CHAPTER TWO

The Respiratory System

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INTRODUCTION

The authors realize that complete coverage of all the diseases that affect the respiratory system is practically impossible within the limitations of one chapter, or even an entire volume. Therefore, we have attempted to include all the primary diseases, as well as the normal structure and function of the respiratory system, while avoiding overlapping description of conditions that predominantly involve other organs or systems.

NORMAL ANATOMY, HISTOLOGY, AND ULTRASTRUCTURE

Gross Anatomy

Recognition and understanding of the normal structure and function of an organ is essential to the interpretation of abnormalities in that organ. Although the function of gaseous exchange is identical in all species described here, there is considerable variation in the gross and microscopic anatomy. Space does not permit a complete discussion of the variations observed in lobar arrangement; however, Figure 2.1 illustrates lobular patterns in the more common laboratory animals. The trachea conducts inhaled and exhaled air between the larynx and bronchi.

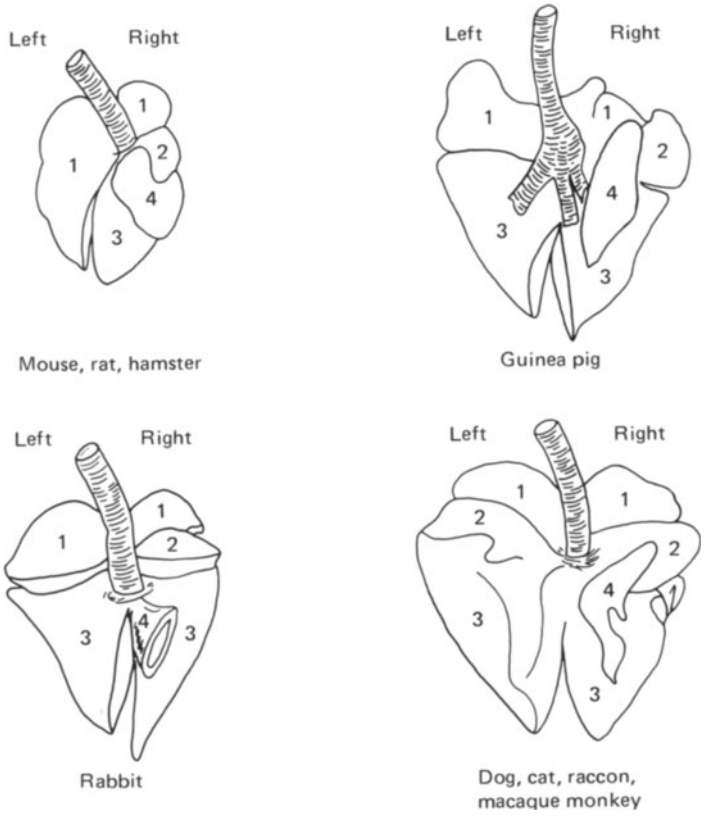


FIGURE 2.1 *Schematic depiction of the lobular arrangement of the lung of selected species. Key: 1, apical lobe; 2, cardiac lobe; 3, diaphragmatic lobe; 4, intermediate lobe.*

The primary bronchi are a continuation of the bifurcation of the trachea and undergo further branching, and a decrease in diameter, to the level of the bronchioles. The bronchioles branch into terminal bronchioles and further into respiratory bronchioles, the gateway leading into numerous alveolar ducts. The alveolar ducts lead to multiple alveolar sacs, each in its tiny compartment, the alveoli, the smallest units of the respiratory system.

Circulation of blood through the lungs is achieved through two separate systems, pulmonary and bronchial. The pulmonary artery carries venous blood directly from the right ventricle to the pulmonary parenchyma for gaseous exchange in the alveolar capillaries. Oxygenated blood is returned to the left atrium via the pulmonary vein. The pulmonary arteries branch in a manner very similar to that of the bronchial tree and are generally parallel to the bronchi and bronchioles. The bronchial arteries are derived from the aorta and carry oxygenated blood to the conducting air tubes and supporting connective tissues of the lung. The vasa vasorum of the pulmonary arteries are derived from the bronchial arteries. Precapillary anastomoses between the pulmonary and bronchial arteries are seen in man (Spencer, 1968) but have not been demonstrated in laboratory animals. The branches of the bronchial artery are tightly applied to the walls of the bronchi and bronchioles they accompany and supply. Most of the venous drainage from the lung is through the pulmonary veins, and only a small amount of blood from the hilus returns through the bronchial veins.

Lymphatic drainage from the lung is accomplished through a subpleural network, in addition to perivascular and peribronchial lymph channels. Flow of lymph from all sources in the lung is centripetal with drainage through the hilar lymph nodes. Direct lymphatic connections have been demonstrated between the lower lobes of lung and the diaphragmatic and coeliac lymph nodes in humans, providing a potential route for direct extension of pathologic processes between the thorax and abdomen. Lymphatic channels are not demonstrable in the alveolar walls.

Preservation and Fixation of Pulmonary Tissue

Intratracheal perfusion is a very useful technique for fixation of lungs for histopathologic examination. The trachea is clamped prior to opening the thoracic cavity. After removal of the lungs from the thorax, the tracheal clamp is removed, and formalin or some other fixative is introduced into the trachea under gentle pressure. Elevation of the larynx and trachea to establish gravitational flow distends the alveoli with fixative. The trachea is ligated after perfusion. The lungs of small laboratory animals can be embedded in paraffin *in toto* for sectioning and mounting with a resultant visualization of all lobes on one slide. This is best accomplished by removing the heart, esophagus, thymus, and mediastinal tissues after fixation and before embedding. Perfusion–fixation of the lung prevents postmortem collapse and allows a more accurate interpretation of pulmonary lesions.

Microscopic Anatomy

The vestibule of the nasal cavity is lined by stratified squamous epithelium, which is continuous with the external skin at the mucocutaneous junction. There is a gradual transition from stratified squamous to the typical pseudostratified, ciliated columnar epithelium, which lines the respiratory passages as far as the terminal bronchioles (Figure 2.2). Mucus-secreting goblet cells are present in varying numbers in the mucosa. Additional secretions for the nasal cavity are provided by the serous, mucus, and mixed tubuloalveolar glands of the lamina propria. Blood vessels, nerves, and occasional lymphoid nodules are embedded in the connective tissues of the nasal submucosa. The mucosa of the olfactory region of the nasal cavity is provided with specialized sensory nerve cells, the olfactory cells, with processes that lead into the olfactory nerve. The paranasal sinuses are continuous with the nasal cavity and very similar in histologic detail. In the nasopharynx, a layer of striated muscle and two layers of fascia are subjacent to a mucosal layer nearly identical to that of the nasal cavity.

The larynx is structurally modified in mammals to permit production of vocal sounds by a special arrangement of the cartilages and striated muscles that comprise the middle and outer layers. Stratified squamous epithelium is the normal lining of the vestibule, to the oral margin of the vocal cords, and care should be taken that it is not interpreted as a metaplasia when observed in the anterior portion of the larynx. The posterior lumen is lined by pseudostratified ciliated epithelium, which may have glands and lymphoid nodules in the submucosa.

The pseudostratified ciliated epithelium of the

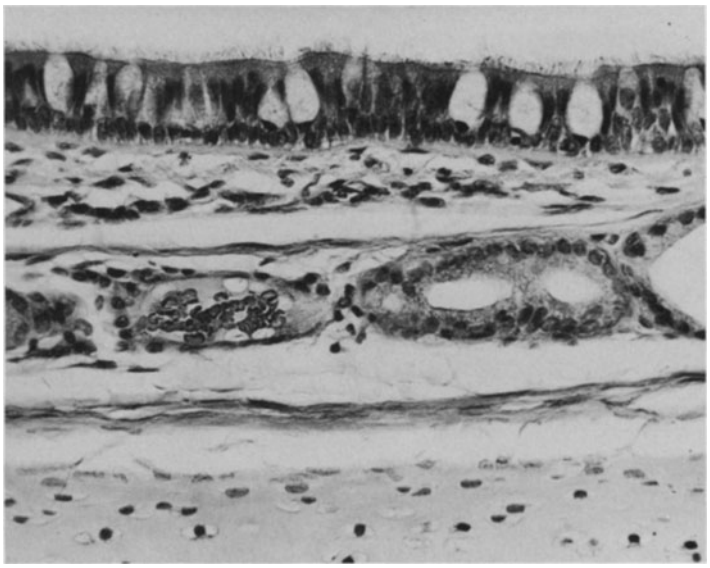


FIGURE 2.2 *Normal trachea from a rhesus monkey. The epithelium is pseudostratified, consisting of ciliated cells, goblet cells, and basal cells. Serous and mucus glands and a blood vessel are seen in the connective tissue of the submucosa. Part of a hyaline cartilage ring is seen at the bottom of the field.* H&E stain.

trachea is continuous with that of the posterior larynx and overlays a submucosa containing connective tissues, blood vessels, lymph channels, nerves, glands, and occasionally, focal or diffuse infiltrations of lymphocytes. The tracheal rings are composed of hyaline cartilage and lend structural support to the trachea. A fibroelastic membrane is closely applied to the cartilaginous rings and forms the annular tracheal ligament in the spaces between the rings. A small smooth muscle, the trachealis, is interposed dorsally between the ends of incomplete tracheal rings. Ossification of the tracheal rings is a common phenomenon in older animals.

The bronchi are similar in histologic structure to the trachea except that the cartilaginous structures are in the form of plates and gradually diminish in size and number with the successive branchings of the bronchi. There is a complete ring of smooth muscle interposed as a layer between the cartilaginous plates and the mucosa. In the rat, mouse, and hamster (Magalhaes, 1968), cartilage is absent from the walls of intrapulmonary (secondary) bronchi. Bronchial glands are inconspicuous in the dog (M. E. Miller *et al.*, 1964), and absent in rats, but very abundant in the cat.

Bronchioles are branched continuations of the bronchi with gradual but striking changes in structure as their diameter becomes narrower. At the level of the terminal bronchiole, there are no goblet cells in the normal pseudostratified, ciliated epithelium. Submucosal glands and cartilaginous plates are not seen. The epithelium is more nearly cuboidal than columnar, and the smooth muscle layer is quite thick at this level. Alveoli open directly through the walls of the respiratory bronchioles. In the distal portions of the respiratory bronchioles, the epithelium is nonciliated and the muscle layer is interrupted by the openings into the alveoli. The walls of alveolar ducts are lined by epithelium similar to that of the alveoli, a few smooth muscle bundles and fibroelastic fibers.

A variable number of alveolar sacs originate from each alveolar duct, and the alveoli, in turn, open into the alveolar sacs. Fine elastic and reticular fibers are interwoven in the walls of the alveolar sacs and alveoli. These fibers are probably important in the reduction of the size of alveolar structures during expiration. The epithelial lining of the alveoli will be described in the section on ultrastructure.

Alveolar capillaries are present within the walls of all alveoli and are similar in all species. Cardiac muscle fibers are normally present in the adventitia of pulmonary veins of rats and mice. It is important to recognize these fibers as a normal feature in these species and also to be aware of their potential pathologic significance. For example, during experimental *Trypanosoma cruzi* infections in mice, the cardiac fibers of the pulmonary veins, as well as those of the heart, may be affected.

The pleura consists of a mesothelial layer overlaying a connective tissue layer, which contains elastic fibers, blood vessels, lymph vessels, and nerves. There are smooth muscle fibers within

the pleura of the guinea pig, and considerable variation in the thickness of the pleura is seen among the species. Most of the common small laboratory animals, carnivores, and primates have a very thin pleura with lungs not separated into lobules. Man (W. S. Miller, 1947) and some of the domestic animals, including the ox and pig, have thicker pleura and septa dividing the lungs into lobules.

Ultrastructure

Over most of the upper respiratory tract, there is a surface lining of ciliated cells and goblet cells. The cilia arise from the basal corpuscle in the supranuclear cytoplasm. There are internal longitudinal filaments coursing parallel to the long axis of each cilium. Nine of the filaments are double and located peripherally in the cilia; two single filaments are central. The unit membrane of the cell continues as the covering for the cilia. The cyclic rostral motion of the cilia, in concert with the mucus layer, functions to propel small foreign objects out of the respiratory system.

Goblet cells contain a prominent Golgi apparatus that appears to be the site of mucus production and storage. During chronic irritation or infection, there is an increase in the number of goblet cells within the respiratory epithelium. Both ciliated and goblet cells are apparently derived from the basal cells that rest upon the basement membrane. Basal cells contain many tonofilaments within their cytoplasm, which are very similar to those observed in stratified squamous epithelial cells. This observation may have some relationship to the phenomenon of squamous metaplasia sometimes noted in pathologic conditions of the airways.

The epithelium gradually changes from its pseudostratified arrangement to become a distinct single layer in the bronchioles. Here, the ciliated cells are intermingled with nonciliated cells, the Clara cells, in the distal bronchioles. (Figure 2.3) Clara cells are characterized by flame-shaped cytoplasmic processes, membrane-bound secretory-type granules, basal nuclei; cilia are absent. The function of the Clara cells is unknown.

Two types of epithelial cells have been identified within the alveolar lining (Figure 2.4). The

FIGURE 2.3 *A flame-shaped Clara cell (arrow), containing electron-dense bodies, is interposed between two ciliated cells in the terminal bronchiole of a mouse.* Uranyl acetate and lead nitrate stain; ×3555. (Electron photomicrograph courtesy of Dr. J. D. White.)

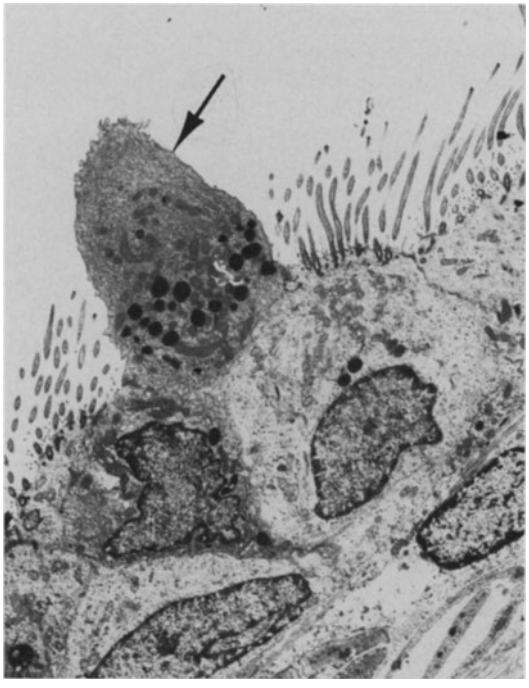
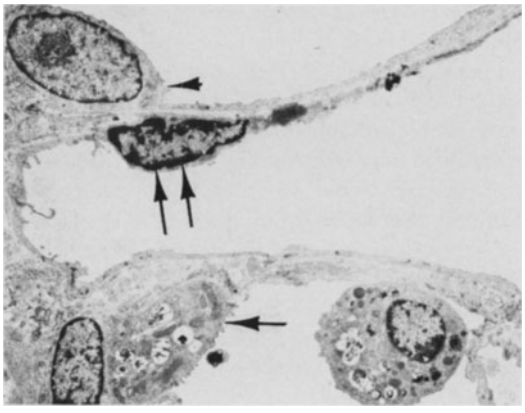


FIGURE 2.4 *This section of an alveolar septum compares a type I pneumocyte (arrowhead), with its delicate cytoplasmic processes, to a type II pneumocyte (single arrow) containing myelin figures. An endothelial cell nucleus (double arrows) lines an alveolar capillary.* Uranyl acetate and lead nitrate stain; ×3645. (Electron photomicrograph courtesy of Dr. J. D. White.)



first of these is the squamous or type I pneumocyte, which covers most of the alveolar surface of the normal lung. The cytoplasmic processes of the type I pneumocytes are extremely thin, measuring 0.1 to 0.2 μ, and, hence, are not visible with the light microscope. Granular, or type II pneumocytes, are larger than type I cells; these two types are connected by junctional complexes. Within the cytoplasm of the type II pneumocytes are lamellar bodies, which probably secrete the phospholipid surfactant found in the alveoli. Type II pneumocytes are thought to be the primary source of this surfactant, which acts to increase surface tension at the tissue–gas interface during inspiration and to decrease surface tension during expiration.

Inhaled or expired gases must traverse the cytoplasmic process of the type I pneumocytes, the epithelial basement membrane, a potential or real interstitial space, the capillary basement membrane, and the cytoplasmic process of the capillary endothelial cells for exchange to occur. An alveolar wall consists of the epithelia of two alveoli, one capillary, and the intervening basement membranes and interstitial space. The interstitial space may contain elastic or reticulin fibers, macrophages, and a few fibroblasts. The macrophages, or septal cells as they are sometimes called, are probably derived from bone marrow and can be seen within the alveolar lumina as alveolar macrophages.

VIRAL DISEASES

Giant Cell Pneumonia (Measles) in Primates

Giant cell pneumonia is a naturally occurring disease of primates. The macaques and most other species of Old World primates are highly susceptible to this disease, but laboratory outbreaks have also been reported in colonies of New World primates (Kwapien, 1972; Abee *et al.*, 1972). The New World species appear to be somewhat more resistant to the disease, but sufficient data are not now available to support this conclusion. In the experience of the authors, and as indicated in report of others (Potkay *et al.*, 1966), giant cell pneumonia occurs in rhesus monkeys within a few weeks of removal from their natural habitat, where the incidence of measles is very low. In a serologic study, it was found that nearly every monkey developed a humoral antibody titer to measles shortly after arrival from southeastern Asia (Shishido, 1966), suggesting widespread infection early in captivity. One report (Manning *et al.*, 1968), however, described onset of giant cell pneumonia in monkeys that had been in captivity over 30 days.

Giant cell pneumonia is generally regarded as being caused by the rubeola virus, one of the paramyxoviruses. This opinion is substantiated by results of experimental infection with rubeola virus, serologic findings, and histopathologic observations (Hall *et al.*, 1971). It must be recognized that other viruses, such as cytomegaloviruses and the respiratory syncytial virus, may cause giant cells to form in pulmonary epithelium and that observation of these cells is not definitive proof of rubeola virus infection.

Clinical signs, although not always obvious, consist of coughing, dyspnea, and a cutaneous maculopapular rash. In many instances, the monkey will die within 24 hours after the clinical signs are first detected.

The lungs of monkeys with giant cell pneumonia are heavier than normal, firm, moist when sectioned, and mottled gray to deep red. Occasionally, a fibrinous exudate is adherent to the visceral pleura. Pleuritis is probably related to secondary infection with *Streptococcus pneumoniae* (formerly *Diplococcus*), the most common bacterial isolate in affected animals. Hilar lymph nodes may be enlarged, soft, and moist.

Microscopically, there is metaplasia of the tracheal, bronchial, and bronchiolar epithelium to nonciliated, low columnar or flattened epithelium. Syncytial cells with up to 20 nuclei or more are often formed in the airway epithelium. Brightly eosinophilic intranuclear and cytoplasmic inclusions are present in these syncytial cells. Within the pulmonary parenchyma there is a tendency for peribronchiolar localization, although involvement may be diffuse in severe cases. The alveolar epithelial cells undergo hyper-

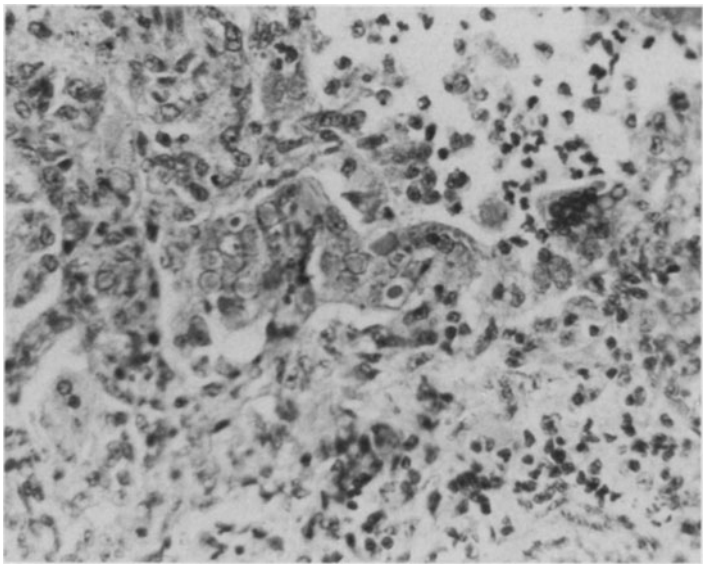


FIGURE 2.5 *Giant cell pneumonia in a rhesus monkey. The large multinucleate syncytial epithelial cell contains numerous nuclear and cytoplasmic inclusions.* H&E stain.

trophy and hyperplasia to form syncytia with inclusions similar to those observed in the trachea and bronchi (Figure 2.5). Inclusions may also be observed in single epithelial cells. In uncomplicated cases, there is infiltration of the interstitium by moderate numbers of mononuclear cells. But, if secondary bacterial infection by *S. pneumoniae* occurs, the exudate is copious. Large, dense pools of neutrophils will be seen in the bronchioles and alveoli, and aggregations of fibrin may fill some alveoli.

Giant cells of lymphoid type (Warthin–Finkeldey cells) and reticular, plasmacytic, or phagocytic giant cells may be observed in the hilar lymph nodes. Epithelial giant cells have been observed in nearly every part of the body including the skin, gastrointestinal tract, liver, pancreas, thyroid, and urogenital system in conjunction with giant cell pneumonia.

Canine Distemper

Any discussion of viral diseases that affect the respiratory system would be incomplete without mentioning canine distemper. This disease, caused by a paramyxovirus, can occur in members of the families Canidae (dogs, wolves, coyotes), Mustelidae (ferret, mink, skunk), Procyonidae (raccoon, lesser panda, kinkajou), and Viverridae (binturong, mongoose). Distemper can be a devastating disease in a laboratory dog colony, particularly in situations in which nonimmune animals are introduced and concentrated (Bjotvedt *et al.,* 1969). In one study (Binn *et al.,* 1970), 86 percent (37 of 43) of nonvaccinated dogs, serologically negative for canine distemper, developed neutralizing antibodies to distemper virus within 6 weeks after introduction into a colony with infected dogs, and 20 susceptible dogs in this study died during the conditioning period. These findings are further evidence of the communicability and high mortality rate associated with canine distemper and emphasize the absolute necessity for prophylactic vaccination against this disease.

In canine distemper infection, there is a biphasic temperature curve, with onset of respiratory signs in the second phase of the temperature curve. Respiratory signs, which predominate over all others in the early stages of distemper, consist of coughing, catarrhal or mucopurulent nasal exudate, and the later development of hyperkeratosis of the bare, pigmented skin of the muzzle.

Gross pathologic changes of distemper are frequently observed in the respiratory system. The nasopharyngeal mucosa is inflamed, and serous or purulent exudate is found in the nasal cavity. The tracheal mucosa may be congested and accompanied by frothy serous or mucopurulent exudate. The most common pulmonary lesions are subcrepitant, patchy yellowish purple subpleural zones and firm, gray areas along the margins of the lobes.

Discussion of the typical microscopic changes associated with distemper in the respiratory system should cover those lesions observed in uncomplicated infections. It seems doubtful, how-

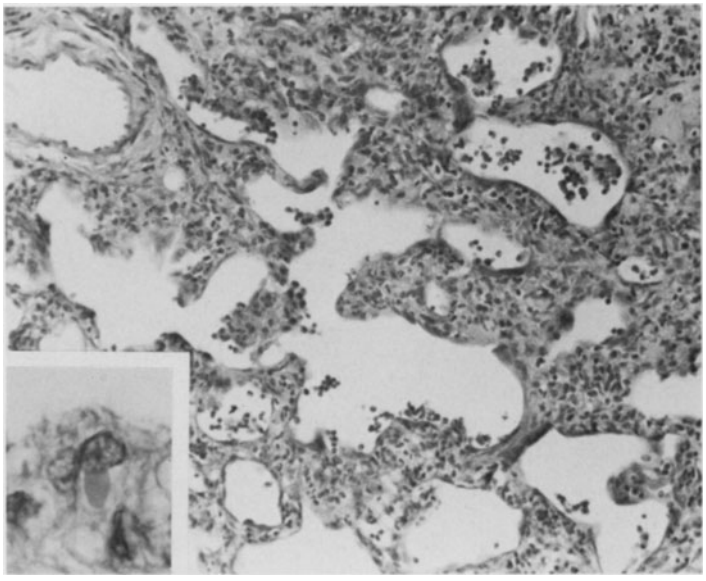


FIGURE 2.6 *Canine distemper. Subacute interstitial pneumonia in which the alveolar septa are infiltrated with neutrophils and macrophages.* The inset shows a typical eosinophilic cytoplasmic inclusion in a bronchial epithelial cell. H&E stain.

ever, that pneumonia caused solely by the distemper virus ever occurs. Pulmonary lesions were not observed during experimental canine distemper in gnotobiotic dogs (Gibson *et al.,* 1965). Despite this evidence, the occurrence of microscopic lesions in the lung following natural infection is a well-known and accepted fact. Interstitial pneumonia, with collections of macrophages in the alveolar septa, is considered to be typical of canine distemper (Figure 2.6). Multinucleate giant cells, similar to those observed in conjunction with measles in monkeys (see discussion in this chapter), are sometimes seen in bronchial and alveolar epithelium. Eosinophilic, homogeneous inclusions occur in the cytoplasm, frequently within vacuoles, and also may be seen occupying most of the nuclear space (Figure 2.6). A search for these inclusions is profitable, in most instances, in the bronchial epithelium. Recent ultrastructural studies (Richter and Moize, 1970) confirmed that the inclusions seen with the light microscope are indeed viral.

Secondary bacterial infections, especially by *Bordetella bronchiseptica,* result in purulent bronchopneumonia. Secondary infection with *Toxoplasma gondii,* a fairly frequent occurrence, results in a predominantly necrotizing process being superimposed on the interstitial pneumonia.

Although the pattern and type of microscopic changes in the respiratory system during distemper may vary, demonstration of the typical inclusion bodies provides a reliable guide for diagnosis of this disease.

Poxviruses

Among the species of concern in this text, natural infection with one or more of the relatively species-specific poxviruses occurs in rabbits, monkeys, mice (Briody, 1965) and several avian species (Cunningham, 1972; and Smith, *et al.,* 1972). In all of these species, cutaneous proliferative lesions are the hallmark of poxvirus infection. The respiratory system may be affected in avians, rabbits, and mice during pox infections. In avian pox, slightly elevated, white nodules may form on the mucosa of the nasal sinuses and pharynx with resultant respiratory signs and distress. Multifocal necrotic lesions may be present in the lung during mousepox (infectious ectromelia) and rabbit pox. The diseases produced by the poxviruses are described in another chapter.

Adenoviruses

Adenoviruses have been associated with respiratory diseases in primates, dogs, mice, and a few avian species. The SV17 strain of adenovirus was isolated from patas monkeys with pharyngoconjunctival involvement and fever; several strains were isolated during and after an outbreak of conjunctivitis and pneumonia in rhesus monkeys; and C_1 serotype was isolated from a chimpanzee following a mild upper respiratory tract infection (Cabasso and Wilner, 1969). Adenovirus strain SV340 has been implicated as

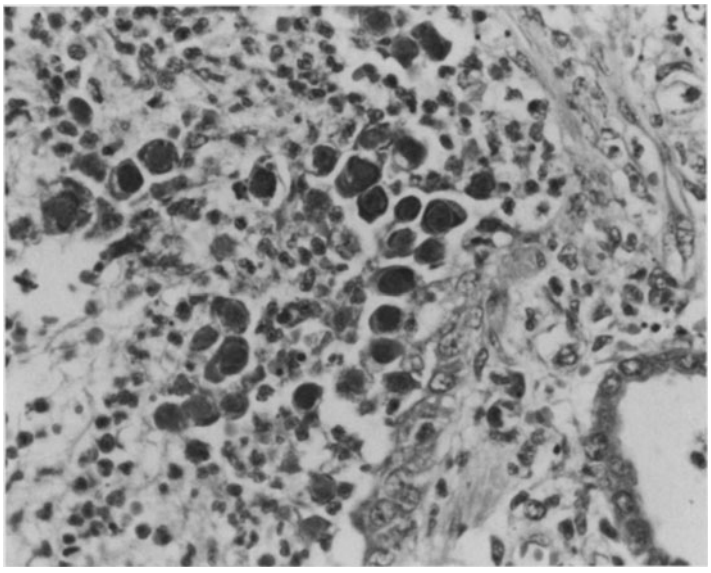


FIGURE 2.7 *Adenovirus infection in the lung of a dog. Numerous detached bronchiolar epithelial cells contain deeply basophilic inclusions that fill the nucleus.* H&E stain.

the cause of pneumoenteritis in six newborn baboons, three of which died (Eugster *et al.,* 1969). Infectious canine hepatitis virus and another adenovirus, Toronto A26/61, are known to be capable of producing respiratory disease in dogs under natural and experimental conditions (Ditchfield *et al.,* 1962; Binn *et al.,* 1970; Swango *et al.,* 1970; Wright *et al.,* 1971). Of interest was the concurrent observation of inclusions typical of adenovirus and canine distemper in tissues of two young dogs subsequently dying of respiratory disease (Figure 2.7) (Stookey *et al.,* 1972). An adenovirus reportedly has caused fatal pneumonia in nursing mice (Hartley and Rowe, 1960).

From our limited present knowledge of adenovirus infections, fatal disease appears to occur at a disproportionately high incidence in newborn and young animals. It is not known whether this is a reflection of the relative immunologic incompetence of this age group, as is apparently the case with fatal adenovirus infections in young horses of the Arabian breed (McGuire and Poppy, 1973).

Quail bronchitis virus causes respiratory disease and significant loss by death in quail, and rarely, in chickens (Cabasso and Wilner, 1969). In quail or chickens infected with this virus, there is a serous to mucoid exudate in the sinuses of the head, and lymphocytic infiltrates are present in the trachea and lungs.

Plum red or gray areas of consolidation are distributed over the edges of the cardiac and apical lobes and the dorsal aspects of the diaphragmatic lobes of dogs with adenovirus pneumonia. These dogs may also have hyperemic enlargement of the tonsils, as well as the retropharyngeal and bronchomediastinal lymph nodes. Microscopically, there is swelling and vacuolation of the bronchiolar epithelium with subsequent epithelial necrosis, bronchiolar occlusion by necrotic debris, and alveolar collapse. Later in the course of adenovirus infection in dogs, the bronchiolar epithelium may be hyperplastic. Typical, basophilic, Cowdry type A nuclear inclusions may be observed in bronchiolar epithelial cells and alveolar macrophages (Figure 2.7). Focal necrosis and inclusion bodies also occur in the nasal and turbinate epithelium. In at least one group of dogs, the bronchi and trachea were not affected.

In baboons, the lungs were affected by diffuse hemorrhagic pneumonia, especially of the apical lobes. Although typical adenovirus inclusion bodies were observed in bronchial epithelium of these baboons, the interstitial infiltration of mononuclear cells differed considerably from the typical necrotizing bronchiolitis observed in dogs. It is interesting to note that baboons also had inclusion bodies in the liver, spleen, and intestine, whereas dogs with respiratory adenovirus infection do not have inclusion bodies in other organs.

A diagnosis of adenovirus infection can be confirmed by virus isolation, demonstration of neutralizing, complement-fixing, or hemagglutinating antibodies in convalescent serum or by electron microscopic examination of viral inclusions in affected tissues.

Herpesviruses

Feline Viral Rhinotracheitis

Since the isolation of a herpesvirus (Crandell and Maurer, 1958) from the respiratory system of cats, the importance of this agent in respiratory diseases of cats has been widely recognized. At the present time, feline viral rhinotracheitis is considered to be one of the most common diseases of domestic cats. The role of feline herpesvirus in this disease has been substantiated by the experimental production of disease by intranasal inoculation of germfree cats (Hoover *et al.*, 1970).

Feline rhinotracheitis is an upper respiratory system disease, manifested by a serous nasal and conjunctival exudate and moderate fever in the early stages of infection. Later there are signs of sneezing, coughing, dyspnea, anorexia, and listlessness. Frequently, ulcers develop on the dorsum and edge of the tongue. Keratitis, panophthalmitis, and corneal ulcers may develop. Although the usual course is about 2 weeks with a gradual return to health in most cases, death due to uncomplicated feline viral rhinotracheitis can occur. As may be surmised from the foregoing remarks on signs, this disease is extremely difficult to distinguish clinically from the other feline viral and bacterial respiratory diseases.

In addition to the exudate and lesions seen during clinical examination, gross lesions consist of a viscid gray–white exudate that fills the nasal cavity, hyperemia of the proximal trachea, mandibular and pharyngeal lymphadenopathy, and occasionally, small areas of atelectasis in the apical and cardiac lobes. Microscopically, there are multifocal zones of epithelial necrosis with neutrophilic infiltration in the nasal mucosa. Eosinophilic intranuclear inclusion bodies in the respiratory epithelial cells are characteristic of feline viral rhinotracheitis, often being accompanied by hydropic degeneration of the cytoplasm (Figure 2.8). Similar, although less severe, lesions may be seen in the epithelium of the tonsils, pharynx, conjunctiva, epiglottis, larynx, trachea, bronchi, and bronchioles. As the disease progresses, inclusions are no longer seen, the inflammatory infiltrate becomes predominantly mononuclear, and epithelial regeneration occurs. The turbinate bones may be resorbed and have increased numbers of osteoclasts in areas subjacent to necrotic epithelium. This last lesion is interesting when correlated with the observation that feline herpesvirus inoculated intravenously in young cats localized in osteoprogenitor cells and caused osteolytic lesions (Hoover and Griesemer, 1971).

Diagnosis may be confirmed by histologic examination, virus isolation in feline kidney cell culture, and serum neutralization test.

Canine Herpesvirus

Two separate diseases, fatal systemic herpesvirus infection in pups less than 2 weeks of age and tracheobronchitis in older dogs, have been associated with canine herpesvirus.

The clinical disease popularly known as tracheobronchitis or "kennel cough" of dogs needs

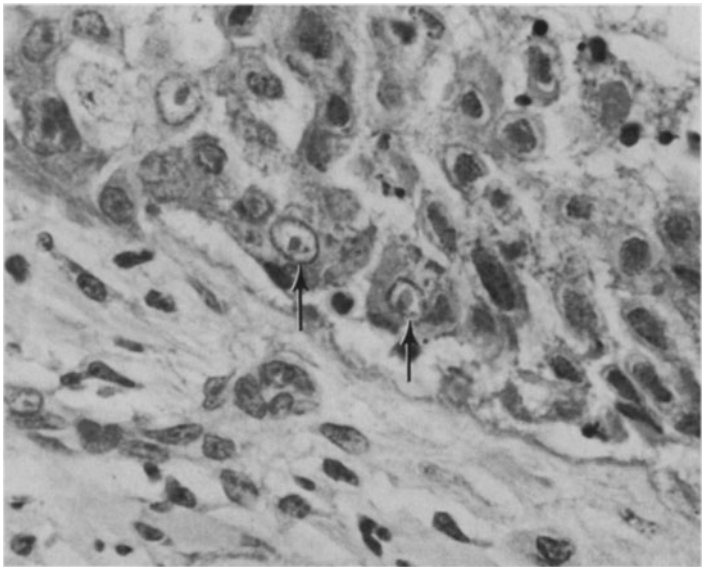


FIGURE 2.8 *Feline rhinotracheitis. Epithelial cells (arrows) containing intranuclear inclusions are present in the mucosa of the nasal cavity.* H&E stain.

little introduction to the veterinarian. In the past decade, the etiologic role of canine herpesvirus in this condition has been investigated by virus isolation, serologic techniques, and experimental infection (Karpas *et al.,* 1968; Binn *et al.,* 1970). Although herpesvirus is probably not the sole etiologic agent for tracheobronchitis, it is recognized as being capable of producing this disease. Canine herpesvirus can be isolated from the nasal cavity of clinically normal dogs, which probably serve as carriers of virus.

The clinical signs observed during infection with canine herpesvirus vary from mild bilateral serous nasal discharge to severe, paroxysmal dry cough. Frequently, the cough can be induced by gentle digital pressure applied to the trachea. Only rarely does tracheobronchitis progress to cause death in dogs over 2 weeks of age, and this outcome is probably related to secondary bacterial infection or other complications.

Most of the reported lesions of tracheobronchitis are those observed during sequential studies of dogs necropsied during experimental infections (Karpas *et al.,* 1968). During the early stages of infection, the lungs have multiple gray or red foci, and the tonsils are enlarged. Both lesions are absent in dogs killed 20 days after intranasal inoculation. Microscopically, the most consistent feature of tracheobronchitis is the presence of eosinophilic intranuclear inclusions in respiratory epithelial cells of the nares, trachea, bronchi, and bronchioles. A few foci of necrosis may be present in bronchioles and adjacent alveoli.

Canine herpesvirus is firmly established as the cause of a fatal systemic disease of pups less than 2 weeks of age (Carmichael, 1970; Huxsoll and Hemelt, 1970; Cornwell and Wright, 1969). Infection may occur in utero, during passage through the birth canal, or by the intranasal route after contact with other infected dogs. The fatal disease in this age group has been attributed to the poor homeothermic control mechanism in young pups and the increased growth rate of canine herpesvirus at 33.5 to 37°C. Affected pups stop nursing, cry persistently, and usually die within 3 days of the first appearance of signs. Elevation of the body temperature of pups by increasing environmental temperature has been used as a method of preventing death in pups less than 2 weeks old (Percy *et al.,* 1971).

The lungs of pups infected with herpesvirus are swollen and moist with frothy, blood-stained fluid in the bronchi and trachea. Focal hemorrhagic or gray necrotic lesions are present throughout the lungs. Numerous hemorrhagic foci, sometimes having gray necrotic centers, are scattered through the renal cortex. Similar necrotizing or hemorrhagic lesions may be present in the intestine, gastric mucosa, liver, spleen, brain, and adrenal gland.

Focal necrosis of the alveolar walls and fibrinous exudation into the alveoli, with occasional accumulations of neutrophils and macrophages, characterize the lung lesions (Figure 2.9). Cells in and near the necrotic foci may contain eosinophilic intranuclear inclusion bodies. Focal necrosis is also characteristic of lesions of canine herpesvirus infection in other organs. Pups that

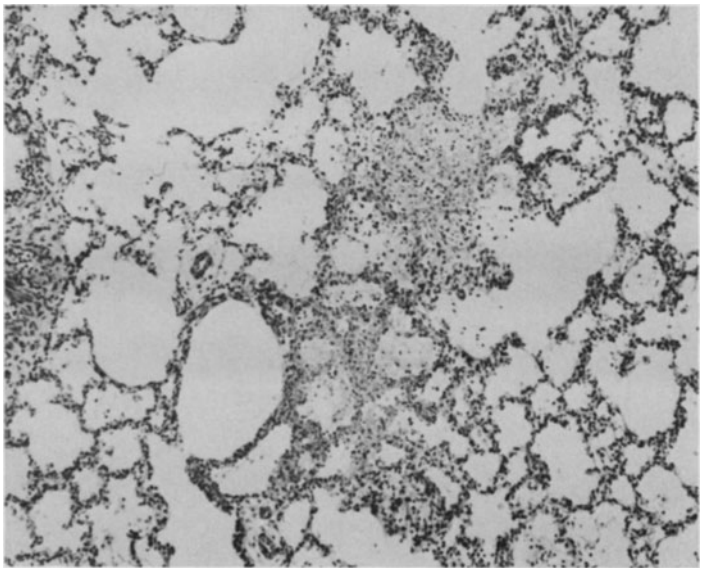


FIGURE 2.9 *Canine herpesvirus infection in the lung of a neonatal Saint Bernard pup. Two foci of coagulation necrosis are present in the pulmonary parenchyma.* H&E stain. (Case material courtesy of Dr. Robert A. Squire.)

survive systemic herpesvirus infection may have interstitial pneumonia and focal granulomatous lesions in the brain, eye, and kidney.

Diagnosis of canine herpesvirus infection can be confirmed by virus isolation, immunofluorescence techniques, or serologic detection of neutralizing antibodies.

Herpes simiae, Herpes tamarinus and *Herpes Infections of Primates*

Although it is important to mention that the respiratory system may be pathologically involved and play a role in the transmission of these herpesviruses, other organs and systems are more significantly affected. The reader is referred to Chapter 13 for a detailed description of these diseases.

Cytomegalovirus

Although there is evidence of widespread cytomegalovirus infection in various species of primates (Swack *et al.,* 1971; Minamishima *et al.,* 1971), systemic disease seems to be an uncommon occurrence. One case report of fatal disease in a gorilla suggests that cytomegalovirus was the causative agent (Tsuchiya *et al.,* 1970). In this gorilla, there was interstitial pneumonia with hypertrophied cells containing nuclear inclusions in the alveoli of the lung. Cytomegaly and inclusions were also present in hepatic parenchyma and the interstitium of the kidney. In the authors' experience, lesions of subclinical infections in primates are most often limited to cytomegaly and nuclear inclusions in renal tubules. Rarely, if ever, are these changes observed in the respiratory system. Disseminated infection, however, is known to occur in immunodeficient human beings and should be considered a potential complication in immunosuppressed primates.

The same comments seem to be true for the guinea pig in which cytomegalovirus infection of the salivary gland is ubiquitous. Spontaneous disseminated infection is almost unknown in the guinea pig.

Feline Picornavirus

Feline picornavirus is recognized as a significant respiratory pathogen of cats (Kahn and Walton, 1971). The name "picornavirus" is derived from the morphologic and biochemical characteristics of this virus; it means "small RNA virus." Infection with feline picornavirus has been reported to occur at the highest incidence in cat colonies, for example, in laboratories. Following recovery from infection, cats may carry the virus in their nasal and pharyngeal mucosa and thus serve as carriers for several weeks. Nonimmune cats become infected upon contact with carriers and perpetuate the infection in a colony. Weanling cats, 4 to 8 weeks of age, frequently have apparent respiratory disease when the infection is enzootic. Mortality is highest in these young cats.

Clinical signs associated with infection are quite similar to those of feline rhinotracheitis, described elsewhere in this chapter. Fever, conjunctivitis, lacrimation, photophobia, mucopurulent nasal discharge, sneezing, and coughing are common signs. Ulcers may develop in the tongue or palatine mucosa. Should the nares become obstructed by exudate or pneumonia develop, dyspnea and mouth breathing will be observed.

In addition to mucopurulent rhinitis and conjunctivitis, ulcerative stomatitis and pneumonia are typical lesions of feline picornavirus infection. Pneumonic involvement is seen as dark red areas of consolidation, often in the ventral portions of the lobes of the lung. The characteristic microscopic lesion of infection is interstitial pneumonia. Presence of pneumonia helps differentiate feline picornavirus infection from feline rhinotracheitis, pneumonia seldom being associated with the latter disease.

A diagnosis of infection may be confirmed by serum neutralization tests or by isolation of the virus in feline tissue culture, in which characteristically rapid cytopathic effects are observed (Kahn and Gillespie, 1970).

Reovirus Infection

Reoviruses (respiratory enteric orphan viruses), formerly included with the ECHO viruses, have been isolated from many mammalian species (Rosen, 1968). Their exact role in etiology of disease is somewhat uncertain. But, one reovirus isolate from a cat induced lacrimation, photophobia, gingivitis, and depression in two other cats inoculated orally and intravenously. Similar signs were observed in another group of cats allowed contact with those inoculated experimentally (Scott *et al.,* 1970). Serum neutralization tests have revealed antibodies against reovirus in the general feline population. Although this infection in cats may resemble other viral infections, reovirus infections can be differentiated by their extremely mild course and tendency to be limited to the conjunctiva. There are very few respiratory signs even though the virus replicates

in the respiratory tract. Fatal respiratory disease and postmortem lesions in cats attributable to reovirus have not been reported.

Reovirus, type 1, has been isolated from a dog with fatal pneumonia (Lou and Wenner, 1963). The lungs had numerous red subcrepitant foci measuring up to 20 mm in diameter. Under microscopic examination, there was a subacute interstitial pneumonia. Dogs have also been reported to be susceptible to experimental respiratory infection with bovine reovirus (Thompson *et al.,* 1970).

Antibody to reovirus, type 3, was discovered in sera from a wide variety of Old and New World primates (Kalter and Herberling, 1971). Antibody to reovirus types 1 and 2 were also detected, but the incidence was much lower than that for antibody to type 3. A reovirus, isolated from chimpanzees during a spontaneous outbreak of rhinitis, produced rhinitis when instilled in the nasal cavity of other chimpanzees (Sabin, 1959).

Spontaneous disease and experimental infection with reovirus in mice have been reported, but lesions in other organs and systems are much more severe than those in the respiratory system.

Feline Pneumonitis

The causative agent of feline pneumonitis, *Chlamydia psittaci,* has also been known as *Miyagawanella felis* and as *Chlamydia felis* (Cello, 1971). Although *C. psittaci* is not a virus, it has some of the properties of viruses, and it is included here because of the similarities of feline pneumonitis to the respiratory diseases of cats caused by viruses. Although pneumonitis was once thought to be the major respiratory disease of cats, feline viral rhinotracheitis and picornavirus infections are now considered more common.

Clinical signs of feline pneumonitis are indistinguishable from those of the other viral respiratory diseases, consisting of sneezing and coughing accompanied by mucopurulent nasal and ocular discharge. Recurrence of infection often occurs, and *C. psittaci* has been isolated from cats following recovery from clinical disease. The usual course is about 2 weeks, with recovery being the usual outcome. In the rare fatal case, catarrhal inflammatory lesions are present in the respiratory tract. In the lung, sharply demarcated gray–pink zones of consolidation are seen, most frequently in the anterior lobes. Microscopic lesions consist of atelectasis and a neutrophilic and mononuclear exudate within the bronchi, bronchioles, and alveoli. Such special stains as Giemsa or Macchiavellos can be used to demonstrate elementary bodies of *C. psittaci* in epithelial cells or leukocytes in tissue sections. Elementary bodies are much more easily demonstrated in impression smears of infected tissues.

Suspect materials can be inoculated into the yolk sac of embryonated chicken eggs for the isolation of *C. psittaci.*

A similar organism, apparently of the chlamydial group, reportedly can produce pneumonia in mice following intranasal instillation, but is not an important cause of spontaneous disease (Brennan *et al.,* 1969). This organism is also known as the mouse pneumonitis agent.

Pneumonia Virus of Mice

Pneumonia virus of mice, an unclassified virus, is evidently of low infectivity but occasionally causes acute focal and enzootic infections in colonies. There is serologic evidence of widespread infection in mouse colonies in the United States (Tennant *et al.,* 1964, 1966). Cotton rats and hamsters may also be infected with pneumonia virus of mice. This pneumonia is characterized as an interstitial pneumonia with mononuclear cell infiltrates surrounding the bronchi and pulmonary blood vessels (Horsfall and Hahn, 1940). Infection with pneumonia virus of mice can be demonstrated by hemagglutination or complement-fixation techniques and by isolation of the virus in cell culture.

Sendai Virus Infection

Sendai virus (parainfluenza 1) is present as a contaminating, latent virus in many mouse breeder colonies. It does not usually cause clinical disease. There is also evidence that rats, hamsters, and guinea pigs become infected when housed in the same buildings as infected mice. Young mice (weanlings) are more susceptible than older mice. Rapid spread of infection through a large proportion of susceptible individuals may occur in a colony of young mice. After recovery from infection, there is an apparent life-long immunity against reinfection. Clinical signs in experimentally infected rats include diminished activity, respiratory distress, rough coat, and temporary reduction of growth rate (Tyrrell and Coid, 1970). Sendai virus infection has become clinically apparent during studies of other respiratory virus infections in mice (Grunert, 1967). Although two plaque-forming units

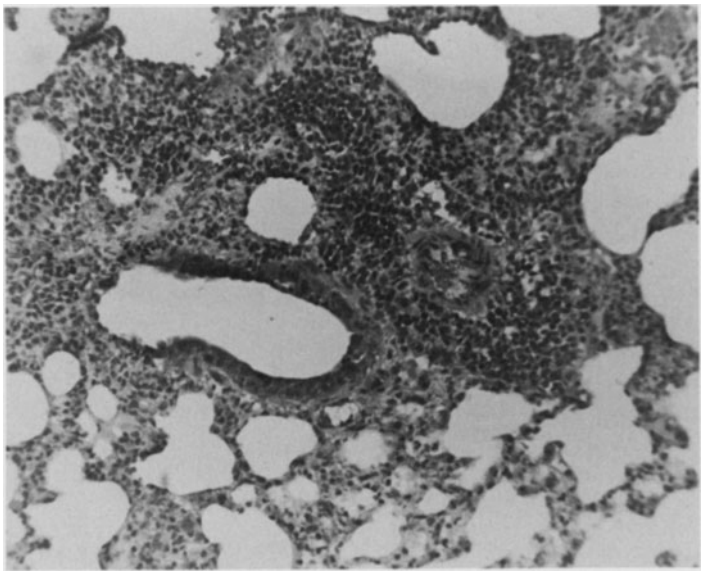


FIGURE 2.10 *Sendai virus infection in a mouse. Bronchial epithelial hyperplasia, perivascular and peribronchial lymphoid infiltration, and inflammation of the interstitium, as shown, are typical of subacute Sendai virus infection.* H&E stain.

(PFU) of virus have been shown to cause infection, considerably higher dosage (2000 to 20,000 PFU) is required to produce deaths (Van Nunen and Van der Veen, 1967).

The lungs of mice dying of Sendai infection are irregularly speckled. Loose adhesions between visceral and parietal pleura have been described (Appell *et al.,* 1971). The bronchi and bronchioles appear to be the site of initial attack; they often exhibit epithelial hyperplasia and metaplasia, with thickened epithelium having a squamous appearance (Figure 2.10). There may also be focal necrotic zones in the epithelium and cellular exudate within the lumen. Eosinophilic cytoplasmic inclusions are frequently observed in epithelial cells; whether these are viral in nature is unknown. Often the alveolar septa surrounding affected bronchioles are infiltrated by neutrophils, macrophages, and lymphocytes (Figure 2.10). Lymphoid cuffs or nodules may be seen adjacent to vessels and airways in pneumonic areas. In severe infections, a cellular infiltrate and edema fluid may be seen in the alveoli.

A diagnosis of Sendai virus infection may be confirmed by virus isolation or by using hemagglutination-inhibition, complement-fixation, or neutralization tests to detect antibody in serum.

K Virus of Mice

At the present time, K virus, a member of the papovavirus group, is not considered to be an important cause of murine pneumonia. Although K virus has been isolated from laboratory mice in the United States and from wild mice in Australia, it was not detected during one serologic survey of mouse colonies (Poiley, 1970). Experimental inoculation of K virus by a variety of routes causes pneumonia in suckling mice but not in adults. Following inoculation with K virus, the respiration of these suckling mice become labored, and they become moribund and die.

The pulmonary alveolar septa are moderately thickened by an infiltrate of lymphocytes and histiocytes. The characteristic microscopic changes are swelling and proliferation of endothelial cells in pulmonary blood vessels. The nuclei of these endothelial cells are enlarged, vacuolated, and contain Feulgen-positive inclusion bodies (Fisher and Kilham, 1953). Viral particles have been demonstrated by electron microscopy in these endothelial cell nuclei (Jordan, 1969). Hemagglutination-inhibition or complement-fixation tests are used to detect antibody to K virus and confirm infection. Intracranial inoculation of mice less than 3 days old may also be used as an effective method for detection and isolation of K virus.

Rat Coronavirus

Rat coronavirus is prevalent in colony-reared and wild rats. Inoculation of the virus causes a fatal pneumonia in newborn rats. Microscopically, there is hyperemia, widespread mononuclear cell infiltration of the alveolar septa, and focal atelectasis (Parker *et al.,* 1970).

MYCOPLASMA DISEASES

Murine Chronic Respiratory Disease —*Mycoplasma pulmonis*

This condition has been known by numerous names in the past, including chronic murine pneumonia, infectious catarrh, and gray lung pneumonia. Murine chronic respiratory disease, however, best describes the whole disease and is gaining acceptance. It is probably the most common disease of rats and mice and has been attributed to a variety of bacteria, viruses, and other factors over the years. Recent opinion and evidence implicate *Mycoplasma pulmonis* as the primary etiologic agent of murine chronic respiratory disease (Brennan *et al.*, 1969; Lindsey *et al.*, 1971, 1973; Jersey *et al.*, 1973). The reader is referred to Chapter 14 for a more complete account of the diseases caused by mycoplasmas.

Clinical signs of murine chronic respiratory disease in rats are variable, including dyspnea, rhonchal breathing, circling, snuffling, and tilting of the head. In addition to these signs, mice sometimes exhibit "chattering." At necropsy, a purulent exudate can often be found in the tympanic cavities of the middle ears and in the larger airways. Lesions in the lung range from diffuse gray–white speckling to consolidation of one or more lobes. Bronchiectasis occurs in some rats during infection and was once thought to be a separate disease, "enzootic bronchiectasis." When it does occur, yellow–white globoid elevations, each representing a bronchus dilated by purulent exudate, are seen on the pleural surfaces of the lung.

The characteristic microscopic lesions of murine chronic respiratory disease are nodular aggregations of lymphocytes in the submucosa of the airways, from the nose to the bronchioles, and perivascular lymphocytic cuffs in the lung (Figure 2.11). Frequently, the respiratory mucosa over these lymphocytic nodules is hyperplastic and may resemble stratified squamous epithelium. There may also be hyperplasia of alveolar epithelium, imparting an "adenomatoid" appearance to the lung. The tympanic cavities of the middle ear and lumina of the airways often contain pools of neutrophils.

Mycoplasma Infections of the Respiratory System of Other Species

Mycoplasmas can sometimes be isolated from the respiratory system of several species of laboratory animals, but their role in causation of disease is often questionable. Mycoplasmas have been associated with respiratory diseases in dogs and cats (Binn *et al.*, 1968; Armstrong *et al.*, 1972;

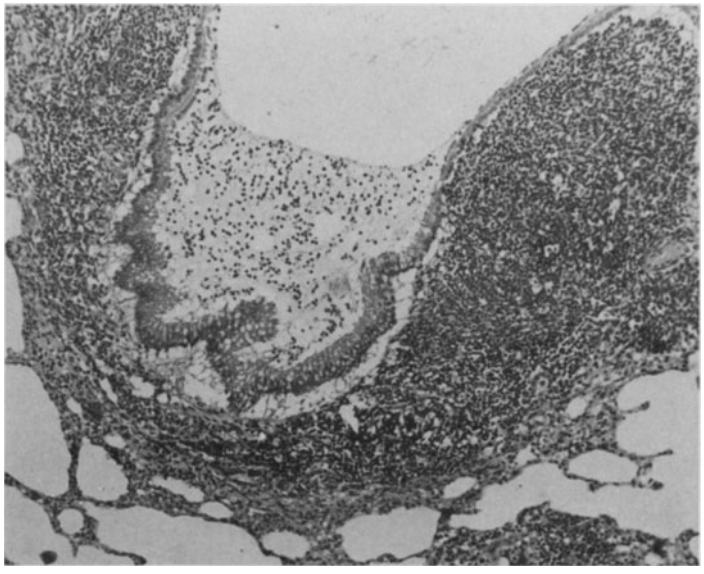


FIGURE 2.11 *Murine chronic respiratory disease in a rat. This secondary bronchus is distended by an exudate composed of neutrophils and mucus. A lymphocytic infiltrate is present in the wall of the bronchus and extends into the surrounding interstitium.* H&E stain.

Schneck, 1972). Further research is required to determine whether mycoplasmas can act as primary respiratory pathogens in laboratory species other than rats and mice (Davidson and Thomas, 1968).

Domestic and wild avians are susceptible to respiratory infection with several species of *Mycoplasma* (Yoder *et al.*, 1972). Nasal sinusitis, air sacculitis, tendosynovitis, and bursitis are some of the clinical and pathologic manifestations of infection in avians. Lymphocytic infiltrations and nodules in the submucosa of the airways are among the characteristic histologic lesions of avian mycoplasmosis.

BACTERIAL DISEASES AND AGENTS

Tuberculosis

In spite of extensive programs aimed at the detection and control of tuberculosis, this disease continues to be a serious one in captive primates. Although tuberculosis occurs more frequently in Old World species of primates, New World species are susceptible, and spontaneous cases have been reported (Moreland, 1970). Primates contract tuberculosis by contact with infected humans or other primates (Capucci *et al.*, 1972). Consequently, the most frequently isolated strain from primates is *Mycobacterium tuberculosis* var. *hominis*. Infected primates must be considered a potential source of tuberculosis for their human handlers.

Reported signs of tuberculosis include dry cough, listlessness, anorexia, weight loss, and dyspnea. In the authors' experience, however, there have been few clinical signs suggestive of tuberculosis. Clinical diagnosis of tuberculosis is best accomplished through use of the intradermal tuberculin test. Koch's old tuberculin (KOT) or purified protein derivative may be injected intradermally to detect hypersensitivity. A major fault of the tuberculin test is the fact that shedding of *M. tuberculosis* precedes the development of hypersensitivity in infected primates (Clarke, 1968). Therefore, infected monkeys serve as a source of infection to their roommates before they can be detected. Radiologic examination can serve as an auxiliary, but much less reliable, diagnostic aid.

Pulmonary lesions of tuberculosis consist of single or multiple, circumscribed, white–yellow, firm nodules in the lung and bronchial lymph nodes. Small lesions are homogeneous on section, whereas larger lesions may have a dry, caseous, cavitated center. Similar lesions may be seen in

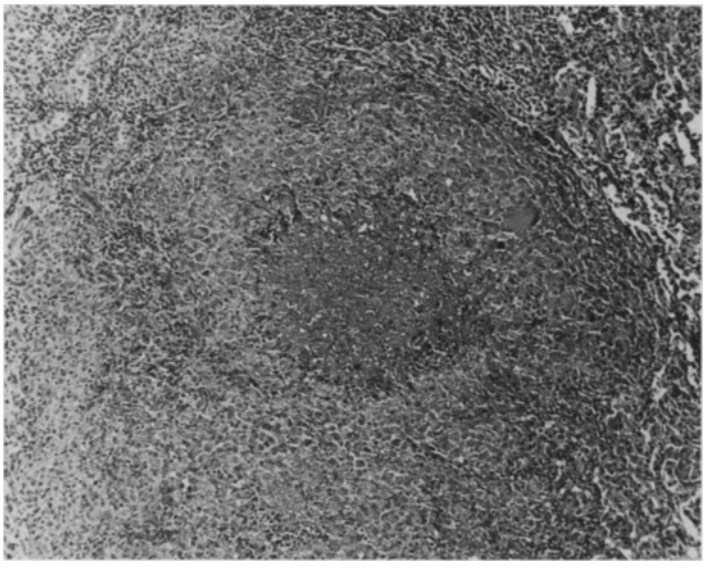


FIGURE 2.12 *Tuberculosis. This microgranuloma in the lung of a rhesus monkey consists of a central necrotic zone, a layer of epithelioid macrophages and Langhans-type giant cells, and lymphocytes located at the periphery.* H&E stain.

any other organ system in the disseminated miliary form of tuberculosis. Liquefaction is occasionally seen. Calcification of tubercles is rarely observed in Old World species but has been reported as having occurred in squirrel monkeys (*Saimiri sciureus*). Microscopically, tubercles consist of a central zone of caseation necrosis surrounded by a layer of Langhans-type giant cells and epithelioid macrophages, a zone of lymphocytes and plasma cells, and occasionally, an outer capsule of connective tissues (Figure 2.12). The Langhans-type giant cells may be few in number or completely absent in some fulminating, miliary forms of simian tuberculosis. *Mycobacterium tuberculosis* is a slender, slightly beaded, acid-fast bacillus. Tubercles from primates frequently contain very few organisms, and extensive searching is required to demonstrate bacilli during histologic examination.

In addition to intradermal tuberculin testing, radiologic examination and histologic examination, culture of *M. tuberculosis* from lesion material will help confirm the diagnosis of tuberculosis.

Other laboratory animals are susceptible to one or more strains of *M. tuberculosis*. Spontaneous tuberculosis, however, is practically unknown in other species at the present time.

Domestic cats are susceptible to the bovine strain of *M. tuberculosis;* there is also a report of infection with the avian strain (Hix *et al.,* 1961).

Tuberculosis can be a devastating disease in avians, particularly in captured wild birds. However, spread is usually enteric, and lesions in the digestive tract, liver, spleen, and bone marrow are more notable than those in the lung (Karlson, 1972).

Pneumococcal Infection

Streptococcus pneumoniae, also known as *Diplococcus pneumoniae* and *Pneumococcus pneumoniae,* is recognized as an important respiratory pathogen in primates, rats (Brennan *et al.,* 1968), and guinea pigs (Kunz and Hutton, 1971). In one survey of a large primate colony, covering ten species of nonhuman primates, *S. pneumoniae* was found to be the second most common cause of respiratory disease (Good and May, 1971). In this colony, the mortality rate was 82 percent of the clinically ill primates from which pneumococci had been isolated. Bacteriologic sampling of conventionally bred rats selected from 22 commercial suppliers revealed that 86 percent of the rats, representing 19 supply sources, were infected with *S. pneumoniae* (Weisbroth and Freimer, 1969). In the experience of the authors, *S. pneumoniae* has been the most common bacterial isolate from cases of giant cell pneumonia of primates caused by the rubeola virus.

Clinical signs of pneumococcal infection include fever, dyspnea, anorexia, and occasionally, mucopurulent nasal discharge. The clinical course is often short, and death occurs within 48 hours of onset. Recovery from one attack of the disease does not necessarily confer immunity.

The hallmark of *S. pneumoniae* is its affinity

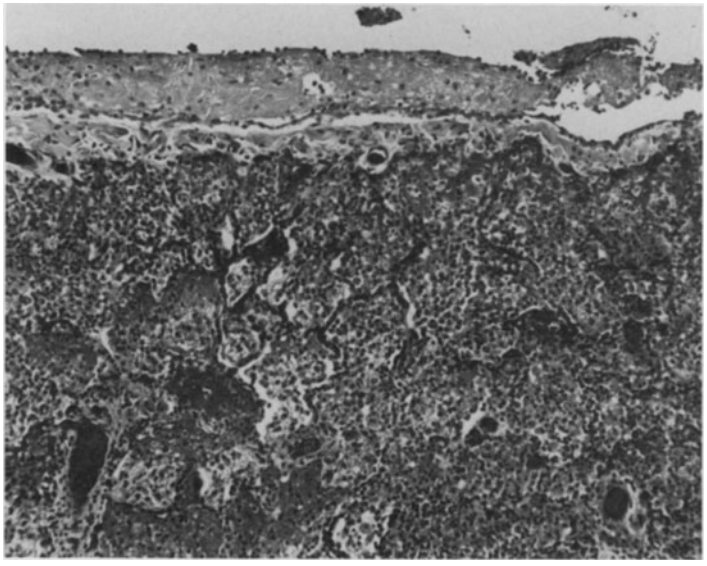


FIGURE 2.13 *Pneumococcal pneumonia (diplococcal pneumonia) in a rhesus monkey. A layer of fibrin is present on the visceral pleura, and the alveoli are filled with neutrophils and casts of fibrin.* H&E stain.

for serous membranes. Fibrinopurulent exudate is observed most frequently on the pleura and meninges and somewhat less commonly on the peritoneum. Conjunctivitis, panophthalmitis, and otitis media are present occasionally. The pattern of pneumonia is usually diffuse, involving all of one or more lobes. Microscopically, the alveoli of the lung are filled with fibrin and neutrophils. A similar exudate is often present on the pleural and peritoneal surfaces (Figure 2.13). It is not unusual to find an animal with a severe pleuritis but no inflammation of the subjacent alveolar tissue of the lung. By carefully searching the less cellular regions of exudation, one can often identify *S. pneumoniae* in tissues stained with hematoxylin and eosin. The organisms, better visualized with the usual tissue Gram stains, are seen as Gram-positive diplococci, each organism measuring 0.5 to 1.25 μ in diameter.

In addition to histopathologic examination, bacteriologic culture is used to confirm the presence of *S. pneumoniae* in tissues. There are numerous serologic subtypes that are differentiated on the basis of the Quellung reaction, but the pathogenicity of all subtypes has not been investigated.

Klebsiella pneumoniae

Klebsiella infections, most often attributed to *Klebsiella pneumoniae,* are most important in nonhuman primates (Good and May, 1971). *Klebsiella* spp. are opportunistic pathogens; it should not be surprising that they can cause disease in a variety of species including dogs, guinea pigs, mice, rats, and muskrats. (Ludford and Stevens, 1958; Kunz and Hutton, 1971; Flamm, 1957; Hartwick and Shouman, 1965; Wyand and Hayden, 1973). These organisms can be cultured from the environment, and it has been speculated that some form of "stress" is required to render the host susceptible to infection. *Klebsiella* spp. were isolated from sawdust bedding during an outbreak of acute mastitis in cows, and such bedding source should be considered a potential risk to laboratory animal colonies when unsterilized (Newman and Kowalski, 1973).

The clinical course during *Klebsiella* infection may vary from prolonged episodes of respiratory disease to a short, septicemic illness, which is often fatal (Schmidt and Butler, 1971; Snyder *et al.,* 1970).

Gross lesions consist of diffuse red–purple discoloration of the pulmonary lobes. The lungs remain uncollapsed; they are firm and may have scattered yellow-white foci throughout the parenchyma. Sometimes the lungs are rather slimy in consistency. Fibrinopurulent exudates may be present on the pleura, meninges, and peritoneum. In septicemic infections, multifocal necrotic areas may be seen in other organs, especially the liver and kidneys. Microscopically, the alveolar septa are thickened and collapsed, and the lung is congested, hemorrhagic, and edematous. Necrosis of

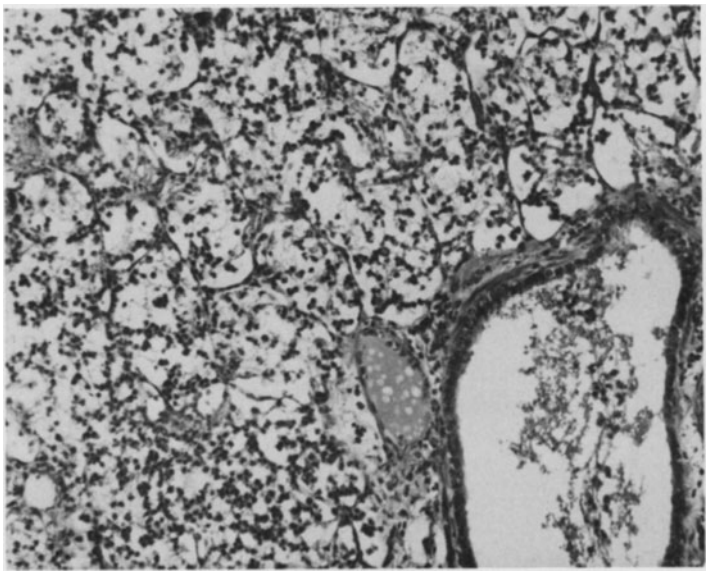


FIGURE 2.14 *Experimentally induced* Klebsiella pneumoniae *infection in a squirrel monkey. The alveolar septa are necrotic, and alveoli are flooded with a mixture of neutrophils and copious amounts of mucoid material produced by* K. pneumoniae. *Numerous bacteria were evident following application of special stains.* H&E stain.

the alveolar walls, with an abundance of neutrophils and fibrin in the alveolar spaces, is characteristic of *Klebsiella* infections (Figure 2.14). Large numbers of Gram-negative bacterial rods can often be found scattered throughout the exudate.

Diagnosis of suspected *Klebsiella* infections can be confirmed by bacteriologic culture.

Pasteurella multocida

The very small, ovoid, Gram-negative bipolar rod, *Pasteurella multocida,* is responsible for severe pneumonic and septicemic disease in a wide variety of animals including both wild and domestic mammals and birds. Its most serious incursion into laboratory animals is the familiar "snuffles" in rabbits. The term "snuffles" applies only to the mild upper respiratory infection characterized by a mucopurulent discharge from the nares and occasional conjunctivitis. The rabbit often exhibits difficulty in breathing, and the characteristic sound associated with this condition gave rise to the term "snuffles." This initial infection may be followed by dissemination of the disease throughout the respiratory system resulting in severe fibrinous pneumonia with pleuritis, subsequent septicemia, and death. In the terminal septicemic stage, the blood may be teeming with organisms. In some acute septicemic forms of this disease, death may occur rapidly with few clinical signs, and the only gross lesions may be petechiae of the heart, pericardium, and serous surfaces.

Rabbits that survive an initial infection of this disease usually fail to make a complete recovery. The organism tends to localize in the respiratory system and adjacent lymphoid tissue and produces abscesses, many of which are very large (Fox *et al.,* 1971). The organism is readily recovered from the thick creamy exudate within these abscesses if they have not been present too long. Chronic abscesses in rabbits usually prove sterile.

The virulence of *P. multocida* varies greatly with the strain. This disease has characteristically been associated with stress, crowding, poor sanitation, or bad management practices; but, highly virulent strains may cause disease outbreaks in the best-managed colony. In addition to the highly susceptible rabbit, other laboratory animals susceptible to respiratory disease caused by *P. multocida* are mice, rats, and primates (Benjamin and Lang, 1971; Good and May, 1971).

Pasteurella pneumotropica

Pasteurella pneumotropica is, as its name implies, a pneumotropic bacterium closely resembling *P. multocida* in its morphologic, cultural, and biochemical characteristics. It has been isolated from the lungs of mice, rats, guinea pigs, and hamsters. The virulence of this organism is apparently quite variable (Burek *et al.,* 1972). It has been isolated from many colonies in which outbreaks of pneumonia have occurred, and it has also been recovered from numerous apparently healthy animals and colonies. Its association with *Mycoplasma* species and chronic respiratory disease in rats and mice is well documented, but its exact role, if any, in the development of this disease remains unclear (Giddens *et al.,* 1971).

Yersinia pseudotuberculosis

The relatively large, Gram-negative coccobacillus *Yersinia pseudotuberculosis* produces a plague-like disease in rodents, primarily guinea pigs. The organism has also been recovered from infections in rabbits, dogs, cats, birds, primates, and man. The disease occurs as an acute septicemia characterized by diarrhea, weight loss, and death. The disease may often follow a more chronic course and is then characterized by diarrhea and a marked lymphadenopathy with nodular abscesses, primarily in the lymph nodes, liver, spleen, and lung. Histologically, these disseminated nodules are typical abscesses containing a core of necrotic cells and neutrophils surrounded by a zone of macrophages (Figure 2.15). If the lesion has been present long enough, a peripheral zone of fibrosis may be present but giant cells are absent. Gram-negative bacteria can usually be demonstrated in the necrotic debris of the abscesses. A definitive diagnosis of pseudotuberculosis depends upon the isolation and identification of the specific organism.

Corynebacterium kutscheri

Corynebacterium kutscheri, a Gram-positive diphtheroid bacterium, has been isolated from outbreaks of fatal disease in both rat (Giddens *et al.,* 1968) and mouse colonies (Weisbroth and Scher, 1967). Morbidity and mortality are usually low in this disease, but infected animals may die within a week. Clinical signs consist of emacia-

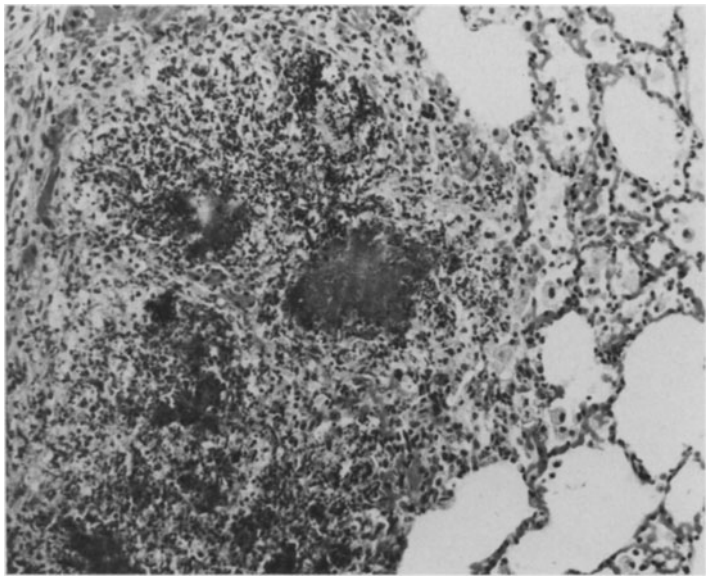


FIGURE 2.15 *Experimentally induced* Yersinia *pneumonia in a rat.* Yersinia enterocolitica *was inoculated subcutaneously 7 days earlier. Aggregations of neutrophils and macrophages surround the colonies of deeply stained bacteria.* H&E stain. (Case material courtesy of Major Charles A. Montgomery, VC, U.S. Army.)

tion, a rough coat, sluggishness, nasal and ocular discharge with encrustations, and arching of the back. On necropsy, the lungs are the most commonly involved organ system, although lesions may be observed in the liver, kidney, spleen, lymph nodes, and joints. Grossly, the lesions appear as small gray–yellow foci that, upon incision, may be caseous or contain a viscous liquid. Microscopically, the lesions consist of disseminated, caseopurulent foci with small, early, somewhat granulomatous lesions (Figure 2.16). Gram-positive diphtheroids, often in colonies, are usually visible in the lesions. The organism is readily cultured from affected tissues.

Staphylococcus Species

Staphylococci are of little primary importance in the respiratory system of laboratory animals. They have been reported as the etiologic agent of sinusitis and tonsillitis in some animals and as a secondary invader in pneumonias. These small

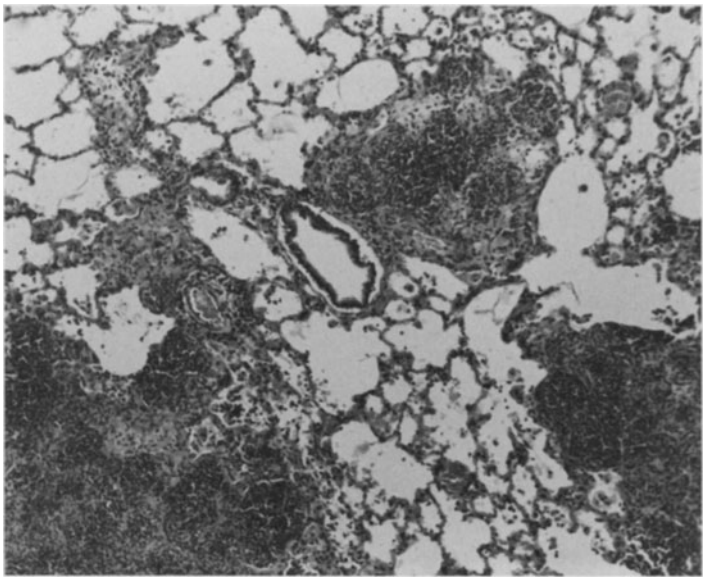


FIGURE 2.16 *Pneumonia in a rat caused by* Corynebacterium kutscheri. *Several dense focal accumulations of neutrophils are present in the pulmonary parenchyma.* H&E stain. (Case material courtesy of Dr. Russell Lindsey.)

Gram-positive cocci are more apt to be associated with suppurative skin lesions, lymph node abscesses, and occasional septicemia.

Melioidosis

Melioidosis is endemic in Southeast Asia, where *Pseudomonas pseudomallei,* the causative agent, can often be isolated from the soil and water. Most species of domestic animals, rodents, and nonhuman primates appear to be susceptible to melioidosis (Omar, 1963; Strauss *et al.,* 1969; Retnasabapathy, 1966; Stedham, 1971; Butler *et al.,* 1971; and Moe *et al.,* 1972). The usual incubation period is unknown but has been reported to be as long as 2 years in humans (Prevath and Hunt, 1957). One should, therefore, suspect that the same situation might prevail in Asian-born primates shipped to other parts of the world. Because so little is known of the transmission of melioidosis, one should handle suspected cases as having a zoonotic potential. Wound contamination and ingestion are the most likely routes of infection.

The clinical course of melioidosis may be acute and fulminant or chronic. In dogs, even the fatal cases tend to run a fairly long course. Clinical signs include fever, dyspnea, and in the case of primates and dogs, dermal abscesses. Palpable enlargement of the testicles is a common finding in dogs.

Gross lesions of melioidosis in the lung consist of focal lesions, each measuring up to 3 cm in diameter, scattered throughout the various lobes (Figure 2.17). A fairly characteristic feature of melioidosis is the presence of a narrow red halo around each focal lesion. Congestion, edema, and bronchopneumonia may also be present. The liver, spleen, kidneys, central nervous system, lymph nodes, testicles, and epididymis may contain focal lesions similar to those seen in the lung.

FIGURE 2.17 *Melioidosis in a dog. Two focal purulent lesions, each with central necrotic zones, are present in the lung.* (AFIP photograph #74–114–05.) (Courtesy of Lt. Colonel Michael A. Stedham, VC, U.S. Army.)

Microscopically, focal lesions have a central zone of necrosis with intense neutrophilic infiltration and an outer rim of hemorrhage (Figure 2.18). Nonspecific microscopic changes in the lungs include alveolar edema and septal infiltration by a mixed cell population.

Pseudomonas pseudomallei can often be cultured from the blood or dermal abscesses during the clinical phase of melioidosis and from internal organs at necropsy. The indirect-hemagglutination or complement-fixation tests can be used for serologic diagnosis of melioidosis (Alexander *et al.,* 1970). Serum antibody titers appear to rise quite early in the recognizable clinical course of melioidosis in dogs.

Bordetella bronchiseptica

Bordetella bronchiseptica, formerly *Brucella bronchisepticus,* has been incriminated in many respiratory disease outbreaks in laboratory animal colonies, particularly bronchopneumonias. It has been isolated from a variety of laboratory animals including rats, guinea pigs, rabbits, primates, dogs, and cats. The organism is not only a cause of primary respiratory disease but is an important secondary invader in viral disease. It is a short, slender, Gram-negative, motile rod, about 2 μ long. Good colony management and quality laboratory animals are still the best preventive but, where the disease is persistent, bacterin has proved useful.

Mycobacterium lepraemurium

Murine leprosy is a spontaneous disease of both rats and mice produced by the Gram-positive, decidedly acid-fast bacillus *Mycobacterium lepraemurium.* This organism is a slender, curved rod, 3 to 5 μ long and often appears in beaded or finely granular forms. The lesions are similar to those of human leprosy with affected tissues heavily infiltrated with large, foamy, phagocytic reticuloendothelial cells literally stuffed with numerous acid-fast bacilli. The skin, subcutis, regional lymph node, and most visceral organs, including the lungs, may be involved. The authors have observed several aged breeder mice with pulmonary lesions that contained acid-fast bacilli. These lesions were confined to the lung, were multifocal, and contained large foamy

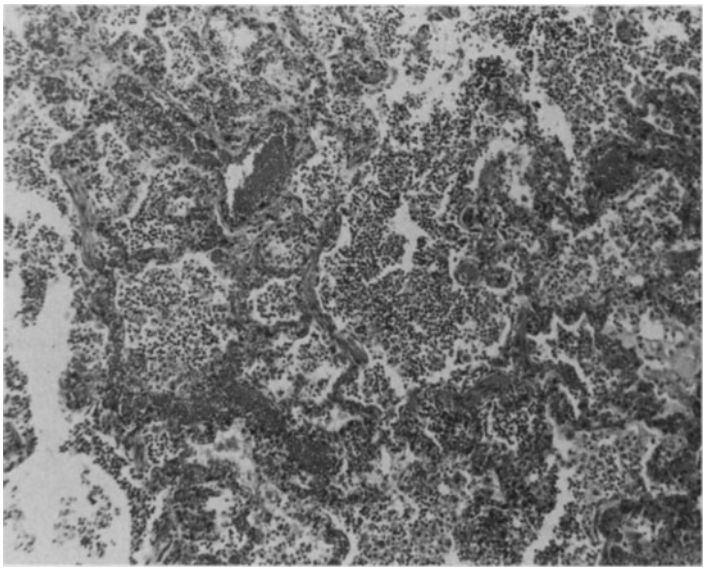


FIGURE 2.18 *Melioidosis in a dog. The alveoli are flooded with neutrophils. Small vessels and alveolar capillaries are congested, with a few hemorrhages at the periphery of the lesion.* H&E stain. (Case material courtesy of Lt. Colonel Michael A. Stedham, VC, U.S. Army.)

macrophages, lymphocytes, and plasma cells. Acid-fast, Gram-positive, slightly beaded bacterial rods were present within macrophages. A tentative diagnosis of pulmonary murine leprosy was rendered, although confirmation was not obtained because only fixed tissue was available.

Streptobacillus moniliformis

Streptobacillus moniliformis is an aerobic, Gram-negative, pleomorphic bacillus that is a normal inhabitant of the upper respiratory tract of both wild and laboratory rats. Although it is apparently nonpathogenic for rats, it has been reported to cause a highly fatal generalized pyogenic infection in mice (Brennan *et al.*, 1969). This is but another reason for keeping rat and mice colonies segregated. *Streptobacillus moniliformis* appears to play no role in the pathogenesis of murine chronic respiratory disease. In addition to the generalized infection in mice, this organism is occasionally incriminated in cases of arthritis.

For general references for bacterial diseases of the respiratory system see Bruner and Gillespie (1973), Davis *et al.* (1973), and Merchant and Packer (1967).

MYCOTIC DISEASES

Mycotic infection of the respiratory system of laboratory animals is rare in well-managed animal colonies, unless the colony happens to contain avian species. Mycotic infections, however, often occur in individual animals or groups of animals involved in prolonged stressful situations, such as experiments involving radiation, steroid, antibiotic or anti-inflammatory drug therapy or research, or any condition that may alter the basic immunologic competence of the animal.

The two mycotic organisms most commonly encountered in these types of situations are *Aspergillus* and *Candida* spp. Candidiasis occurs primarily in the upper respiratory tree, especially the pharynx, whereas aspergillosis occurs in the lungs. Avian species are particularly susceptible to certain types of mycotic infection, especially with *Aspergillus fumigatus*. Aspergillosis can become a serious, disseminated respiratory infection in an avian colony, and it is one of the few mycotic diseases for which animal to animal transmission has been confirmed.

If the avian species is excluded, the dog is the most likely laboratory animal in which the more common systemic mycoses can be encountered. This applies only to those canines that

are acquired from various animal dealers and generally referred to as "pound dogs." Because of the varied backgrounds, crowded holding conditions, and stress of transportation, these dogs occasionally run the gamut of mycotic respiratory infections. Higher bacteria and mycotic agents isolated from the respiratory system of dogs include *Actinomyces bovis, Nocardia asteroides, Aspergillus fumigatus, Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis,* and *Cryptococcus neoformans.*

The domestic cat is probably second to the dog in reported cases of systemic mycoses of the respiratory system. The same statements concerning the "pound dog" apply to the "pound cat." Both dogs and cats bred specifically as laboratory animals are seldom involved in cases of mycotic infection.

Laboratory primates have become spontaneously infected with a variety of higher bacteria and mycotic agents. The literature contains reports of actinomycosis, nocardiosis, aspergillosis, coccidioidomycosis, histoplasmosis, and cryptococcosis of the respiratory system of a variety of primate species. Again these diseases are rare, but they continue to be reported.

Geotrichum candidum in the Dog

A rare systemic mycosis, *Geotrichum candidum,* has been reported only in the dog (Lincoln and Adcock, 1968). The authors have encountered three individual infections with this organism in the respiratory system of dogs from widely separated geographic areas of the United States. One was from the Pacific northwest, one from the desert southwest, and one from the east. As with the majority of systemic mycotic infections, the diagnosis in all three of these cases was based on the morphology and staining characteristics of individual organisms in tissue sections. The only way a positive diagnosis can be obtained in mycotic infections is to culture the organism. Unfortunately, more often than not, the first time a mycotic infection of the respiratory system is suspected is when the organisms are observed on microsections. By then it is too late to culture them. In our three cases of geotrichosis, diagnoses were based upon the host response to the organisms and their location, morphology, and staining characteristics in formalin-fixed tissues. On hematoxylin and eosin stained sections, the *Geotrichum* species have many characteristics that suggest an infection with *Histoplasma capsulatum.* Both organisms are small yeastlike forms in the 1 to 7 μ range and are found abundantly throughout the pneumonic lung parenchyma, usually within the cytoplasm of macrophages (Figure 2.19). The application of such special stains as Gomori's methenamine–silver technique or the PAS reaction reveal additional fungal structures; these include short mycelial elements, chains of the yeast form, and budding "pseudohyphae" (Figure 2.19). The yeast form does not contain a central body or nucleus as seen in *H. capsulatum* with the PAS

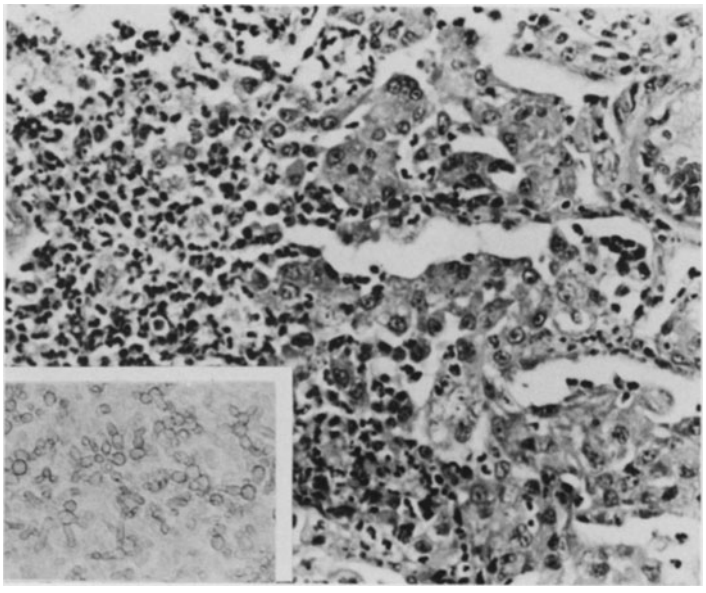


FIGURE 2.19 *Geotrichosis in a dog. The alveoli are filled with neutrophils and large macrophages containing small basophilic dots.* H&E stain. Inset is a Gomori's methenamine-silver stained section, which illustrates budding and short chain forms of *Geotrichum candidum.* GMS stain.

reaction. These variations in morphology easily differentiate the two mycoses and illustrate the value of selective additional staining in all cases of mycotic infection.

Again, it is important to repeat that systemic mycotic infections of the respiratory system are not a problem in well-managed colonies containing animals bred specifically for the research environment.

A detailed description of mycotic diseases, including respiratory involvement is presented in Chapter 4.

PROTOZOAN DISEASES

Of the variety of protozoan diseases reported, only two are of any consequence in the respiratory system of laboratory animals. They are pneumocystosis and toxoplasmosis. Although pneumocystosis is confined to the lungs of infected animals, toxoplasmosis may not only be observed in respiratory tissue but in a variety of other organ systems. Both of these diseases are discussed in greater detail in Chapter 16 of this text.

Pneumocystosis

Pneumocystosis is a pulmonary disease of the lungs of mammals in which the alveolar sacs are filled with the sporozoan parasite *Pneumocystis carinii*. The disease has been reported in a variety of animals including man, dog, rat, mouse, guinea pig, rabbit, and various nonhuman primates (Long *et al.*, 1975). Its occurrence in animals is invariably associated with a natural or induced immunologic deficiency, the use of cytotoxic agents or steroids, or a prolonged debilitating condition (Barton and Campbell, 1969) (Frenkel *et al.*, 1966). The disease does not occur in healthy immunocompetent animals, although the organisms have been recovered from apparently normal lungs.

This disease is characterized by a diffuse interstitial pneumonia with infiltration of lymphocytes and macrophages into the alveolar septa and a foamy, eosinophilic, reticular material filling the alveolar sacs (Figure 2.20). The organisms, *P. carinii,* are contained within this foamy alveolar material, but the use of special stains is required to visualize them (Figure 2.20). Gomori's methenamine-silver is the stain of choice, but various modifications of the PAS reaction are satisfactory. The organisms are quite numerous and appear in clusters. The individual organisms vary in morphology from round to ovoid to crescent shaped and range in diameter from 3 to 12 μ.

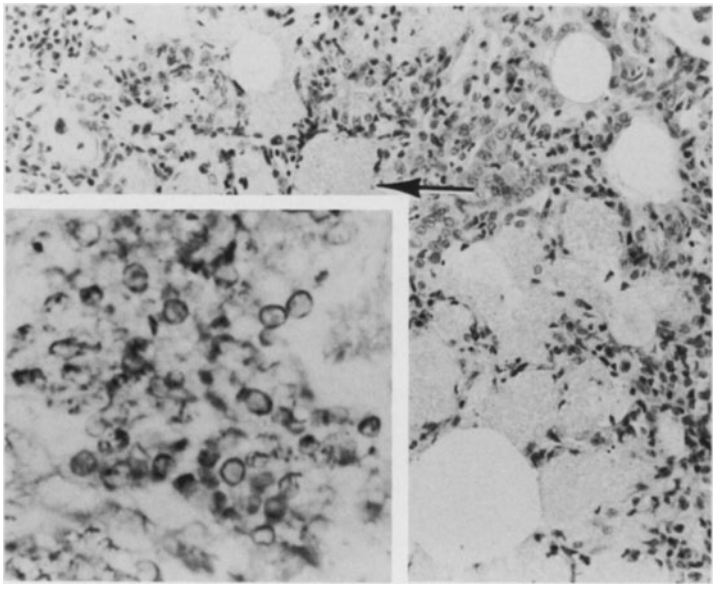


FIGURE 2.20 *Pneumocystosis in a rat. Many of the alveoli are filled with a pale, bubbly appearing material (arrow).* H&E stain. Inset shows numerous *Pneumocystis carinii* in an alveolus. GMS stain.

Toxoplasmosis

Toxoplasmosis is a universal disease affecting both mammals and birds. This coccidian parasite, *Toxoplasma gondii,* although apparently widespread in a variety of animal hosts, is seldom incriminated in clinical illness. It is the uncommon generalized or disseminated toxoplasmosis that involves the respiratory system and produces pneumonia. The authors have observed several cases of disseminated toxoplasmosis with concomitant pneumonia in both dogs and cats, but its spontaneous occurrence in the respiratory system of other laboratory animals is considered rare.

The pneumonia associated with toxoplasmosis is considered to be interstitial with the organisms arriving in the lung via lymphatics or blood vessels. In the cases we have observed, the interstitial pneumonia was nonsuppurative with numerous plump macrophages and other large reticuloendothelial cells crowding the alveolar septa (Figure 2.21). Alveolar edema was common. Numerous aggregates or clusters of the typical small, ovoid, banana-shaped organisms, with one pointed end, were both free and phagocytized throughout the lung (Figure 2.21). These nonencysted free forms, once considered to be trophozoites, are now termed tachyzoites (Frenkel, 1971; Jones, 1973). It should be remembered that pulmonary toxoplasmosis in the dog often accompanies canine distemper, the hypothesis being that canine distemper debilitates the animal and activates any latent or encysted toxoplasma organisms that may be present.

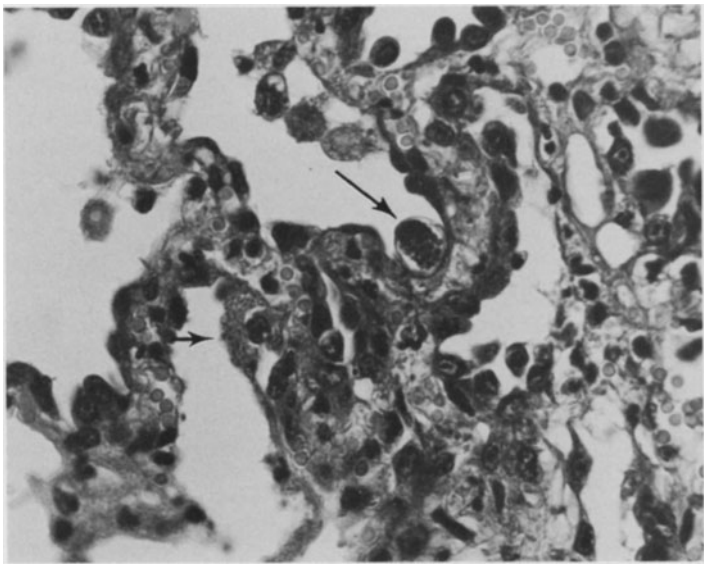


FIGURE 2.21 *A cyst of* Toxoplasma gondii *(arrow) is present in an alveolus, and nonencysted forms (arrowhead) appear to be within the cytoplasm of an alveolar macrophage in the lung of a cat.* H&E stain.

MISCELLANEOUS DISORDERS OF THE RESPIRATORY SYSTEM

Pneumoconiosis and Aspiration of Foreign Material

Animals reared in an environment in which there are significant quantities of dust in the air will inhale and retain these particles within their lungs. The general term for this condition is pneumoconiosis. More specific terms, such as silicosis, asbestosis and anthracosis, are used when the specific nature of the inhaled dust is known. Important factors influencing the effect of pneumoconiosis on the host are the particle size, chemical nature, and quantity of the material inhaled. Optimum particle size for retention in the alveoli is 0.5 to 5.0 μ, although many particles that do not fall into this range may be retained. Mucociliary action of the airway epithelium and phagocytosis by alveolar macrophages are the principal mechanisms for removal of particles from the lung. When these mechanisms fail, and the inhaled particles are sufficiently irri-

tating, an inflammatory response, which is predominantly fibrotic, occurs.

Anthracotic (soot) pigment is extremely common in the lungs of animals reared in industrial metropolitan areas. The pigment is seen as a brown or black birefringent material phagocytized by macrophages in alveolar septa (septal cells), in the peribronchiolar adventitia, and in regional lymph nodes. Seldom is there any identifiable lesion attributable to the pigment deposits. Massive quantities of anthracotic pigment have been observed by the authors in the lungs of wild skunks, presumably attributable to the behavior and habitat of this species.

Anthracotic or other inhaled environmental dusts are seldom seen in the lungs of commercially raised laboratory animals, since air filtering and air conditioning apparatus are commonly used in modern facilities.

Aspiration of gastric contents produces severe and often fatal pneumonia. Clinical observations and experimental results indicate that most of the lesions of aspiration pneumonia are produced by gastric hydrochloric acid. Other experiments suggest that highly alkaline solutions are equally damaging. Particulate aspirates, regardless of pH, are capable of inducing aspiration pneumonia, especially if the particles are of sufficient size to obstruct a bronchus or bronchiole. Aspiration of gastric contents can occur during vomition while animals are under general anesthesia or restrained in a dorsal recumbent position. It has also been observed as a sequela to acute gastric dilation in the rhesus monkey.

Lungs with aspirated gastric contents have numerous yellow–brown foci surrounded by areas of hyperemia. Distribution of the lesions is a function of the position of the animal at the time of aspiration. In addition to hydrochloric acid, which causes the primary damage in the lung, many saprophytic bacteria are carried in with the particulate aspirate. These saprophytes flourish in the necrotic tissue and further complicate the course of disease.

Microscopically, large particles of aspirates are seen in conjunction with necrosis in the airways and surrounding alveoli. Proteinaceous fluid is present in the alveoli, and although there may be hemorrhage, neutrophils are seldom seen. Chains and colonies of large bacteria are present within the aspirates and necrotic parenchyma. Provided the animal survives, the necrotic foci may be resolved and replaced by a granulomatous response or progress to pulmonary abscesses.

Kaolinite Aspiration and Granulomas in Primates

Kaolin (aluminum, silicate, China clay) is widely used in antidiarrheal medicaments. When accidentally introduced into the trachea, these preparations cause a severe histiocytic reaction in the lung, and frequently, death of the animal. Firm, gray–white circumscribed lesions are present in the affected lobes, which may be collapsed or heavy, firm, and uncollapsed. Distribution of lesions is related to the position of the monkey at the time the kaolinite suspension is aspirated.

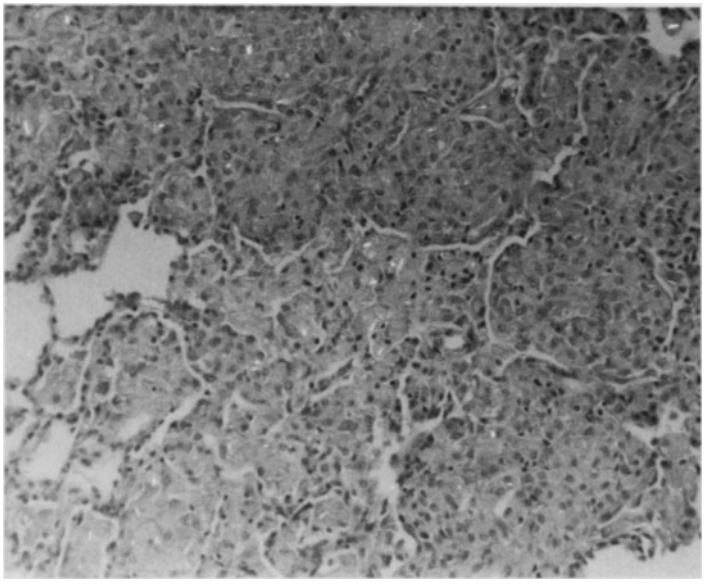


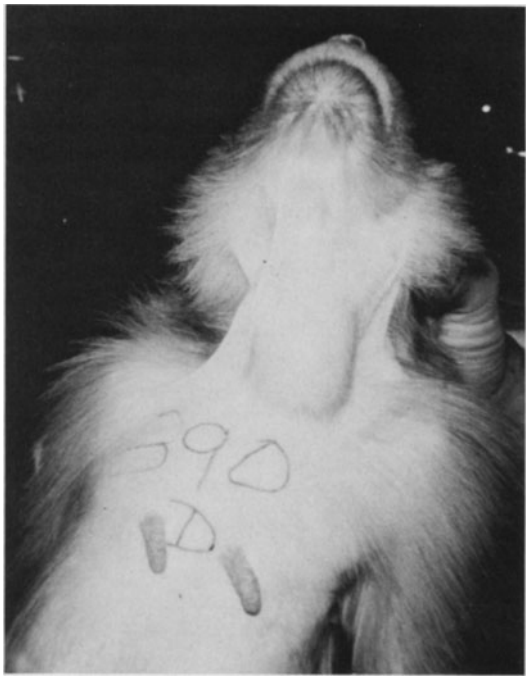
FIGURE 2.22 *Kaolinite granuloma in the lung of a rhesus monkey. Most alveoli are filled with macrophages, which contain birefringent crystals of kaolinite in their cytoplasm.* Photographed with polarizing filters partially crossed. H&E stain.

Lesions may be dispersed throughout all lobes as a result of excitement and rapid, harsh respiratory movements during treatment.

Although there is a tendency for peribronchial localization, the microscopic pattern of involvement is often fairly diffuse in the acute lesion. In the acute lesion, the alveoli are flooded with a dull eosinophilic material containing varying numbers of macrophages and neutrophils. Admixed with the exudate and phagocytized by macrophages are the characteristic kaolin crystals. These crystals are highly birefringent under polarized light and slightly refractile under reduced light (Figure 2.22). Irregular needle-shaped crystals, up to 16 μ long, are usually found. X-ray diffraction analysis of these crystals will definitively identify them as kaolinite. Histologic lesions vary considerably, since death can occur any time from a few minutes to several days following aspiration of the kaolin suspension. Death does not always follow aspiration of kaolin suspensions, and aspiration may go undetected until necropsy is performed at some later time. Granulomas are then observed as incidental findings. Diagnosis is based on identifying the birefringent crystals with a granulomatous response principally in alveolar tissue (Figure 2.22). Differential diagnoses include lung mite pigment and anthracotic pigment. These latter crystals are usually located in the peribronchiolar lymphatics, and no granulomatous response is present.

Kaolinite granulomas may be found in subcutaneous and deeper connective tissues of the neck and anterior thoracic cavity of monkeys (Figure 2.23). They are probably the result of traumatic penetration of the oral cavity or pharynx by a rigid dose cannula during administration of kaolin suspensions (Reed *et al.*, 1970). The suspension then gravitates and collects to elicit a granulomatous response. These masses occasionally are large enough to cause respiratory distress. They can be manifested as small cystic spongy masses or firm masses of various sizes. Some larger, fluctuant lesions may undergo cavitation and contain a creamy gray, nonodorous, pastelike material. Microscopic examination reveals the typical crystals and granulomatous response, occasionally with giant cells. It is important to recognize these masses as being iatrogenic in nature so that the basic cause can be eliminated.

FIGURE 2.23 *Subcutaneous cervical kaolinite granuloma in a* Macaca arctoides. (AFIP photograph #69–10461.) (Photograph from Reed (1970). Reprinted by permission of the author, Dr. R. E. Reed, and *Laboratory Animal Care,* now *Laboratory Animal Science.*)



Amyloidosis

Amyloidosis of the respiratory system is infrequently encountered, but recently, a case of localized amyloidosis of the larynx in a dog was reported (Dill *et al.*, 1972). A nodular mass that partially obstructed the laryngeal inlet consisted of masses of amyloid enmeshed in a granulomatous stroma (Figure 2.24). This form of amyloidosis has been reported occasionally in the upper respiratory system in horses but seldom in other species.

Amyloid deposits are encountered within pulmonary vessels and alveolar septa of animals affected by systemic amyloidosis, especially in certain strains of mice. As a general rule, however, amyloid is observed in the respiratory system much less frequently than in other viscera. Microscopically, amyloid is characterized by its pale eosinophilic appearance upon staining with hematoxylin and eosin, and specific staining and birefringence with Congo red, PAS reaction, metachromatic staining, and iodine reaction. The significance of amyloid deposits in tissues is uncertain. It may be observed in conjunction with chronic illness or neoplasia (secondary), or it may be without obvious associated changes (primary). Spontaneous amyloidosis has been reported in a

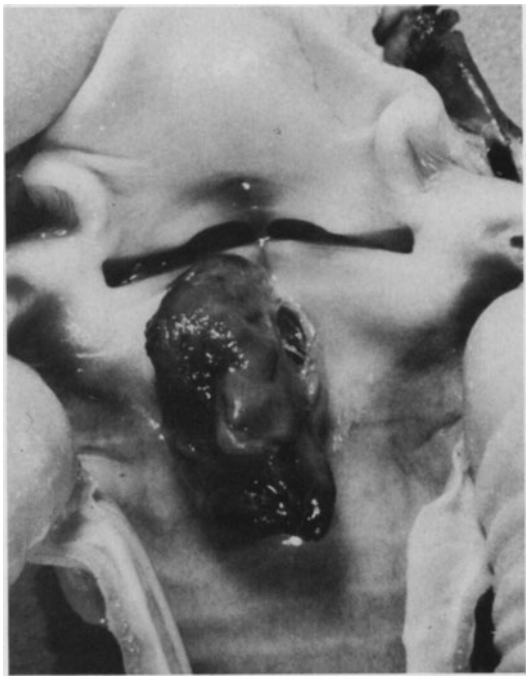


FIGURE 2.24 *Nodular amyloidosis in the larynx of a dog. The dark mass is composed of amyloid and connective tissue.* (Photograph courtesy of Major G. S. Dill, Jr., VC, U.S. Army and with permission of the publisher of the journal, *Veterinary Pathology*.)

wide variety of mammals including baboons, squirrel monkeys, rabbits, guinea pigs, Syrian golden hamsters, gerbils, mice, dogs, and cats. Amyloidosis is rarely, if ever, observed in rats or rhesus monkeys (Jakob, 1971).

Lipid Pneumonia

Lipid pneumonia is a form of aspiration pneumonia in which the foreign material is an oily substance accidentally introduced into the lung. Frequently, the oily substance is a base or component of a medicament or nutritional supplement administered orally. Aspiration into the lung may result from faulty administration of the material or depressed swallowing reflexes. The type of reaction in the lung is influenced by the amount and nature of the aspirated oil. Oils of animal origin are hydrolyzed by lipases present in the lung to liberate free fatty acids, which cause a severe inflammatory response. Chemically inert mineral oils, such as liquid paraffin, are not hydrolyzed, and limited quantities can be expectorated or removed through the lymphatics. Any residual mineral oil will produce a granulomatous, fibrotic response. Vegetable oils are emulsified and removed by expectoration with very little damage to the lung.

The gross pathologic pattern is that of a dependent pneumonia with sharply defined, darkened zones of lung, which have a fleshy consistency. Microscopically, there is a hemorrhagic bronchopneumonia, with leukocytic response, following aspiration of animal oils. With the mineral oils, there is a macrophage response within the alveoli and interstitial fibrosis. Numerous globoid clear spaces, of varying size, are seen in paraffin-embedded sections. The clear spaces represent locations of lipid droplets, which dissolve during processing of the tissues. If these same tissues are frozen, sectioned, and stained with a lipid stain, such as oil red O, the lipid droplets can be visualized. When these observations are recorded, retrospective examination of the clinical history will often reveal the cause of lipid pneumonia.

Fat Embolism

This condition is included here because of similarities to the lipid pneumonias. Fat embolism is the condition whereby particles of adipose tissue enter the circulation and eventually lodge in a vessel of appropriate size. The small arterioles and capillaries of the lung provide an excellent filter for retaining fat emboli. Trauma, as in the case of a fracture, is often implicated as the cause of liberation of these particles. Fatty degeneration of the liver, with subsequent fatty embolism, occurs in dogs and has been observed by the authors in association with pregnancy toxemia of a guinea pig. Under gross examination, the lungs of this guinea pig were diffusely reddened. Fat droplets were demonstrable within the alveolar walls, associated with a moderate macrophage response (Figure 2.25).

Pulmonary Edema

Gross or microscopic evidence of pulmonary edema is frequently encountered during postmortem examination of various laboratory animals. Although the ultimate mechanism of pulmonary edema is extravasation of plasma fluids, there are numerous preliminary causes. Among these causes are capillary pressure changes, as in

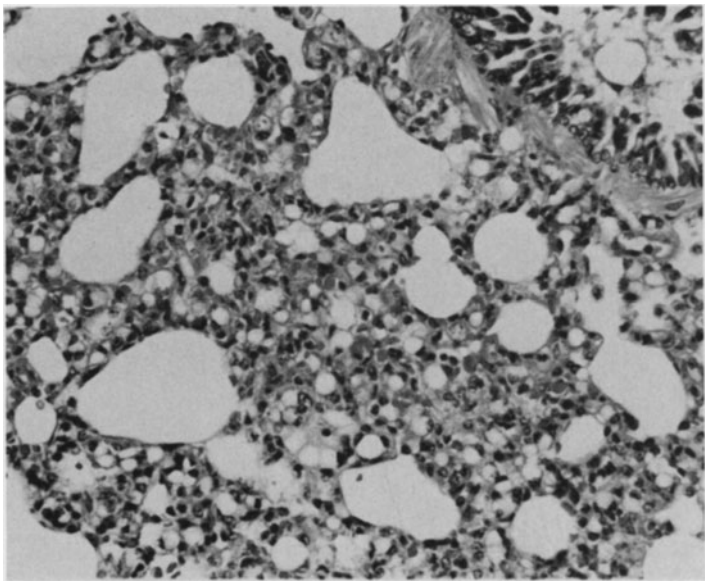


FIGURE 2.25 *Lipid pneumonia in a guinea pig. Numerous globoid vacuoles, each representing a fat droplet, are present in the interstitium. There is a moderate histiocytic response.* H&E stain.

congestive heart failure; capillary damage by anoxia, irritating gases, alphanaphthyl thiourea, and many other irritating chemicals; and altered plasma osmotic pressure, which may be seen in transfusional edema. Lymphatic obstruction is a potential cause of pulmonary edema, although it is seldom observed in domestic animals. Adrenalin administered subcutaneously to mice causes pulmonary edema and mice so treated can be used as experimental models (Wang *et al.*, 1970).

Edematous lungs are gray–pink, voluminous to the point of occasionally bearing rib imprints, heavy, and wet when sectioned. Often the trachea contains a white or pink (blood-tinged) froth. Observations made during gross examination of the cadaver are probably more valid in substantiating a diagnosis of pulmonary edema than microscopic findings. Especially important is the weight of the lung relative to the weight of the entire cadaver.

Microscopically, the alveoli of edematous lungs are filled by eosinophilic, proteinaceous material of varying concentration, which contains trapped air bubbles. The perivascular lymphatic channels and adventitia may be distended by a similar material. These microscopic findings may be observed in rats and rabbits killed by various methods and are the result of agonal or postmortem occurrences. There are no certain criteria for confidently identifying pulmonary edema as having occurred antemortem or postmortem. But, if euthanasia is performed by a method, such as exsanguination, known to be less likely to produce edema, and necropsy is performed immediately after death, more accurate interpretation is possible.

Histiocytosis

Occasionally, accumulations of cells resembling histiocytes have been observed in the subpleural parenchyma of lungs of rats, deer mice, and wild skunks. Small, firm, brown–white nodules ranging from 1 to 3 mm, which are sometimes confluent, may be seen in the subpleura.

Microscopically, the lesions consist of alveoli distended by accumulations of foamy macrophages (Figure 2.26). The macrophages, or histiocytes, are characterized by foamy cytoplasm and a single small dark nucleus. Occasional multinucleated giant cells with cholesterol-like clefts are present. In a systematic study of these lesions in rats, the macrophages invariably contained lipid when frozen sections were stained with oil red O, sudan IV, Nile blue sulfate-saphranin, or Nile blue sulfate (Yang *et al.*, 1966). About 15 percent of the macrophages contained an iron-positive brown pigment. Many cells also contained brown granules, which were positive with Schmorl's reaction for lipofuscin and Ziehl-Neelsen's acid-fast technique but negative to PAS reaction. Mast cells can also be identified within the alveolar septa. Histiocytosis is not related to

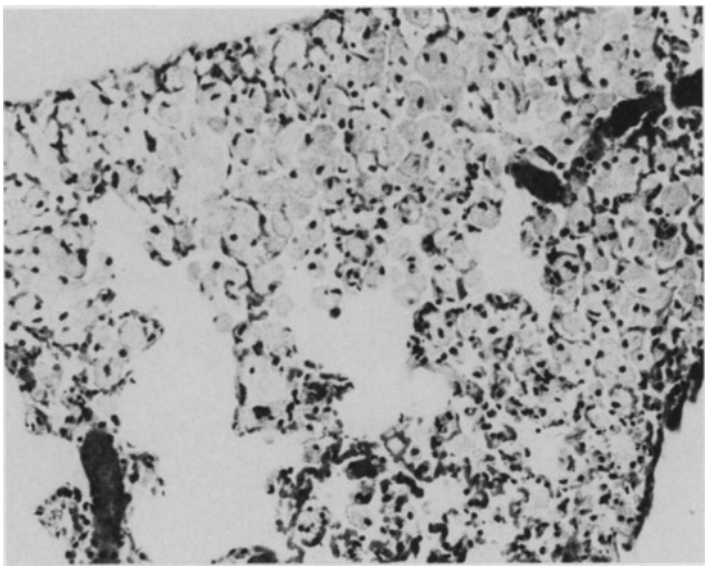


FIGURE 2.26 *Histiocytosis in the lung of a deer mouse. Large, foamy macrophages fill many of the subpleural alveoli.* H&E stain.

any specific infective agent and is seen mainly in older rodents and germfree rats. The principal significance of histiocytosis is that it be recognized as an incidental, nonspecific change in older rodents.

Hemothorax

Hemothorax, the presence of blood in the pleural cavity, is often the result of traumatic rupture of a major vessel. It may also be associated with hemorrhagic diatheses, neoplasms, or pleural tuberculosis, in which the serous effusion is contaminated by large quantities of blood. Hemothorax was observed by the authors during necropsy of young beagle dogs experimentally poisoned with a high dosage of warfarin, a commonly used rat poison. The apparent site of extravasation of blood was the thymus and mediastinum, which were extremely hemorrhagic.

Pulmonary Arterial Hypertrophy and Hyperplasia

Increased thickness of the media of the pulmonary arteries (Figure 2.27) is seen most frequently in three species: guinea pigs, rabbits, and domestic cats. Since it is debatable whether

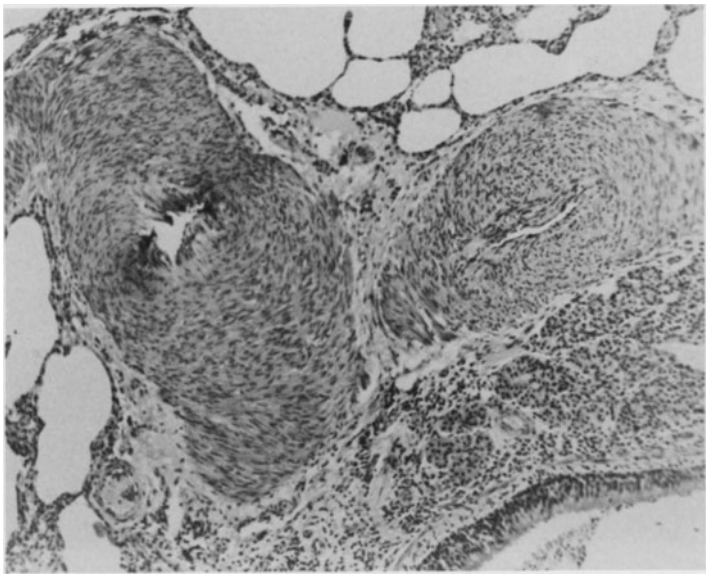


FIGURE 2.27 *Pulmonary arterial hypertrophy and hyperplasia in a cat. The tunica media of both arteries are extremely thick, due to an increase in number and size of smooth muscle cells. The abundance of bronchial glands seen in this field is normal for the cat.* H&E stain.

smooth muscle is capable of hyperplasia, the term hypertrophy may be preferred to indicate an increase in thickness, although both terms are used in the literature. In guinea pigs, medial hypertrophy is universally present in all but extremely young individuals. It is somewhat less common in rabbits but should be considered a normal variant in both species.

Pulmonary artery medial hypertrophy and hyperplasia in cats has commonly been attributed to the presence of the cat lungworm *Aelurostrongylus abstrusus,* but recent studies indicate that the condition may be seen in the absence of *A. abstrusus* (Rogers *et al.,* 1971). Additionally, it has been found that migrating larvae of *Toxocara cati* are capable of producing the condition and may be its most common cause in cats (Swerczek *et al.,* 1970).

PARASITES

Parasites of the respiratory system generally are encountered in only a small percentage of laboratory animals, and lesions related to such infections are usually minimal. Notable exceptions are "lung mites" (*Pneumonyssus simicola*) in Old World subhuman primates with incidence approaching 100 percent in some species, and medial hypertrophy of pulmonary vessels, which is encountered in a high percentage of domestic cats. The latter condition is attributed by some to the migration of larval forms of *A. abstrusus.* Recent evidence suggests that any parasitic larval migration through the lung may elicit this vascular change. In general, respiratory parasites are not a problem in well-managed colonies. Laboratory rats, hamsters, and guinea pigs are considered to be free of pulmonary parasites and only rarely are they encountered in the respiratory system of mice and rabbits.

Occasionally, parasites are observed that are not normally encountered in the respiratory tissue. An example is the presence of adult *Dirofilaria immitis,* the dog heartworm, in the pulmonary arteries of the lung. These parasites may also be encountered free in the lung parenchyma, presumably arriving there via a ruptured pulmonary artery. Another example is *Angiostrongylus vasorum,* which normally resides in the pulmonary artery and occasionally causes perivascular sclerosis and pulmonary emphysema. Migrating nematode larvae, especially those of ascarids, are also occasionally observed in the lung parenchyma of some laboratory animal species.

Space does not permit a lengthy discussion, description, and life cycle of each parasite of the respiratory system. This discussion will center around the significant parasites, their impact on affected species, and the lesions associated with their presence (Becklund, 1964; Chitwood and Lichtenfels, 1972).

Cestodes

Larval cestodes are occasionally encountered in the respiratory system of laboratory animals, principally primates. Adult cestodes are not seen in the lungs.

The larval forms most often observed in the respiratory tree are hydatid cysts caused by *Echinococcus granulosus,* cysticercus, coenurus (multiceps), and tetrathyridium.

The hydatid cyst is observed most frequently probably because the lung is one of the normal sites of development, and almost any mammal is a susceptible host. Significant histologic guidelines to the identification of *E. granulosus* cysts are the presence of numerous brood capsules that arise from the germinal epithelium lining the cyst and the diagnostic concentrically laminated, hyaline outer wall (Figure 2.28).

The cysticercus, the larval stage of *Taenia* spp., contains a single invaginated scolex. Although the lung is not the normal site of development, cysticerci are found occasionally within the respiratory system of primates, dogs, and small rodents. Histologic identification of various species is impractical or impossible due to close species similarities and variations in plane of cut.

The coenurus, the intermediate form of *Multiceps serialis* or *Multiceps cerebralis,* differs from the cysticercus in that each cyst contains multiple scolices arising from the inner wall. Like the cysticercus, it is not normally found in the respiratory tract but may be occasionally encountered there or associated with adjacent structures. These cysts are most often observed in primates and rabbits but may occur in several species of rodents.

Tetrathyridium is the larval stage of *Mesocestoides* species. It resembles the cysticercus but has a long slender body and may be confused

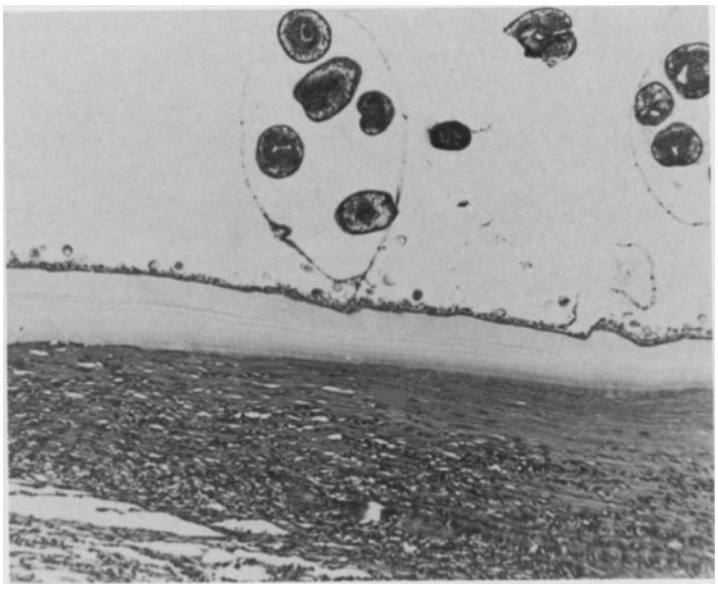


FIGURE 2.28 *Section of* Echinococcus granulosus *cyst in the lung of a rhesus monkey. The laminated outer wall, germinal layer, and brood capsules containing several scolices are characteristic of* E. granulosus. H&E stain.

with a sparganum, the larval stage of *Pseudophyllidean* cestodes. Tetrathyridium may be found free in serous cavities or encysted in various organs and have been observed in lungs of Old World primates.

In histologic preparations, larval cestodes have certain characteristics that distinguish them from other parasites. They all have a smooth cuticle, contain at least one scolex, lack a true body cavity and intestinal tract, and contain numerous small calcareous corpuscles or bodies. These calcareous bodies contain calcium. Special stains specific for calcium salts, such as Alizarin red S, demonstrate the presence of calcareous bodies within the parasite and aid in confirmation.

The severity of lesions produced by larval cestodes depend upon their numbers, size, and location. Within the respiratory system, damage is usually minimal, and the presence of larval cestodes is commonly not detected until necropsy. The rupture of *E. granulosus* cysts not only results in seeding of scolices throughout the host and establishment of numerous new hydatid cysts but is considered to cause death of primates, in some cases as a result of anaphylactic shock.

Trematodes

The only flukes normally inhabiting the respiratory system of laboratory mammals are of the Genus *Paragonimus*. The two species most commonly encountered are *Paragonimus westermanii* and *Paragonimus kellicotti,* both being very similar and virtually indistinguishable histologically. *Paragonimus westermanii,* the Oriental lung fluke, is usually found in various species of macaques for which the environment and eating habits include crustacea. *Paragonimus kellicotti* has been reported in dogs, cats, and several other mammals. Infection results from ingestion of crustacea, primarily crayfish containing infected metacercariae. The lesions produced by the two species are similar. The mature flukes, usually in pairs, are found in cysts within the lung parenchyma (Figure 2.29). These cysts are often observed at necropsy and may be elevated, raising the pleural surface of the lung. Host response to the parasites is localized but marked. Cysts are surrounded by a leukocytic infiltrate, a fibrous capsule, and an outer area of hemorrhage. Numerous, golden brown, single operculate ova from the parasites are usually scattered throughout the inflammatory exudate of this capsule (Figure 2.29). The characteristic golden brown color of all trematode ova, except those of the schistosomes, is very helpful in identifying the parasites as flukes, especially in histologic sections where only portions of ova may be present and the operculum is not in the plane of cut. Other factors that aid in the microscopic differentiation of flukes from other metazoan parasites in tissue section are the absence of a body cavity, presence and location of suckers, and hermaphroditism, the presence of both testes and ovaries in each parasite. Not all of these criteria may be present in a single microsection, however.

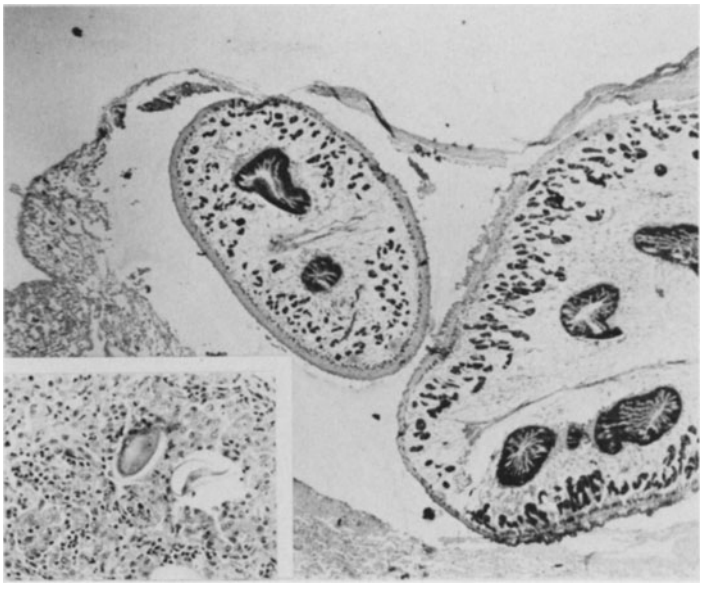


FIGURE 2.29 Paragonimus kellicotti *within a subpleural cyst in the lung of a cat.* H&E stain. Inset shows two ova of this parasite in the lung and a typical granulomatous response. H&E stain.

Schistosomiasis has been reported in primates. Although schistosomes are not normally found in the lung, the presence of large numbers of their ova within alveolar capillaries can produce severe lesions.

Nematodes

A few nematodes species are encountered in the respiratory tract of a number of laboratory animals. They range from the nares to the alveoli, and the host response is variable depending upon the specific parasite involved.

Aelurostrongylus abstrusus

This nematode parasite of cats is probably the most controversial lung parasite to be discussed. First, the normal habitat of the adult form is in question; some reports indicate the right ventricle of the heart and pulmonary arteries, whereas others say the small bronchioles of the lung. In any event, the visualization of adult *Aelurostrongylus abstrusus* in infected cats, wherever their location, can be difficult. Second, the etiologic role of these parasites in the incidence of medial hypertrophy of pulmonary arteries, seen in a high percentage of cats, is uncertain. This condition was previously discussed under miscellaneous respiratory disorders.

Adult female *A. abstrusus,* depending upon their location, deposit their ova either into the pulmonary circulation or the adjacent alveolar tissue. If deposition is in the pulmonary circulation, the ova are carried to the alveolar capillaries where they break through into the alveoli. The ova hatch, liberating larvae that migrate up the respiratory tree, are swallowed, pass out in the feces, and are ingested by certain molluscs. Infected molluscs may perpetuate the life cycle directly if eaten by a cat. The ingestion of such transport hosts as frogs, snakes, lizards, or birds by a cat also perpetuates the cycle.

Localization of individual adult *A. abstrusus* may be difficult, but the gross and histopathologic diagnosis, in moderately or heavily infected cats, is not. Grossly, the lungs of infected cats contain one or more firm, yellowish nodules, 1 to 5 mm in diameter. These represent nests of large numbers of ova and larvae. Upon incision of a nodule, a small amount of creamy exudate may be expressed. Microscopically, these nodules contain both ova and larvae within alveoli and bronchioles. A moderate host response is present, consisting of a mononuclear infiltrate, occasional giant cells, and epithelialization of alveolar walls. Lymphoid nodules associated with adjacent arteries are common. Cats usually tolerate this parasite well, but very heavy infections can debilitate and kill.

Filaroides milksi

Filaroides milksi is an apparently rare, very small lung parasite of the dog. In the single case observed by the authors, these nematodes were present in alveolar sacs adjacent to a bronchiole. There was no response on the part of the host to

the presence of the few parasites. The size of the parasites, approximately 30 μ in diameter, and the absence of any host response, makes them difficult to visualize on casual observation of tistue specimens and may be one factor in their apparent low incidence. Some reports describe a mild mononuclear response to the adult form. The females are ovoviviparous, and the presence of the larvae incites a marked eosinophilic, granulomatous reaction. Larval granulomas have been found in organs other than the lung. The life cycle of the parasite is unknown, but terrestrial gastropods are thought to serve as intermediate hosts.

Filaroides osleri

This parasite, another infrequently reported nematode, is found within nodular masses arising from the mucosa of the trachea and bronchi of dogs. It has also been observed within the lung parenchyma. The adult parasites live in or under the mucosa of the trachea or bronchi; their presence stimulates the formation of a nodular mass up to 1 cm in diameter that protrudes into the lumen. The nodule contains a cavity in which the parasites reside. The most common site of nodules is the tracheal bifurcation; and if present in large numbers, they may interfere with respiration. Young dogs are most often affected, and if the infection is severe, a persistent rasping cough may develop. Diagnosis may be confirmed by observing the nodules by bronchoscopic examination or by demonstrating ova in the sputum or larvae in feces. The life cycle of the parasite is unknown, but certain snails may serve as intermediate hosts.

Filaroides gordius

The lungworm *Filaroides gordius* is a classic example of *Metastrongylidae* in nonhuman primates. Lungworms are primarily encountered in New World primates. Of the several *Filaroides* species, *F. gordius* appears to be most commonly reported. These parasites inhabit the bronchioles and alveoli, where their presence elicits a mild host response characterized by a focal granulomatous pneumonitis. Grossly, the location of the parasites is indicated by a slightly raised, irregular, dark purple focus beneath the pleural surface of the lung. The complete life cycle is unknown, but the first stage larvae are coughed up, swallowed, and passed in the feces. An intermediate host appears to be necessary. Lungworms in primates do not appear to be associated with a debilitating condition and are tolerated well by the host.

Angiostrongylus cantonensis

This is the lungworm of the rat and is mentioned here only because of its public health significance. This parasite does not occur in the continental United States but is found in Hawaii, numerous other Pacific Islands, Australia, and the Far East. Like most other lungworms, *Angiostrongylus cantonensis* requires an intermediate host to complete its life cycle. Several species of land snails serve as suitable intermediate hosts, with species of shrimp and fish serving as transport host. In man, an aberrant host, ingestion of land snails or any transport host containing viable, infective larvae of *A. cantonensis* may result in a severe, often fatal, eosinophilic meningitis due to the migration of the larvae. In the rat, the normal migration is through the central nervous system, where there is little reaction, to the lung.

Crenosoma vulpis

Although primarily a parasite of the fox, *Crenosoma vulpis* is found in the dog (Stockdale and Hulland, 1970), wolf, badger, and wolverine. The parasites inhabit the bronchi and bronchioles of these hosts. In severe infections, clinical signs similar to those observed with *Capillaria aerophila* are present. Female parasites are ovoviviparous, larvae being passed in the feces or nasal discharges. Land snails or slugs act as intermediate hosts, and the life cycle is completed when snails containing infective larvae are ingested by a susceptible host.

Gongylonema species

Nematodes of this genus are most frequently found in the epithelium of the esophagus, tongue and buccal cavity, but they have also been observed in the trachea, bronchi, and lungs of some animals. They elicit little response in the host. Various species occur in primates, rats, mice, and other rodents, plus a wide variety of wild animals. Their life cycle requires that their ova be ingested by an arthropod host, commonly cockroaches and beetles. The presence of the arthropod vectors in a colony environment may result in transmission of this parasite within the colony.

Capillaria aerophila

This small parasite is found in the trachea, bronchi, bronchioles, and occasionally the nasal sinuses of dogs, foxes, cats, and several small wild mammals. In mild infections, there are no clinical signs. The parasites are only superficially imbedded in the mucosa of the respiratory tract, and host response is minimal or absent. In heavy infections, however, a different picture is presented. Clinically, the animal exhibits a chronic cough, frequently accompanied by dyspnea. Tracheitis and bronchitis are evident and may be severe enough to predispose the animal to a secondary bacterial bronchopneumonia. Diagnosis is based on demonstrating typical double operculate ova in respiratory discharge or feces. Caution should be exercised in differentiating the ova from *Trichuris vulpis* and other *Capillaria* species. The life cycle of *C. aerophila* is direct. Ova are deposited in the upper respiratory passages, expectorated and swallowed, and passed in the feces; they embryonate and, in 35–50 days, become infective. Infection is by ingestion of embryonated ova by a suitable host.

Anatrichosoma cutaneum and *Anatrichosoma cynamolgi*

These nematodes normally inhabit the nasal mucosa near the external nares. They have only been reported in primates and then only rarely. *Anatrichosoma cutaneum* may be found in cutaneous locations other than the nares and has been associated with subcutaneous granulomatous nodules and serpentine blisters of the palms and soles. It is not clear whether these parasites are truly rare or whether their location in the nares shields them from the eyes of clinicians and pathologists, since few routinely examine the nares of any animal unless a complaint is received. Results of a survey in progress by one of the authors suggest that the incidence of these parasites is greater than previously reported. A 5 percent incidence of an *Anatrichosoma* species parasite was encountered in a survey of 400 *Macaca mulatta*. The presence of the parasite was diagnosed clinically by swabbing the nares with a wet, cotton-tipped applicator stick and examining a smear for the presence of characteristic ova. An examination of histologic sections of the nares from 133 *M. mulatta* revealed an incidence of 12 percent infection. The variance in the two incidence figures may be partially explained by the fact that a positive result from the swabbing technique depends on the presence of mature gravid females for a diagnosis. Several histologic sections contained only male parasites in the deeper subcutaneous tissues. The parasites are small, threadlike, and found primarily in hyperplastic epidermis of the nasal mucosa (Figure 2.30); males are occasionally observed in deeper subcutaneous tissue, however. The host response is minimal, and aside from the hyperplastic epidermis, the subcutis may be lightly infiltrated with neutrophils and histiocytes and an occasional eosinophil and lymphocyte. The females deposit large, rough, double operculate ova

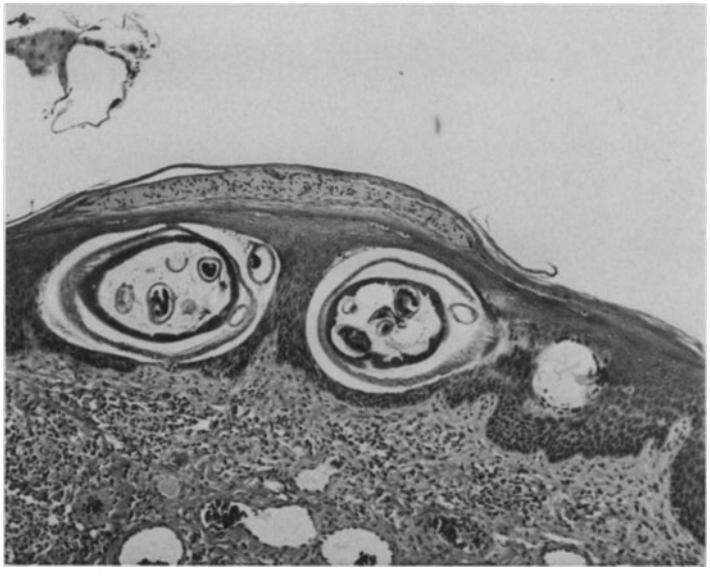


FIGURE 2.30 *Two sections of* Anatrichosoma cynomologi *within the nasal epithelium of a rhesus monkey. There is a moderate lymphocytic infiltrate in the submucosa.* H&E stain.

within the migrating channels they inhabit. As the superficial epithelium sloughs, the ova are released into the nares. The life cycle has not been established.

Pentastomes

Linguatula serrata

Few pentastomes are encountered in laboratory mammals. They are found more commonly in carnivorous reptiles, primarily snakes. *Linguatula serrata* is the principal exception, the adults residing in the nasal and respiratory passages of the dog, fox, and wolf. This parasite has also rarely been reported in man, horse, goat, and sheep. The adults are commonly referred to as the "tongue-worm," due to the slightly curved, flat, convex dorsal end of the parasite, which resembles a tongue. The life cycle of pentastomes is interesting and explains the variety of both hosts and intermediate hosts. Ova are expelled from the respiratory tract and deposited on ground vegetation. When ingested by the intermediate host, the ova hatch and larvae migrate through the viscera. After several molts and migrations, the infective nymphal stage encysts. The life cycle is completed when the definitive host ingests the intermediate hosts or the infective nymph. In the case of *L. serrata,* such herbivores as cattle, sheep, and goats are the most common intermediate hosts. Dogs infected with adult *L. serrata* present clinical signs of sneezing and coughing due to local irritation to the nares. A mucinous, blood-tinged nasal discharge may be present. Diagnosis is confirmed by swabbing the external nares and demonstrating ova.

Other pentastomes of the genera *Porocephalus* and *Armillifer,* as well as *Linguatula,* are important in nonhuman primates because these animals serve as intermediate hosts. Adults of the first two genera, *Porocephalus* and *Armillifer,* are seen in the lungs and air sacs of carnivorous snakes. These snakes prey upon various species of primates and become infected when they ingest primates containing infective nymphal forms. Distribution is widespread; the pentastomes are generally found wherever suitable reptile hosts and primate intermediate host occur together. Encysted larvae may be found in almost any organ system, including the brain, but are most commonly encountered in the lungs, liver, and serosa of visceral organs. Usually there is a very minimal host response to the presence of these parasites.

Arthropods

Mites within the respiratory passages of laboratory animals are, with one notable exception, rare. The exception is the genus *Pneumonyssus,* and its various species are reported in a variety of nonhuman primates and the dog. Other arthropods of genera *Pneumonyssoides* and *Rhinophaga* have been reported from the lungs and nasal passages, respectively, of primates, but space does not permit a comprehensive discussion of these or the great number of species of *Pneumonyssus.* The incidence of lung mite infection in primates varies with the simian species examined. The incidence of *Pneumonyssus simicola* in the rhesus monkey (*M. mulatta*) is virtually 100 percent. Infections with lung mites in other simian species varies downward to the New World primates in which the incidence is rare to nonexistent. The life cycle of these mites is not clearly understood but animal to animal infection is probable. Experience indicates that primate species with a negative or low incidence of lung mites, kept in close proximity to rhesus monkeys, will later have a high incidence of lung mite infection. This is another reason to segregate various species of primates.

Clinically, there is no way to diagnose lung mite infections or assess the degree of lung involvement. Radiographs are of little value and do not correlate with necropsy findings. Clinical signs are almost nonexistent, and monkeys with severe lung involvement have appeared healthy prior to necropsy examination.

The pulmonary lesions produced by these mites is rather characteristic and only varies with the severity of infection. Grossly, mite lesions appear as discrete, ovoid, pale yellow nodules, rarely larger than a few millimeters in diameter. Upon initial examination, the nodules appear to be subpleural, but sectioning of the lobes reveals their presence at all levels of the lung parenchyma. The pulmonary tissue adjacent to the nodules is usually normal under gross examination. In cross section, the nodules have a small cavernous space, which often contains the parasite. Microscopically, the mites (Figure 2.31) reside in various levels of the bronchial tree distal to the secondary bronchi. In some sections, the mites may appear to reside in alveolar spaces, not associated with bronchioles, but this is considered to be an artifact, due to the plane of the section. The lesion consists of a dilated thickened bronchiole with eroded epithelium, which often

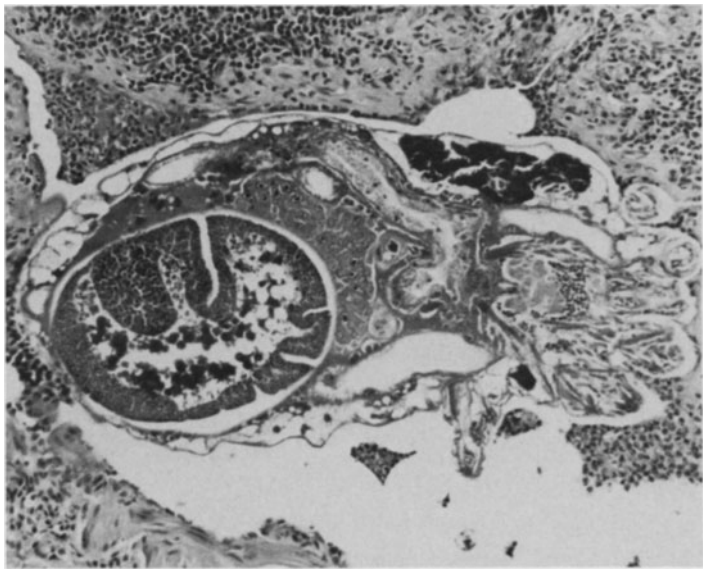


FIGURE 2.31 *A section of the lung mite,* Pneumonyssus simicola, *in a bronchiole of a rhesus monkey. The wall of the bronchiole and the surrounding pulmonary tissue are infiltrated by lymphocytes and macrophages.* H&E stain.

contains sections of the mite, surrounded by a zone of lymphocytes, eosinophils, and numerous macrophages containing the characteristic birefringent crystalline, golden brown to black mite pigment (Figure 2.31). This pigment, thought to be excreta of the mites, may be found throughout the lungs and regional lymph nodes. It is so characteristic of lung mites that its presence even in the absence of mites is considered to be virtually diagnostic.

The mite *Pneumonyssus caninum* lives in the nasal passage and sinuses of dogs. Its presence is generally not associated with any significant clinical signs or lesions.

Treatment for infections with the various species of lung and nasal mites is generally unsatisfactory.

Annelida

Leeches of the class Hirudinea are mentioned here because they are occasionally seen in primates and were present in military dogs in Southeast Asia (Bywater and Mann, 1960; Pryor *et al.,* 1971; Moe and Paclik, 1970). The presence of leeches in the nares of numbers of these dogs was a significant veterinary problem. The usual clinical history was of paroxysmal sneezing and unilateral epistaxis. Examination of the nares revealed varying numbers of leeches firmly attached to the nasal mucosa. Treatment consisted of anesthetizing the dog, passing an intratracheal tube, and continued flushing of the nares with 15 to 20 percent ethanol until all the leeches were detached and washed out into the oral cavity. Light spraying of the nasal cavity with pyrethrin insecticide has also been used to remove the leeches. The leeches ranged up to 10 cm in length. Infection is usually acquired from drinking water. These leeches are not host specific and will attach to any mammal, including man or nonhuman primates. For this reason, nonhuman primates obtained in endemic areas may arrive in the colony environment infected with leeches. Leeches of the genera *Limnatis* and *Dinobdella* have been identified in the nasal cavity of monkeys. Monkeys may have signs similar to those observed in dogs. There is only a mild, chronic inflammation at the site of attachment, and this is resolved following removal of the leeches. Treatment similar to that employed in the dog would be indicated.

NEOPLASMS

The incidence of respiratory system neoplasia in the majority of laboratory animals is very low. This is true in the rat, hamster, guinea pig, rabbit, cat, and nonhuman primates. Both the dog and mouse have an incidence of pulmonary neoplasia greater than the aforementioned species, which often varies with the individual breed or strain studied. This is particularly true of the different strains of mice in which variations in the incidence of neoplasia are dramatic.

Pulmonary Adenomatosis

This is a term generally applied to a histologic alteration of cells lining the pulmonary alveoli. It is characterized by the metaplastic transformation, hypertrophy, and hyperplasia of the alveolar lining cells into cuboidal or columnar cells, which often contain mucus. The specific cell involved is in dispute; however, it is probably one of the two types of epithelial pneumocytes related to the epithelial cells lining the bronchi and bronchioles. Recent investigations suggest the great alveolar epithelial cell or type II granular pneumocyte is capable of mitosis and is probably the progenitor cell of the more abundant type I pneumocyte; this cell is most likely responsible for alveolar adenomatosis. Another cell considered by some to be involved is the alveolar septal cell; this is a phagocytic type cell not normally found on the surface of the alveolar sacs, however, and it is unlikely to contain or secrete mucus.

Histologically, adenomatosis is characterized by the uniform transformation of cells lining the alveoli into cords of cuboidal or columnar nonciliated cells (Figure 2.32). The basic alveolar architecture may be distorted. Lesions may be focal, involving only a few alveoli, or they may be very diffuse. Other terms applied to this change are alveolar fetalization, alveolar adenoma, and alveolar cell hyperplasia.

Adenomatosis has been observed in virtually all laboratory mammals. The authors have seen adenomatoid lesions in lungs of all of the major laboratory mammals discussed in this chapter. Although adenomatosis is a significant disease problem in sheep and cattle in certain geographic areas, the significance of similar lesions in laboratory animals is at best minimal because of their low incidence. In sheep, this condition involves a group of specific transmissible diseases, one of which, jaagsiekte, has virtually become a synonym for adenomatosis.

There is no single specific etiologic agent for pulmonary adenomatosis. A variety of infectious agents, parasites, plants, chemicals, toxins, gases, and irritants have produced adenomatosis in animal lungs. For example, it has been seen associ-

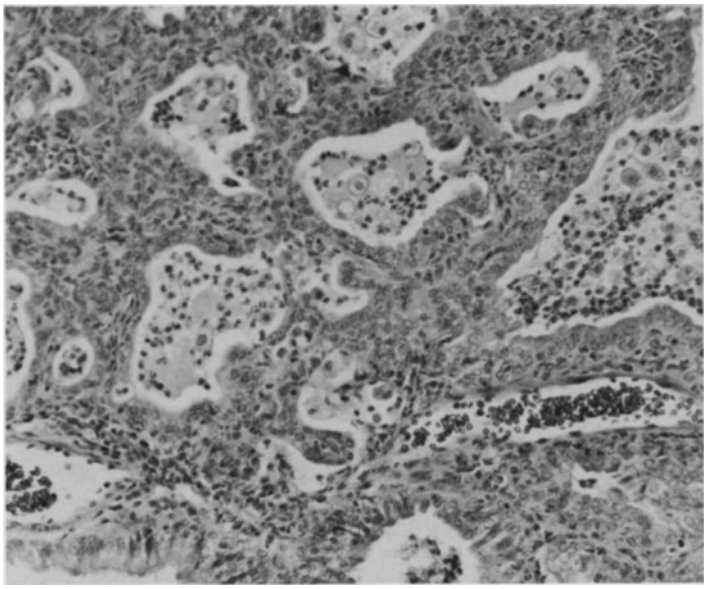


FIGURE 2.32 *Pulmonary "adenomatosis" in a mouse 3 weeks after experimental aerosol infection with a mouse-adapted strain of influenza virus. The alveoli are lined by cuboidal epithelial cells, and there is a mixed inflammatory cell infiltrate in the interstitium.* H&E stain.

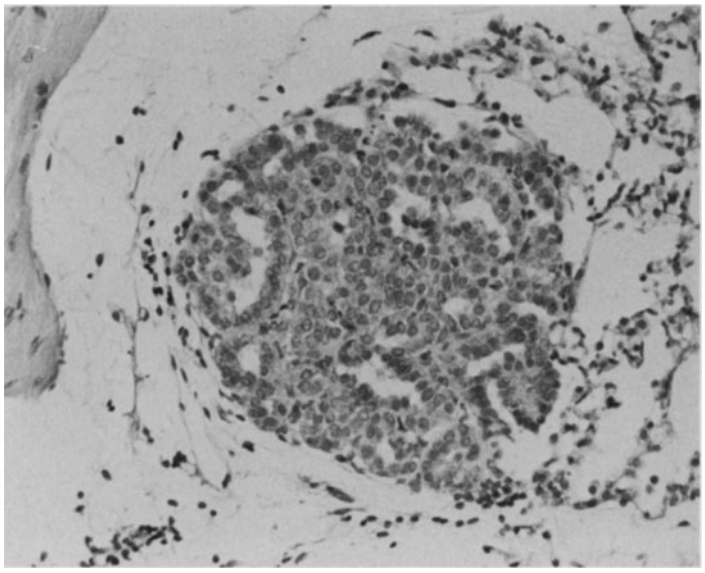


FIGURE 2.33 *A pulmonary adenoma in the lung of a mouse. Neoplastic cells are arranged in short cords or around small spaces.* H&E stain.

ated with various verminous pneumonias, bacterial pneumonias, experimental influenza in mice, prolonged oxygen therapy in dogs, and feeding of various plants. It has also been seen in apparently normal colony rats, mice, and other species.

Finally, the relationship of adenomatosis to neoplasia should be mentioned. In sheep, various forms of "adenomatosis" have metastasized to regional lymph nodes. In man, alveolar cell adenomas, which are histologically compatible with the diagnosis of adenomatosis, are considered benign neoplasms. These are the exceptions, and pulmonary adenomatosis, as encountered in laboratory animals, is at best a hyperplastic change and at the very worst a preneoplastic lesion. So as not to completely close the door on a neoplastic process, it is appropriate to quote a wise old sage who observed, "one man's hyperplasia is another man's neoplasia."

Primary Neoplasms of the Respiratory System

A variety of primary neoplasms have been reported in the respiratory system of laboratory animals. Carcinomas easily predominate over sarcomas. All types of benign neoplasms appear

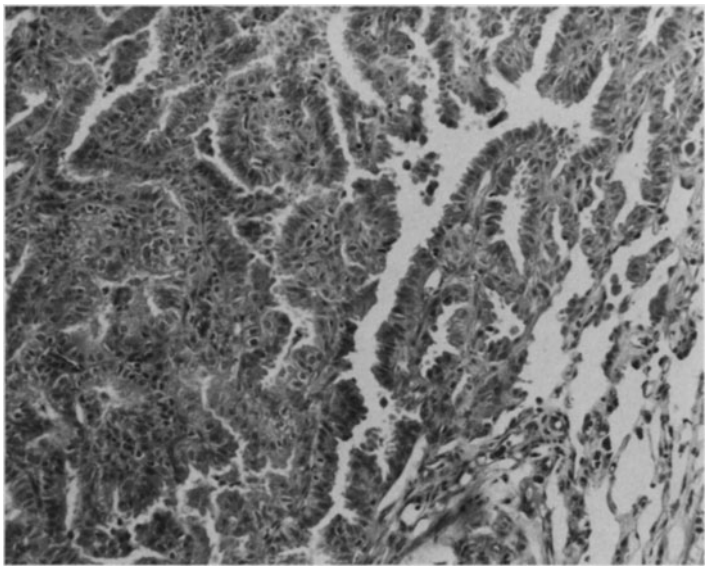


FIGURE 2.34 *A primary pulmonary carcinoma, probably of alveolar origin, in the lung of a dog. In the deeper aspects of the neoplasm, neoplastic cells are arranged in cords, whereas at the edges, small tufts of cells appear to be invading alveoli by extension.* H&E stain.

to be rare, except in mice, where pulmonary adenomas are relatively common (Figure 2.33). By far the highest incidence of primary respiratory tract neoplasia is reported in the dog, with certain strains of mice a close second. Rats, cats, and other common laboratory animals have a low incidence of respiratory neoplasia.

The two most common carcinomas of the lung are the bronchiolar or alveolar cell carcinoma and the bronchiogenic carcinoma (Figure 2.34). Carcinomas arising from respiratory epithelium of the nares, sinuses, pharyngolaryngeal region and trachea have all been reported.

A variety of sarcomas have been reported from the entire respiratory system. These include fibrosarcomas, osteosarcomas, and lymphosarcomas. The incidence of primary lymphosarcoma in the lung and that of chronic respiratory disease sometimes appear to be correlated; it is theorized that the heavy deposition of lymphocytes in the lungs of rats affected with chronic respiratory disease may predispose them to lymphosarcoma.

Metastatic Neoplasms of the Respiratory System

Aside from regional lymph nodes draining the site of a primary neoplasm, the lungs are the most common site of metastases. For this reason, it is impractical to list all of the neoplasms that have metastasized to the lung. But, allowing for variations in species incidence of neoplasia, mammary gland neoplasms, hemangiosarcomas, osteosarcomas, and melanomas are most commonly encountered in the lungs.

For general references for neoplastic disease of the respiratory system, see Cotchin and Roe (1967), Franks and Chesterman (1963), Moulton (1961), and Stewart *et al.* (1970).

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