tuberculosis is an important disease in domestic and wild pigs that has a much greater prevalence in pigs than in cattle or other domestic mammals in many countries. Porcine tuberculosis is attributed to infection with *Mycobacterium bovis* and porcine mycobacteriosis to infection with *Mycobacterium avium* complex. A common scenario in small mixed-farming operations is the diagnosis of avian tuberculosis at the time that pigs are slaughtered, and the source is ingestion of tuberculous chickens or contaminated litter. As would be expected, granulomas are found in the mesenteric, mandibular, and retropharyngeal lymph nodes; to a lesser extent in the intestine, liver, and spleen; and only in rare cases in the lung. The route of infection in pulmonary tuberculosis and mycobacteriosis of pigs is most often hematogenous after oral exposure and intestinal infection. Lung lesions are those of a granulomatous pneumonia. The microscopic lesions are basically those of tubercles (granulomas), but the degree of encapsulation, caseation, and calcification varies with the type of mycobacterium, age of the lesion, and host immune response.

Other Bacterial Pneumonias of Pigs. Septicemias in pigs often cause petechial hemorrhages in the lung and pulmonary edema. Salmonellae, *Escherichia coli*, and *Listeria monocytogenes* can cause severe interstitial pneumonia in very young animals. *Salmonella* Choleraesuis causes a necrotizing fibrinous pneumonia similar to porcine pleuropneumonia, and *Salmonella* Typhisuis causes a chronic suppurative bronchopneumonia. In high health herds, *Actinobacillus suis* may cause fibrinohemorrhagic pleuropneumonia and is easily confused with porcine pleuropneumonia.

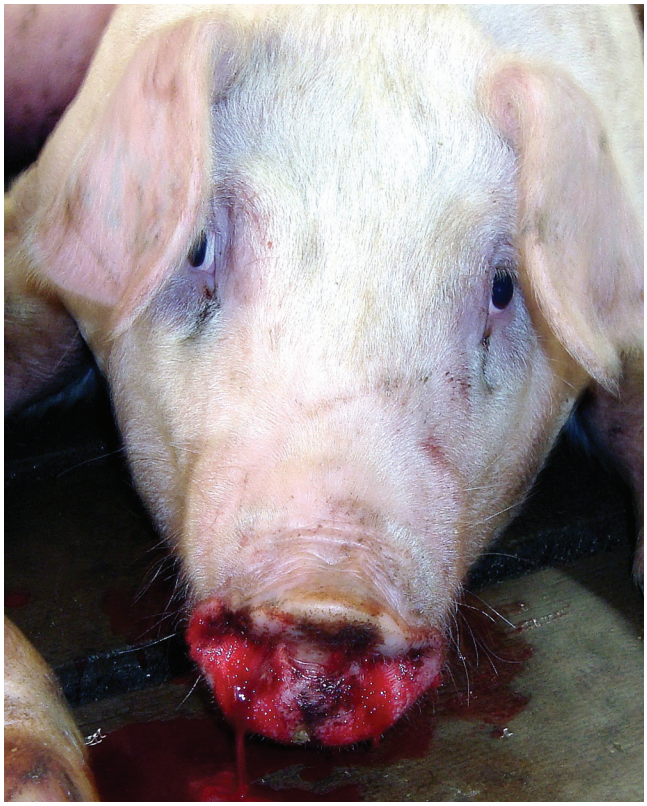
Parasitic Pneumonias of Pigs

Metastrongylosis. *Metastrongylus apri* (*elongatus*), *Metastrongylus salmi*, and *Metastrongylus pudendotectus* (lungworms) of domestic and feral pigs occur throughout most of the world and require earthworms as intermediate hosts for transmission. The incidence of disease has therefore decreased with development of confinement housing. The importance of pig lungworms is mainly because infection results in growth retardation of the host. Clinical signs include coughing because of parasitic bronchitis.

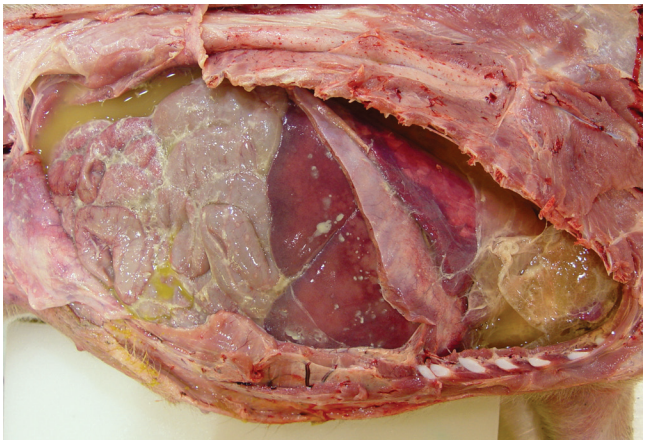
The gross lesions, when noticeable, consist of small gray nodules, particularly along the ventral borders of the caudal lobes. The adult worms are grossly visible in bronchi, and microscopically, the parasites cause a catarrhal bronchitis with infiltration of eosinophils and lobular atelectasis (Fig. 9-99).

Ascaris suum. The larvae of *Ascaris suum* can cause edema, focal subpleural hemorrhages, and interstitial inflammation (see Fig. 9-77). Along their larval migration tracts, hemorrhages also occur in the liver and, after fibrosis, become the large white "milk spots" seen so frequently as incidental findings at necropsy. It has been reported that *Ascaris suum* may cause immunosuppression in severely affected pigs. Pigs can be killed if exposed to an overwhelming larval migration.

Other Causes of Pneumonia. Foreign body granulomatous pneumonia occurs frequently in pigs after inhalation of vegetable material (starch pneumonia), presumably from dusty (nonpelleted) feed. Lesions are clinically silent but are often mistaken for other pneumonic processes during inspection at slaughterhouses. Microscopically, pulmonary changes are typical of foreign body granulomatous inflammation in which variably sized feed particles are surrounded by macrophages and neutrophils, and often have been phagocytosed by multinucleated giant cells. Feed (vegetable) particles appear as thick-walled polygonal cells that stain positive with PAS because of their rich carbohydrate (starch) content (see E-Fig. 9-12).



E-Figure 9-24 **Porcine Pleuropneumonia, Hemorrhagic Froth in Nostrils, *Actinobacillus pleuropneumoniae,* Pig.** Note abundant hemorrhagic froth coming out of the nostrils and on the floor. Pneumonic lesions are notably hemorrhagic, and fluid with blood is coughed out of the lungs. (Courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México.)



E-Figure 9-25 **Polyserositis, Subacute, Lung and Peritoneum, Pig.** The thoracic and abdominal cavities contain turbid yellow fluid, and thick plaques of fibrin cover the peritoneal and pleural surfaces, respectively. (Courtesy Dr. A. López, Atlantic Veterinary College.)

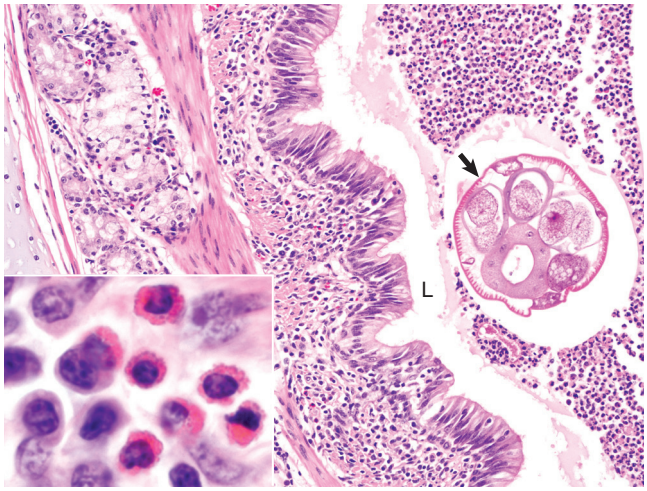


Figure 9-99 Acute Verminous Bronchitis (*Metastrongylus apri*), Bronchus, Cross Section, Pig. Cross section of a nematode (*Metastrongylus apri*) *(arrow)* admixed with mucus, neutrophils, and eosinophils (not visible at this magnification) within the lumen *(L)* of the bronchus. H&E stain. *Inset,* Eosinophils with distinct red granules infiltrate the lamina propria. H&E stain. (Courtesy Dr. S. Martinson and Dr. A. Lopez, Atlantic Veterinary College.)

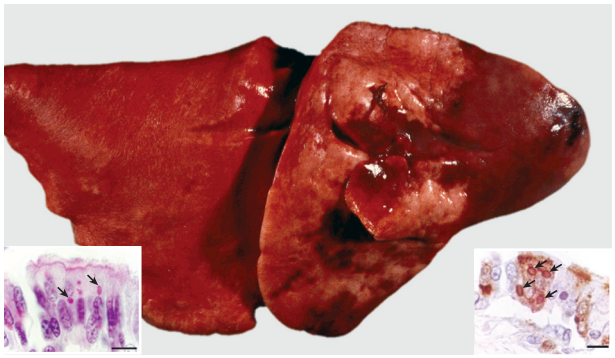


Figure 9-100 Interstitial Pneumonia, Canine Distemper, Lungs, Dog. The lungs are heavy, edematous, and rubbery, with costal (rib) imprints on the pleural surface. *Inset, left,* Bronchial epithelial cells contain intracytoplasmic eosinophilic inclusion bodies *(arrows)*. H&E stain. *Inset, right,* Immunohistochemistry revealing canine Morbillivirus antigen *(arrows)* in the cytoplasm and apical borders of bronchial epithelial cells. Immunoperoxidase stain. Bars = 20 µm. (From Berrocal A, López A: *J Vet Diagn Invest* 15:292-294, 2003.)

Pneumonias of Dogs

In general, inflammatory diseases of the lungs are less of a problem in dogs than in food-producing species and can be subdivided in two major groups, infectious and noninfectious pneumonias. "*Canine infectious respiratory disease*" (CIRD) is the term currently used by clinicians to describe a heterogeneous group of respiratory infections in dogs; these diseases were previously clustered under the name of infectious tracheobronchitis or "kennel cough." CIRD is the canine counterpart of BRD and PRD complexes in cattle and pigs, respectively. The most common viruses in CIRD include canine parainfluenza virus (CPIV), canid herpesvirus 1 (CaHV-1), canine adenovirus-2 (CAV-2), canine respiratory coronavirus (CRCoV), canine distemper virus (CDV), and canine influenza virus (CIV). *Bordetella bronchiseptica*, *Streptococcus equi* ssp. *zooepidemicus*, and *Mycoplasma* spp. are the most frequent bacterial isolates in CIRD. It has been recently recognized that animal shelters are an important source of viral and bacterial infections for dogs and cats. Uremia and paraquat toxicity are perhaps the two most notable noninfectious causes of canine respiratory disease.

Viral Pneumonias

Canine Distemper. Canine distemper is an important and ubiquitous infectious disease of dogs, other Canidae, wild Felidae, Mustelidae, and marine mammals throughout the world. It is caused by a Morbillivirus that is antigenically related to the human measles, rinderpest (officially eradicated in 2011), "peste de petit ruminants," and phocine distemper viruses. Canine distemper virus (CDV) is transmitted to susceptible puppies through infected body fluids. The virus invades through the upper respiratory tract and conjunctiva, proliferates in regional lymph nodes, becomes viremic, and in dogs with an inadequate antibody response, infects nearly all body tissues (pantropic), particularly the epithelial cells. Distemper virus hampers the immune response, downregulates cytokine production, and persists for a long time in some tissues. CDV can target the lungs either directly as a viral pneumonia or indirectly by its immunosuppressive effects rendering the lungs susceptible to secondary bacterial and protozoal infections, or as a coinfection with other viruses such as canine adenovirus-2 and canid herpesvirus 1.

Gross lesions in the acute stages include serous to catarrhal to mucopurulent nasopharyngitis and conjunctivitis. The lungs are edematous and have a diffuse interstitial pneumonia (Fig. 9-100) microscopically characterized by necrotizing bronchiolitis, necrosis and exfoliation of pneumonocytes, mild alveolar edema, and, several hours later, thickening of the alveolar walls because of interstitial mononuclear cell infiltrates and hyperplasia of type II pneumonocytes. Secondary infections with *Bordetella bronchiseptica* and mycoplasmas are common and induce life-threatening suppurative bronchopneumonia. The thymus may be small relative to the age of the animal because of viral-induced lymphocytolysis.

Microscopically, eosinophilic inclusions are present in the epithelial cells of many tissues, in the nuclei or cytoplasm, or in both (see Fig. 9-100). They appear early in the bronchiolar epithelium but are most prominent in the epithelium of the lung, stomach, renal pelvis, and urinary bladder, making these tissues good choices for diagnostic examination. Viral inclusions are rarely seen in the later stages of this disease. The suppurative secondary bronchopneumonias often hinder the detection of viral lesions in the lung, particularly because bronchiolar cells containing inclusion bodies exfoliate and mix with the neutrophils recruited by the bacterial infection. Distemper virus antigens can be readily demonstrated in infected cells by the immunoperoxidase technique (see Fig. 9-100), which can also be used in skin biopsies for the antemortem diagnosis of canine distemper.

Distemper virus also has a tendency to affect developing tooth buds and ameloblasts, causing enamel hypoplasia in dogs that recover from infection. Of all distemper lesions, demyelinating encephalomyelitis, which develops late, is the most devastating (see Chapter 14). Sequelae to distemper include the nervous and pneumonic complications mentioned previously and various systemic infections, such as toxoplasmosis and sarcocystosis, because of depressed immunity. Persistent viral infection occurs in some dogs that survive the disease, and they may become carriers and the source of infection for other susceptible animals.

Clinical signs consist of biphasic fever, diarrhea, vomiting, weight loss, mucopurulent oculonasal discharge, coughing, respiratory distress, and possible loss of vision. Weeks later, hyperkeratosis of the foot pads ("hard pad") and the nose are observed, along with nervous signs, including ataxia, paralysis, convulsions, or residual myoclonus (muscle twitches, tremors, and "tics").

Canine Adenovirus Type 2 Infection. CAV-2 infection is a common but transient contagious disease of the respiratory tract of dogs, causing mild fever, oculonasal discharge, coughing, and poor weight gain. The portal of entry is generally by inhalation of infected aerosols followed by viral replication in the surface cells of the upper respiratory tract, mucous cells of the trachea and bronchi, nonciliated bronchiolar epithelial cells, and type II pneumonocytes. Pulmonary lesions are initially those of bronchointerstitial pneumonia, with necrosis and exfoliation of bronchiolar and alveolar epithelium, edema, and, a few days later, proliferation of type II pneumonocytes, mild infiltration of neutrophils and lymphocytes in the alveolar interstitium, and hyperplastic bronchitis and bronchiolitis. Large basophilic intranuclear viral inclusions are typically seen in bronchiolar and alveolar cells (Fig. 9-101). Infection with CAV-2 is clinically mild unless complicated with a secondary bacterial infection or coinfections with other viruses such as distemper virus. Experimental work suggests CAV-2 reinfection may lead to hyperreactive airways, a nonspecific condition in which the bronchial mucosa becomes highly "responsive" to irritation such as that caused by cold air, gases, or cigarette smoke. However, it is not clear if this outcome is true in natural infections.

Canid Herpesvirus 1. Canid herpesvirus 1 (CaHV-1) can cause fatal systemic disease in newborn puppies and is probably a contributing factor in "fading puppy syndrome." Hypothermia has been suggested as a pivotal component in the pathogenesis of fatal infections in puppies. Many dogs are seropositive, suggesting that transient or subclinical infections are more common than realized; the virus remains latent in the trigeminal and other ganglia and can be reactivated after stress, resulting in asymptomatic transmission of CaHV-1 virus to offspring via the placenta, thus resulting in abortion or stillbirths. In puppies, CaHV-1 causes ulcerative tracheitis, interstitial pneumonia (E-Fig. 9-26), and focal necrosis and inflammation in the kidneys, liver, and brain. Eosinophilic intranuclear inclusion bodies occur within epithelial cells in early lesions. CaHV-1 has also been identified as a cause of ulcerative keratoconjunctivitis in older dogs.

Canine Influenza (Canine Flu). Canine influenza is an emerging contagious respiratory infection of dogs that was first described in the United States and subsequently in other countries. It has a high morbidity (close to 100%), but the mortality, as with most other influenza infections, is relatively low (less than 8%). This disease, first diagnosed in greyhounds, is caused by a novel influenza-A virus (canine influenza virus or CIV), a mutation from a previously recognized H3N8 strain of equine influenza virus. Dog-to-dog transmission does occur and therefore this infection must be distinguished from other viruses of the canine infectious respiratory disease (CIRD) group. Pulmonary lesions are generally mild and transient, but infected dogs are susceptible to secondary bacterial bronchopneumonia. The most relevant lesions in dogs dying unexpectedly from canine influenza are pleural and pulmonary hemorrhages. Microscopically, there is necrotizing tracheitis, bronchitis, and bronchiolitis with exudation of neutrophils and macrophages. In severe cases, hemorrhagic interstitial or bronchointerstitial pneumonia may be accompanied by vasculitis and thrombosis. Influenza antigen can be demonstrated by immunohistochemistry in airway epithelium and alveolar macrophages. Clinically, dogs with canine influenza are lethargic, inappetent, and hyperthermic and frequently cough and show nasal discharge. These signs resemble those seen in dogs with kennel cough or secondary bacterial pneumonia. In addition, there are confirmed cases of canine influenza caused by the porcine H1N1 presumably transmitted from infected pet owners.

Bacterial Pneumonias. Dogs generally develop bacterial pneumonias when the pulmonary defense mechanisms have been impaired. *Pasteurella multocida*, *Streptococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, and *Bordetella bronchiseptica* can be involved in pneumonia secondary to distemper or after aspiration of gastric contents (Fig. 9-102 and E-Fig. 9-27). *Streptococcus zooepidemicus* can cause acute and fatal hemorrhagic pleuropneumonia with

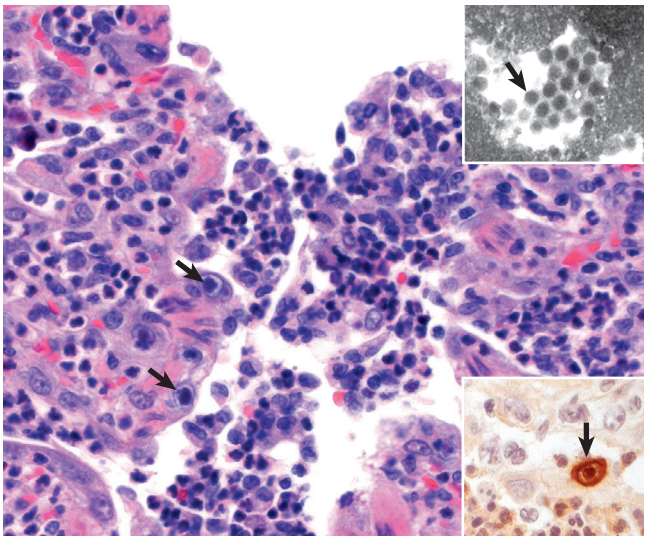


Figure 9-101 Necrotizing Bronchiolitis, Canine Adenovirus-2, Puppy. Note necrosis and exfoliation of bronchiolar epithelial cells and the neutrophilic infiltrates in the mucosa and bronchiolar lumen. Large basophilic inclusion bodies are present in nuclei of some bronchiolar cells *(arrows)*. H&E stain. *Inset top right corner,* Paracrystalline arrays of electron dense particles typical of adenovirus *(arrow)* in a transmission electron photomicrograph. Uranyl acetate and lead citrate stain. *Inset, right bottom corner,* Immunopositive staining for CAV-2 antigen *(arrow)*. Immunoperoxidase stain. (From Rodríguez LE, Ramírez-Romero R, Valdez-Nava Y, et al: *Can Vet J* 48:632-634, 2007.)

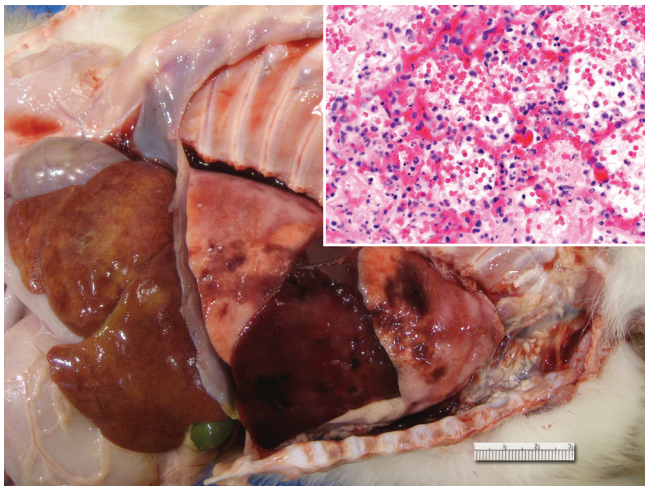
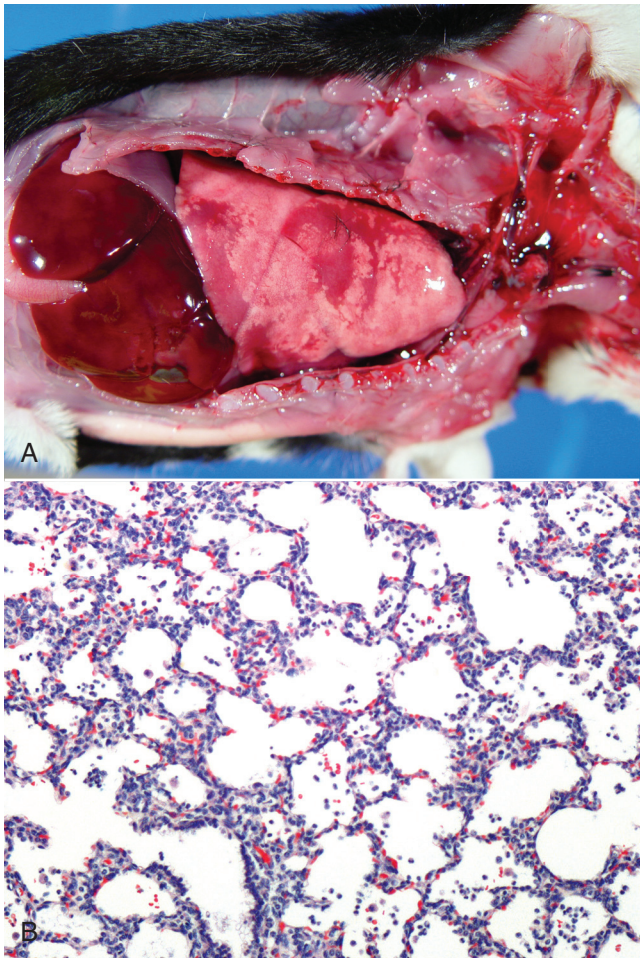
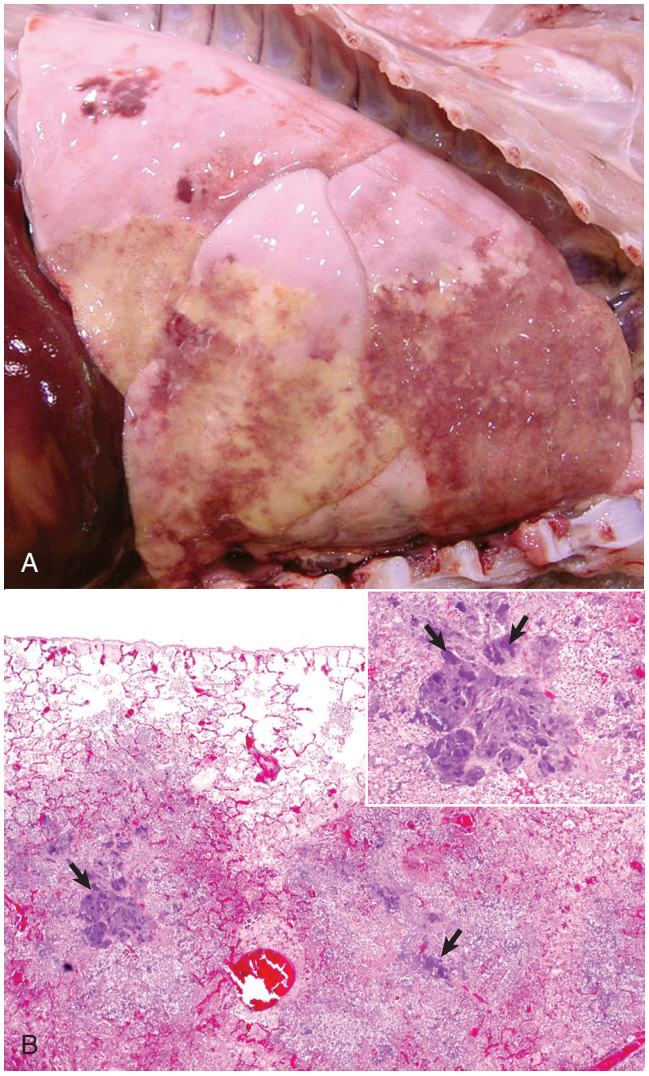


Figure 9-102 Aspiration Pneumonia, Bronchopneumonia, Right Lung, Dog. Acute to subacute bronchopneumonia. The right middle lung lobe and portions of the cranial and caudal lung lobes are dark red and consolidated. Aspiration pneumonia starts as an acute necrotizing bronchitis and bronchiolitis caused by aspiration of irritant materials such as gastric acid or a caustic material administered by mouth. Acute lesions caused by caustic damage are hemorrhagic and necrotizing. *Inset,* Alveolar spaces filled with erythrocytes, fibrin, and inflammatory infiltrates. (Courtesy Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-26 Interstitial Pneumonia, Chronic, Lymphohistiocytic, Lung, Canine Herpesvirus, 3-Day-Old Puppy. A, The lungs do not collapse, show costal rib imprints on the pleura, and have locally extensive areas of congestion and edema. **B,** The alveolar walls are thickened with infiltrates of lymphocytes and macrophages. The alveoli contain few inflammatory and exfoliated cells. Lung tissue tested positive for canine herpesvirus. H&E stain. (Courtesy Dr. J. Haruna and Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-27 Aspiration Pneumonia, Bronchopneumonia, Subacute, Right Lung, Dog. A, The cranioventral portions of the lung are firm and contain purulent exudate (*yellow areas*). Aspiration pneumonia starts as an acute necrotizing bronchitis and bronchiolitis caused by aspiration of irritant materials such as gastric acid or a caustic material administered by mouth. The aspirate also contains potentially pathogenic bacteria, and because the mucociliary apparatus is damaged and these bacteria are not removed, they settle into the ventral portions of the lung (from gravity) and provoke a fibrinosuppurative and necrotizing bronchopneumonia. **B,** Bronchoalveolar spaces are filled with neutrophils, macrophages, and bacteria (*arrows*). H&E stain. *Inset*, Large colonies of bacteria (*arrows*). H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

hemorrhagic pleural effusion in dogs. Death is generally a consequence of severe sepsis and septic shock or from β-hemolytic streptococcal bacteremia causing emboli in the lungs, liver, brain, and lymph nodes. The primary source of the infection cannot be determined in most cases. Dental disease in dogs may be a source of systemic and pulmonary infection, a concept well-recognized in human medicine for many years. The role of mycoplasmas in canine pneumonia is still uncertain because these organisms are frequently isolated from normal nasopharyngeal flora.

Tuberculosis is uncommon in dogs because these animals appear to be quite resistant to infection; most cases occur in immunocompromised dogs or in dogs living with infected human beings. Dogs are susceptible to the infection with *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium avium* complex, and therefore canine infection presupposes contact with human or animal tuberculosis. The clinicopathologic manifestation is pulmonary after inhalation or alimentary after oral exposure, but in most cases infection is disseminated to lymph nodes and visceral organs. The gross lesions are multifocal, firm nodules with necrotic centers, most often seen in the lungs, lymph nodes, kidneys, and liver. Diffuse granulomatous pleuritis and pericarditis with copious serofibrinous or sanguineous effusion are common. Microscopically, granulomas are formed by closely packed macrophages but with very little connective tissue.

Mycotic Pneumonias. Mycotic pneumonias are serious diseases seen commonly in animals in some regions. There are two main types: those caused by opportunistic fungi and those caused by a group of fungi associated with systemic "deep" mycoses. All of these fungi affect human beings and most domestic animals but are probably not transmitted between species.

Aspergillosis. Opportunistic fungi, such as *Aspergillus* spp. (particularly *Aspergillus fumigatus*), are important in birds, but in domestic animals, they mainly affect immunosuppressed individuals or those on prolonged antibiotic therapy. The pulmonary lesion is a multifocal, nodular, pyogranulomatous, or granulomatous pneumonia. Microscopically, there is necrosis and infiltrates of neutrophils, macrophages, and lymphocytes, with proliferation of fibroblasts eventually leading to encapsulation of the granuloma. Fungal hyphae are generally visible in the core of the lesion and in the walls of blood vessels.

Systemic Mycoses (Dimorphic Fungal Infections). Systemic (deep) mycoses are caused by *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Cryptococcus neoformans/Cryptococcus gatti* (see Fig. 9-35). Blastomycosis mainly affects dogs and is discussed here, whereas cryptococcosis is discussed in the section on Pneumonias of Cats. In contrast to other fungi, such as *Aspergillus* spp., organisms of the systemic mycosis group are all primary pathogens of human beings and animals and thus do not necessarily require a preceding immunosuppression to cause disease. These fungi have virulence factors that favor hematogenous dissemination and evasion of immune and phagocytic responses. Systemic dissemination is often exacerbated by the administration of immunosuppressant drugs such as corticosteroids. These fungi are usually detected by cytological evaluation of affected tissues.

Blastomycosis. Blastomycosis occurs in many countries of the North American continent, Africa, the Middle East, and occasionally in Europe. In the United States, it is most prevalent in the Atlantic, St. Lawrence, and Ohio-Mississippi River Valley states, compared with the Mountain-Pacific region. *Blastomyces dermatitidis* is a dimorphic fungus (mycelia-yeast) seen mainly in young dogs and occasionally in cats and horses. This fungus is present in the soil, and inhalation of spores is considered the principal route of infection; thus it most frequently affects outdoor and hunting dogs. From the lung, infection is disseminated hematogenously to other organs, mainly bone, skin, brain, and eyes.

Pulmonary lesions are characterized by multifocal to coalescing pyogranulomatous pneumonia, generally with firm nodules scattered throughout the lungs (Fig. 9-103). Microscopically, nodules are pyogranulomas with numerous macrophages (epithelioid cells), some neutrophils, multinucleated giant cells, and thick-walled yeasts (see Fig. 9-35, C). Yeasts are 5 to 25 μm in diameter and are much better visualized when they are stained with PAS reaction or Gomori's methenamine silver stain. Nodules can also be present in other tissues, chiefly lymph nodes, skin, spleen, liver, kidneys, bones, testes, prostate, and eyes. This fungus can be easily identified in properly prepared and stained transtracheal washes or lymph node aspirates.

Clinical signs can reflect involvement of virtually any body tissue; pulmonary effects include cough, decreased exercise tolerance, and terminal respiratory distress.

Coccidioidomycosis. Coccidioidomycosis (San Joaquin Valley fever), caused by the dimorphic fungus *Coccidioides immitis*, occurs mainly in animals living in arid regions of the southwestern United States, Mexico, and Central and South America. It is a primary respiratory tract (aerogenous) infection commonly seen at slaughterhouses in clinically normal feedlot cattle. In dogs, coccidioidomycosis also has an aerogenous portal of entry and then

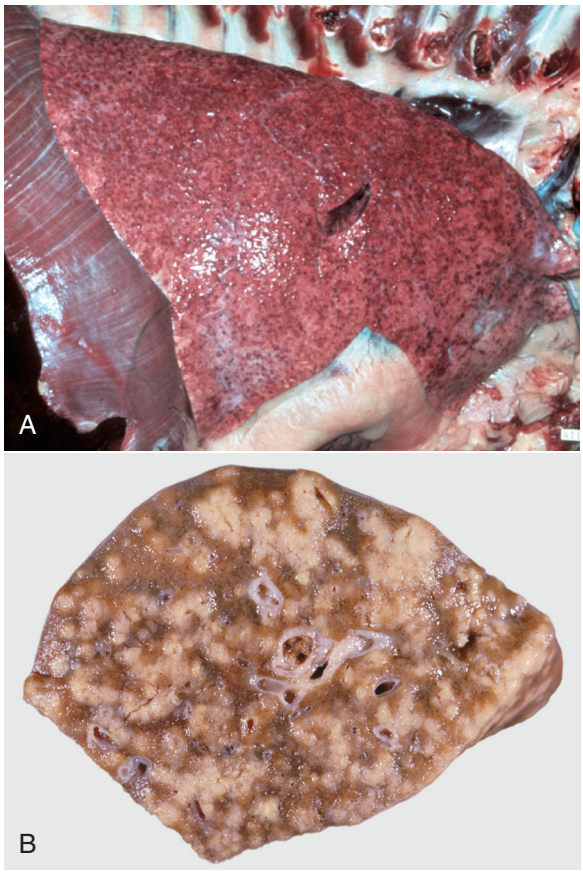


Figure 9-103 Granulomatous Pneumonia, Blastomycosis (*Blastomyces dermatitidis*), Right Lung, Dog. A, The lung contains large numbers of small granulomas distributed throughout all pulmonary lobes. **B,** The cut surface of the lung shows multiple discrete and coalescing gray-white granulomas distributed randomly throughout the lung. (**A** courtesy Ontario Veterinary College. **B** courtesy College of Veterinary Medicine, University of Illinois.)

disseminates systemically to other organs. Clinical signs relate to the location of lesions, so there can be respiratory distress, lameness, generalized lymphadenopathy, or cutaneous lesions, among others.

The lesions caused by *Coccidioides immitis* consist of focal granulomas or pyogranulomas that can have suppurative or caseated centers. The fungal organisms are readily seen in histologic or cytologic preparation as large (10 to 80 μm in diameter), double-walled, and highly refractile spherules containing numerous endospores (see Fig. 9-35, *D*).

Histoplasmosis. Histoplasmosis is a systemic infection that results from inhalation and, in dogs, possibly ingestion of another dimorphic fungus, *Histoplasma capsulatum*. Histoplasmosis occurs sporadically in dogs and human beings and, to a lesser extent, in cats and horses. Bats often eliminate *Histoplasma capsulatum* in the feces, and droppings from bats and birds, particularly pigeons, heavily promote the growth and survival of this fungus in the soil of enzootic areas.

Pulmonary lesions are grossly characterized by variably sized, firm, poorly encapsulated granulomas and, sometimes, more diffuse involvement of the lungs. Microscopically, granulomatous lesions typically have many macrophages filled with small (1 to 3 μm), punctiform, intracytoplasmic, dark oval bodies (yeasts) (see Fig. 9-35, *A*) that are best demonstrated with PAS reaction or Gomori's methenamine silver stain. Similar nodules or diffuse involvement can be present in other tissues, chiefly lymph nodes, spleen, intestine, and liver.

Parasitic Pneumonias

Toxoplasmosis. Toxoplasmosis is a worldwide disease caused by the obligate intracellular, protozoal parasite *Toxoplasma gondii*. Cats and other Felidae are the definitive hosts in which the mature parasite divides sexually in the intestinal mucosa. Human beings, dogs, cats, and many wild mammals can become intermediate hosts after accidental ingestion of fertile oocysts shed in cat feces or ingestion of undercooked or raw meat containing tissue cysts, and fetuses can be infected transplacentally from an infected dam. In most instances, the parasite infects many cells of different tissues and induces an antibody response (seropositive animals) but does not cause clinical disease. Toxoplasmosis is often triggered by immunosuppression, such as that caused by canine distemper virus. Toxoplasmosis is characterized by focal necrosis around the protozoan.

Pulmonary lesions are severe, multifocal necrotizing interstitial pneumonia with notable proliferation of type II pneumonocytes and infiltrates of macrophages and neutrophils. Other lesions in disseminated toxoplasmosis include multifocal necrotizing hepatitis, myocarditis, splenitis, myositis, encephalitis, and ophthalmitis. The parasites appear microscopically as small (3 to 6 μm) basophilic cysts that can be found free in affected tissues or within the cytoplasm of many epithelial cells and macrophages (see E-Fig. 8-8). Similar findings can be seen sporadically in dogs infected with *Neospora caninum* and *Sarcocystis canis*, and immunohistochemistry would be required to differentiate those protozoal organisms from *Toxoplasma gondii*.

Filaroides hirthi. *Filaroides hirthi*, a lungworm of the alveoli and bronchioles of dogs, has long been known as a cause of mild subclinical infection in large colonies of beagle dogs in the United States. However, it can on occasion cause severe and even fatal disease in individual pets, presumably as a result of immunosuppression. Clinical signs may include coughing and terminal respiratory distress. Grossly, the lesions are multifocal subpleural nodules, often with a green hue because of eosinophils, scattered throughout the lungs. Microscopically, these nodules are eosinophilic granulomas arising from the alveolar interstitium associated with larvae or dead worms because little reaction develops to the live adults.

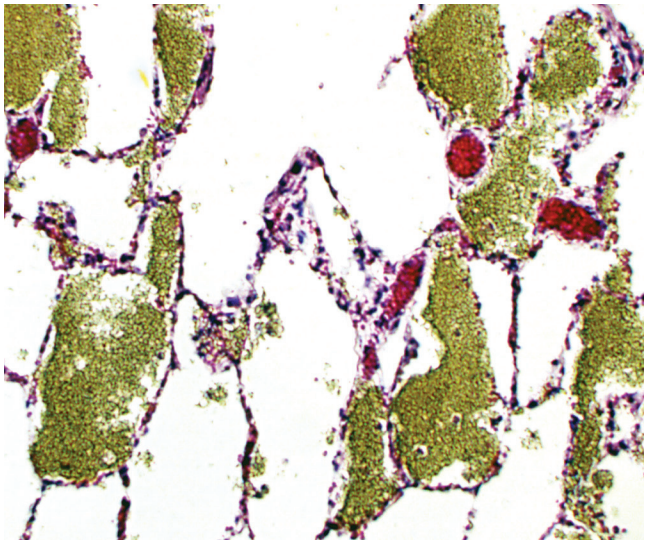
Crenosoma vulpis. *Crenosoma vulpis* is a lungworm seen commonly in foxes and sporadically in dogs with access to the intermediate hosts—slugs and snails. The adult lungworms live in small bronchi and bronchioles in the caudal lobes, causing eosinophilic and catarrhal bronchitis manifested grossly as gray areas of inflammation and atelectasis. In some animals, *Crenosoma vulpis* causes bronchiolar goblet cell metaplasia and mucous obstruction, resulting in lobular atelectasis due to the valve effect of the mucous plug.

Eucoleus aerophilus. *Eucoleus aerophilus* (*Capillaria aerophila*) is a nematode parasite typically found in the trachea and bronchi of wild and domestic carnivores. In some cases, this parasite may also involve the nasal passages and sinuses. Although generally asymptomatic, some dogs cough because of the local irritation caused by the parasites on the tracheal or bronchial mucosa.

Paragonimus spp. *Paragonimus kellicotti* in North America and *Paragonimus westermani* in Asia are generally asymptomatic fluke infections in fish-eating species. The life cycle involves two intermediate hosts, the first a freshwater snail and the second a freshwater crab or crayfish; in North America, cats and dogs acquire infection by eating crayfish. Gross lesions include pleural hemorrhages where the metacercariae migrate into the lungs. Later, multifocal eosinophilic pleuritis, and subpleural cysts up to 7 mm long containing pairs of adult flukes, are found along with eosinophilic granulomas around clusters of eggs. Like many other parasitic pneumonias, lesions and scars are more frequent in the caudal lobes. Pneumothorax can occur if a cyst that communicates with an airway ruptures to the pleural surface.

Other Parasitic Infections. *Angiostrongylus vasorum* and *Dirofilaria immitis* are parasites of the pulmonary arteries and right ventricle and, depending on the stage, can produce different forms of pulmonary lesions. Adult parasites can cause chronic arteritis that leads to pulmonary hypertension, pulmonary arterial thrombosis, interstitial (eosinophilic) granulomatous pneumonia, pulmonary interstitial fibrosis, congestive right-sided cardiac failure, and eventually caudal vena caval syndrome. Other lesions include pleural petechial hemorrhages and, in later stages, diffuse pulmonary hemosiderosis and multifocal pulmonary infarcts. Larvae and eggs also cause alveolar injury, thickening of the alveolar walls with eosinophils and lymphocytes (interstitial pneumonia), and multifocal or coalescing granulomas with giant cells (parasitic granulomas). *Pneumocystis carinii* has been reported as a sporadic cause of chronic interstitial pneumonia in dogs with a compromised immune system (see Pneumonias of Horses; also see Fig. 9-20).

Aspiration Pneumonia. Aspiration pneumonia is an important form of pneumonia that occurs in dogs when vomit or regurgitated materials are aspirated into the lungs, or when drugs or radiographic contrast media are accidentally introduced into the airways (E-Fig. 9-28). As in other animal species, aspiration pneumonia may be unilateral or may more often affect the right cranial lobe (Fig. 9-104). The severity of lesions depends very much on the chemical and microbiologic composition of the aspirated material. In general, aspiration in monogastric animals, particularly in dogs and cats, is more severe because of the low pH of the gastric contents (chemical pneumonitis). In severe cases, dogs and cats die rapidly from septic shock and ARDS (see Fig. 9-63), which is microscopically characterized by diffuse alveolar damage, protein-rich pulmonary edema, neutrophilic alveolitis, and formation of typical hyaline membranes along the alveolar walls (see Fig. 9-104). In animals that survive the acute stages of aspiration, pulmonary lesions progress to bronchopneumonia. Aspiration pneumonia is a common sequela to



E-Figure 9-28 **Aspiration of Contrast Media, Dog.** Lung section of a dog that died unexpectedly following improper administration of contrast media for radiology. Alveoli are filled with homogenous green granular material (contrast media). H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

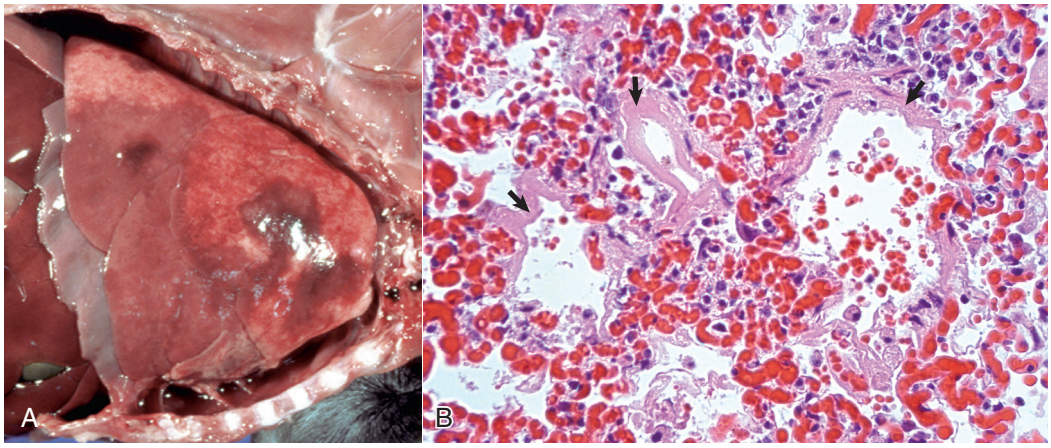


Figure 9-104 Acute Hemorrhagic Bronchopneumonia, Acute Respiratory Distress Syndrome (ARDS), Lungs, 4-Week-Old Puppy (Also See Fig. 9-63). A, Note that the lungs did not collapse when the thorax was opened (loss of negative pressure) and as a result fill almost the entire thoracic cavity. The cranioventral aspects of the lung are consolidated with hemorrhage. **B,** Alveolar capillary congestion, thick hyaline membranes along the alveolar septa *(arrows)*, and intraalveolar hemorrhage. These microscopic changes are typical of the diffuse alveolar damage seen in lungs with ARDS. H&E stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

cleft palate, and in dogs with megaesophagus secondary to either myasthenia gravis or persistent right aortic arch. It is also an important complication of general anesthesia or neurologic diseases affecting laryngeal function.

Toxic Pneumonias

Paraquat. Paraquat, a broad-spectrum herbicide widely used in gardening and agriculture, can cause severe and often fatal toxic interstitial pneumonia (pneumonitis) in dogs, cats, human beings, and other species. After ingestion or inhalation, this herbicide selectively accumulates in the lung where paraquat toxic metabolites are produced by Club (Clara) cells. These metabolites promote local release of free radicals in the lung, which causes extensive injury to Club cells and to the blood-air barrier, presumably through lipid peroxidation of type I and II pneumonocytes and alveolar endothelial cells (see Fig. 9-89). Paraquat toxicity has been used experimentally as a model of oxidant-induced alveolar injury and pulmonary fibrosis. Soon after poisoning, the lungs are heavy, edematous, and hemorrhagic because of extensive necrosis of epithelial and endothelial cells in the alveolar walls. The lungs of animals that survive acute paraquat toxicosis are pale, fail to collapse when the thorax is opened, and have interstitial emphysema, bullous emphysema, and occasionally pneumomediastinum. Microscopic findings in the acute and subacute phases include necrosis of type I pneumonocytes, interstitial and alveolar edema, intraalveolar hemorrhages, and proliferation of type II pneumonocytes. In the chronic stages (4 to 8 weeks later), the lesions are typically characterized by severe interstitial and intraalveolar fibrosis.

Uremic Pneumopathy. Uremic pneumonopathy (pneumonitis) is one of the many extrarenal lesions seen in dogs with chronic uremia. Lesions are characterized by a combination of pulmonary edema and calcification of vascular smooth muscle and alveolar basement membranes. In severe cases, alveolar calcification prevents lung collapse when the thorax is opened. In the more advanced cases, the lungs appear diffusely distended, pale red or brown in color, and show a rough pleural surface with rib imprints (see Fig. 9-51). On palpation, the pulmonary parenchyma has a typical "gritty" texture because of mineralization of the alveolar and vascular walls, which are best visualized microscopically by using special stains such as von Kossa (see Fig. 9-51). Because this is not primarily an inflammatory lesion, the term *pneumonitis* should not be used.

Other Pneumonias. *Idiopathic pulmonary fibrosis* is a rare condition of uncertain etiology reported in the West Highland white terrier breed that shares similarities with human and feline idiopathic pulmonary fibrosis. Microscopically, there is diffuse interstitial pneumonia and progressive alveolar fibrosis with capillary obliteration, hyperplasia of type II cells, some of which exhibit cellular atypia, and finally hypertrophy and hyperplasia of smooth muscle. The interstitial fibrosis eventually spills over alveolar spaces causing conspicuous intraalveolar fibrosis.

Pneumonias of Cats

Although upper respiratory tract infections are common and important in cats, pneumonias are uncommon except when there is immunosuppression or aspiration of gastric contents. Viral infections such as feline rhinotracheitis and calicivirus may cause lesions in the lungs, but unless there is secondary invasion by bacteria, they do not usually cause a fatal pneumonia.

Viral Pneumonias

Feline Rhinotracheitis. Feline rhinotracheitis is an important viral disease of cats caused by the ubiquitous felid herpesvirus 1 (FeHV-1). This infection affects primarily young or debilitated cats causing inflammation in the nasal, ocular, and tracheal mucosa and, to a much lesser extent, the lung (see Species-Specific Diseases of the Nasal Cavity and Paranasal Sinuses). When lungs are affected, FeHV-1 causes bronchointerstitial pneumonia with necrosis of bronchiolar and alveolar epithelium, thickening of the alveolar walls, and extensive permeability edema. Eosinophilic intranuclear inclusion bodies may be seen in infected epithelial cells early in infection.

Feline Calicivirus. Feline calicivirus (FCV) causes upper respiratory disease, stomatitis, conjunctivitis, and, to a lesser extent, interstitial pneumonia. Microscopically, affected lungs exhibit the typical pattern of bronchointerstitial pneumonia with necrotizing bronchiolitis, thickening of alveolar walls, occasionally hyaline membranes, hyperplasia of type II pneumonocytes, and macrophages admixed with cellular debris in the alveolar lumens. Because pulmonary lesions are similar to those caused by FeHV-1, isolation or in situ detection is required for final diagnosis.

Feline Infectious Peritonitis. Feline infectious peritonitis (FIP) is caused by FIP virus (FIPV), a mutated form of feline enteric

coronavirus (FECV), and is one of a few viral infections of domestic animals that result in pyogranulomatous pneumonia. This disease is microscopically characterized by a vasculitis affecting many tissues and organs (Fig. 9-105).

Other Viral Pneumonias. Other viruses sporadically incriminated in feline interstitial pneumonia are cowpox virus (CPXV) and influenza A H1N1.

Bacterial Pneumonias

Pasteurellae. Bacteria from the nasal flora such as *Pasteurella multocida* and *Pasteurella*-like organisms are occasionally associated with secondary bronchopneumonia in cats (Fig. 9-106). *Pasteurella multocida* also causes otitis media and meningitis, but its role as a respiratory pathogen is mainly associated with pyothorax. Interestingly, there are reports of *Pasteurella multocida* pneumonia in older or immunosuppressed human beings acquired through contact with domestic cats.

Mycoplasmas. Mycoplasmas are often isolated from the lungs of cats with pulmonary lesions but are not definitively established as primary pathogens in feline pneumonias.

Feline Pneumonitis. The term *feline pneumonitis* is a misnomer because the major lesions caused by *Chlamydophila felis* (formerly *Chlamydia psittaci*) are severe conjunctivitis and rhinitis (see Species-Specific Diseases of the Nasal Cavity and Paranasal Sinuses). The elucidation of the importance of feline viral rhinotracheitis and feline calicivirus has removed *Chlamydophila felis* from its previously overstated importance as a lung pathogen.

Tuberculosis. Cats are susceptible to three types of mycobacterial infections: classic tuberculosis, feline leprosy, and atypical mycobacteriosis. Classic tuberculosis in cats is rare and generally caused by *Mycobacterium bovis* and *Mycobacterium microti* but also, to a lesser extent, by *Mycobacterium tuberculosis*. Nosocomial tuberculosis (*Mycobacterium bovis*) in cats has been reported with increased frequency. The usual route of infection for feline tuberculosis is oral, through infected rodents/meat or unpasteurized milk, so the granulomatous lesions are mainly in the intestine and mesenteric lymph nodes where they may disseminate through infected phagocytes to other organs. The solid and noncaseated appearance of tuberculous nodules is grossly similar to that of neoplasms, so they must be differentiated from pulmonary neoplasms (e.g., lymphoma). Classic tuberculosis with dermal lesions in cats should be differentiated from feline leprosy (localized skin granulomas) caused by *Mycobacterium lepraemurium* and other nonculturable species of acid-fast bacilli. Atypical mycobacteriosis is caused by contamination of a skin wound with saprophytic and nonsaprophytic mycobacteria such as those of the *Mycobacterium avium* complex. Advances in PCR techniques have notably reduced the time required for etiologic diagnosis of mycobacteriosis in veterinary diagnostic laboratories.

Mycotic Pneumonias

Cryptococcosis. Cryptococcosis (pulmonary *Cryptococcus neoformans* or *Cryptococcus gatti*) is the most frequent systemic mycosis in cats, and lesions are akin to those discussed in the section on mycotic pneumonias of dogs. It occurs worldwide in all species but is diagnosed most frequently in cats, horses, dogs, and human beings. Some healthy dogs and cats harbor *Cryptococcus* in the nasal cavity and become asymptomatic carriers. Clinical infection may occur in immunocompetent cats and in cats that are immunologically compromised, such as by FeLV, FIV, malnutrition, or corticosteroid treatment. Lesions can occur in nearly any tissue, resulting in a wide

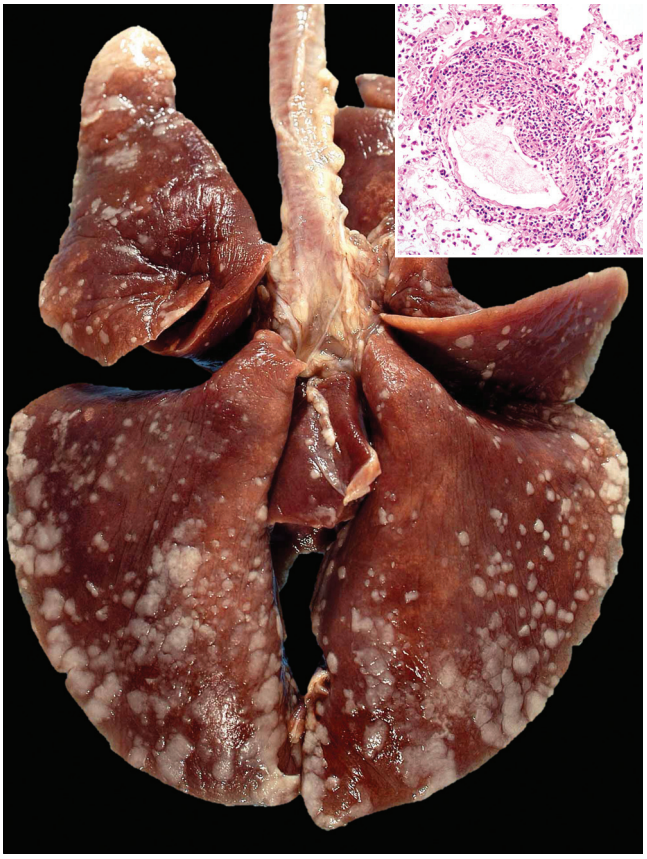


Figure 9-105 Feline Infectious Peritonitis, Granulomatous Pneumonia, Cat. Multifocal to coalescing granulomas scattered throughout all pulmonary lobes. *Inset,* Pulmonary vasculitis with transmural infiltrates of macrophages, neutrophils, and lymphocytes. H&E stain. (Courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. *Inset* courtesy Dr. A. López, Atlantic Veterinary College.)

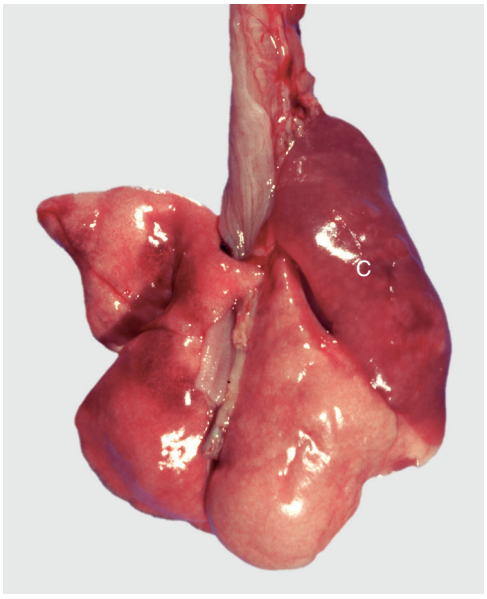


Figure 9-106 Fibrinopurulent Bronchopneumonia, Lungs, 5-Month-Old Kitten with History of Conjunctivitis, Rhinitis, and Bacterial Pneumonia. Cranioventral consolidation (C) of the right lung involves approximately 40% of its parenchyma. The consolidated lung is firm. (Courtesy Dr. S. McBurney, Atlantic Veterinary College.)

variety of clinical signs. However, granulomatous rhinitis, sinusitis, otitis media and interna, pneumonia, ulcerative dermatitis, and meningoencephalitis are most common.

The pulmonary lesion in cryptococcosis is a multifocal granulomatous pneumonia and, like those occurring in other internal organs, they are small, gelatinous, white foci. The gelatinous appearance is due to the broad mucous capsule around the yeast (see Fig. 9-35, *B*). Microscopically, lesions contain great numbers of fungal organisms (4 to 10 µm in diameter without the capsule) and only a few macrophages, lymphocytes, and multinucleated giant cells. This thick polysaccharide capsule does not stain well with H&E, and thus there is a large empty space or halo around the yeast.

Parasitic Pneumonias of Cats

Feline Lungworm. *Aelurostrongylus abstrusus*, known as *feline lungworm*, is a parasite that occurs in cats wherever the necessary slug and snail intermediate hosts are found. It can cause chronic respiratory disease with coughing and weight loss and, sometimes, severe dyspnea and death, particularly if there are secondary bacterial infections. The gross lesions are multifocal, amber, and subpleural granulomatous nodules up to 1 cm in diameter throughout the lungs. On incision, these nodules may contain viscous exudate. Microscopically, the adult parasites, eggs, and coiled larvae are in the bronchioles and alveoli, where they cause catarrhal bronchiolitis, hyperplasia of submucosal glands, and, later, granulomatous alveolitis, alveolar fibrosis, and fibromuscular hyperplasia (Fig. 9-107). During routine examination of feline lungs, it is quite common to find fibromuscular hyperplasia in bronchioles and arterioles in otherwise healthy cats. It was alleged in the past that this fibromuscular hyperplasia was a long-term sequela of subclinical infection with *Aelurostrongylus abstrusus*. However, this view has been challenged; thus the pathogenesis and significance of pulmonary fibromuscular hyperplasia in healthy cats remains uncertain. In severe cases, fibromuscular hyperplasia is grossly visible in the lungs as white subpleural nodules.

Other Parasitic Pneumonias. *Toxoplasma gondii*, *Paragonimus kellicotti*, and *Dirofilaria immitis* can also affect cats (see the section on Parasitic Pneumonias of Dogs). *Cytauxzoon felis* is an apicomplexan hemoparasite that affects domestic and wild Felidae. The organism infects erythrocytes in the erythrocytic stage of disease and multiplies in intravascular macrophages/monocytes, including those in the alveolar capillaries (E-Fig. 9-29), during the leukocytic stage of disease.

Aspiration Pneumonia. Aspiration pneumonias are common in cats as a result of vomiting, regurgitation, dysphagia, or anesthetic complication or after accidental administration of food, oral medicaments, or contrast media into the trachea (iatrogenic). Pulmonary lesions are similar to those described for dogs, and the type of lung lesion depends on the chemical and bacterial composition of the aspirated material (see the section on Aspiration Pneumonia of Dogs).

Other Pneumonias

Feline Idiopathic Pulmonary Fibrosis. Feline idiopathic pulmonary fibrosis is a rare, progressive, and fatal disease of cats of uncertain etiology characterized by multifocal fibrotic nodules subpleurally and randomly in the lung making the pleural surface resemble nodular cirrhosis of the liver (Fig. 9-108). Microscopically, the affected alveolar and peribronchiolar interstitium is thickened by excessive fibrosis, abundant deposition of extracellular matrix, and hypertrophy of smooth muscle. Some investigators suggest an intrinsic cellular defect in type II pneumonocytes as the underlying cause. The alveolar walls are diffusely lined by cuboidal hyperplastic type II pneumonocytes, and the alveolar lumens often contain exfoliated cells and necrotic debris. This feline condition has morphologic features similar to "equine multinodular pulmonary fibrosis" and "cryptogenic pulmonary fibrosis" in human beings.

Fetal and Perinatal Pneumonias

Fetal Pneumonias. Pneumonia is one of the most frequent lesions found in fetuses submitted for postmortem examination, particularly in foals and food-producing animals. Because of autolysis, lack of inflation, and the lungs being at various stages of development, fetal lesions are often missed or misdiagnosed. In the nonaerated fetal lung, the bronchoalveolar spaces are filled with a viscous, locally produced fluid known as *lung fluid* or *lung liquid*. It has been estimated that an ovine fetus produces approximately 2.5 mL of "lung fluid" per kilogram of body weight per hour. In the

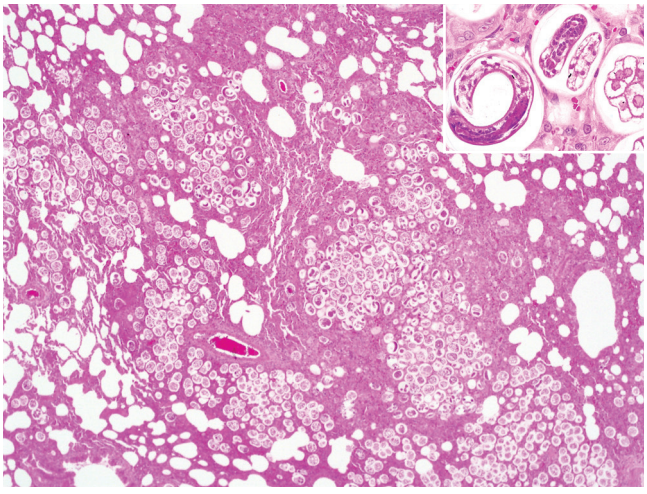


Figure 9-107 Verminous Pneumonia, *Aelostrongylus abstrusus*, Lung, Cat. Pulmonary nodules containing numerous larvae and eggs, and interstitial thickening due to fibrosis and smooth muscle hypertrophy of arteries and bronchioles. *Inset*, Coiled *Aelostrongylus* larvae. (Courtesy Dr. D.L. Dungworth and Dr. A. López, Atlantic Veterinary College.)

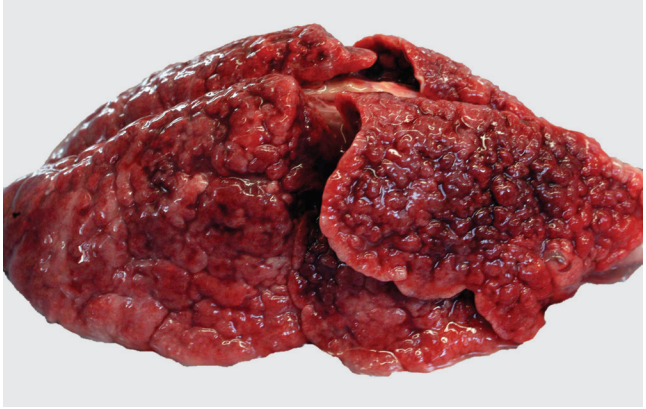


Figure 9-108 Idiopathic Nodular Pulmonary Fibrosis, Lung, Cat. The lung contains large numbers of nodules distributed throughout all pulmonary lobes. These nodules are formed by focal areas of fibrosis with retraction of the pulmonary parenchyma admixed with focal areas of pulmonary hyperinflation. This cat had a history of chronic respiratory problems. (Courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México.)

fetus, this fluid normally moves along the tracheobronchial tree, reaching the oropharynx, where a fraction is swallowed into the gastrointestinal tract, and a small portion is released into the amniotic fluid. At the time of birth, the lung fluid is rapidly reabsorbed from the lungs by alveolar absorption and lymphatic drainage.

Aspiration of amniotic fluid contaminated with meconium and bacteria from placentitis is the most common route by which microbial pathogens reach the fetal lungs. This form of pneumonia is secondary to fetal hypoxia and acidosis ("fetal distress"), which cause the fetus to relax the anal sphincter, release meconium into the amniotic fluid, and, in the terminal stages, inspire deeply with open glottis, resulting in the aspiration of contaminated fluid (Fig. 9-109). Gross lesions are only occasionally recognized, but microscopic changes are similar to those of a bronchopneumonia. Microscopically, bronchoalveolar spaces contain variable numbers of neutrophils, macrophages, epidermal squames, and pieces of meconium that appear as bright yellow material because of its bile content. In contrast to postnatal bronchopneumonia, lesions in fetuses are not restricted to the cranioventral aspects of the lungs but typically involve all pulmonary lobes.

In cattle, *Brucella abortus* and *Trueperella* (*Arcanobacterium*) *pyogenes* are two of the most common bacteria isolated from the lungs of aborted fetuses. These bacteria are usually present in large numbers in the amniotic fluid of cows with bacterial placentitis. Inflammation of the placenta interferes with oxygen exchange between fetal and maternal tissue, and the resultant fetal hypoxia induces the fetus to "breathe" with an open glottis and aspirate the amniotic fluid. *Aspergillus* spp. (mycotic abortion) and *Ureaplasma diversum* cause sporadic cases of placentitis, which results in fetal pneumonia and abortion.

In addition to the respiratory route (aspiration), pathogens, such as bacteria and viruses, can also reach the lungs via fetal blood and cause interstitial pneumonia. Listeriosis (*Listeria monocytogenes*), salmonellosis (*Salmonella* spp.), and chlamydiosis (*Chlamydophila abortus* [*C. psittaci*]) are the best known examples of blood-borne diseases that cause fetal pneumonia in farm animals. Gross lesions in the lungs are generally undetected, but microscopic lesions include focal necrotizing interstitial pneumonia and focal necrosis in the liver, spleen, or brain. Fetal bronchointerstitial pneumonia also occurs in some viral abortions, such as those caused by infectious bovine rhinotracheitis (IBR) virus and bovine parainfluenza virus 3 (BPIV-3) in cattle and equine viral rhinopneumonitis (EVR) in horses. Fetal pneumonias in dogs and cats are infrequently described, perhaps because aborted puppies and kittens are rarely submitted for postmortem examination. With advancements in molecular biology techniques, the etiologic diagnosis of abortions and their association with pulmonary fetal lesions is rapidly improving.

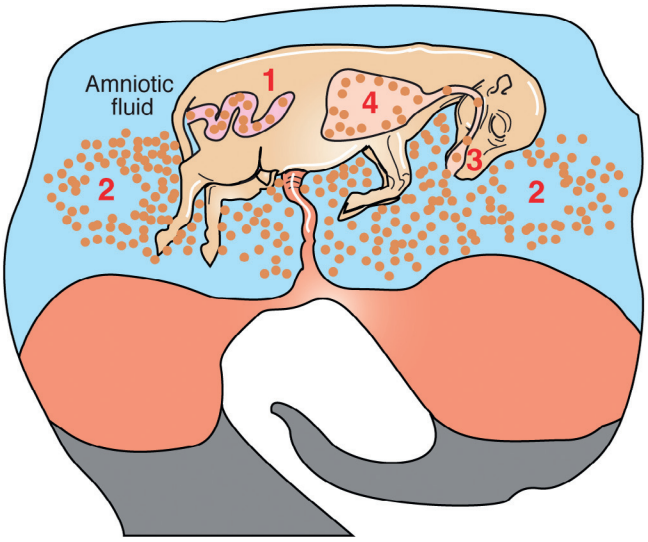


Figure 9-109 Meconium Aspiration Resulting From Intrauterine Hypoxia. *1*, Increased peristalsis and relaxation of anal sphincter. *2*, Meconium contamination of amniotic fluid. *3*, Meconium in the oropharynx. *4*, Intrauterine gasping with open glottis causing aspiration of meconium and amniotic fluid into fetal lung. (Redrawn with permission from Dr. J. Martinez-Burnes, Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma de Tamaulipas, México.)

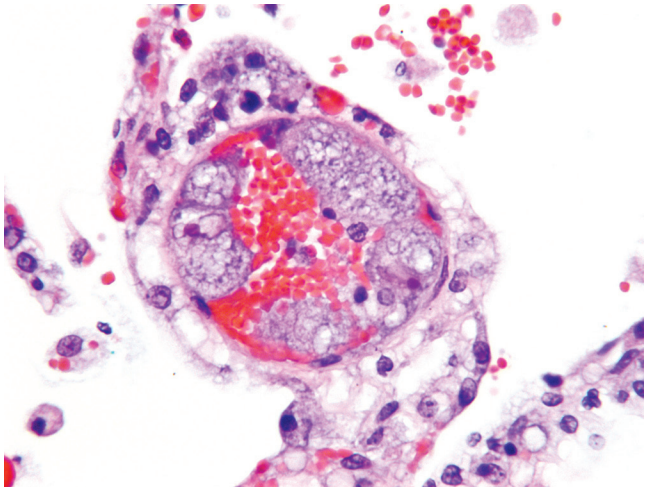
Neonatal Pneumonias and Septicemias. These entities are rather common in newborn animals lacking passive immunity because of the lack of either ingestion or absorption of maternal colostrum (failure of passive transfer or hypogammaglobulinemia). In addition to septicemias causing interstitial pneumonia, farm animals with hypogammaglobulinemia can develop bronchopneumonia by inhalation of bacterial pathogens. These include *Histophilus somni* and *Pasteurella multocida* in calves; *Streptococcus* spp. in foals; and *Escherichia coli*, *Listeria monocytogenes*, and *Streptococcus suis* in pigs.

Meconium Aspiration Syndrome. Meconium aspiration syndrome (MAS) is an important but preventable condition in human babies that originates when amniotic fluid contaminated with meconium is aspirated during labor or immediately after birth. The pathogenesis of MAS is basically the same as in those of fetal bronchopneumonia (see Fig. 9-109). Fetal hypoxia, a common event during dystocia or prolonged parturition, causes the fetus to relax the anal sphincter and release meconium into the amniotic fluid. Aspiration of meconium can occur directly from aspirating contaminated amniotic fluid before delivery (respiratory movements with an open glottis) or immediately after delivery when the meconium lodged in the nasopharynx is carried into the lung with the first breath of air. This latter form of aspiration is prevented in delivery rooms by routine suction of the nasopharynx in meconium-stained babies. MAS is well known in human babies, but the occurrence and significance in animals remains largely unknown. MAS has been reported in calves, foals, piglets, and puppies. Although pulmonary lesions are generally mild and transient, aspiration of meconium can be life-threatening for newborn babies and animals because it typically occurs in compromised neonates already suffering from intrauterine hypoxia and acidosis. Neonatal acidosis is known to impair colostrum absorption in calves. Common MAS sequelae are lobular atelectasis, pulmonary hypertension, and possibly airway hyperreactivity.

In the most severe cases of MAS, focal (patchy) atelectasis can be observed grossly in the lung, indicating failure of the lungs to be fully aerated because of the mechanical obstruction and the chemical effect of meconium on pulmonary surfactant (see Fig. 9-52). Microscopically, meconium and keratin exfoliated from skin of the fetus into the amniotic fluid are present in bronchi, bronchioles, and alveoli and accompanied by mild alveolitis characterized by infiltration of leukocytes followed by alveolar macrophages and occasional giant cells (E-Fig. 9-30).

Neoplasms of the Lungs

Lung cancer in animals is rare, unlike in human beings, in which the incidence is alarming and continues to be the number one cause of death due to cancer in Canada, the United States, and Europe. Interestingly, prostatic and breast cancers, so much feared by men



E-Figure 9-29 Cytauxzoonosis, *Cytauxzoon felis*, Lung, Cat. Lung section showing a distended and partially occluded blood vessel *(center of figure)* containing large granular cells. These large cells are macrophages, and their cytoplasm is filled with myriad merozoites. H&E stain. (Courtesy Dr. Sylvia Ferguson, University of Tennessee.)

and women, are a distant second. To say that cigarette smoking is responsible for this epidemic of lung cancer is unnecessary. Although dogs have been proposed as valuable "sentinels" for environmental hazards, such as exposure to passive smoking, asbestos, dyes, and insecticides, it is not known if the prevalence of canine lung tumors has increased in geographical areas with high contamination. Alterations in genes (oncogenes) and chromosomes and changes in biologically active molecules have been linked to lung cancer in recent years. As with many other forms of cancer, epidemiologic studies indicate that the incidence of pulmonary neoplasms increases with age, but there are still insufficient data to confirm that particular canine or feline breeds have a higher predisposition to spontaneous lung neoplasms.

A standard nomenclature of pulmonary neoplasms in domestic animals is lacking, and as a consequence, multiplicity of names and synonyms occur in the veterinary literature. Some classifications are based on the primary site, whereas others emphasize more the histomorphologic type. The most common types of benign and malignant pulmonary neoplasms in domestic mammals are listed in Box 9-2.

Clinically, the signs of pulmonary neoplasia vary with the degree of invasiveness, the amount of parenchyma involved, and locations of metastases. Signs may be vague, such as cough, lethargy, anorexia, weight loss, and perhaps dyspnea. In addition, paraneoplastic syndromes, such as hypercalcemia, endocrinopathies, and pulmonary hypertrophic osteoarthropathy, have been associated with pulmonary neoplasms.

Primary Neoplasms of the Lungs. Primary neoplasms of the lungs arise from cells normally present in the pulmonary tissue and can be epithelial or mesenchymal, although the latter are rare.

Box 9-2 Classification of Pulmonary Neoplasms

PRIMARY EPITHELIAL ORIGIN
Benign
Papilloma
Adenoma

Malignant
Adenocarcinoma (acinar or papillar)
Squamous cell carcinoma
Adenosquamous carcinoma
Bronchiolar-alveolar carcinoma (this term is being abandoned by some pathologists)
Small cell and large cell carcinomas
Anaplastic (undifferentiated) carcinoma
Carcinoid tumor (pulmonary neuroendocrine tumor)
Ovine (retroviral) pulmonary carcinoma

PRIMARY MESENCHYMAL ORIGIN
Benign
Hemangioma

Malignant
Osteosarcoma, chondrosarcoma
Hemangiosarcoma
Histiocytic sarcoma
Lymphomatoid granulomatosis
Granular cell tumor
Mesothelioma

SECONDARY (METASTATIC) LUNG TUMORS
Any malignant tumor metastatic from another body location (e.g., osteosarcoma in dogs, uterine carcinoma in cows, and malignant melanoma in horses)

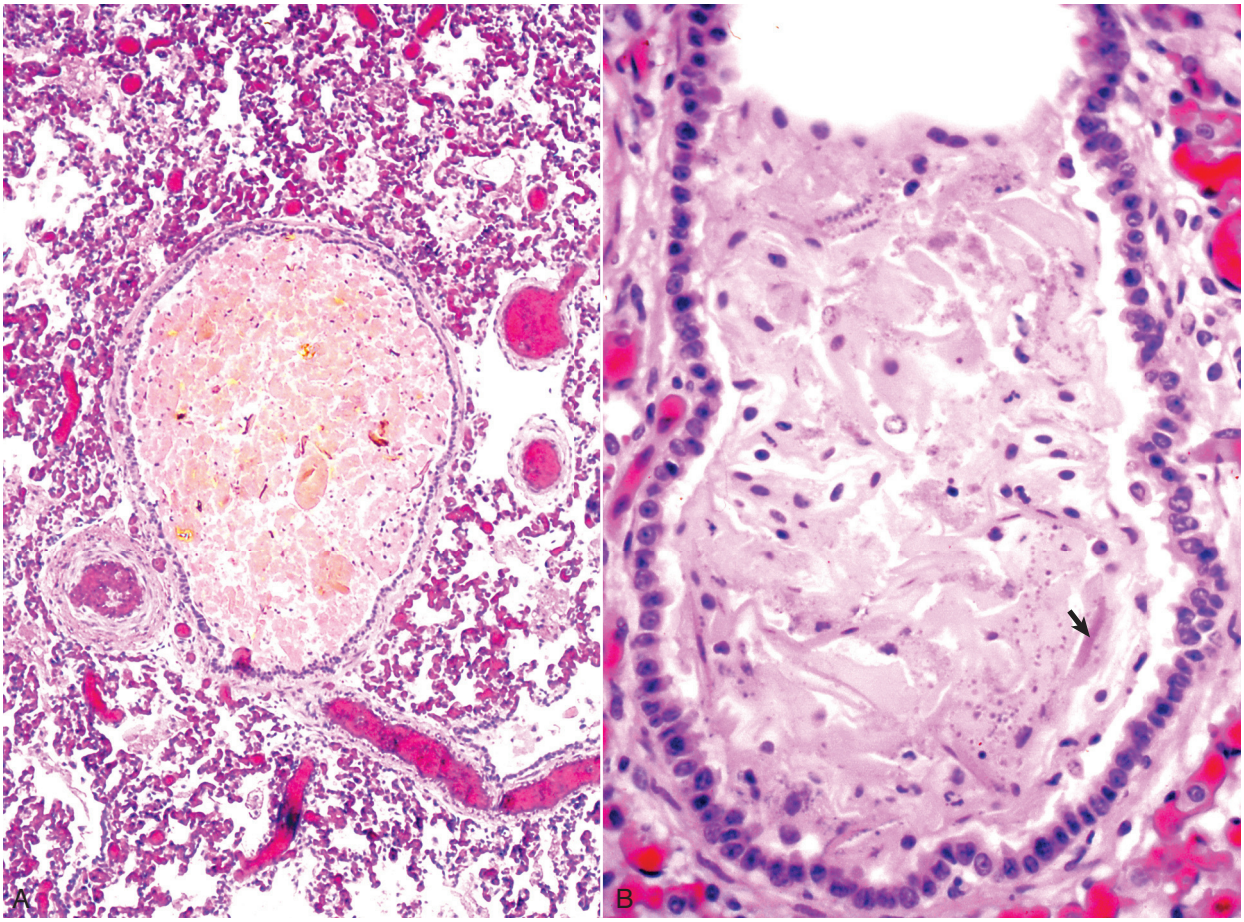
Primary benign neoplasms of the lungs, such as pulmonary adenomas, are highly unusual in domestic animals. Most primary neoplasms are malignant and appear as solitary masses of variable size that, with time, can metastasize to other areas of the lungs and to distant organs. It is sometimes difficult on gross and microscopic examination to differentiate primary lung cancer from pulmonary metastasis resulting from malignant neoplasms elsewhere in the body.

It is often difficult to determine the precise topographic origin of a neoplasm within the lungs—for example, whether it originates in the conducting system (bronchogenic carcinoma), transitional system (bronchiolar carcinoma), exchange system (alveolar carcinoma), or bronchial glands (bronchial gland carcinoma). According to the literature, pulmonary carcinomas in animals arise generally from Club (Clara) cells or type II pneumonocytes of the bronchioloalveolar region, in contrast to those in human beings, which are mostly bronchogenic. Tumors located at the hilus generally arise from major bronchi and tend to be a solitary large mass with occasional small metastasis to the periphery of the lung. In contrast, tumors arising from the bronchioloalveolar region are often multicentric with numerous peripheral metastases in the lung parenchyma. Because of histologic architecture and irrespective of the site of origin, many malignant epithelial neoplasms are classified by the all-encompassing term of pulmonary adenocarcinomas.

Dogs and cats are the species most frequently affected with primary pulmonary neoplasms, largely carcinomas, generally in older animals. The mean age for primary lung tumors is 11 years for dogs and 12 years for cats. Pulmonary carcinomas in other domestic animals, except for retrovirus-induced pulmonary carcinoma in sheep, are less common, possibly because fewer farm animals are allowed to reach their natural life span. These neoplasms can be invasive or expansive, vary in color (white, tan, or gray) and texture (soft or firm), and often have areas of necrosis and hemorrhage, which result in a "craterous" or "umbilicate" appearance. This umbilicate appearance is frequently seen in rapidly growing carcinomas in which the center of the tumoral mass undergoes necrosis as a result of ischemia. Some lung neoplasms resemble pulmonary consolidation or large granulomas. Cats with moderately differentiated neoplasms had significantly longer survival time (median, 698 days) than cats with poorly differentiated neoplasms (median, 75 days). Dogs with primary lung neoplasms, grades I, II, and III, had survival times of 790, 251, and 5 days, respectively.

Ovine Pulmonary Adenocarcinoma (Ovine Pulmonary Carcinoma). Ovine pulmonary adenocarcinoma, also known as *pulmonary adenomatosis* and *jaagsiekte* (from the South African Afrikaans word for "driving sickness"), is a transmissible, retrovirus-induced neoplasia of ovine lungs caused by Jaagsiekte sheep retrovirus (JSRV). It occurs in sheep throughout the world, with the notable exception of Australia and New Zealand; its incidence is high in Scotland, South Africa, and Peru and unknown but probably low in North America. This pulmonary carcinoma behaves very much like a chronic pneumonia, and JSRV shares many epidemiologic similarities with the ovine lentivirus responsible for maedi and the retrovirus responsible for enzootic nasal carcinoma in small ruminants. Pulmonary adenomatosis has been transmitted to goats experimentally but is not known to be a spontaneous disease in that species.

Ovine pulmonary adenocarcinoma affects mainly mature sheep but can occasionally affect young stock. Intensive husbandry probably facilitates horizontal transmission by the copious nasal discharge and explains why the disease occurs as devastating epizootics with 5% to 80% mortality when first introduced into a flock. Differential diagnosis between maedi and pulmonary adenomatosis can prove difficult because both diseases often coexist in the same flock



E-Figure 9-30 Meconium and Amniotic Fluid Aspiration, Lung, Neonatal Calf. A, Large plug of meconium totally fills the lumen of a bronchiole *(center of figure)*. Meconium is composed of amorphous material and keratin and stains yellow because of the bile. H&E stain. **B,** Bronchiole containing a large sheet of squamous epithelial cells (squames), several pieces of keratin *(arrow)*, and a few neutrophils. (From Lopez A, Bildfell R: *Vet Pathol* 29:104-111, 1992.)

or in the same animal. Death is inevitable after several months of the initial onset of respiratory signs, and a specific humoral immune response to JSRV is undetectable in affected sheep.

During the early stages of ovine pulmonary carcinoma, the lungs are enlarged, heavy, and wet and have several firm, gray, variably sized nodules that in some cases can be located in the cranioventral lobes mimicking a bronchopneumonic lesion (Fig. 9-110, *A*). In the later stages, the nodules become confluent, and large segments of both lungs are diffusely, but not symmetrically, infiltrated by neoplastic cells. On cross section, edematous fluid and a copious mucoid secretion are present in the trachea and bronchi (Fig. 9-110, *B*). Microscopically, the nodules consist of cuboidal or columnar epithelial cells lining airways and alveoli and forming papillary or acinar (glandlike) structures (see Fig. 9-110, *A*). Because the cells have been identified ultrastructurally as originating from both type II alveolar epithelial cells and Club (Clara) cells, the neoplasm is considered a "bronchioloalveolar" carcinoma. Sequelae often include secondary bronchopneumonia, abscesses, and fibrous pleural adhesions. Metastases occur to tracheobronchial and mediastinal lymph nodes and, to a lesser extent, to other tissues such as pleura, muscle, liver, and kidneys. Neoplastic cells stain strongly positive for JSRV using immunohistochemistry.

Clinically, ovine pulmonary adenocarcinoma is characterized by a gradual loss of condition, coughing, and respiratory distress, especially after exercise (e.g., herding or "driving"). Appetite and temperature are normal, unless there are secondary bacterial infections. An important differentiating feature from maedi (interstitial pneumonia) can be observed if animals with pulmonary adenomatosis are raised by their hind limbs; copious, thin, mucoid fluid, produced by neoplastic cells in the lungs, pours from the nostrils of some animals.

Carcinoid (Neuroendocrine) Tumor of the Lungs. Carcinoid tumor of the lungs is a neoplasm presumably arising from neuroendocrine cells and is sporadically seen in dogs as multiple, large, firm pulmonary masses close to the mainstem bronchi. It has also been reported in the nasal cavity of horses. Tumor cells are generally polygonal with finely granular, pale, or slightly eosinophilic cytoplasm. Nuclei are small, and mitotic figures are absent or rare.

Granular Cell Tumor. Granular cell tumor is a rare and locally invasive tumor that has been reported mainly in human beings and older horses. The cell origin of this tumor was thought to be the myoblast, but it is currently presumed to be Schwann cells, which are normally present in the bronchovascular bundles of the lung. Microscopically, neoplastic cells are large, polyhedron-shaped with abundant cytoplasm containing numerous acidophilic granules, which are positive for PAS and for S-100 protein using immunohistochemistry. Although this tumor can cause bronchial obstruction and respiratory signs, in most cases, it is an incidental finding in older horses submitted for postmortem examination.

Lymphomatoid Granulomatosis. Lymphomatoid granulomatosis is a rare but interesting pulmonary disease of human beings, dogs, cats, and possibly horses and donkeys characterized by nodules or large solid masses in one or more lung lobes. These frequently metastasize to lymph nodes, kidneys, and liver. Microscopically, tumors are formed by large pleomorphic mononuclear (lymphomatoid) cells with a high mitotic rate and frequent formation of binucleated or multinucleated cells. Tumor cells have a distinct tendency to grow around blood vessels and invade and destroy the vascular walls.

Lymphomatoid granulomatosis has some resemblance to lymphoma and is therefore also referred to as angiocentric lymphoma; phenotypic marking confirms that neoplastic cells are a mixed population of plasma cells, B and T lymphocytes, and histiocytes. Cerebral and cutaneous forms of lymphomatoid granulomatosis have also reported in human beings, dogs, and cats.

Secondary Neoplasms of the Lungs. Secondary neoplasms of the lungs are all malignant by definition because they are the result of metastasis to the lungs from malignant neoplasms elsewhere. Because the pulmonary capillaries are the first filter met by tumor emboli released into the vena cava or pulmonary arteries, secondary neoplasms in the lung are relatively common in comparison to primary ones. Also, secondary tumors can be epithelial or mesenchymal in origin. Common metastatic tumors of epithelial origin are mammary, thyroid (Fig. 9-111), and uterine carcinomas. Tumors of mesenchymal origin are osteosarcoma (Fig. 9-112, *A*); hemangiosarcoma (Fig. 9-112, *B*); malignant melanoma in dogs; lymphoma in cows, pigs, dogs, and cats (Fig. 9-113); and vaccine-associated sarcoma in cats. Usually, secondary pulmonary neoplasms are multiple; scattered throughout all pulmonary lobes (hematogenous dissemination); of variable size; and, according to the growth pattern, can be nodular, diffuse, or radiating (E-Fig. 9-31).

The appearance of metastatic neoplasms differs according to the type of neoplasm. For example, dark red cystic nodules containing blood indicate hemangiosarcoma, dark black solid nodules indicate melanoma, and hard solid nodules (white, yellow, or tan color) with bone spicules indicate osteosarcoma. The gross appearances of

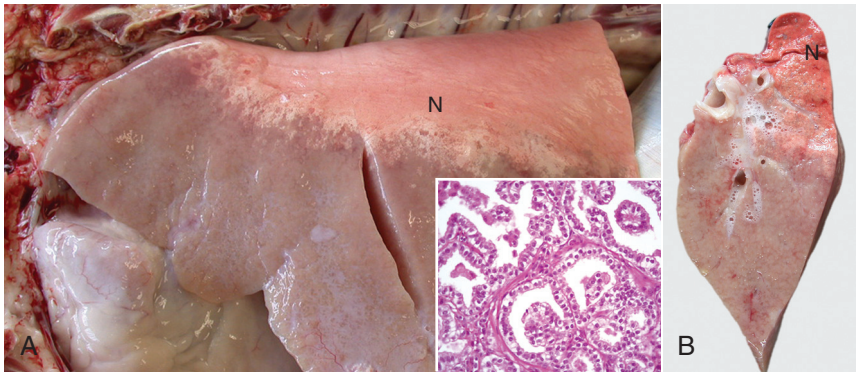
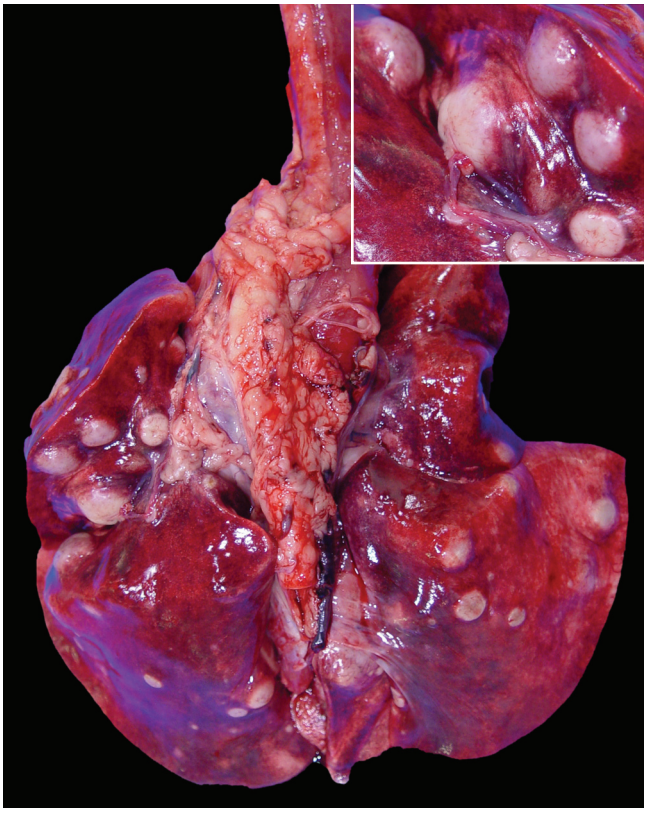


Figure 9-110 Ovine Pulmonary Carcinoma (Pulmonary Adenomatosis, Jaagsiekte), Lung, 3-Year-Old Sheep. A, Neoplastic cell infiltration involving the cranial and ventral portions of the lung and mainly sparing the dorsal portions of the caudal lung lobe *(N)*. The affected lung is enlarged and firm. *Inset,* Papillary proliferation of cuboidal epithelial cells (presumed type II pneumonocytes). H&E stain. **B,** Transverse section of the cranial lobe. Note the solid appearance of the ventral portion *(bottom)* of the lung and the frothy fluid (edema) that originates in the alveolar walls. *N*, Normal lung. (Courtesy Dr. M. Heras, Facultad de Veterinaria, Universidad de Zaragoza, Spain.)



E-Figure 9-31 Metastatic Anal Sac Gland Carcinoma, Lung, Dog. Numerous white to tan bulging masses randomly distributed throughout all lobes of the lung. The primary site of this canine carcinoma is the anal sac. *Inset*, Close-up of tumoral masses, some of which show a slightly umbilicated center. (Courtesy Dr. C. Legge and Dr. M. Buote, Atlantic Veterinary College.)

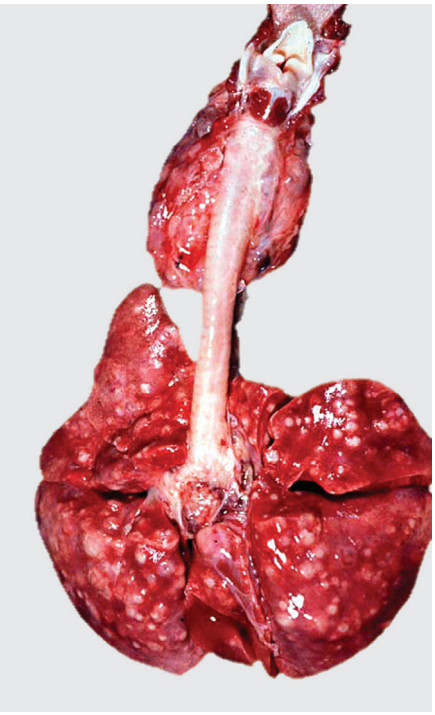


Figure 9-111 **Metastatic Thyroid Carcinoma, Lungs, Adult Dog.** The lungs contain multiple randomly distributed white-pink metastatic nodules, which originated from the enlarged and neoplastic left thyroid gland. (Courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University.)

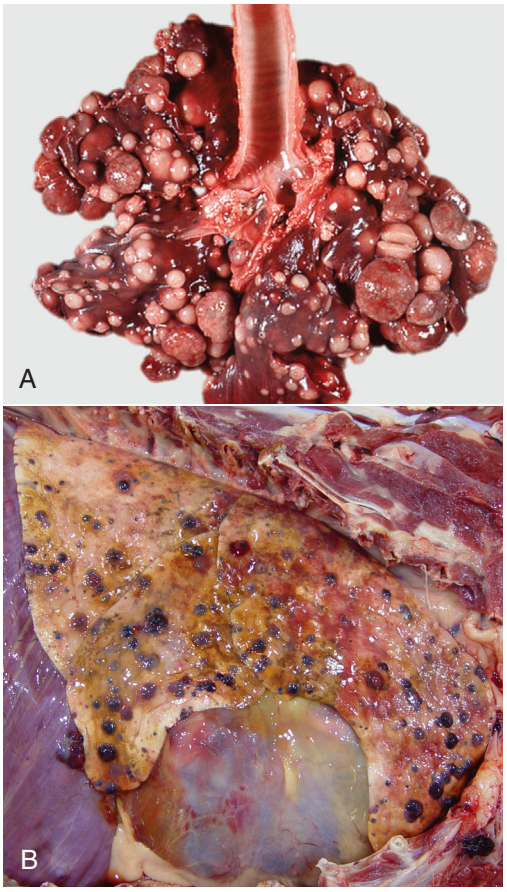


Figure 9-112 **Lung, Metastatic Neoplasms, Dog. A,** Metastatic sarcoma (primary site unknown). Large numbers of gray-white metastatic nodules are randomly distributed throughout all lung lobes. **B,** Metastatic hemangiosarcoma. Note the red to dark red masses throughout the lung parenchyma. If these masses were black, metastatic melanoma would be the likely diagnosis. (**A** courtesy Dr. J.M. King, College of Veterinary Medicine, Cornell University. **B** courtesy Dr. A. Bourque and Dr. A. López, Atlantic Veterinary College.)

metastatic carcinomas are generally similar to the primary neoplasm and sometimes have umbilicated centers. Proper diagnoses of pulmonary neoplasms in live animals require history, clinical signs, radiographs, cytologic analysis of BAL fluid, and, when necessary, a lung biopsy. Identification of a specific lineage of neoplastic cells in biopsy or postmortem specimens is often difficult and requires electron microscopy or immunohistochemical techniques. Electron microscopy allows identification of distinctive cellular components such as osmiophilic lamellar phospholipid nephritic bodies in alveolar type II epithelial cells or melanosomes in melanomas. Immunohistochemical staining is also helpful in identifying tumor cells.

Thoracic Cavity and Pleura

The thoracic wall, diaphragm, and mediastinum are lined by the parietal pleura, which reflects onto the lungs at the hilum and continues as the visceral pleura, covering the entire surface of the lungs, except at the hilus where the bronchi and blood vessels enter. The space between the parietal and visceral pleura (pleural space) is only minimal and under normal conditions contains only traces of clear fluid, which is a lubricant, and a few exfoliated cells. Samples of this fluid are obtained by thoracocentesis, a simple procedure in which a needle is passed into the pleural cavity. Volumetric, biochemical, and cytologic changes in this fluid are routinely used in veterinary diagnostics.

Disorders of the Thoracic Cavity and Pleura

Anomalies[7]

Congenital defects are rare and generally of little clinical significance. Cysts within the mediastinum of dogs and, less often, cats

[7]See E-Box 1-1 for potential, suspected, or known genetic disorders.

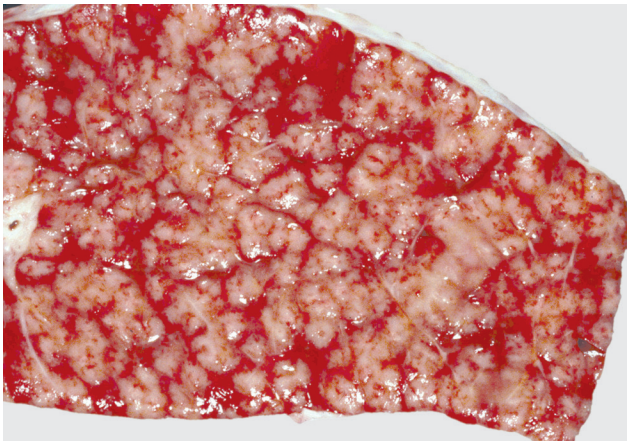


Figure 9-113 **Metastatic Lymphoma (Lymphosarcoma), Lungs, Cut Surface, Cow.** Note the numerous discrete and confluent metastatic nodules with the smooth texture and gray color characteristic of lymphoma. (Courtesy College of Veterinary Medicine, University of Illinois.)

can be large enough to compromise pulmonary function or mimic neoplasia in thoracic radiographs. These cysts may arise from the thymus (thymic branchial cysts), bronchi (bronchogenic cysts), ectopic thyroid tissue (thyroglossal duct cysts), or from remnants of the branchial pouches, and they are generally lined by epithelium and surrounded by a capsule of stromal tissue. Anomalies of the thoracic duct cause some cases of chylothorax.

Degenerative Disturbances

Pleural Calcification. Pleural calcification is commonly found in dogs and less often in cats with chronic uremia. Lesions appear as linear white streaks in parietal pleura, mainly over the intercostal muscles of the cranial part of the thoracic cavity. The lesions are not functionally significant but indicate a severe underlying renal problem. Vitamin D toxicity (hypervitaminosis D) and ingestion of hypercalcemic substances, such as vitamin D analogs, can also cause calcification of the pleura and other organs.

Pneumothorax. Pneumothorax is the presence of air in the thoracic cavity where there should normally be negative pressure to facilitate inspiration. Human beings have a complete and strong mediastinum so that pneumothorax is generally unilateral and thus not a serious problem. In dogs, the barrier varies, but in general it is not complete, so often some communication exists between left and right sides.

There are two main forms of pneumothorax. In spontaneous (idiopathic) pneumothorax, air leaking into the pleural cavity from the lungs occurs without any known underlying disease or trauma. In secondary pneumothorax, movement of air into the pleural cavity results from underlying pulmonary or thoracic wall disease. The most common causes of secondary pneumothorax in veterinary medicine are penetrating wounds to the thoracic wall, perforated esophagus, iatrogenic trauma to the thorax and lung during a transthoracic lung biopsy or thoracoscopy, tracheal rupture from improper intubation, and rupture of emphysematous bullae or parasitic pulmonary cysts (*Paragonimus* spp.) that communicate with the thoracic cavity. Pneumothorax and pneumomediastinum caused by high air pressure (barotrauma) are also well documented in cats after equipment failure during anesthesia. Clinical signs of pneumothorax include respiratory distress, and the lesion is simply a collapsed, atelectatic lung. The air is readily reabsorbed from the cavity if the site of entry is sealed.

Circulatory and Lymphatic Disturbances

Pleural Effusion. Pleural effusion is a general term used to describe accumulation of any fluid (transudate, modified transudate, exudate, blood, lymph, or chyle) in the thoracic cavity. Cytologic and biochemical evaluations of pleural effusions taken by thoracocentesis are helpful in determining the type of effusion and possible pathogenesis. Based on protein concentration and total numbers of nucleated cells, pleural effusions are cytologically divided into transudates, modified transudates, and exudates.

Hydrothorax. When the fluid is serous, clear, and odorless and fails to coagulate when exposed to air, the condition is referred to as *hydrothorax* (*transudate*). Causes of hydrothorax are the same as those involved in edema formation in other organs: increased hydrostatic pressure (heart failure), decreased oncotic pressure (hypoproteinemia, as in liver disease), alterations in vascular permeability (inflammation), or obstruction of lymph drainage (neoplasia). In cases in which the leakage is corrected, if the fluid is a transudate, it is rapidly reabsorbed. If the fluid persists, it irritates the pleura and causes mesothelial hyperplasia and fibrosis, which thickens the pleura.

In severe cases, the amount of fluid present in the thoracic cavity can be considerable. For instance, a medium-size dog can have 2 L of fluid, and a cow may accumulate 25 L or more. Excessive fluid in the thorax causes compressive atelectasis resulting in respiratory distress (see Fig. 9-54). Hydrothorax is most commonly seen in cattle with right-sided heart failure or cor pulmonale (hydrostatic) (E-Fig. 9-32); dogs with congestive heart failure (hydrostatic), chronic hepatic disease (hepatic hydrothorax) (Fig. 9-114), or nephrotic syndrome (hypoproteinemia); pigs with mulberry heart disease (increased vascular permeability); and horses with African horse sickness (increased vascular permeability).

Hemothorax. Blood in the thoracic cavity is called *hemothorax*, but the term has been used for exudate with a sanguineous component. Causes include rupture of a major blood vessel as a result of severe thoracic trauma (e.g., hit by car); erosion of a vascular wall by malignant cells or inflammation (e.g., aortitis caused by *Spirocerca lupi*); ruptured aortic aneurysms; clotting defects, including coagulopathies; warfarin toxicity; disseminated intravascular coagulation (consumption coagulopathy); and thrombocytopenia. Hemothorax is generally acute and fatal. On gross examination, the thoracic cavity can be filled with blood, and the lungs are partially or completely atelectatic (Fig. 9-115).

Chylothorax. The accumulation of chyle (lymph rich in triglycerides) in the thoracic cavity (Fig. 9-116) is a result of the rupture of major lymph vessels, usually the thoracic duct or the right lymphatic duct. The clinical and pathologic effects of chylothorax are similar to those of the other pleural effusions. Causes include thoracic neoplasia (the most common cause in human beings but a distant second to idiopathic cases in dogs), trauma, congenital lymph vessel anomalies, lymphangitis, dirofilariasis, and iatrogenic rupture of the thoracic duct during surgery. The source of the leakage of chyle is rarely found at necropsy. When the leakage of chyle occurs in the abdominal cavity, the condition is referred to as *chyloabdomen*. Cytologic and biochemical examination of fluid collected by thoracocentesis typically reveals large numbers of lymphocytes, lipid droplets, few neutrophils in chronic cases, and high triglyceride content.

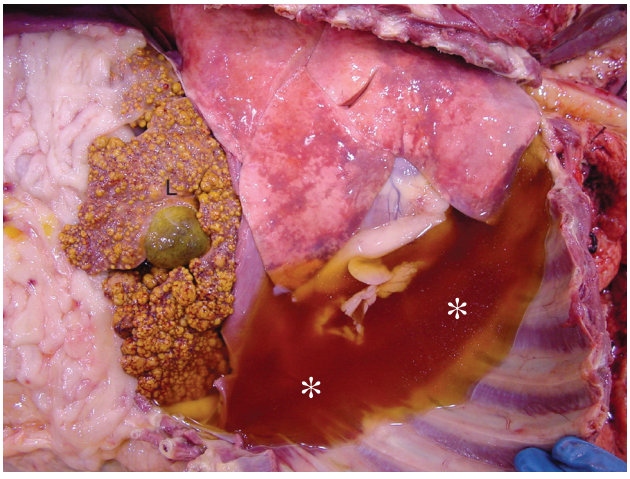
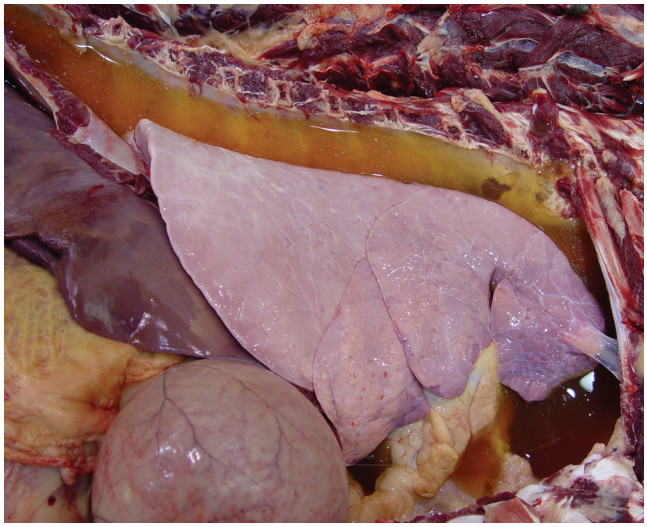


Figure 9-114 Hydrothorax, Pleural Cavity, 8-Year-Old Dog. The pleural cavity contains a large amount of deep yellow transudate *(asterisks)* (ventrally). Scattered foci of atelectasis are visible on the surface of the lung. Fluid in the pleural cavity usually compresses the ventral portions of the lung, resulting in a compressive atelectasis. Also note the nodular surface of the cirrhotic liver *(L)*. (Courtesy Dr. S. McBurney and Dr. A. López, Atlantic Veterinary College.)



E-Figure 9-32 **Hydrothorax, Pleural Cavity, 11-Month-Old Steer.** The pleural cavity contains a large amount of a clear yellow transudate. This animal also had hydropericardium and hydroperitoneum, but the underlying cause for the effusions could not be determined. (Courtesy Dr. C. Legge and Dr. A. Bourque, Atlantic Veterinary College.)

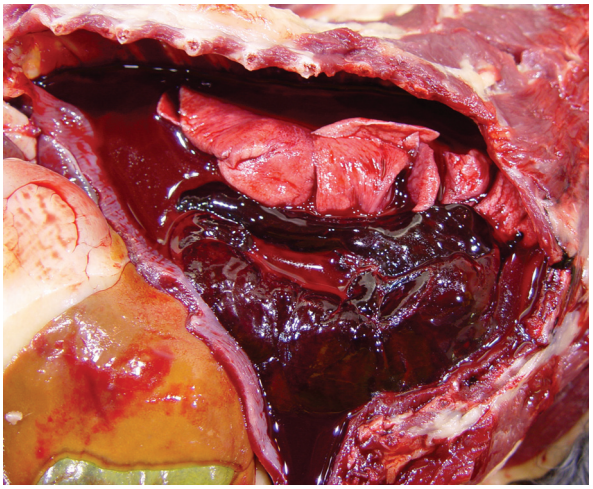


Figure 9-115 **Hemothorax, Right Pleural Cavity, Dog.** The right pleural cavity is filled with a large clot of blood from a ruptured thoracic aortic aneurysm, which caused unexpected death. Canine aortic aneurysms are associated with migration of *Spirocerca lupi* larvae along the aortic wall before their final migration into the wall of the adjacent esophagus. In other cases, like in this dog, the cause remains unknown (idiopathic aortic aneurysm). (Courtesy Dr. L. Gabor and Dr. A. López, Atlantic Veterinary College.)

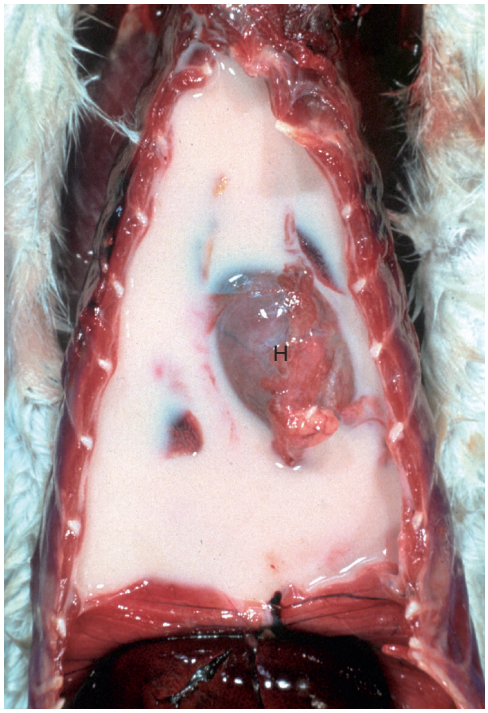


Figure 9-116 **Chylothorax (Cause Unknown), Thoracic (Pleural) Cavity, Mink.** Lymph (chyle) fills both left and right pleural cavities. The heart *(H)* and pericardium are essentially normal because the chyle does not adhere to the outer surface of the pericardial sac, as typically happens with suppurative and fibrinous exudates in the thoracic cavity. (Courtesy Western College of Veterinary Medicine.)

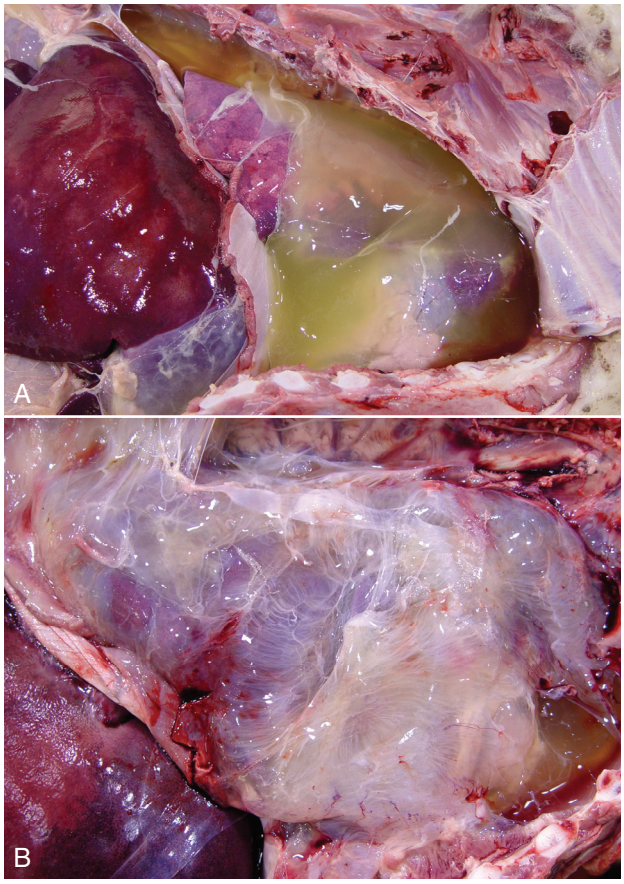


Figure 9-117 **Acute and Chronic Pleuritis, Sheep. A,** A large amount of slightly turbid straw-colored fluid is present in the thorax, and sheets and large clumps of tan-yellow friable material (fibrin and clotted protein) are loosely adhered to the right lung. **B,** The visceral and parietal pleura are covered with a thick layer of immature fibrous connective tissue. (**A** courtesy Dr. S. Martinson, Atlantic Veterinary College. **B** from Muckle A, López A, et al: *Can Vet J* 55:946-949, 2014.)

Inflammation of the Pleura

Pleural tissue is readily susceptible to injury caused by direct implantation of an organism through a penetrating thoracic or diaphragmatic wound; by hematogenous dissemination of infectious organisms in septicemias; or by direct extension from an adjacent inflammatory process, such as in fibrinous bronchopneumonia or from a perforated esophagus. Chronic injury typically results in serosal fibrosis and tight adhesions between visceral and parietal pleurae (see Fig. 9-71). When extensive, these adhesions can obliterate the pleural space.

Pleuritis or Pleurisy. Inflammation of the visceral or parietal pleurae is called *pleuritis*, and according to the type of exudate, it can be fibrinous, suppurative, granulomatous, hemorrhagic, or a combination of exudates. Acute fibrinous pleuritis can progress with time to pleural fibrosis (Fig. 9-117). When suppurative pleuritis results in accumulation of purulent exudate in the cavity, the lesion is called *pyothorax* or *thoracic empyema* (Fig. 9-118). Clinically, pleuritis causes considerable pain, and in addition, empyema can result in severe toxemia. Pleural fibrous adhesions (between parietal and visceral pleura) and fibrosis are the most common sequelae of chronic pleuritis and can significantly interfere with inflation of the lungs.

Pleuritis can occur as an extension of pneumonia, particularly in fibrinous bronchopneumonias (pleuropneumonia), or it can occur alone, without pulmonary involvement (Fig. 9-119). Bovine and ovine pneumonic mannheimiosis and porcine and bovine pleuropneumonia are good examples of pleuritis associated with fibrinous bronchopneumonias. Polyserositis in pigs and pleural empyema, particularly in cats and horses, are examples of pleural inflammation in

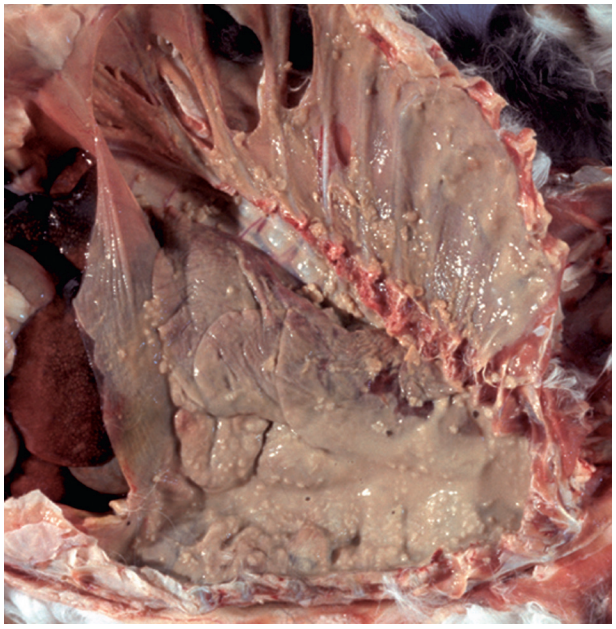


Figure 9-118 Pyothorax (*Pasteurella multocida*), Right Pleural Cavity, Cat. Pus in the thoracic cavity is called pyothorax or pleural empyema. Purulent gray-brown exudate also covers the visceral and parietal pleurae. This lesion is also referred to as *suppurative pleuritis*. (Courtesy Dr. A. López, Atlantic Veterinary College.)

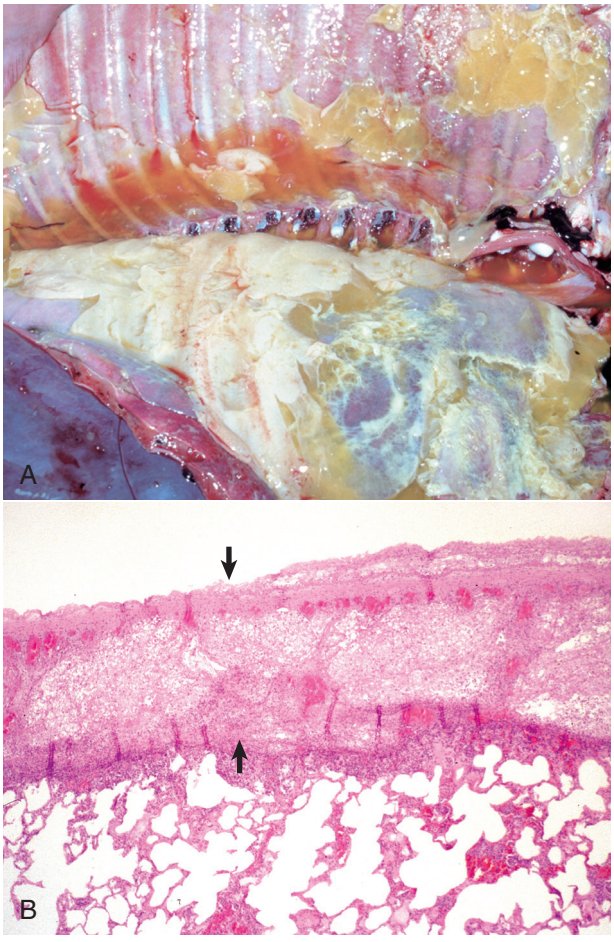


Figure 9-119 Fibrinous Pleuritis, Right Pleural Cavity, Horse. A, Large masses of yellow fibrin cover the visceral and parietal pleurae. The lungs are normal. **B,** The visceral pleura is covered by a thick layer of fibrin *(between arrows)*. Subjacent alveoli are essentially normal. H&E stain. (**A** courtesy Dr. A. López, Atlantic Veterinary College. **B** courtesy College of Veterinary Medicine, University of Illinois.)

which involvement of the lungs may not accompany the pleuritis. Pleural inflammation is most frequently caused by bacteria, which cause polyserositis reaching the pleura hematogenously. These bacteria include *Haemophilus parasuis* (Glasser's disease) (see E-Fig. 9-25), *Streptococcus suis*, and some strains of *Pasteurella multocida* in pigs; *Streptococcus equi* ssp. *equi* and *Streptococcus equi* ssp. *zooepidemicus* in horses; *Escherichia coli* in calves; and *Mycoplasma* spp. and *Haemophilus* spp. in sheep and goats. Contamination of pleural surfaces can be the result of extension of a septic process (e.g., puncture wounds of the thoracic wall and, in cattle, traumatic reticulopericarditis) and ruptured pulmonary abscesses (e.g., *Trueperella pyogenes*).

In dogs and cats, bacteria (e.g., *Nocardia*, *Actinomyces*, and *Bacteroides*) can cause pyogranulomatous pleuritis, characterized by accumulation of blood-stained pus ("tomato soup") in the thoracic cavity. This exudate usually contains yellowish flecks called *sulfur granules* (Fig. 9-120), although these are less common in nocardial empyema in cats. Many species of bacteria, such as *Escherichia coli*, *Trueperella pyogenes*, *Pasteurella multocida*, and *Fusobacterium necrophorum*, can be present in pyothorax of dogs and cats. These bacteria occur alone or in mixed infections. The pathogenesis of pleural empyema in cats is still debatable, but bite wounds or penetration of foreign material (migrating grass awns) are likely. Pyogranulomatous pleuritis with empyema occurs occasionally in dogs, presumably associated with inhaled small plant material and penetrating (migrating) grass awns. Because of their physical shape (barbed) and assisted by the respiratory movement, aspirated grass awns can penetrate airways, move through the pulmonary parenchyma, and eventually perforate the visceral pleura causing pyogranulomatous pleuritis.

Cats with the noneffusive ("dry") form of feline infectious peritonitis (FIP) frequently have focal pyogranulomatous pleuritis, in contrast to those with the effusive ("wet") form, in which thoracic involvement is primarily that of a pleural effusion. Cytologic evaluation of the effusion typically shows a low to moderate cellularity with degenerated leukocytes, lymphocytes, macrophages, and mesothelial cells, and a pink granular background as a result of the high protein content.

Pleuritis is also an important problem in horses. *Nocardia* spp. can cause fibrinopurulent pneumonia and pyothorax with characteristic sulfur granules. Although *Mycoplasma felis* can be isolated from the respiratory tract of normal horses, it is also isolated from horses with pleuritis and pleural effusion, particularly during the early stages of infection. The portal of entry of this infection is presumably aerogenous, first to the lung and subsequently to the pleura.

Neoplasms

The pleural surface of the lung is often involved in neoplasms that have metastasized from other organs to the pulmonary parenchyma and ruptured the visceral pleura to seed the pleural cavity. Mesothelioma is the only primary neoplasm of the pleura.

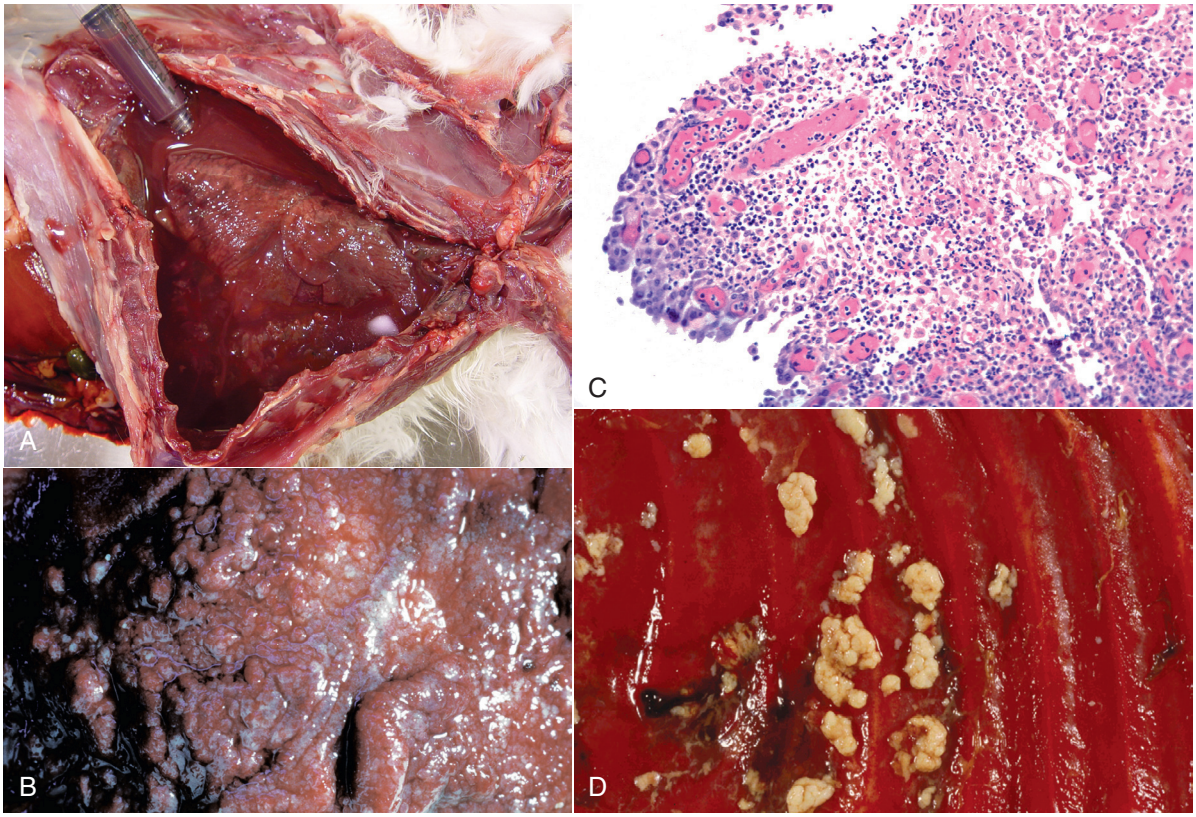


Figure 9-120 **Nocardiosis. A,** Chronic pleuritis (*Nocardia asteroides*), pleural cavity, cat. The pleural cavity is covered with abundant red-brown ("tomato soup") exudate" (syringe). Once considered to be pathognomonic of *Nocardia* spp. infection, it is no longer regarded as being diagnostic of nocardiosis. The fluid contains abundant protein, erythrocytes, granulomatous inflammatory cells, and sulfur granules. **B,** Chronic pleuritis (*Nocardia asteroides*), visceral pleura, dog. The thickened pleura has a granular pink-gray appearance because of granulomatous inflammation and the proliferation of fibrovascular tissue of the pleura. **C,** Chronic pleuritis (*Nocardia asteroides*), dog. The pleura has been thrown up into villous-like projections composed of abundant fibrovascular tissue and granulomatous inflammation. Leakage from the neocapillaries of the fibrovascular tissue is responsible for the hemorrhagic appearance of the pleural exudate. H&E stain. **D,** Chronic pleuritis (*Nocardia asteroides*), thoracic cage, parietal pleura, cat. Large pieces of exudate, which contain yellow sulfur granules, are present on the thickened pleura. (**A** courtesy Dr. F. Marrón-López and Dr. A. López. **B** and **C** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **D** courtesy College of Veterinary Medicine, University of Illinois.)

Primary Neoplasms of the Pleura: Mesothelioma. Mesothelioma is a rare neoplasm of the thoracic, pericardial, and peritoneal mesothelium of human beings that is seen most commonly in calves, in which it can be congenital. In human beings, it has long been associated with inhalation of certain types of asbestos fibers (asbestos mining and ship building) alone or with cigarette smoking as a probable cocarcinogen; no convincing association between the incidence of mesothelioma and exposure to asbestos has been made in domestic animals. In animals, there may be pleural effusion with resulting respiratory distress, cough, and weight loss.

Mesothelioma initially causes a thoracic effusion, but cytologic diagnosis can be difficult because of the morphologic resemblance of malignant and reactive mesothelial cells. During inflammation, mesothelial cells become reactive and not only increase in number but also become pleomorphic and form multinucleated cells that may be cytologically mistaken for those of a carcinoma.

Grossly, mesothelioma appears as multiple, discrete nodules or arborescent, spreading growths on the pleural surface (Fig. 9-121). Microscopically, either the mesothelial covering cells or the supporting tissue can be the predominant malignant component, so the neoplasm can microscopically resemble a carcinoma or a sarcoma. Although considered malignant, mesotheliomas rarely metastasize to distant organs.

Secondary Neoplasms of the Pleura. Secondary tumors may also spread into the visceral and parietal pleura. Thymomas are rare neoplasms that grow in the cranial mediastinum of adult or aged dogs, cats, pigs, cattle, and sheep. Thymomas are composed of thymic epithelium and lymphocytes (see Chapter 13).

Aging Changes of the Respiratory Tract

Old age, both in human beings and in animals, is known to be a risk factor for pulmonary infections, but the precise mechanisms involved in this increased susceptibility are still under investigation. Some studies have shown that in aged individuals the antibacterial properties provided by surfactant proteins, proinflammatory cytokines, and complement are altered.

Pulmonary hyperinflation (often referred to as senile emphysema) has been reported as an age-related change in human and canine lungs. Other age-related changes described in canine lungs include mineralization of bronchial cartilage, pleural and alveolar

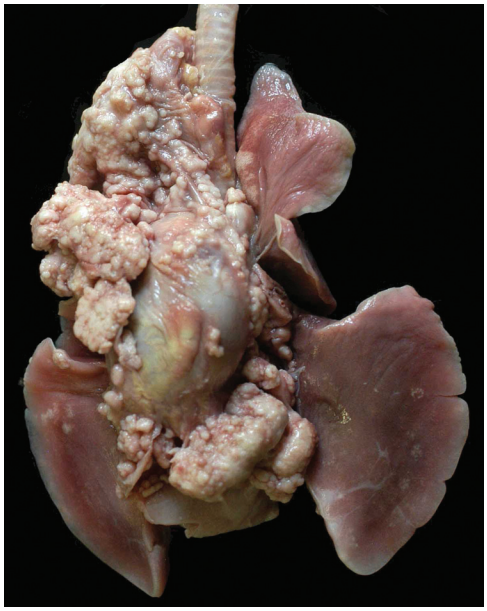


Figure 9-121 Mesothelioma, Lungs and Heart, Cat. The tumor (*top left*) has proliferated and extended over the ventral parietal pleurae and pericardium. The pericardial sac was subsequently opened (not shown here), and the epicardium appeared normal, indicating that the tumor, although on the pericardium, had not invaded the pericardial sac to involve the epicardium. (Courtesy Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México.)

fibrosis, and heterotopic bone formation (so-called "pulmonary osteomas").

Acknowledgments

We thank all pathologists at the Atlantic Veterinary College, University of Prince Edward Island for providing case material.

Suggested Readings

Suggested Readings are available at www.expertconsult.com.

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