

Non-proliferative Lesions of the Respiratory Tract in Rats

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INTRODUCTION

A standardized nomenclature of proliferative lesions occurring in the rat respiratory tract has been previously published by the Society of Toxicologic Pathology (STP) (74). Consideration of non-proliferative lesions will follow a similar anatomical approach to that previously used. Consequently, nasal cavity, larynx and trachea, major airways, and lung parenchyma have been listed separately in this nomenclature scheme even though there can be considerable redundancy regarding responses at various levels. Non-proliferative lesions, in general, are associated with either experimental perturbation or a result of degenerative changes frequently associated with aging. Modern laboratory animal management practices within rodent facilities are such that spontaneous infectious processes should be infrequently encountered; thus the lesions related to infectious respiratory tract diseases are not described in detail in this chapter. Excellent reviews are published on the effects of infectious disease, diet, and environmental factors on the rat respiratory tract (2, 14, 19).

MORPHOLOGY

NASAL CAVITY

The nasal cavity is structurally complex, reflecting the diverse physiological functions associated with this anatomical site. St. Clair and Morgan (78) provide an overview of normal development, growth, and age-related changes in the rat nasal passages. Various articles detail the anatomy (28, 81, 85) and physiology (3, 53, 63) of the rodent nasal cavity tissues. Identification of metabolic functions of nasal epithelia has enhanced morphological interest in nasal passages and consequently the recognition of chemically-induced lesions has become more frequent in recent years (1, 5, 15, 40, 66). The location of lesions is likely related to several factors, including: dose to affected area, site-specific susceptibility, local metabolism, or a combination of these factors. Localization and documentation of lesions are quite dependent upon consistency of sampling and preparation of nasal tissues (25, 56). Diagrams for recording distribution of nasal lesions have been published (51, 56). Careful description of lesion distribution is important to help understand the nature of the toxic compound (25, 51).

CONGENITAL LESIONS

Congenital lesions of the upper respiratory tract are uncommon. Cleft palate is a longitudinal defect in bone and

mucosa of the midline of the hard palate resulting from failure of fusion of the lateral palatine shelves from the maxillary processes (38). Cleft palate has been induced in fetal rats exposed to triamcinolone (82) or vitamin A palmitate (31).

DISTURBANCE OF GROWTH

Odontodysplasia (dental dysplasia) is a lesion particularly involving the incisor teeth and may occur secondary to malocclusion or food impaction (55). Large dysplastic lesions may distort the adjacent nasal cavity. Severe prolonged malocclusion may lead to overgrowth of the incisors, resulting in ulceration of the palate and secondary inflammatory lesions in the nasal cavity.

EPITHELIAL CHANGES

Atrophy (Figure 1)

Atrophy of nasal epithelium secondary to degeneration of sensory cells has been observed following exposure to dimethylamine (11, 55). Affected areas of mucosa become thin, possibly to a single cell layer in depth, and composed of featureless elongated epithelium. Atrophy of portions of the olfactory epithelium may result from inhalation of metals such as zinc or nickel compounds (4, 20).

Degeneration (Figures 2-4)

Degenerative changes in nasal tissue have been reported as sequelae to toxic agent exposure (27, 55, 57) and as a consequence of aging (78). Loss of cilia, epithelial blebbing, and increased intercellular spaces are early indications of a response to injury. Dilatation (ectasia) of nasal glands may occur with accumulation of secretory material, either spontaneously or as a sequel to toxic damage to the ductal epithelium. Accessory nasal structures and surrounding tissues can also undergo a variety of degenerative changes. The vomeronasal organ, a specialized sensory organ thought to be responsible for pheromone recognition and food flavor perception, is composed of sensory and columnar epithelia. This organ can undergo degenerative and atrophic changes following either exposure to toxic agents or as a consequence of aging (76, 81).

Eosinophilic Inclusions (Globules, Droplets) (Figure 5)

A common degenerative change, particularly as a spontaneous lesion in aged rats, is the accumulation of eosinophilic inclusions in nasal epithelium. These inclusions occur in sustentacular cells of olfactory epithelium, respiratory epithelial cells, and epithelium of the nasal seromucous glands, especially near the junction of olfactory and respiratory epithelia (57). These inclusions are negative for a number of special stains. Ultrastructurally they present as amorphous flocculent (presumably proteinaceous) material in membrane-bound vacuoles. The accumulation

of inclusions may be seen in association with loss of sensory cells. Increases in size and number of eosinophilic inclusions in respiratory and olfactory epithelium were observed in rats exposed to dimethylamine (11, 23) or cigarette smoke (46). Inclusions in nasal epithelium of smoke-exposed rats reacted with antibodies for carboxylesterase, an enzyme induced by exposure to some toxic compounds.

Corpora Amylacea (Figure 6)

Another common degenerative change in the nasal cavity is the presence of small basophilic or amphophilic concretions, referred to as corpora amylacea in the lamina propria or nasal gland lumina (55).

Necrosis (Figures 7-9)

Necrosis of mucosal epithelium is characterized by pyknosis or karyorrhexis of nuclei and exfoliation of cells. Respiratory or transitional epithelium lining the dorsal medial, middle medial, and lateral meatuses are often the first areas affected after exposure to irritant gases. Continued exfoliation of cells results in erosion or ulceration. The subsequent inflammatory response with exudation of fibrin and cellular debris may set the stage for adhesion of turbinates to adjacent structures. In olfactory epithelium, the first indication of injury may be increased intracellular or extracellular space, the latter being attributed to swelling of sustentacular cells. The most rostral olfactory epithelium lining the dorsal medial meatus is the area of olfactory epithelium most frequently affected by inhalation of direct-acting gaseous irritants (10, 25). Chemicals requiring metabolism to a toxic intermediate to damage olfactory epithelium usually induce lesions throughout the olfactory epithelium (20). A consequence of loss of sensory cells (either through aging or toxic injury) is atrophy of nerve bundles within the lamina propria.

Toxic injury may affect the nasal glands with subsequent loss of epithelium and replacement with fibrous connective tissue. This may also occur spontaneously, perhaps as an aging phenomenon.

Erosion/Ulceration (Figure 10)

Loss of nasal epithelium only (erosion) or complete penetration of underlying basement membrane (ulceration) is observed in all types of nasal epithelium in response to inhaled toxicants (55). One must use care to differentiate erosion or ulceration from artifactual loss of epithelium related to experimental procedures or autolysis. A serofibrinous or suppurative exudate is usually visible covering areas of ulcerated epithelium. Metaplasia to squamous or respiratory epithelium may occur following repeated loss of respiratory or olfactory epithelium, respectively.

Regeneration (Figure 11)

The morphologic sequelae to injury of nasal epithelium depend on extent and duration of the injury as well as the length of time post-injury that tissues are fixed. Sequelae range from regeneration of epithelium identical to the original epithelium, to atrophy (see above), to metaplasia to a different epithelial type. Loss of surface respiratory or transitional epithelium with retention of an intact basement membrane is followed by formation of a layer of fibrin and inflammatory cells covering the affected area (36). Adjacent undamaged epithelium undergoes rapid proliferation in response, and depending on the size of the lesion, migrates to form a layer of slightly flattened cuboidal epithelium completely or partially covering the defect. If the injury is not repeated, the affected area will be recovered with epithelium of the same type as the original. Epithelial degeneration and regeneration are often present together in nasal tissues repeatedly exposed to injurious chemicals, resulting in a disorganized histologic picture (20, 25). Repeated loss of epithelium leads to metaplasia to a more resistant type: squamous metaplasia in transitional or respiratory epithelium; and squamous or respiratory metaplasia in olfactory epithelium (36). Metaplastic nasal lesions are described in detail and illustrated in the SSNDC Guide on Proliferative Lesions of the Respiratory Tract (74). It is important to differentiate true squamous metaplasia from the comparatively thin layer of flattened epithelium present in early regeneration of ulcerated nasal epithelium. Schlage, *et al* (72, 73) have published information on changes in cytokeratin expression patterns in the various nasal epithelia which were useful in demonstrating subtle effects of inhaled smoke on these tissues.

INFLAMMATION (RHINITIS)

Inflammatory changes can be observed in response to infectious disease, chemical exposure, or foreign bodies. Mycoplasma species, sialodacryoadenitis virus, and Sendai virus are the most common murine pathogens affecting the upper respiratory tract (2). The nasal mucosa is a well-known site for chemically induced injury. Foreign bodies, generally either food particles or bedding material, are occasionally found in the nasal cavity. Associated nasal cavity structures can also be affected by inflammatory processes. Lesions commonly observed in the nasolacrimal duct include inflammatory cells, hyperplasia of mucosal epithelium, and squamous metaplasia with or without keratinization. In rodents exhibiting open-mouth or noisy "clicking" respiration, it may be useful to examine a longitudinal section of posterior nasal meatus and nasopharynx as inflammatory, hyperplastic or neoplastic lesions may be occlusive.

Acute Inflammation (Figures 12-13)

Acute inflammation is characterized by edema of the lamina propria, accumulations of a serous, mucous, or

fibrinous exudate in airways, and accumulation of leukocytes, primarily neutrophils, in the mucosa. The tips of the maxillary and nasal turbinates are frequently the areas first, and most severely, affected by inhaled irritants. Emigration of neutrophils into airways produce a suppurative exudate. Eosinophils in exudate or mucosal infiltrate may indicate an immunologic element to the inflammatory response (35).

Granulomatous Inflammation (Figure 14)

Foreign bodies in nasal cavity tissues elicit an initial suppurative inflammatory response, accompanied or followed by influx of macrophages. If the foreign body remains, the inflammatory response will gradually evolve to a granulomatous inflammation dominated by macrophages and varying amounts of fibrosis.

Chronic Inflammation

Chronic inflammation is characterized by infiltration of lymphocytes and fibroblasts into the lamina propria, hyperplasia of nasal-associated lymphoid tissue (NALT) and hyperplasia or metaplasia of overlying nasal epithelium (74). Chronic inflammation of the mucosa covering the turbinates frequently leads to atrophy of the maxilloturbinate and nasoturbinate bones. In severe cases, the atrophy may be complete (55).

Osteofibrosis

Extensive lesions affecting nasal mucosa may extend into and involve the adjacent turbinates. Osteofibrosis, with remodeling of the turbinates, has been observed as a sequel to necrosis of nasal mucosa induced by inhalation of potent toxicants such as 3-methylfuran (29), or as a part of the inflammatory response to repeated inhalation of toxicants such as chloroform (44). Osteopetrosis of turbinates may occur as a spontaneous lesion. Criteria for diagnosis of osteopetrosis are presented in the portion of this Guide covering non-proliferative lesions of bone (47).

VASCULAR CHANGE

Congestion of the richly vascular nasal mucosa may be observed in rats dying or killed while moribund, related to terminal pooling of blood in the nasal cavity. Hyperemia, edema, and/or hemorrhage in the nasal mucosa may be the earliest response observed to inhaled nasal toxicants or traumatic injury to the nose. Small amounts of free blood may be observed in the nasolacrimal duct or nasal lumen following antemortem blood collection via the retroorbital plexus in the medial canthus of the eye. Thrombosis of vessels in the nasal cavity is observed occasionally in Fischer rats with severe leukemia.

LARYNX, TRACHEA, AND BRONCHI

Although less complex than the epithelium lining nasal airways, the mucosal epithelium lining the laryngeal lumen consists of several distinct anatomic subtypes with varying susceptibility to damage from inhaled toxicants (45, 68). The most frequent site of induced laryngeal lesions is the zone of transition between squamous and respiratory epithelium at the base of the epiglottis. This critical area for interpretation of toxic effects is rather small, and it is important to use histologic procedures that insure it is consistently available for microscopic examination (45, 67, 71). Other sites frequently affected are the medial aspect of the arytenoid projections and the area anterior and lateral to the ventral pouch (45, 54).

The trachea and bronchi of rats are lined predominantly by ciliated columnar (respiratory) epithelium, with lesser numbers of basal, serous, and mucous goblet cells (48). Globule leucocytes are scattered among respiratory epithelium lining the larynx and trachea of rats. Height of the pseudostratified tracheal epithelium decreases caudally to simple epithelium in the bronchi. The walls of only the extrapulmonary mainstem bronchi of rats contain supporting cartilage. Nodules of bronchus-associated lymphoid tissue (BALT) are closely associated with the proximal intrapulmonary bronchi.

The anatomical structure of the tracheobronchial tree determines, in part, the dose of an inhaled irritant delivered to a specific airway. The epithelium lining the medial surfaces at the tip of the tracheal bifurcation (carina) is a likely site to observe lesions induced by inhaled irritants, presumably because this area receives a higher dose from direct aerosol impaction (21). Therefore, the carina should be included in airway sections examined microscopically for toxicologic lesions.

Systematic sampling and careful fixation by airway perfusion are prerequisites to identifying lung lesions. There are 12 to 20 monopodal branching airway segments from the trachea to the terminal bronchiole, depending upon the lobe (84). The right primary bronchus branches to a cranial lobar bronchus, followed by a middle lobar bronchus and accessory and caudal lung lobes, respectively. The left primary bronchus serves the single large left lobe (32). Intralobular septa and lobules are absent in the rat lung.

EPITHELIAL CHANGES

Degeneration (Figure 15)

Degeneration of epithelium lining the laryngeal lumen is a frequently observed effect of inhaled materials of low toxicity or of lower concentrations of potent toxicants (54). Subtle changes, including loss of cilia and rounding of normally cuboidal or columnar epithelial cells, are most often observed at the base of the epiglottis. Care must be

taken to differentiate these changes from cuboidal or rounded, non-ciliated epithelial cells normally present in the transition zone of the epiglottis (45, 54). Decreases in number, or complete loss of globule leucocytes normally present in laryngeal and tracheal epithelium of rats, are frequently-observed responses to inhaled chemicals (45).

Necrosis

As in the nasal cavity, necrosis of mucosal epithelium lining the larynx, trachea, or bronchi is characterized by pyknosis or karyorrhexis of nuclei and sloughing of affected cells and debris into the lumen. Although necrosis is seen most frequently in the transition zone at the base of the epiglottis, inhalation of strong irritants can induce severe lesions in the entire lumen, with ulceration and severe inflammation (54). Severe necrosis of the upper respiratory tract and bronchial mucosa has been induced by inhalation exposure to strong irritants such as methyl isocyanate (6).

Ectasia of Submucosal Glands (Figure 16)

Ectasia of submucosal glands of the epiglottis may occur following blockage of excretory ducts due to squamous metaplasia and hyperplasia of the overlying luminal epithelium or accumulation of exudate (45). Rupture of the ectatic glands with release of accumulated necrotic debris induces a granulomatous inflammatory response that can progress to severe polypoid lesions, partially occluding the laryngeal lumen (9, 74). Dilatation of submucosal glands of the larynx or trachea may also occur spontaneously (22).

Erosion/Ulceration (Figure 17)

Morphology of erosions and ulcerations of the larynx, trachea, and bronchi is similar to that described above for nasal respiratory epithelium. Ulceration of mucosal epithelium may result in necrosis and mineralization of underlying cartilage. The "U-shaped" cartilage at the entrance to the ventral pouch is particularly susceptible to necrosis related to ulceration. Subtle lesions may persist in this cartilage after the overlying epithelium has returned to normal (26, 45).

Accidental introduction of a gavage tube into the airway lumen or poor technique in intratracheal instillation can induce laryngeal or tracheal injury, resulting in stertor and serous or hemorrhagic nasal discharge. Severe laceration of laryngeal or tracheal tissues can result in subcutaneous emphysema due to air escaping into adjacent tissues. At microscopic examination, submucosal edema, congestion, or hemorrhage may be present in association with ulceration of the laryngeal or tracheal mucosa.

Regeneration

Sequelae to injury of laryngeal, tracheal, or bronchial

epithelium are similar to those described above for nasal epithelium. Sequelae range from rapid regeneration of epithelium identical to the original epithelium to squamous metaplasia. Epithelial degeneration and regeneration may be present together in laryngeal or tracheal tissues repeatedly exposed to injurious chemicals, resulting in a disorganized histologic picture. Repeated loss of transitional or respiratory epithelium leads to squamous metaplasia. Squamous metaplasia is described in detail and illustrated in the proliferative lesions section of this guide (74). As was noted above for nasal epithelium, it is important to attempt to differentiate well established squamous metaplasia following repeated injury to respiratory epithelium from the temporary squamous epithelium covering areas of recently denuded respiratory epithelium (41). Schlage *et al.* (72, 73) have published information on normal cytokeratin expression patterns in the epithelia lining the larynx, trachea, and lung that could aid in differentiating established squamous metaplasia from epithelial repair.

INFLAMMATION (LARYNGITIS, TRACHEITIS, BRONCHITIS)

Acute Inflammation (Figure 18)

A variable inflammatory response characteristically accompanies degenerative or proliferative lesions induced in the rat larynx, trachea, or bronchi. The site of inflammation, and type and severity of inflammatory response, depends on the physical characteristics of the toxic material and the duration of exposure. A mild suppurative inflammatory infiltrate typically is present in areas of laryngeal epithelial degeneration, becoming more severe and often accompanied by bacterial colonization when ulceration of mucosal epithelium occurs (45). Infectious agents affecting the nasal cavity can also cause inflammatory lesions in the larynx, trachea, and bronchi, creating problems in differential diagnosis of subtle lesions in these sites. Inhalation of highly irritating compounds can induce fatal inflammatory lesions in laryngeal mucosa. Severe laryngeal edema and fibrin or mucus accumulation caused death from airway occlusion in rats inhaling high concentrations of red phosphorus smoke or combustion products of sodium and lithium (12, 54, 65).

Chronic Inflammation (Figure 19)

Chronic inflammation of the larynx, trachea, or bronchi has similar features to those described above for the nasal cavity: infiltration of predominantly mononuclear inflammatory cells, hyperplasia of associated lymphoid tissue, and metaplasia or hyperplasia of affected epithelium. Epithelial metaplasia and hyperplasia are described and illustrated in the section on Proliferative Lesions of Respiratory Tract in these Guides (74).

Mineralized debris, hairs, or inhaled food material

accompanied by a mixed inflammatory cell exudate are frequently observed in the lumen of the ventral pouch of rat larynges, occurring more frequently in aged animals (45, 54). Similar cystic lesions can occur in submucosal glands of the trachea secondary to inflammation or squamous metaplasia of luminal epithelium.

Bronchiectasis (Figure 20)

Bronchiectasis is a common feature of bronchopneumonia caused by *Mycoplasma pulmonis*, now a very rarely observed disease of laboratory rats. A mucopurulent exudate partially or completely fills the airways. Severe dilatation of bronchi occurs to fill the intrathoracic space created by atelectasis of lung parenchyma distal to the blocked airways. Fibrosis is present in the tissue around affected bronchi.

BRONCHIOLES, ALVEOLI, AND PLEURA

The rat lacks a well-developed respiratory bronchiole; thus the transition from conducting to respiratory airways is abrupt. Each terminal bronchiole, alveolar duct, and associated alveoli make up a pulmonary acinus. Ciliated columnar epithelial cells are the predominant cell type in bronchioles, with fewer numbers of Clara cells and serous cells. Type I pneumocytes cover the majority of the surface of alveoli and alveolar ducts; Type II cells, progenitors of Type I cells, produce pulmonary surfactant. Detailed descriptions of the cells making up the bronchioles and the pulmonary acinus, their ability to differentiate, and their metabolic capabilities and distribution, are described in detail elsewhere (6, 61, 62, 79). The visceral pleura and interstitial connective tissue of rats is relatively thin compared to domestic species and primates (80).

Alveolar Type I cells are more susceptible to injury than alveolar Type II cells with the exception of situations in which the role of Type II cells in phospholipid metabolism makes them more vulnerable, as in phospholipidosis induced by amphiphilic cationic drugs (60, 61). Ciliated bronchiolar epithelial cells are highly sensitive to direct-acting inhaled toxicants. High concentrations of metabolizing enzymes in Clara cells make them the most sensitive cells to inhaled or ingested chemicals requiring metabolic activation to be cytotoxic (77). However, Clara cell enzymes may also decrease toxicity by deactivation of cytotoxic chemicals.

The location and microscopic appearance of induced lesions in lung parenchyma depends on a number of factors, including the route of exposure to the inducing agent, the physical and chemical properties and concentration of the inhaled toxicant, and the duration of exposure. Water solubility and reactivity are the most critical determinants of the depth of penetration and location of lesions from inhaled gases. The location of airway lesions induced by inhaled aerosols and particulates depend on particle size, shape, biopersistence, and chemical reactivity. The

primary effects of particles less than three microns in aerodynamic diameter will usually be seen in the alveolar ducts and alveoli.

Lesions induced in lung parenchyma by inhalation of toxicants are most often distributed in a pattern consistent within pulmonary acinar units, consisting of terminal bronchioles, alveolar ducts, and alveoli. Many environmental toxicants induce lesions at the junction of terminal bronchioles and alveolar ducts (centriacinar region).

CONGENITAL LESIONS

Cysts

Isolated cystic spaces in lung parenchyma are rarely seen in rats and are of uncertain origin. These cysts are lined only by fibrous tissue, with no evidence of inflammation.

Pulmonary Hypoplasia

Hypoplasia of lung parenchyma in neonatal rats induced by oral gavage exposure of dams to the herbicide Nitrofen has been utilized as an animal model for human pulmonary hypoplasia (42). This induced abnormality is characterized by decreased total lung volume and lung tissue volume, decreased development of alveoli, and retarded differentiation of alveolar Type II pneumocytes into Type I cells (8).

EPITHELIAL CHANGES

Degeneration

Subtle degenerative changes in bronchiolar and alveolar epithelium are similar to those in the upper respiratory tract. Loss of cilia, rounding of normally cuboidal or columnar epithelial cells, and loss of normal apical blebs from Clara cells are typical early degenerative lesions seen in response to common urban pollutants such as ozone or nitrogen dioxide (6, 30, 61). Compounds requiring metabolism to exert their toxic effect, such as bromobenzene, carbon tetrachloride, or acetaminophen, induce degeneration and necrosis in Clara cells (30, 61).

Necrosis (Figure 21)

Necrosis of bronchiolar epithelium is characterized by karyorrhexis or pyknosis of nuclei, and sloughing of affected cells into the lumen. Necrosis and sloughing of bronchiolar epithelium and/or alveolar Type I cells releases inflammatory mediators (16) which stimulate an acute inflammatory response, influx of macrophages, and proliferation of Type II cells and Clara cells to replace lost alveolar and bronchiolar epithelium.

Regeneration

Sequelae to loss of epithelium lining bronchioles are similar to those described above for upper airway epithelium. They range from regeneration to the original epithe-

lial cell types following a single insult; to luminal or peribronchiolar fibrosis (see below); to squamous and/or goblet cell metaplasia, hyperplasia, and neoplasia following repeated injury. Loss of the epithelium lining terminal bronchioles, alveolar ducts, and alveoli stimulates replacement by proliferation of alveolar Type II cells and bronchiolar epithelium. This important lesion in rodents is designated in the current literature as bronchiolization, bronchioloalveolar hyperplasia, or Type II cell hyperplasia (18, 74). Lost alveolar epithelium is replaced by peripheral extension of bronchiolar epithelial cells into alveolar ducts and alveoli as well as metaplasia of Type II alveolar epithelium (18). Metaplasia and hyperplasia of bronchiolar and alveolar epithelia are described in detail and illustrated in the Proliferative Lesions section of these Guides (74).

INTRA-ALVEOLAR LESIONS

Alveolar Histiocytosis (Alveolar Macrophage Aggregates) (Figures 22-23)

Small intra-alveolar aggregates of macrophages containing foamy cytoplasm are occasionally observed in untreated rats. These aggregates are most frequently observed in the subpleural area and in aged animals. Some macrophages may contain hemosiderin. Macrophage aggregates may be associated with intra-alveolar collections of degenerated phospholipid surfactant material forming cholesterol clefts. The term "alveolar histiocytosis" is used to describe a continuum of lesions ranging from: small foci of alveolar macrophages; to mixtures of inflammatory cells in which macrophages predominate; to lesions in which fibrosis is a major feature (17).

Accumulation of macrophages in alveoli is one primary response to inhaled toxicants. It is a prominent feature of the response to necrosis of pulmonary parenchyma. Aggregates of macrophages may be present without accompanying increases in extracellular surfactant or progression to a prominent inflammatory lesion. Large numbers of macrophages migrate to pulmonary alveoli in response to chemotactic factors released through complement fixation and possibly other processes stimulated by inhalation of cytotoxic materials (83). Phagocytosis of cytotoxic particles and subsequent death of macrophages release other chemotactic factors for granulocytes, fibroblasts, and macrophages (30).

Alveolar Lipoproteinosis (Phospholipidosis) (Figure 23)

Continuation of the inflammatory process described above creates a cascade which may lead to extensive granulomatous inflammation (see below) or to a more degenerative lesion characterized by filling of alveoli with acellular, pale eosinophilic material identified with electron microscopy as the phospholipid surfactant material secreted by

alveolar Type II cells. The latter disease process, designated as alveolar lipoproteinosis (17, 33, 34), is readily induced in rats by repeated exposure to cytotoxic materials such as quartz. Intra-alveolar accumulation of surfactant and macrophages is also induced in rats by alteration of endogenous lipid metabolism by certain cationic amphiphilic drugs (34) or by hypophysectomy (43). Macrophages filled with surfactant are relatively scarce in fully-developed alveolar lipoproteinosis induced by inhalation of cytotoxic particles, whereas in drug-induced phospholipidosis, foamy macrophages persist (17).

Pigments/Dusts (Figures 24-25)

Endogenous pigments, exogenous pigments, and exogenous dusts in lung parenchyma are usually found within macrophages in alveoli. The most frequently observed lung pigment in untreated, aged rats is hemosiderin. Hemosiderin is a brown, iron-positive pigment usually found within subpleural alveolar macrophages. Lipofuscin may also be found within macrophages in alveoli. Large hemoglobin crystals are occasionally observed free in alveoli. Various exogenous dusts may be found in lung parenchyma, again usually within macrophages. Carbonaceous materials in diesel exhaust or other hydrocarbons retain their dark color through tissue processing, and are visible in alveoli. Other dusts, such as silica or talc, may be located by their birefringence with polarized light. The presence of relatively inert materials such as corn oil vehicle accidentally instilled in the lung may cause minimal response and be difficult to detect (6).

INFLAMMATION (BRONCHIOLITIS, PNEUMONITIS, PNEUMONIA, PLEURITIS)

Pulmonary inflammation can be divided into lesions primarily oriented around alveoli and interstitium (alveolar/interstitial pattern) and lesions centered around or originating in the terminal airways (bronchioloalveolar pattern). This division is useful in understanding the pathogenesis and root causes of lesions in the lung parenchyma (17).

Acute Alveolar/Interstitial Inflammation (Figure 26)

Acute alveolitis may be present without concurrent inflammation of adjacent terminal bronchioles. Acute alveolitis is usually related to either a hematogenous insult or inhalation of very high concentrations of toxicants (especially gases) that do not enable a dosimetric gradient to be detected between bronchioles and alveoli in distal portions of the acini (17). Inhalation of mildly toxic particles or vapors may induce only a transient serous, fibrinous, or suppurative exudate, and/or increased numbers of macrophages in alveoli. Hemorrhage and serofibrinous exudate predominate in acute diffuse alveolar damage caused by shock-like states, chemicals, and some acute systemic viral infections. Systemic bacterial infections

affecting lung parenchyma via the bloodstream stimulate a suppurative alveolitis and perivascular infiltrate; viral infections may induce suppurative or mononuclear perivascular and alveolar infiltrates.

Chronic Interstitial Inflammation

The most prominent interstitial changes in chronic pulmonary inflammation in rats are septal and interstitial fibrosis (see below), and accumulations of perivascular and peribronchiolar mononuclear inflammatory cells. Hyperplasia of bronchus-associated lymphoid tissue (BALT) and perivascular lymphocytic cuffs in the absence of other pulmonary lesions may indicate a previous infection with murine respiratory viruses or *Mycoplasma pulmonis*.

Acute Bronchioloalveolar Inflammation (Figures 27-28)

Toxic or infectious agents sufficiently potent to induce necrosis of parenchymal cells (see above) stimulate an acute inflammatory response at the site of cell damage. The bronchioloalveolar pattern of inflammation is related in part to the fact that the terminal bronchioles, alveolar ducts, and adjacent alveoli are the sites of maximum deposition of inhaled small particles (61). The other factor in this pattern is the fragile epithelium covering the terminal bronchioles and the more susceptible alveolar Type I cells lining the alveolar ducts and alveoli.

Necrosis and ulceration of bronchiolar, alveolar duct, and alveolar epithelium stimulate a predominantly intraluminal exudate which will vary from serous to fibrinous to mucopurulent, depending on severity and time frame. Lesser numbers of acute inflammatory cells and macrophages surround affected airways and adjacent blood vessels. Macrophages are a prominent feature of inflammatory infiltrates in lesions induced by particles and in resolving lesions in which epithelial necrosis has occurred.

Introduction of highly irritant materials into the lung parenchyma may induce localized acute necrosis with a pronounced suppurative inflammatory response (abscess), or a more slowly evolving granulomatous inflammatory response (see below). Pulmonary abscesses in rats in response to highly virulent pyogenic bacteria are very rare due to modern husbandry practices.

Acute inflammation in the lung parenchyma in response to infection with pathogenic murine respiratory viruses is characterized by a variable amount of epithelial necrosis and a suppurative inflammatory exudate in bronchioles and alveoli. This is often followed by a perivascular and peribronchiolar infiltrate of lymphocytes and plasma cells and hyperplasia of BALT.

The presence of numerous eosinophils in exudates and infiltrating the submucosa of airways, accompanied by perivascular infiltrates of lymphocytes and plasma cells is suggestive of, but not diagnostic for, an immuno-

logic or allergic basis for inflammatory lesions in lung parenchyma.

Chronic Inflammation

Continuous exposure or inability to clear toxic or infectious agents from lung parenchyma leads to more severe and widespread cellular and interstitial inflammation in an attempt to eliminate or sequester the etiologic agent. In rat lungs repeatedly exposed to cytotoxic or irritant materials, degeneration and necrosis of epithelial surfaces, and inflammatory infiltration and exudation induced by the initial exposure persists. However, it may decrease in severity and evolve into interstitial fibrosis, metaplasia, and hyperplasia of damaged bronchiolar and alveolar epithelium. Bronchiolization is a frequent feature of chronic inflammation induced in the centriacinar areas of the lungs of rats by repeated inhalation of toxicants (see above). Hyperplasia and neoplasia of respiratory tract tissues are illustrated in the Proliferative Lesions portion of this publication (74). Continued severe epithelial hyperplasia, remodeling, and metaplasia may progress to malignant epithelial neoplasia in rats repeatedly exposed to either high concentrations of relatively inert particles, or to very cytotoxic particles such as beryllium or nickel subsulfide. The significance of this carcinogenic response in rat lungs, with regard to prediction of toxicity of inhaled particles in humans, is the subject of controversy (50).

Granulomatous Inflammation (Figure 29)

Inflammatory lesions dominated by large numbers of macrophages, fibrosis, and lymphocytes are classified as granulomatous. Interlacing palisades of macrophages with abundant, finely granular cytoplasm (epithelioid cells) are the defining factor for a diagnosis of granulomatous inflammation. Multinucleated giant cells, formed from amitotic nuclear division or fusion of macrophages (24), are another hallmark of granulomatous inflammation. Granulomatous inflammation in the lung parenchyma can be caused either by infectious agents or by inhalation of foreign materials such as metals or dusts (24, 38). The type and severity of inflammatory response to foreign materials in the lung depends upon the physical characteristics and the amount of the material present. Pneumoconiosis is a generic term for the complex non-neoplastic granulomatous response of the lung to inhaled particles (38, 70). Crystalline silica, a material frequently used to study the pathogenesis of granulomatous inflammation in the lungs, has a range of cytotoxicity which varies widely with surface chemistry (59, 70).

A frequent cause of granulomatous inflammation in the lungs of laboratory rats is intentional exposure via inhalation or intratracheal instillation to insoluble or poorly soluble respirable particles in toxicity studies. Crystalline silica (quartz), titanium dioxide, diesel exhaust, and beryllium are examples of materials that have been studied

extensively in rats (7, 24). Accidental injection of foreign materials into the lung is also an important cause of pulmonary lesions in rats in toxicology studies. This may occur through improper gavage technique (6), or secondary to excessive salivation and laryngeal paralysis caused by anesthesia with barbiturates (21). Highly irritant foreign bodies may induce severe pulmonary edema, a fatal acute suppurative bronchopneumonia or a variable granulomatous inflammatory response in which foreign material may be visible within well-developed granulomas (17).

Pulmonary Fibrosis (Figures 30-32)

Pulmonary fibrosis may be defined morphologically as an observable increase in amount or abnormal location of collagen in lung parenchyma, resulting in disruption of the normal lung architecture (69), or an abnormality in the nature of collagen in the lung (30). Marked intraluminal fibrosis has been described in bronchioles of rats inhaling methyl isocyanate, a strong irritant. Fibrosis occurring as a sequel to lung injury has been reported most frequently in alveolar septa, interstitium, and pleura. Since fibrosis is considered an irreversible change, it is important to differentiate increases in the amount of mature, cross-linked collagen in these areas from increases in septal or interstitial thickness due to edema or inflammation without substantial protein cross-linking. Richards *et al.* (69) use the term fibrogenesis to describe potentially reversible fibroblast proliferation and minimal cross-linking of protein, as compared to true pulmonary fibrosis in which extensive cross-linking has occurred and lesions are not reversible.

The critical event in the pathogenesis of pulmonary fibrosis is generally considered to be the release of potentially fibrogenic cytokines and fibronectin from macrophages activated as part of the inflammatory response to injury of lung parenchyma. Pulmonary fibrosis in laboratory rats is most frequently observed as part of a chronic inflammatory response to repeated injury to lung parenchyma. However, severe acute lung injury from a single exposure may induce a relatively rapid fibrogenic response that may or may not be reversible. Diffuse interstitial fibrogenesis appears rapidly following single exposures to bleomycin or carmustine (BCNU), but resolves within 90 days. However, repeated exposure to these toxicants induces irreversible pulmonary fibrosis (69). The fibrogenic potential of inhaled particles varies widely; crystalline silica (quartz) is the classic model for induced pulmonary fibrosis in rats. Septal fibrosis is readily demonstrated in the lungs of rats repeatedly exposed to cytotoxic quartz particles and held for a prolonged post-exposure period. Slowly progressive increases in interstitial collagen have been demonstrated during repeated exposures to ozone. Subpleural and pleural fibrosis may be prominent in rats chronically exposed via inhalation to respirable mineral fibers. The issue of reversibility of

interstitial fibrosis in post-exposure periods following repeated exposures to ozone is not clear (18). Trichrome, Van Gieson's collagen stain, or other special stains are used to identify and quantify collagen in lung parenchyma. Biochemical and morphometric techniques are available to quantitatively determine collagen content in lungs of experimental animals (69).

ABNORMAL DILATATION/DESTRUCTION OF ALVEOLI

Pulmonary Acinar Ectasia (Hyperinflation) (Figure 33)

Pulmonary acinar ectasia, a mild dilatation of alveoli and alveolar ducts, most frequently subpleural, is seen in aged rats. The lesion can result in an increase in internal surface area of the lung and reduced gas exchange efficiency (49). It has been suggested that this is a "remodeling" of the lung associated with aging. This lesion has been classified as emphysema, but is not consistent with the definition of alveolar emphysema, as there is no destruction of alveolar walls (17).

Another morphologic change that may appear as emphysema is an artifact related to improper instillation of fixative through the airways. The disproportionate filling of pulmonary alveoli results in apparent dilatation. This artifactual change should not be mistaken for emphysema.

Alveolar Emphysema (Figure 34)

Pulmonary emphysema, strictly defined as abnormal enlargement of the air spaces distal to the terminal bronchiole accompanied by destructive changes of the alveolar walls, does not occur as a spontaneous lesion in rats. Alveolar emphysema in rats can result from various injuries to the lung. Intratracheal instillation of pancreatic elastase or papain is used to induce emphysema in rats for experimental purposes (13, 37). Inhalation of cytotoxic particles, such as various nickel compounds, will also induce emphysema by causing intense focal inflammation. The prevailing theory of pathogenesis of this disease is that inflammation involving lung parenchyma leads to an excess of elastase relative to its inactivating protein, with eventual degeneration of matrix. Sendai virus infection in neonatal rats has been reported to induce alveolar emphysema by four months of age (14). The lungs of rats continue to grow until about ten months of age (49). The inflammation induced by the viral infection in a rapidly growing lung may represent another way for emphysema to develop in the rat.

Atelectasis

Atelectasis refers to collapse of all, or a portion of, pulmonary alveoli. It is most often observed as a focal collapse of alveoli distal to airways obstructed by inflammatory exudates or tumors. Atelectasis may be observed

in alveoli distal to severe bronchiectasis (see above), and has been reported to occur in rats with rat coronavirus infection (58).

VASCULAR CHANGES

Pulmonary Congestion and Hemorrhage (Figure 35)

Diffuse dilatation of pulmonary capillaries is difficult to differentiate from agonal changes in the lungs of rats that are necropsied following a delay of 20 minutes or longer after having died spontaneously, or rats that are euthanized with carbon dioxide (75). This change is of no significance in the absence of other evidence of an antemortem lesion in the lungs or vasculature. Small hemorrhages, usually in subpleural alveoli, may also occur as an agonal event in rats that die spontaneously or rats that are euthanized with 100% carbon dioxide. The severity of these intra-alveolar hemorrhages is roughly proportional to the chamber concentration of carbon dioxide (R. Renne, unpublished data). The use of 70% carbon dioxide, although occasionally inducing small areas of hemorrhage in alveoli, does not interfere with routine evaluation of rat lung morphology by light microscopy. Pulmonary hemorrhage due to primary damage to endothelium has been described in rats experimentally poisoned with paraquat (38).

Pulmonary Edema (Figures 36, 37)

Pulmonary edema results from either alteration in pulmonary hemodynamics or damage to the air-blood barrier in alveolar walls. Mild or early interstitial pulmonary edema may be detected by light microscopy as a widening of the perivascular and interlobar spaces. If the primary cause of edema is direct damage to alveolar walls, or if interstitial edema is severe and prolonged enough to overwhelm the capability of the lymphatics to remove fluid, alveolar edema will result. Edema fluid in alveoli is visible as a pink-staining homogenous material; depth of pink staining is proportional to the protein content of the fluid. Detection of fibrin in alveolar fluid (indicative of a more severe lesion than simple edema) is aided by staining with phosphotungstic acid hematoxylin (PTAH). Simple edema of alveoli may be differentiated from accumulated surfactant material in alveolar lipoproteinosis by the presence of numerous intra-alveolar macrophages in lipoproteinosis.

Pleural effusion of edema fluid occurs relatively frequently in rodent lungs; fluid readily passes through stomata in the thin pleura (30). Critical assessment of the location and severity of alveolar edema in rat lungs fixed via intratracheal instillation of fixative is complicated by the instilled fixative changing the distribution of the edema fluid (17). Severe pulmonary edema may be acutely lethal in an organ as vital and as richly vascular as the lung.

Pulmonary Emboli (Figure 38)

Emboli consisting of fragments of hair or skin in pulmo-

nary arteries or capillaries have been reported to occur in over 20% of rats repeatedly injected intravenously in toxicology studies (39). These foreign bodies induce a suppurative or granulomatous response of variable size, including multinucleated giant cells. The keratinized tissue (hair) is readily identifiable by its birefringence in polarized light.

Medial Hypertrophy of Pulmonary Arteries (Figure 39)

Chronic pulmonary hypertension has been induced in rats by chronic hypoxia, hyperoxia, and monocrotaline (52, 64). The pulmonary vascular lesions characterizing this disease at the light level include hypertrophy of smooth muscle and increased connective tissue in tunica media and increased connective tissue in adventitia of normally muscular intra-acinar arteries. The internal elastic lamina is visible in affected arteries. Smooth muscle is present in the walls of normally nonmuscular peripheral arteries due to hypertrophy and hyperplasia of pericytes and intermediate cells. Using special fixation and preparation techniques (52), it is possible to quantify the changes in wall thickness in affected rats.

Mineralization (Figure 40)

Focal mineralization of the walls of pulmonary arteries is frequently observed in older rats, usually with no apparent effect on the lung parenchyma. This material is subintimal, but may affect the media in more severe cases (17). Mineralization of alveolar walls and pulmonary vessels is present in severe cases of chronic nephropathy of aged rats, and may be accompanied by increased numbers of macrophage aggregates, or acute serous inflammation (6).

DISCUSSION

Non-proliferative lesions of the rat respiratory tract are often more subtle and thus more difficult to detect and interpret than proliferative lesions in these tissues. Mild or early degenerative epithelial lesions may be easily overlooked without close comparison to normal tissues from unexposed control animals of the same age and sex. Conversely, it is important to make sure that observed differences in morphology are not variations within the normal range of microscopic anatomy related to age, sex, or simply individual variation. These potential pitfalls point out the importance of maintaining uniformity in necropsy and histology techniques, methods of microscopic examination, as well as genetics, age, husbandry, and exposure parameters for experimental animals.

Diagnosis and evaluation of non-proliferative lesions in the respiratory tract are critically important in the conduct and interpretation of any rodent toxicity study. This is obvious for detection of the irritant, sensitizing, or

necrotizing properties of test compounds for purposes of safety evaluation. It is also important for early detection and evaluation of the potential for test materials to induce carcinogenesis in respiratory tract tissues. Repeated loss and regeneration of affected cells is a critical step in the process of epigenetic carcinogenesis. Detection of subtle changes leading to loss of cells as a result of single exposures to xenobiotics may be the first indication of processes which evolve with repeated exposure to proliferative lesions and culminate in neoplasia in the same cell population.

RECOMMENDED NOMENCLATURE WITH DIAGNOSTIC CRITERIA

NASAL CAVITY

Congenital Lesions

Cleft Palate

1. Longitudinal defect of bone and mucosa in midline of hard palate, opening into nasal cavity

Disturbances of Growth

Odontodysplasia

1. Disorderly growth of tooth bud elements
2. Loss of normal dental microscopic architecture
3. May cause compression of adjacent nasal cavity

Epithelial Changes

Atrophy

1. Single cell layer of flattened, featureless epithelium

Degeneration

1. Cellular swelling, blebbing and increased intercellular spaces
2. Dilatation (ectasia) of nasal glands with accumulation of secretory material

Eosinophilic Inclusions (Globules, Droplets)

1. Amorphous eosinophilic material, negative for special stains
2. Present in respiratory, olfactory or glandular epithelium

Corpora Amylacea

1. Small basophilic or amphiphilic concretions in the lamina propria or nasal gland lumens

Necrosis

1. Karyorrhexis or pyknosis of nuclei
2. Exfoliation of affected epithelial cells

3. Transitional or respiratory epithelium lining the dorsal medial, middle medial, and lateral meatuses are often the first areas affected
4. Continued necrosis leads to ulceration, fibrinous exudates
5. Atrophy of axons in adjacent lamina propria is sequel to necrosis of olfactory epithelium
6. Necrosis of nasal glands leads to replacement with fibrous tissue
7. Olfactory epithelium lining dorsal medial meatus most often affected by direct-acting toxicants

Erosion/Ulceration

1. Erosion: Loss of epithelium but basement membrane intact
2. Ulceration: Loss of epithelium, basement membrane
3. Fibrinous or suppurative inflammation over affected area

Regeneration

1. Sequel to loss of epithelium with intact basement membrane is rapid replacement with same epithelial type if injury is not repeated
2. Concurrent regeneration and degeneration may create disorganized histologic appearance (rosette-like formation in olfactory epithelium)
3. Squamous or respiratory metaplasia are possible sequelae to repeated damage
4. Must differentiate flattened regenerative epithelium from squamous metaplasia

Inflammation

Acute Inflammation

1. Edema of lamina propria
2. Accumulation of neutrophils in mucosa
3. Serous, fibrinous, mucous, or suppurative exudate in lumen
4. Eosinophils in exudate or mucosa may indicate immunologic factor in lesion

Granulomatous Inflammation

1. Macrophages, epithelioid cells, giant cells are predominant cell types
2. Inflammation, fibrosis centered around foreign body or organisms

Chronic Inflammation

1. Infiltration of lymphocytes, fibroblasts, and macrophages into lamina propria
2. Hyperplasia/metaplasia of epithelium
3. Fibrosis and adhesion of nasal turbinates
4. Atrophy of turbinates

Osteofibrosis

1. Fibrous tissue of variable density (depending on duration) involving turbinates adjacent to areas of

prolonged severe necrosis and inflammation

Vascular Changes

Congestion/Hyperemia/Edema

1. Pooling of blood in mucosal vessels and extravasation of eosinophilic edema fluid related to moribund condition, acute inflammation

Hemorrhage/Thrombosis

1. Free blood in lumen of nasolacrimal duct or nasal cavity following antemortem blood collection via retroorbital plexus
2. Thrombi in nasal vessels seen in severe leukemia in F344 rat

LARYNX, TRACHEA, AND BRONCHI

Epithelial Changes

Degeneration

1. Loss of cilia in columnar epithelial cells
2. Rounding of normally cuboidal/columnar epithelium
3. Decrease in numbers of globule leucocytes

Necrosis

1. Pyknosis or karyorrhexis of nuclei
2. Exfoliation of affected epithelial cells
3. Laryngeal necrosis occurs most frequently in transition zone at base of epiglottis

Ectasia, Submucosal Glands

1. Squamous metaplasia of overlying epithelium blocks ducts
2. Rupture of ectatic glands induces inflammatory response

Erosion/Ulceration

1. Erosion: Loss of epithelium but basement membrane intact
2. Ulceration: Loss of epithelium and basement membrane
3. Fibrinous or suppurative inflammation over eroded area

Regeneration

1. Sequel to loss of epithelium with intact basement membrane is rapid replacement with same epithelial type if injury is not repeated
2. Squamous metaplasia is possible sequel to repeated damage
3. Must differentiate flattened regenerative epithelium from squamous metaplasia

Inflammation

Acute Inflammation

1. Mild serous to suppurative infiltrate accompanies epithelial damage
2. Mucosal necrosis, inflammation may lead to necrosis of underlying cartilages
3. Severe edema, fibrinous inflammation can occlude lumen
4. Infectious agents induce lesions similar to those in nasal cavity

Chronic Inflammation

1. Foreign bodies induce chronic suppurative exudate in ventral pouch
2. Cystic lesions in submucosal glands due to squamous metaplasia of overlying mucosal epithelium

Bronchiectasis

1. Severe bronchial dilatation, lumen filled with mucopurulent exudates
2. Alveolar atelectasis and various degrees of alveolar inflammation and fibrosis
3. Fibrosis in and around bronchial walls

BRONCHIOLES, ALVEOLI, AND PLEURA

Congenital Lesions

Cysts

1. Isolated large cyst in lung parenchyma, lined only by fibrous tissue
2. No evidence of inflammation

Pulmonary Hypoplasia

1. Decreased total lung volume
2. Decreased total lung tissue volume
3. Decreased development of alveoli
4. Retarded differentiation of alveolar Type I cells to Type II cells

Epithelial Changes

Degeneration

1. Loss of cilia from bronchiolar epithelium
2. Rounding of normally cuboidal/columnar epithelial cells
3. Loss of apical blebs in Clara cells

Necrosis

1. Karyorrhexis or pyknosis of nuclei
2. Exfoliation of epithelial cells into bronchiolar or alveolar lumen
3. Cytokine release stimulates influx of macrophages, inflammation

Regeneration

1. Sequel to loss of bronchiolar epithelium with intact basement membrane is rapid replacement with same epithelial type if injury is not repeated
2. Must differentiate flattened regenerative epithelium from squamous metaplasia
3. Alveolar duct and alveolar epithelium are replaced by proliferation of bronchiolar and/or alveolar Type II epithelium

Intra-Alveolar Lesions

Alveolar Histiocytosis (Alveolar Macrophage Aggregates)

1. Small aggregates of macrophages are seen frequently in subpleural alveoli of aged rats
2. Macrophages may contain degenerated phospholipid and/or phagocytized particles

Alveolar Lipoproteinosis (Phospholipidosis)

1. Alveoli filled with acellular, eosinophilic, PAS(+) material and numerous macrophages filled with foamy cytoplasm

Pigments/Dusts

1. Endogenous pigments: hemosiderin, lipofuscin
2. Exogenous pigments: carbonaceous pigments retain dark color in processing

Inflammation

Acute Alveolar/Interstitial Inflammation

1. Serous, fibrinous, or mucopurulent exudate in alveoli

Chronic Interstitial Inflammation

1. Septal and interstitial fibrosis
2. Perivascular and peribronchiolar mononuclear inflammatory cell infiltrates
3. Hyperplasia of BALT

Acute Bronchioloalveolar Inflammation

1. Serous, fibrinous, or mucopurulent exudate in terminal bronchioles, alveolar ducts, and alveoli (centriacinar deposition)
2. Eosinophils, mast cells in exudate or submucosa suggest immunologic basis for inflammation

Chronic Inflammation

1. Perivascular and peribronchiolar lymphocytes may persist or replace acute inflammatory cells
2. Replacement of alveolar duct and alveolar epithelium with bronchiolar epithelium (bronchiolization)
3. Bronchiolar and alveolar (Type II cell) epithelial hyperplasia
4. Squamous metaplasia of bronchiolar and/or alveolar epithelium

5. Metaplasia of Clara cells, alveolar Type II cells to goblet cells
6. Septal, interstitial, and pleural fibrosis
7. Hyperplasia of BALT

Granulomatous Inflammation

1. Macrophages are predominant inflammatory cells
2. Presence of epithelioid cells

Pulmonary Fibrosis

1. Increased amount, abnormal location, or abnormal nature of collagen in lung parenchyma
2. Intraluminal fibrosis in bronchioles seen as sequel to severe necrosis
3. Special stains may be required to demonstrate changes in collagen
4. The term *fibrogenesis* may be used to differentiate potentially reversible fibroblast proliferation with minimal protein cross-linking from irreversible pulmonary fibrosis with extensive cross-linking

Abnormal Dilatation/Destruction of Alveoli

Pulmonary Acinar Ectasia (Hyperinflation)

1. Mild dilatation of alveoli
2. Usually subpleural in aged rats
3. No morphologic evidence of alveolar wall destruction
4. May be related to overinflation with intratracheally instilled fixative

Alveolar Emphysema

1. Abnormal enlargement of airspaces distal to terminal bronchiole
2. Morphological evidence of alveolar wall destruction

Atelectasis

1. Collapse of all or portion of alveoli
2. Usually focal lesion distal to obstructed airway
3. Component of severe suppurative airway inflammation
4. Reported in Rat Coronavirus infection

Vascular Changes

Pulmonary Congestion and Hemorrhage

1. Dilatation of alveolar capillaries widens alveolar septa
2. Variable sized intra-alveolar hemorrhages in subpleural alveoli

Pulmonary Edema

1. Widening of perivascular and interlobar spaces (interstitial edema)
2. Present in alveoli as faintly pink-staining homogenous material
3. Differentiate from fibrin using PTAH stain
4. Differentiate from extracellular pulmonary

surfactant by presence of numerous macrophages phagocytizing surfactant and particulate material

5. Pleural effusion frequently occurs with severe pulmonary edema in rat

Pulmonary Emboli

1. Suppurative or granulomatous inflammation surrounding hair shaft in vessel
2. Keratin visible with polarized light

Medial Hypertrophy of Pulmonary Arteries/Pulmonary Hypertension

1. Hypertrophy of smooth muscle and increased connective tissue in tunica media of normally muscular intra-acinar arteries
2. Increased connective tissue in adventitia of normally muscular arteries
3. Increased ratio of thickness of media/total diameter of intra-acinar arteries
4. Presence of muscle in wall of normally nonmuscular peripheral arteries due to hyperplasia and hyperplasia of pericytes and intermediate cells
5. Presence of visible internal elastic lamina in affected peripheral arteries

Mineralization

1. Linear mineralization of alveolar septa and pulmonary vessels
2. May be accompanied by macrophages, inflammation

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Fig. 1 - Focal atrophy, olfactory epithelium. (H&E).

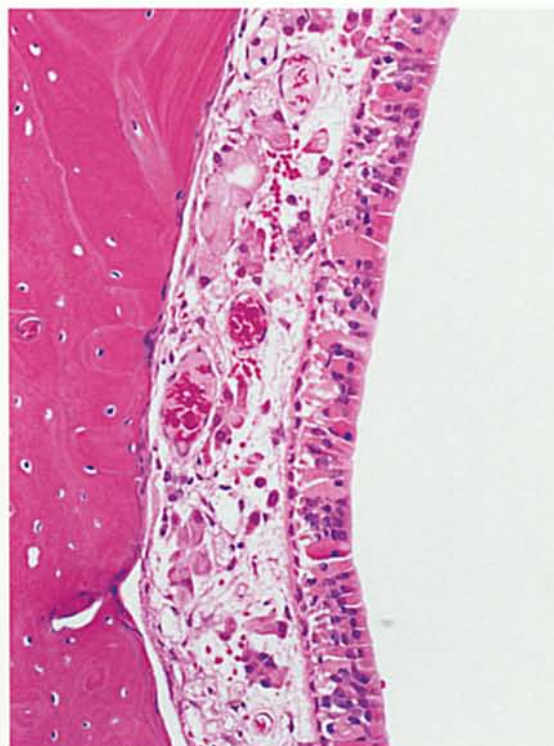


Fig. 2 - Degeneration of olfactory epithelium and axonal atrophy. (H&E).



Fig. 3 - Ectasia of submucosal glands, chronic inflammation. (H&E).



Fig. 4 - Degeneration of epithelium, vomeronasal organ. (H&E).

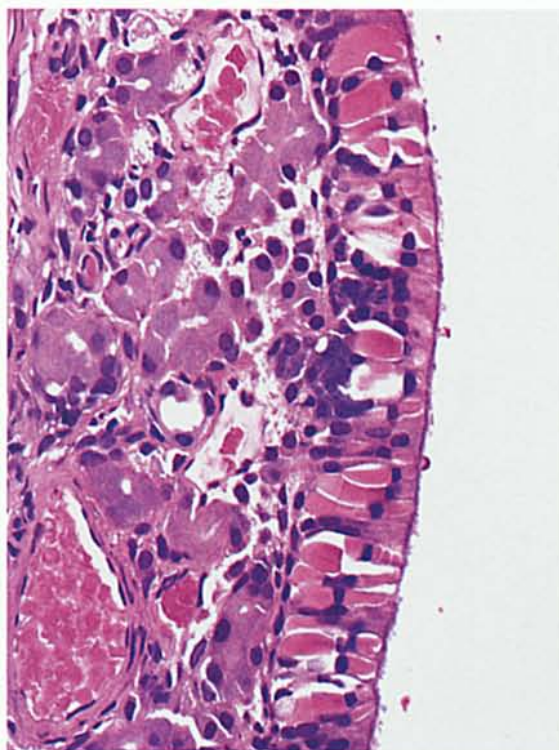


Fig. 5 - Eosinophilic inclusions in olfactory epithelium. (H&E).

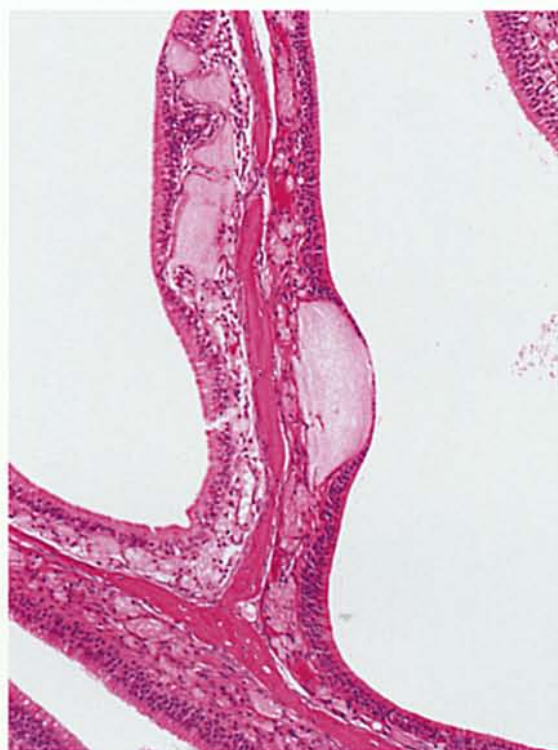


Fig. 6 - Corpora amylacea, ethmoidal turbinates. (H&E).



Fig. 7 - Early/mild necrosis, olfactory epithelium. (H&E).



Fig. 8 - Synechia, osteofibrosis, chronic inflammation, ethmoidal turbinates. (H&E).



Fig. 9 - Fibrosis of submucosal glands. (H&E).

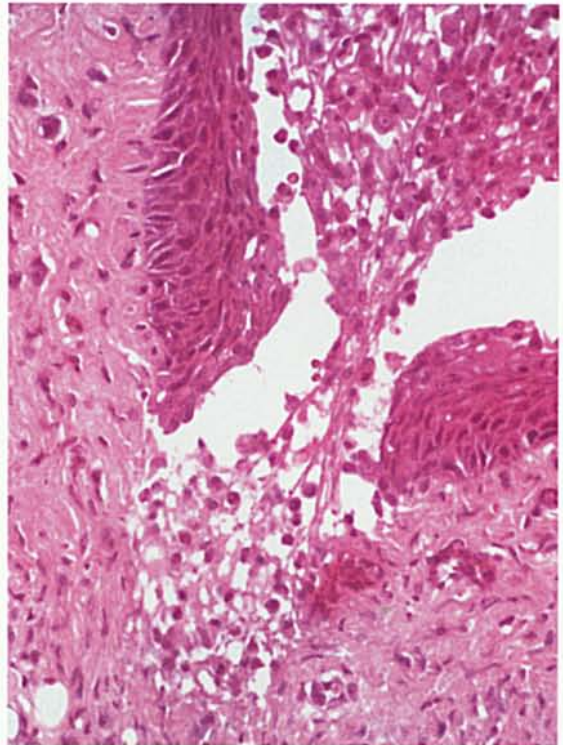


Fig. 10 - Ulceration of squamous epithelium, fibrinopurulent exudate. (H&E).

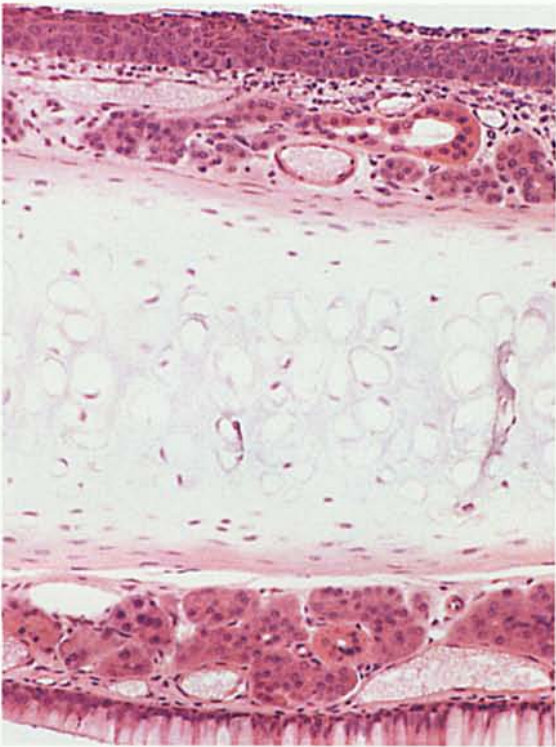


Fig. 11 - Necrosis, regeneration of nasal respiratory epithelium, suppurative inflammation. (H&E).

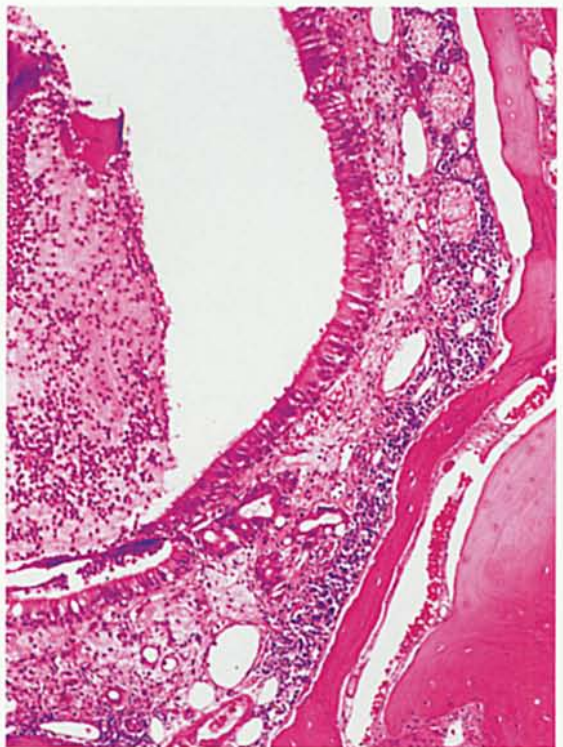


Fig. 12 - Suppurative inflammation, nasal respiratory mucosa. (H&E).

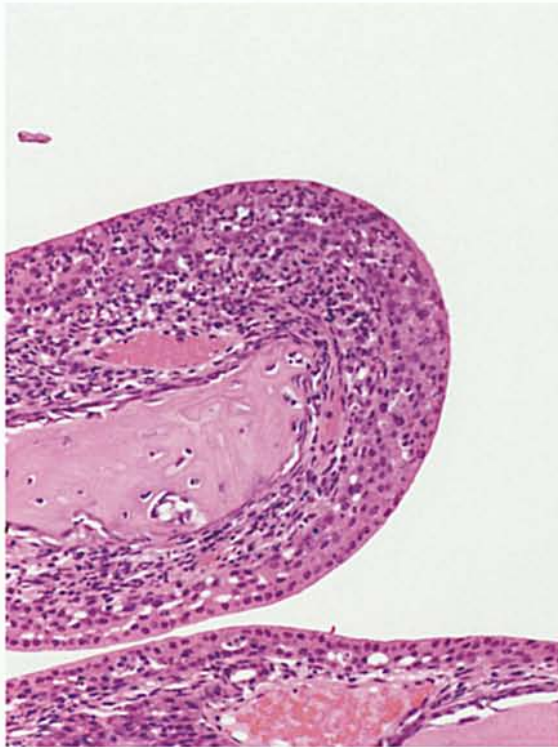


Fig. 13 - Suppurative inflammation, tip of nasal turbinate. (H&E).

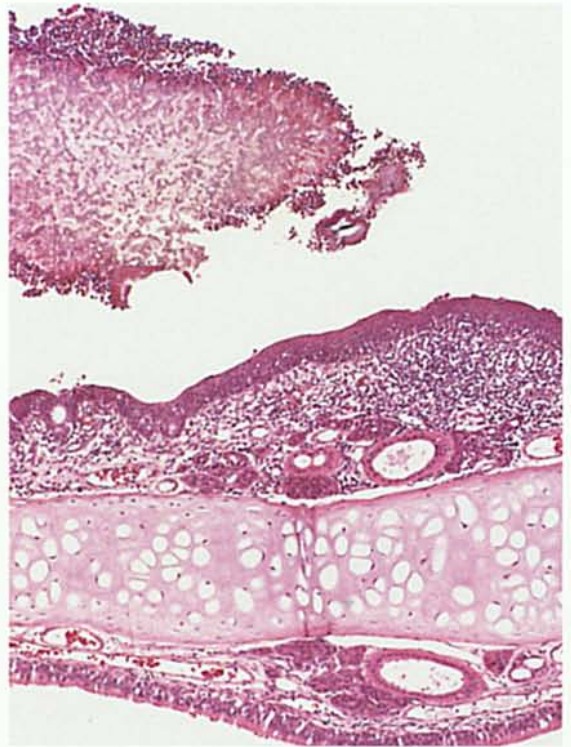


Fig. 14 - Granulomatous inflammation, nasal cavity. (H&E).

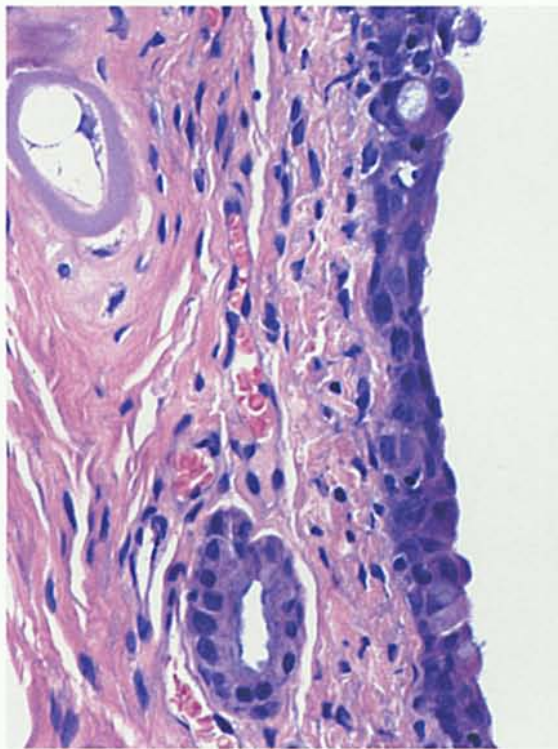


Fig. 15 - Degeneration of mucosal epithelium of base of epiglottis with loss of cilia. (H&E).

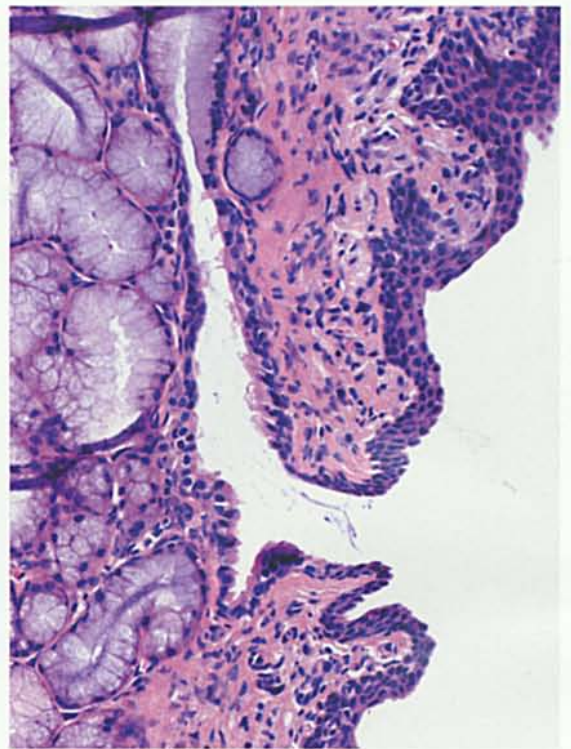


Fig. 16 - Squamous metaplasia of submucosal gland excretory duct at base of epiglottis. This predisposes to obstruction of duct, ectasia of glands. (H&E).

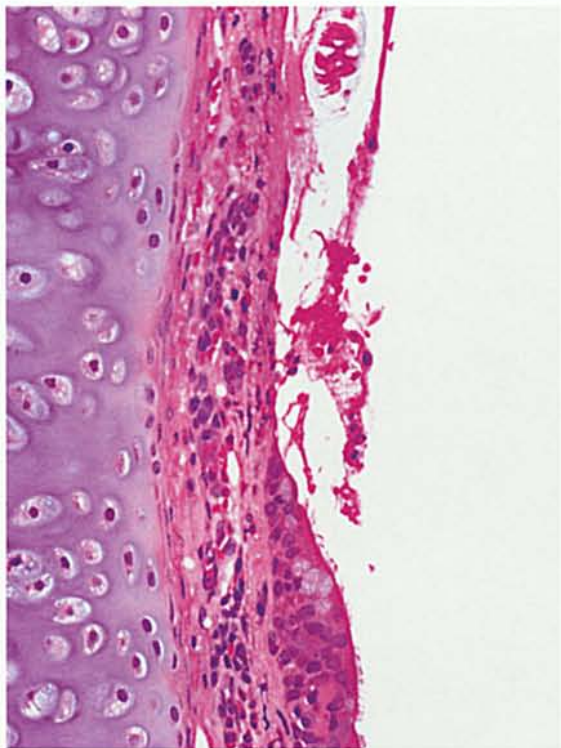


Fig. 17 - Ulceration of tracheal epithelium. (H&E).

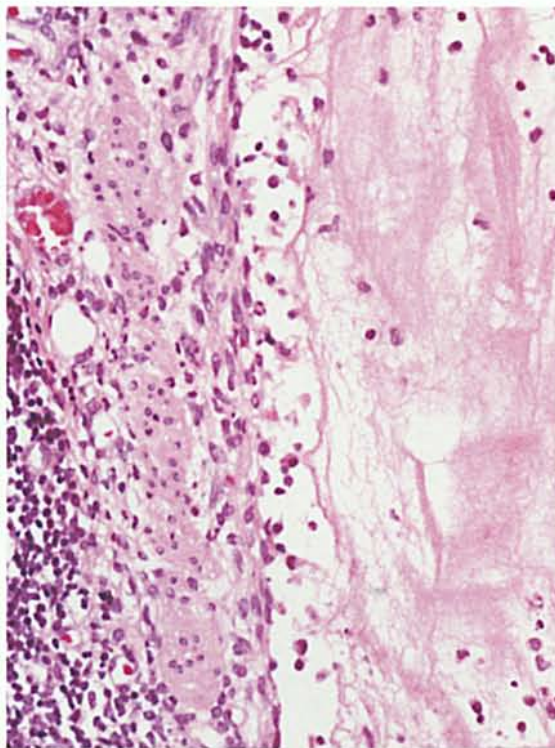


Fig. 18 - Acute fibrinopurulent inflammation in bronchial mucosa with ulceration. (H&E).

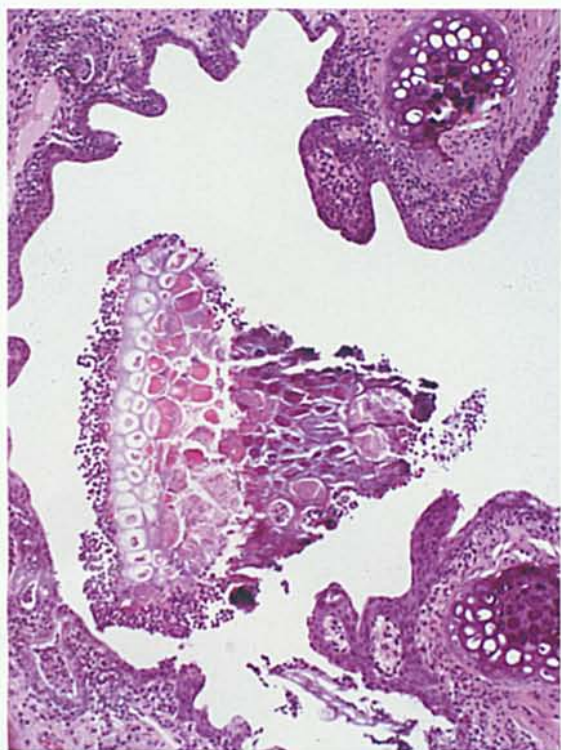


Fig. 19 - Chronic inflammation in ventral pouch of larynx due to presence of foreign body. (H&E).

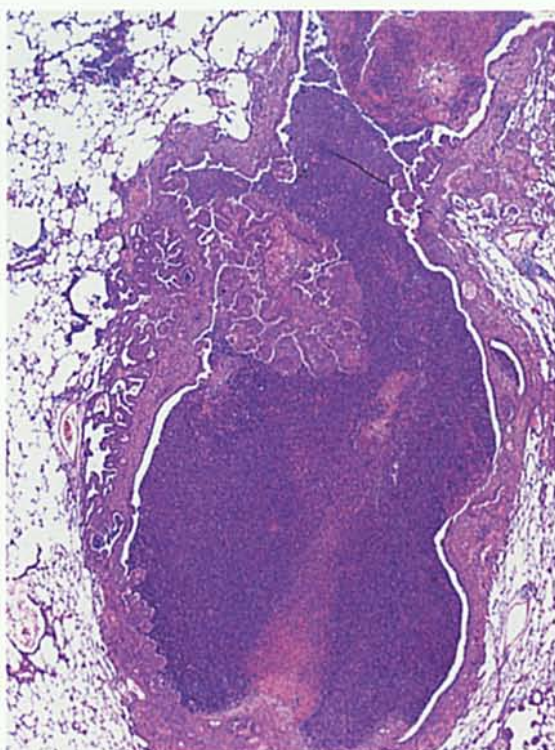


Fig. 20 - Bronchiectasis with suppurative exudate secondary to Sendai virus infection. (H&E).

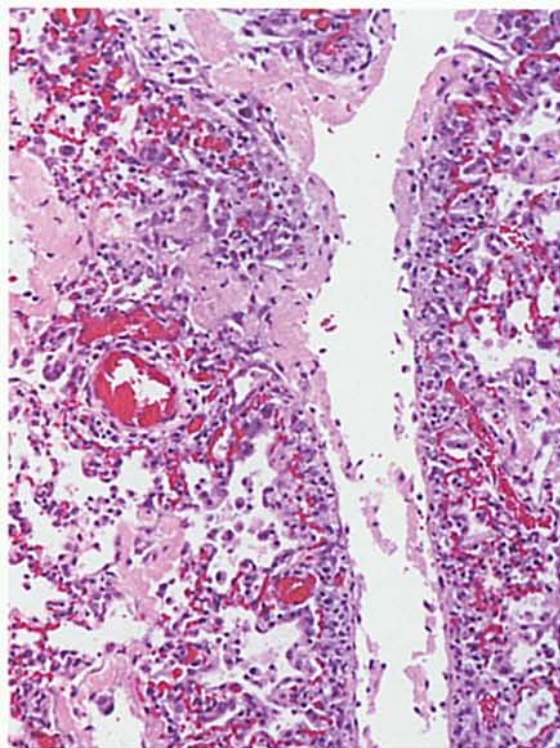


Fig. 21 - Necrotic epithelium sloughing into bronchiolar lumen. (H&E).

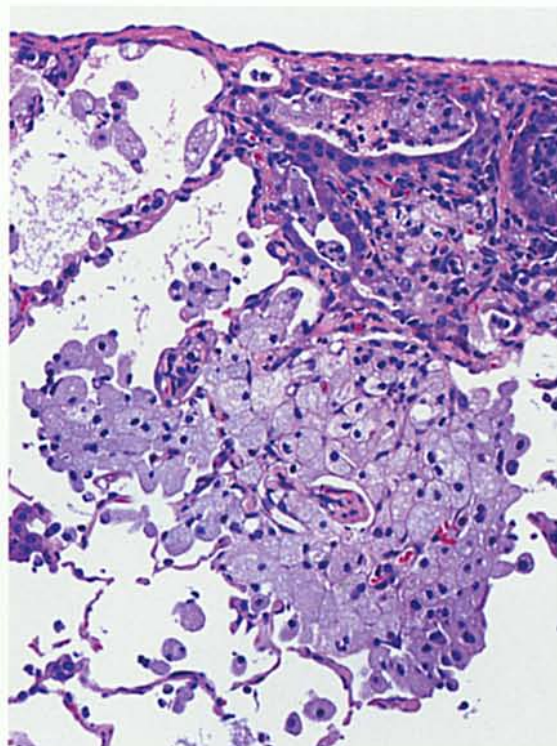


Fig. 22 - Subpleural alveolar macrophage aggregates. (H&E).

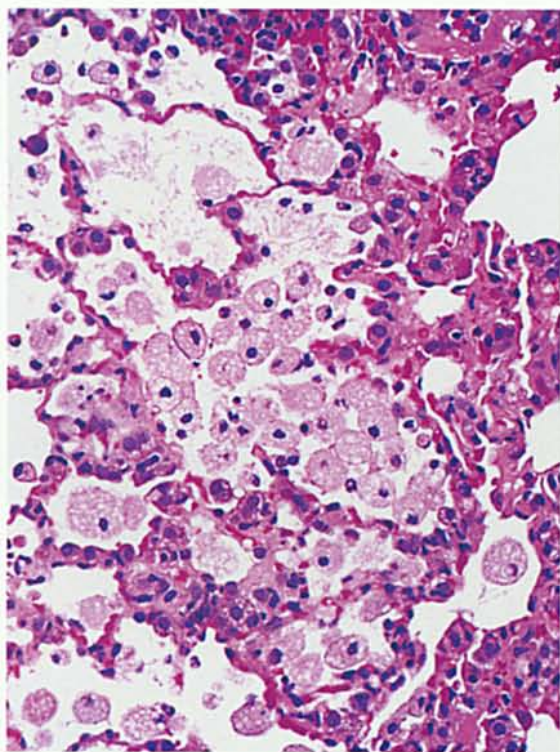


Fig. 23 - Alveolar histiocytosis and lipoproteinosis. (H&E).

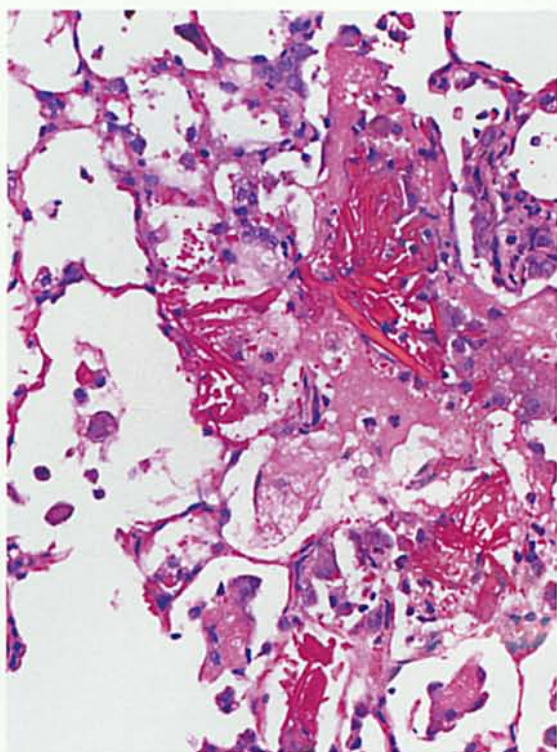


Fig. 24 - Hemoglobin crystals in alveoli. (H&E).

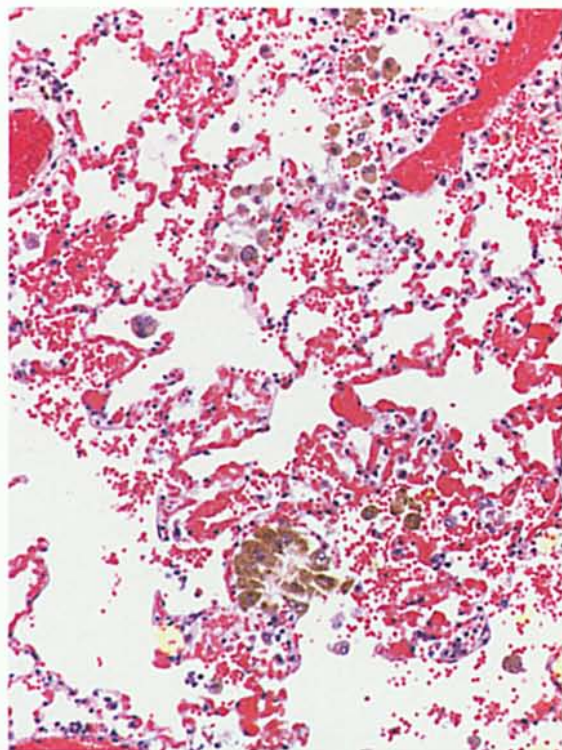


Fig. 25 - Phagocytized foreign material (corn oil) in alveoli. (H&E).

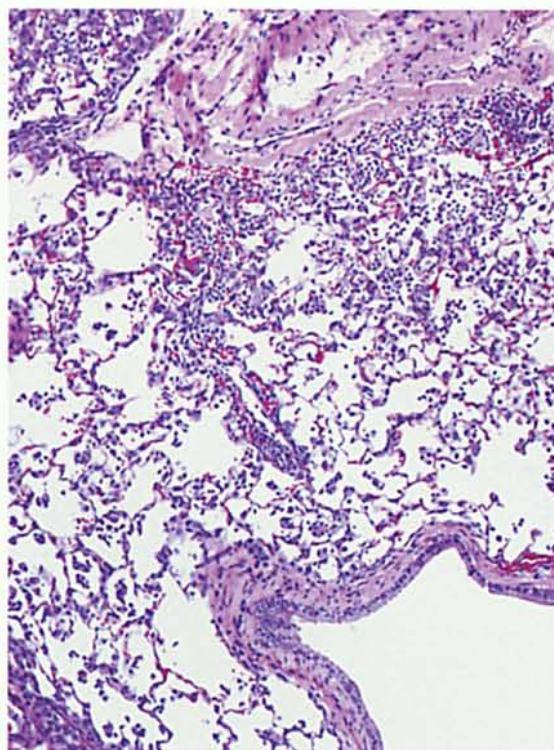


Fig. 26 - Suppurative inflammation, alveoli. (H&E).

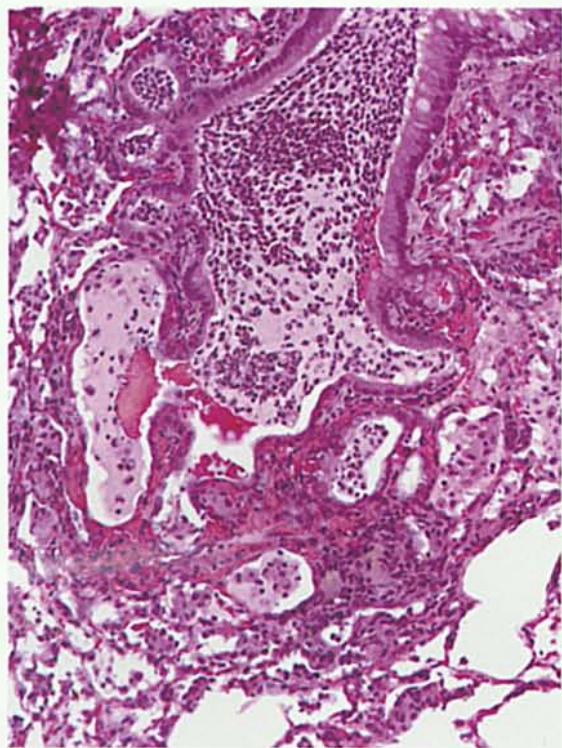


Fig. 27 - Suppurative inflammation, bronchiole and adjacent alveoli (bronchopneumonia). (H&E).

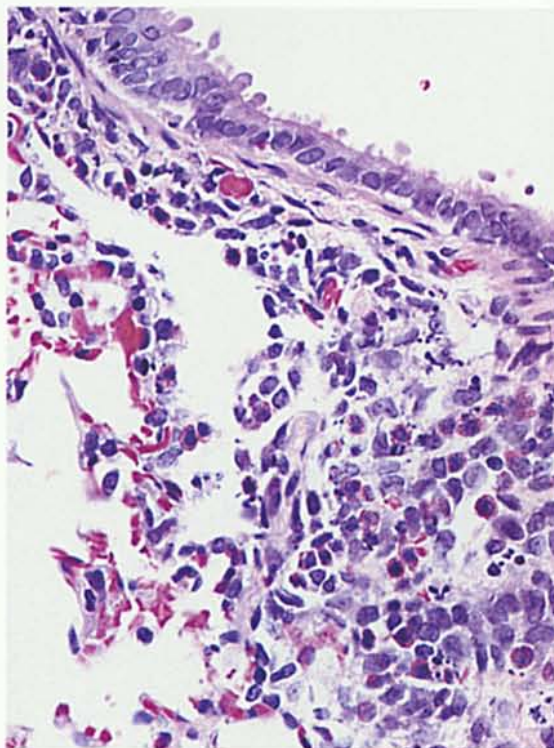


Fig. 28 - Eosinophils around bronchiole. (H&E).

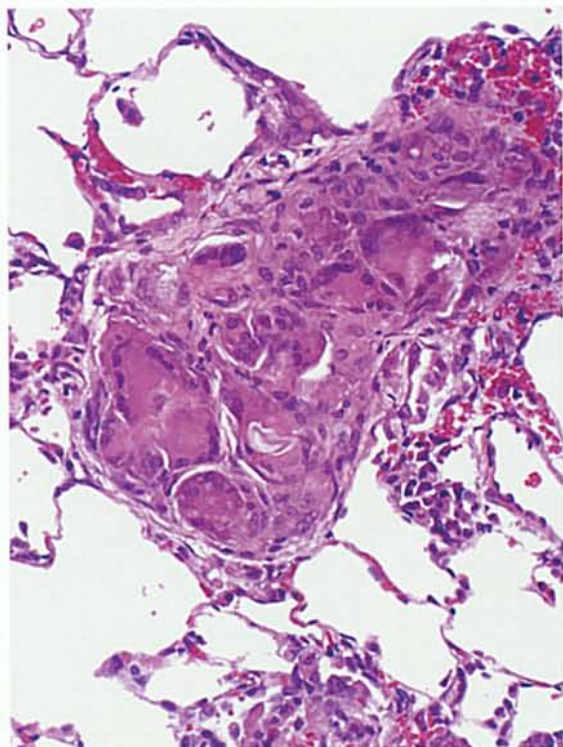


Fig. 29 - Multinucleated giant cells in lung parenchyma. (H&E).

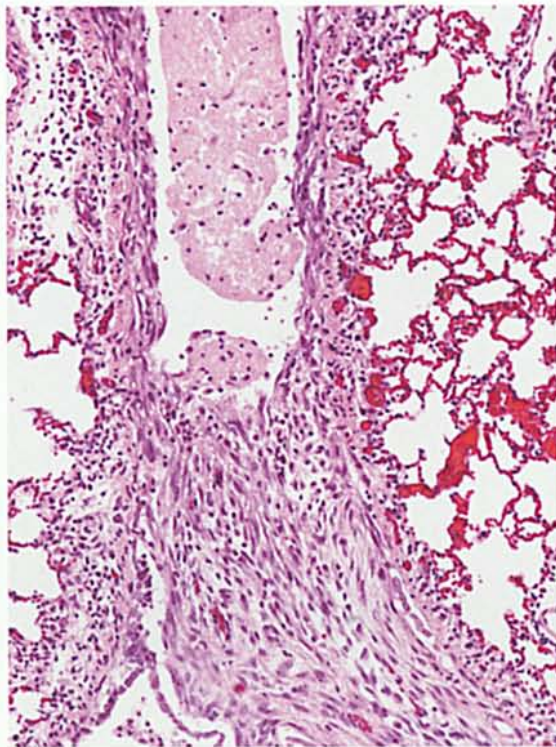


Fig. 30 - Fibrosis and necrotic debris in bronchiolar lumen. (H&E).

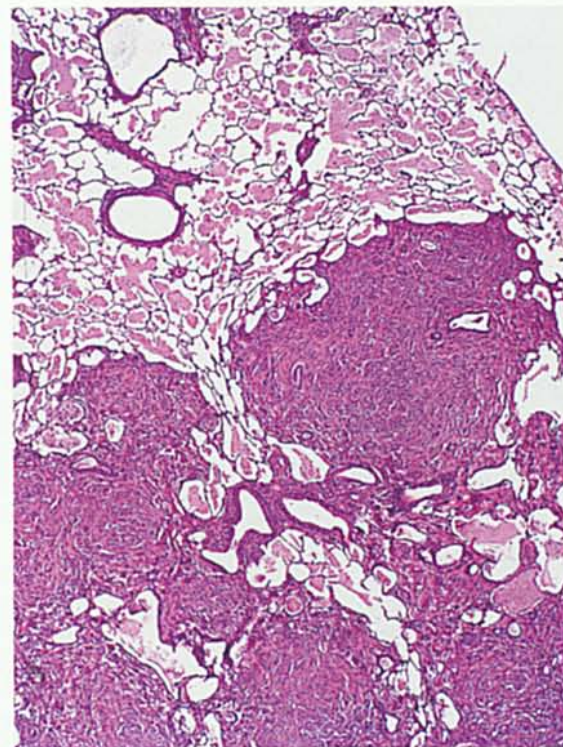


Fig. 31 - Severe pulmonary fibrosis and alveolar lipoproteinosis. Rat exposed to quartz. (H&E).

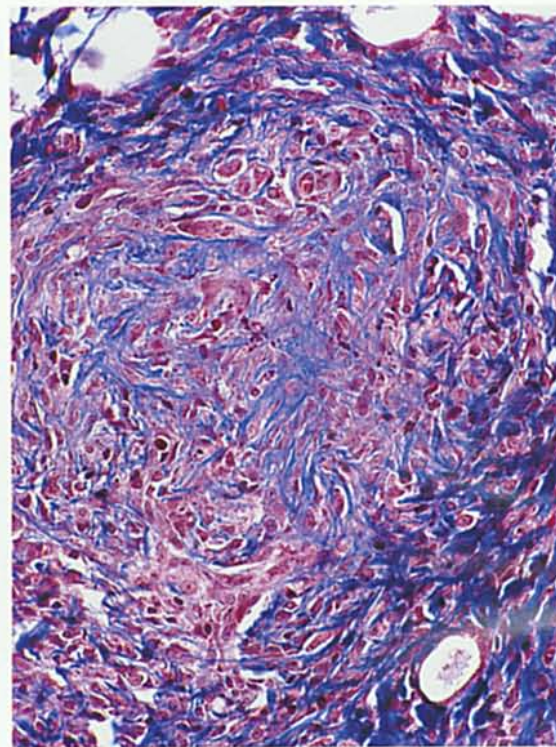


Fig. 32 - Pulmonary fibrosis. Trichrome stain.



Fig. 33 - Pulmonary acinar ectasia due to overinflation with fixative. (H&E).

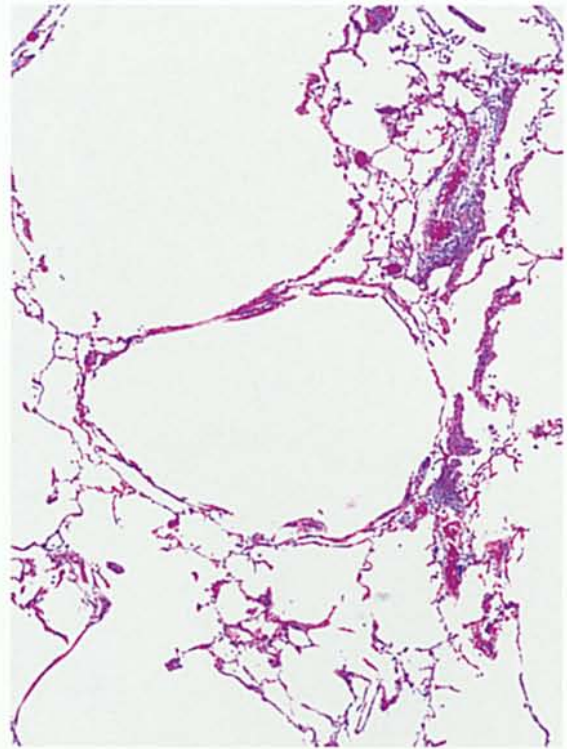


Fig. 34 - Alveolar emphysema induced by exposure to elastase. (H&E).

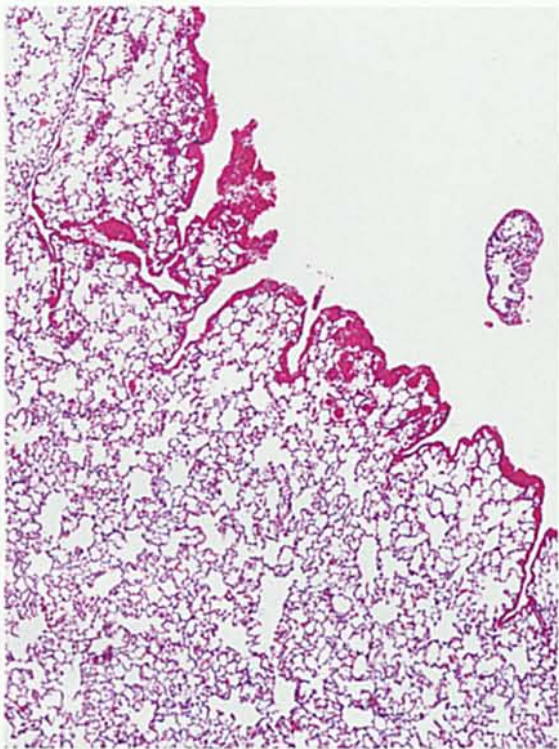


Fig. 35 - Subpleural hemorrhage due to euthanasia with 100% carbon dioxide. (H&E).

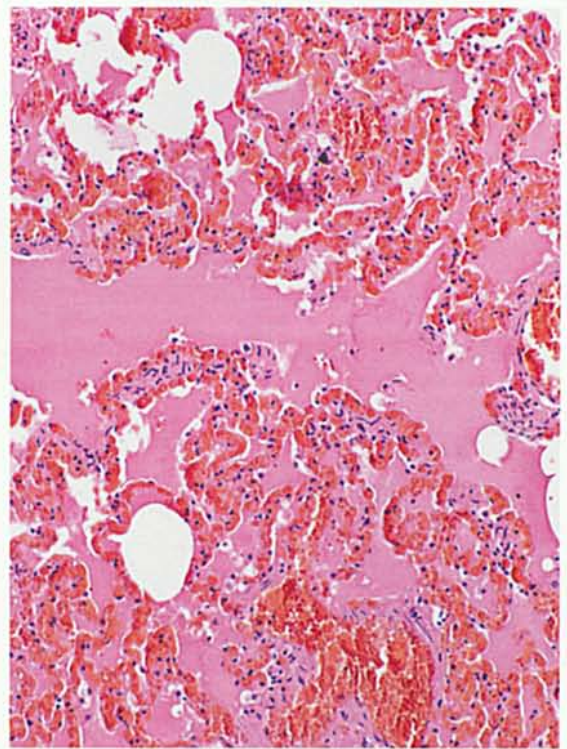


Fig. 36 - Congestion and edema, alveoli. (H&E).



Fig. 37 - Perivascular edema, lung. (H&E).

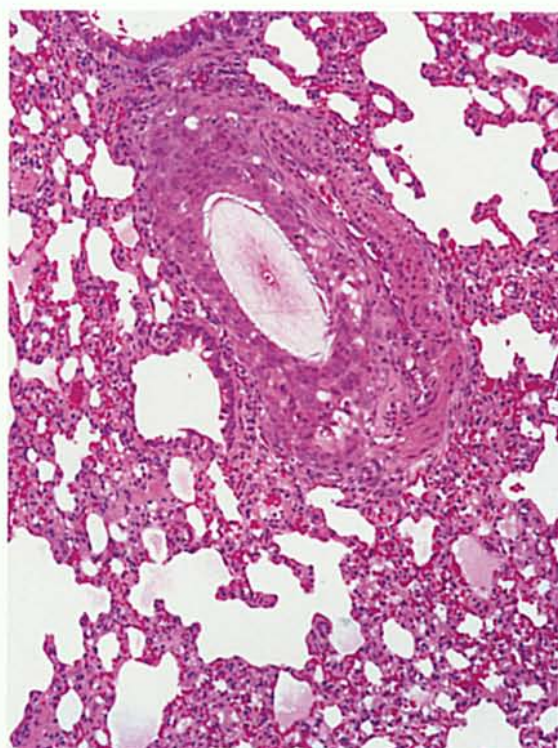


Fig. 38 - Hair embolus, pulmonary artery. (H&E, polarized light).

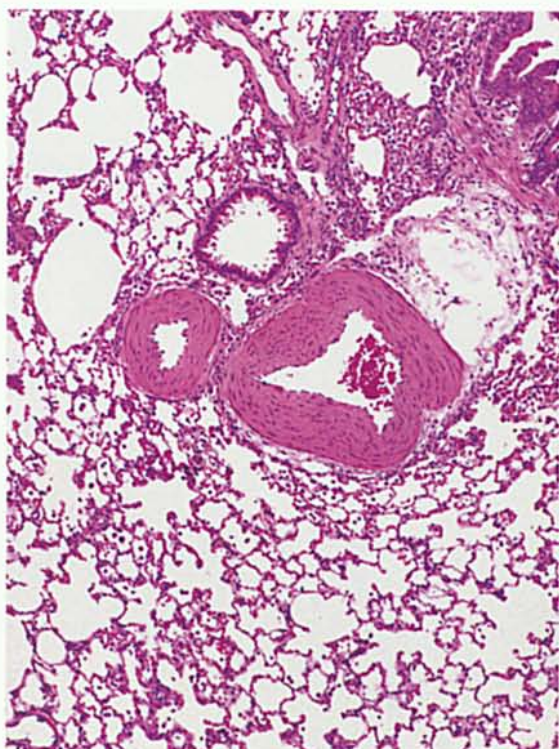


Fig. 39 - Medial hypertrophy, pulmonary artery. (H&E).

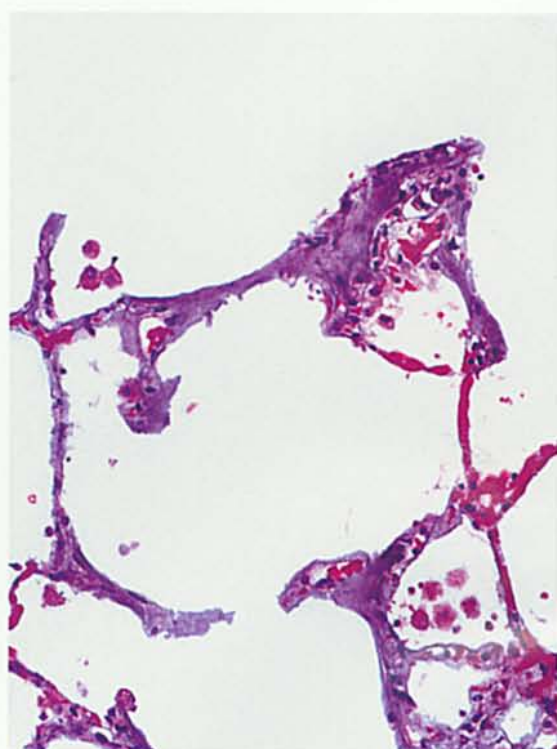


Fig. 40 - Mineralization, alveolar septa. (H&E).