

Proliferative Lesions of the Rat Respiratory Tract

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INTRODUCTION

The respiratory tract is an important site of injury in toxicological studies. In addition to the direct effects caused by the inhalation of gases and particles, ingested chemicals can also affect the respiratory tract. There are several reasons for this susceptibility to toxic insult, but one that appears quite important is the metabolic potential of the nose and lung, which presumably results in the conversion of many xenobiotics into highly reactive intermediates. Considering the anatomic complexity of the respiratory system, the multiplicity of cell types at various levels, their potential for morphologic alteration, and the surface area of this organ system exposed to potential toxicants from inhalation or from systemic circulation, the paucity of respiratory tract neoplasia in the rat is particularly noteworthy. In studies sponsored by the National Toxicology Program (NTP) evaluating approximately 300 chemicals using various routes of administration, a total of 150 positive carcinogenic responses were observed. Yet, only four identified the rat lung as a target tissue.

This chapter provides an outline of the proliferative lesions that occur in the rat nasal cavity, larynx, trachea, bronchi, and lung either as spontaneous or treatment-related lesions. This Society of Toxicological Pathologists (STP)-standard system of nomenclature and diagnostic criteria (SSNDC) is recommended after

review of the nomenclature scheme proposed by the World Health Organization (WHO) and the nomenclature scheme used by the NTP. 2, 3, 12, 34, 38

MORPHOLOGY

NASAL CAVITY:

The varied anatomical features of the nasal passages and the encasement within a bony cavity require special attention for fixation and histological sampling in order to obtain uniform and standard sections. Typically, three or four levels of nose are examined. The details of histological preparation and anatomical features of importance to toxicologic pathologists have been published.^{19, 36, 40, 48, 49, 51}

Examples of normal respiratory and olfactory epithelium are provided for comparison to the abnormal (Figs. 1, 5).

Mucous (Goblet) Cell Hypertrophy and Hyperplasia (Figures 2, 3)

These changes are common after injury to the respiratory epithelium of the nasal cavity. The respiratory epithelium will appear thickened, the nuclei are close together, and the surface appears undulating due to this increased cellularity. The mucous cells are taller and contain an abundance of mucus, which results in the typical appearance of large goblet cells. Clusters of goblet cells surrounding extruded mucus may give the

appearance of an intraepithelial gland. Ciliated cells are less evident or form clusters within areas of goblet cell hyperplasia. Hypertrophy and hyperplasia of mucous and serous glands in the lamina propria can be seen in response to mucosal injury. Karyomegaly and nuclear atypia have been observed in nasal glands following exposure to chemicals. ^{3, 16, 17}

Squamous Cell Hyperplasia

Hyperplasia of stratified squamous epithelium in the anterior portion of the nasal passages is characterized by a focal increase in the number of cell layers. The cells in the affected area may have larger nuclei with more prominent nucleoli and a more abundant cytoplasm. Since the thickness of the epithelium varies slightly depending upon the location in the nasal vestibule, careful comparisons with controls are critical to identify mild lesions. Squamous hyperplasia in these areas rarely occurs as a spontaneous event. Cellular atypia in foci of squamous hyperplasia is characterized by irregular size and shape of the cells, nuclei, and nucleoli. ^{3, 8, 9, 35}

Squamous Metaplasia (Figure 4)

Squamous metaplasia of the respiratory or olfactory epithelium occurs after prolonged insult. It may occasionally occur within the nasolacrimal duct or nasal glands. Squamous metaplasia is characterized by three or more layers of epithelial cells with relatively prominent cell boundaries and moderately abundant eosinophilic cytoplasm. More advanced lesions may contain intercellular bridges and abundant keratinization. The epithelium is generally orderly, and a normal pattern of differentiation from the basal layer to the surface is present. Cellular pleomorphism, atypia, and epithelial disorganization may occur in chemically induced squamous metaplasia. ^{3,9,35}

Respiratory Epithelial Metaplasia (Figures 6–8)

Focal atrophy and degeneration of the olfactory epithelium with loss of sensory cells and a predominance of sustentacular cells is occasionally seen in aged rats as a spontaneous change or after exposure to an irritant chemical. This lesion is common in the dorsal meatus, but with more severe injury the ethmoid turbinates will also be affected. In more severe or advanced lesions, there may be complete loss of sensory and sustentacular cells, with replacement of these cells by ciliated and nonciliated columnar respiratory epithelium. This change is referred to as respiratory epithelial metaplasia of the olfactory epithelium. ^{3, 8, 9, 17, 35}

Epithelial Hyperplasia with Cellular Atypia (Atypical Hyperplasia, Basal Cell Hyperplasia, Dysplasia) (Figures 9–14)

Epithelial hyperplasia with cellular atypia is used

to describe proliferative lesions with varying amounts of altered differentiation and cellular atypia in the respiratory and olfactory epithelium and in glands of the nasal cavity. Epithelial hyperplasia with cellular atypia is characterized by increased thickness of the epithelium, a disorganized appearance, and variable numbers of ciliated and secretory columnar cells in the respiratory epithelium, or sustentacular and sensory cells in the olfactory epithelium that may be interspersed with or overlie basal cells. The basal cells may be relatively uniform or pleomorphic. Proliferation of atypical or pleomorphic basal or undifferentiated cells may extend into the underlying glands, forming nodular clusters in the lamina propria. ^{3, 15, 35}

Epithelial hyperplasia with cellular atypia should not be confused with regenerative hyperplasia, which follows mild or limited injury.

Hyperplasia of the transitional respiratory epithelium located on the lateral wall and lateral surfaces of the nasal and maxillary turbinates has a slightly different appearance. Normally, respiratory epithelium in this location is cuboidal, pseudostratified, and 1-2 cells thick. In response to injury, hyperplastic epithelium at this location is 3 or more cell layers thick with a flattened surface. With prolonged injury, squamous metaplasia occurs. ²⁰

Adenoma (Polypoid or Villous Adenoma, Adenomatous or Villous Polyp) (Figures 15–17)

Adenomas usually occur in the anterior portion of the nasal cavity and arise from either the respiratory epithelium or nasal glands. Adenomas of the respiratory epithelium are usually exophytic masses that grow into the lumen of the nasal cavity and may cause obstruction and/or pressure atrophy of adjacent structures. They may be quite large with a relatively small stalk or broad-based and sessile in their attachment to the mucosa. Adenomas may have a villous (papillary) pattern with a few invaginating gland-like structures or tubules, or they may be polypoid with an irregular surface and tubular or gland-like structures. The villous and tubular structures consist of pseudostratified epithelium overlying a scant fibrovascular stroma. The epithelium is generally moderately- to well-differentiated with typical ciliated and/or secretory cells but it can also contain varying numbers of undifferentiated cells and may form small microcysts. Adenomas are well circumscribed with minimal cellular pleomorphism and atypia and do not appear to commonly progress to nasal adenocarcinoma. A polypoid adenoma has been reported as occurring spontaneously in the Fischer 344 rat. ²⁴

Adenomas of nasal glands are usually circumscribed areas of epithelium with an acinar pattern; acini may be smaller or larger than normal and may be solid. The mitotic rate is low. ⁹

Squamous Cell Papilloma (Figure 18)

Spontaneous squamous cell tumors of the rat nose are extremely rare, but are occasionally seen in rats exposed to carcinogens. While squamous cell papillomas may arise from the stratified squamous epithelium in the anterior portion of the nose, they generally arise from the areas of squamous metaplasia in the respiratory or olfactory epithelium. Squamous cell papillomas consist of exophytic papillary projections of stratified squamous epithelium overlying a thin core of connective tissue stroma. In the nose, the papillae are short and show little branching.^{3,9}

Squamous Cell Carcinoma (Figures 19–20)

The growth features and morphologic appearance of squamous cell carcinoma are similar to those at other sites. This is an invasive, destructive neoplasm that can protrude dorsally or laterally through the overlying bones and induce considerable nasal-ocular discharge and marked dyspnea. This malignant neoplasm may arise from the squamous epithelium of the anterior nose or from metaplastic squamous epithelium in respiratory or olfactory portions of the nasal cavity. Excessive keratinization, local invasion, and/or metastasis to the regional lymph nodes may occur. Extension into the brain is less common. These tumors generally consist of well-differentiated, malignant, squamous epithelium with prominent intercellular bridges and abundant keratin that may induce a marked scirrhous response. Spontaneous squamous cell carcinomas in the nasal cavity are rare in the rat, but this type of neoplasm has been induced by a variety of chemicals administered either by inhalation, oral, or parenteral routes.^{9,17,25}

Adenocarcinoma (Figures 21–23)

Adenocarcinomas may arise from the respiratory epithelium of the anterior naso- or maxillary turbinates, the septal glands, Bowman's glands, or Steno's gland. Adenocarcinomas of the olfactory region may arise from normal or metaplastic respiratory epithelium in that area or from Bowman's glands. Adenocarcinomas of the respiratory epithelium may have an exophytic villous or polypoid growth pattern, or they may grow by lateral extension along the walls of the nasal cavity. Their size varies, but they may progress to fill the nasal passage, compress the nasal septum and/or the turbinates, and induce dyspnea. Cellular atypia, pleomorphism, or prominent stratification of the cells with a solid growth pattern are necessary features for the diagnosis of adenocarcinoma in the absence of invasion or metastasis. Local invasion has been described.^{8,9} Adenocarcinomas with invasive, endophytic growth are readily identified. Well-differentiated adenocarcinomas consist of glandular structures composed of columnar secretory epithelial cells with a moderate amount of loosely organized

supporting stroma. PAS-positive mucus may be present in the glandular epithelium. Poorly differentiated adenocarcinomas are composed of incompletely formed acinar structures or disorganized sheets or cords of round to polyhedral pleomorphic cells. Poorly differentiated or undifferentiated carcinomas may occur either in respiratory or olfactory epithelium. Some undifferentiated carcinomas have spindle-shaped cells. These undifferentiated carcinomas are usually very pleomorphic with numerous mitotic figures and necrosis; invasion into the adjacent tissues, including bone, may occur.³ Adenocarcinomas of nasal glands are present in a glandular pattern or as sheets or nests of cells. Nuclear pleomorphism, a high mitotic rate, and local invasion have been noted.^{9,45}

Spontaneous adenocarcinomas in the rat are extremely uncommon. Exposure to different carcinogens has induced adenocarcinomas and undifferentiated carcinomas of the nasal respiratory epithelium. Care must be taken to distinguish this tumor type from olfactory neuroblastoma (esthesioneuroblastoma).

Olfactory Neuroblastoma (Esthesioneuroblastoma, Olfactory Neuroepithelioma, Olfactory Neuroepithelial Carcinoma) (Figures 24–25)

Neoplasms of the olfactory epithelium have not been reported as spontaneous lesions in the rat; however, they have been induced by exposure to carcinogens and are associated with an increased frequency of focal hyperplastic changes in the olfactory epithelium. Olfactory neuroblastoma can be invasive and destructive with extension through the cribriform plate. It is important to distinguish olfactory neoplasms from poorly differentiated adenocarcinomas, since potent nasal carcinogens often induce multiple types of neoplasms that arise from different types of epithelium. Olfactory neuroblastomas are often anaplastic neoplasms that are difficult to classify without the use of special immunohistochemical stains or electron microscopy.⁴⁶

The neoplastic cells of olfactory neuroblastoma are arranged in lobules or solid sheets with a scant fibrovascular stroma. Some neoplastic cells are oriented parallel to their long axis, giving the impression of ribbons or narrow cords. The neoplastic cells are usually uniform with scant cytoplasm and round to oval nuclei. The nuclei contain moderately abundant heterochromatin and may be hyperchromatic. True rosettes with lumens are occasionally found and consist of columnar cells with abundant pale cytoplasm and basally located nuclei. Pseudorosettes consist of rounded clusters of cells with peripherally located nuclei and cytoplasm oriented towards a central area. Ultrastructural evaluation may be necessary to identify neurogenic features such as electron-dense neurosecretory granules, neurofilaments, or axons. Immunohistochemical localization of neuronal

components may also prove to be useful distinguishing characteristics.³

Boorman *et al*³ notes "A number of terms have been applied to the neoplasms of the olfactory neuroepithelium. In humans the term esthesioneuroepithelioma is used for neoplasms that contain 'true rosettes' (Flexner-Wintersteiner type with a central lumen), whereas those with pseudorosettes (Homer-Wright type without a true lumen) are called esthesioneuroblastoma. Esthesio-neurocytoma is used for neoplasms without rosettes but having a neurofibrillary background and a lobular pattern. The Armed Forces Institute of Pathology Fascicle uses the term olfactory neuroblastoma for all malignant tumors arising from the olfactory epithelium." Since there is relatively little information concerning the histogenesis of olfactory neoplasms in the rat, the single term of olfactory neuroblastoma seems appropriate until a greater understanding of the histogenesis of these tumors is obtained.

Mesenchymal Neoplasms (Figures 26–28)

Mesenchymal tumors of the nasal cavity of the rat have the morphological characteristics of similar neoplasms in other sites. Fibroma, fibrosarcoma, hemangioma, hemangiosarcoma, chondroma, chondrosarcoma, osteoma, osteosarcoma, and schwannoma may occur as rare, spontaneous neoplasms in the nasal cavity. Rhabdomyosarcomas have been observed in rats exposed to potent carcinogens.^{3, 9, 32}

LARYNX, TRACHEA, AND BRONCHI (Figures 29–30)

The mucosal surface of the larynx consists of a number of regionally specific epithelia²⁹; because of this, care must be taken in the preparation of sections from the larynx. Histological evaluation of the larynx should include the base of the epiglottis, the ventral pouch, and the medial aspects of the arytenoid cartilage.^{30, 39} The lamina propria of the larynx contains serous/mucous glands that are also numerous in the upper third of the trachea but less evident in the lower third of the trachea. The ciliated and non-ciliated columnar epithelium of the trachea is pseudo-stratified while that of the intrapulmonary bronchi is simple. The different cell types comprising this epithelium are complex as are their potential pathways of differentiation.^{23, 27, 28, 40, 42} The anatomical structure of the tracheobronchial tree determines, in part, the dose of an inhaled irritant delivered to a specific airway. Experimental studies have established that the sites of bifurcation (carina) are often the first areas to respond to an inhaled irritant, presumably because these receive a higher dose from aerosol impaction. Therefore, the carina should be included in the systematic examination of the respiratory tract for toxicologic lesions.

Squamous Hyperplasia/Metaplasia (Figure 31)

The rat larynx, upper trachea, and bifurcations (carina) are particularly sensitive to the development of hyperplastic and squamous metaplastic changes following inhalation exposure. Squamous metaplasia is characterized by three or more layers of epithelial cells with relatively prominent cell boundaries and moderately abundant eosinophilic cytoplasm. More advanced lesions may contain intercellular bridges and abundant keratinization. The epithelium is generally orderly, and a normal pattern of differentiation from the basal layer to the surface is present. These hyperplastic and metaplastic changes are frequently associated with epithelial degenerative changes, and it is not unusual to see mucous differentiation (mucous cell hyperplasia/metaplasia) occurring in airways that also have evidence of squamous differentiation (hyperplasia/metaplasia). The histogenesis of these lesions has been a subject of extensive experimental studies.^{3, 23, 28, 29, 42}

Mucous Cell Hyperplasia (Goblet Cell Hyperplasia/Metaplasia)

With some types of inhalation injury (prolonged irritation) the pseudostratified or simple cuboidal epithelium of the trachea or bronchi may respond with mucus (goblet) cell hyperplasia, metaplasia, dysplasia, or neoplasia. The hyperplastic mucous epithelium may be irregular and folded due to crowding of the secretory cells. The mucous cells are taller and contain an abundance of mucus, which results in the typical appearance of large goblet cells. Clusters of goblet cells surrounding extruded mucus may give the appearance of an intraepithelial gland. In rats the serous cell will take on the characteristics of mucous cells containing acidic mucosubstances. Ciliated cells are less evident or lacking in these lesions. These hyperplastic and metaplastic changes are frequently associated with epithelial degenerative changes, and it is not unusual to see mucous differentiation occurring in airways that also have evidence of squamous differentiation.^{3, 9, 22, 31}

Papilloma (Papillary Adenoma, Papillary Polyp) (Figures 32–35)

Papillomas, polyps, and adenomas are benign tumors that arise in airways. In contrast to humans, where pulmonary neoplasms frequently arise in the large conducting airways, tracheal and bronchial neoplasms are extremely rare as spontaneous lesions in the rat, but may be induced. The majority of these neoplasms are exophytic papillary or polyp-like masses that protrude into the airway lumen and occasionally may obstruct the airway. These benign lesions generally have a uniform growth pattern, which may have papillary, glandular, or mixed epithelial differentiation and a distinct connective

tissue stalk covered with a uniform stratified squamous epithelium or a cuboidal to columnar respiratory epithelium with little or no cellular pleomorphism or atypia. Occasionally, ciliated and/or mucous cells are identified within a stratified squamous epithelial component.

Bronchial Carcinoma

Bronchial carcinomas may have a papillary or glandular growth pattern and project into the airway lumen, or they may invade into the bronchial wall. Malignant neoplasms are distinguished from benign ones on the basis of anaplasia or evidence of invasion. Since mucosal glands do not occur in the rats' distal airways, bronchial carcinomas most likely originate from the respiratory epithelium lining the bronchus.

Mesenchymal Neoplasms (Figures 36–37)

The mesenchymal neoplasms described as occurring occasionally in the nasal cavity likewise have the potential to occur in the trachea and bronchi, although they have been rarely reported. Granular cell tumors of the tracheal submucosa are rare neoplasms that have also been reported as spontaneous tumors.^{3, 9, 32}

LUNG

Systematic sampling and careful fixation by perfusion are prerequisites to identifying proliferative lesions in the lung.^{13, 42} There are 12 to 20 monopodal branching airway segments from the trachea to the terminal bronchiole, depending upon the lobe. The right primary bronchus branches to a cranial lobar bronchus, followed by a middle lobar bronchus and an accessory, lobar bronchus and finally a caudal lobar bronchus. These bronchi serve the cranial, middle, accessory and caudal lung lobes, respectively. The left primary bronchus serves the single large left lobe. Intralobular septa are absent in the rat lung, as are lobules. The rat lacks a well-developed respiratory bronchiole; thus, the transition from conducting to respiratory airways is abrupt. The terminal bronchiole, alveolar duct, and associated alveoli are often referred to as the centriacinar region. The cellular elements comprising these anatomical structures, their ability to differentiate, and their metabolic capabilities and distribution are described elsewhere.^{31, 43, 47}

Hyperplasia, Bronchiolo-alveolar (Type II Cell Hyperplasia) (Figures 38–40)

Regenerative hyperplasia of the alveolar type II pneumocyte is a common response to epithelial injury. Care must be taken to distinguish hyperplasia from an early stage in the development of a bronchiolo-alveolar neoplasm. It should be remembered that spontaneous neoplasia in the rat lung occurs at an extremely low

incidence in most strains and that male rats have a slightly higher incidence than females.^{2, 31, 43, 47}

Regenerative hyperplasia of alveolar epithelium in the centriacinar region is a common response to numerous toxic injuries. In its simplest form it is recognized as simple cuboidal epithelium. Metaplasia of this epithelium may result in the appearance of ciliated cells, Clara cells, mucous cells, or squamous epithelium. Mitotic figures are infrequent. There is generally no distortion of adjacent alveolar architecture. Since the type II alveolar pneumocyte provides the proliferative and reparative capacity to the alveolar epithelium, it is likely that most of these lesions represent focal areas of alveolar repair. The important feature in distinguishing bronchiolo-alveolar hyperplasia from an adenoma is that the underlying alveolar structure is maintained within the foci of epithelial hyperplasia. If the normal alveolar architecture is retained, a diagnosis of hyperplasia rather than adenoma is indicated.⁶ In addition, attention must be given to the degree of architectural disruption, the distinctiveness of the margins of the lesions, and the magnitude of the associated inflammatory response.

Squamous Metaplasia (Figure 41)

Squamous metaplasia may occur in the alveolar parenchyma and is usually related to prolonged insult. Examples of such insults are large burdens of inhaled irritant dusts or insoluble material implanted or injected in the lung. Squamous metaplasia of alveolar parenchyma is usually associated with chronic inflammation, fibrosis of alveolar septa, or focal scarring. The metaplasia is characterized by several layers of flattened epithelial cells with prominent cell borders and moderately abundant eosinophilic cytoplasm. More advanced lesions show intercellular bridges, hypercellularity, and abundant keratinization. Keratinization may become exaggerated so that squamous (epidermal) cysts are formed.

Squamous Cysts (Benign Cystic Keratinizing Squamous Cell Tumor) (Figure 42–43)

Squamous cysts may be found as incidental lesions, but occurrence is generally associated with exaggerated squamous metaplasia after prolonged exposure to inert particles.^{13, 14} Although the morphological features are relatively distinctive, classification of this lesion remains controversial. This lesion has been referred to as a benign cystic keratinizing squamous cell tumor by the International Agency for Research on Cancer (IARC) and given a synonym of squamous cyst.¹² The cyst wall is composed of stratified squamous epithelium that is several cell layers thick; this epithelium has an orderly differentiation, with a peripherally oriented basilar cell layer. The cyst may contain an abundance of keratin and necrotic debris and may be large enough to occupy much of an entire lung lobe.

Until the biologic behavior of the epithelium lining these cysts is better defined, the STP preferred terminology for this lesion is squamous cyst.

Squamous cell carcinoma may arise from the wall of squamous cysts, especially those that are exposure induced. The important criteria for differentiating squamous cysts from a squamous cell carcinoma are the presence of a well-differentiated epithelial lining and the lack of cellular atypia, dysplasia, and invasion.

Adenoma, Bronchiolo-alveolar (Pulmonary Adenoma)
(Figures 44–46)

Bronchiolo-alveolar adenomas may be macroscopically visible as solitary gray to white distinct nodules along the peripheral border of a lung lobe, usually 1–5 mm in diameter. In contrast to hyperplasia, microscopic features include distortion of the underlying alveolar structure and epithelial arrangement in irregular, papillary, glandular, or solid patterns of cuboidal to columnar epithelial cells overlying a delicate fibrovascular stroma. The cuboidal cells are relatively uniform with round to oval nuclei and moderately abundant cytoplasm; some cells may have apical cytoplasmic vacuoles. The columnar cells have more basal nuclei and basophilic cytoplasm. This epithelium is relatively uniform with little pleomorphism or atypia. Mitotic figures are occasionally observed. Electron microscopy of bronchiolo-alveolar adenomas has shown that the epithelial component contains lamellar cytoplasmic inclusions typical of those seen within type II alveolar pneumocytes and that some have ultrastructural features of nonciliated secretory bronchiolar cells (Clara cells). These lesions are therefore referred to as bronchiolo-alveolar adenomas. 2, 4, 11, 34, 37, 38

Carcinoma, Bronchiolo-alveolar (Figure 47–48)

Bronchiolo-alveolar carcinomas are sufficiently large to be observed macroscopically as white to pink masses with occasional yellow to brown foci of necrosis. These malignant neoplasms tend to occur in peripheral portions of lung lobes and are poorly demarcated from adjacent tissue. Entire lobules may be involved. These tumors compress surrounding parenchyma and may invade airways, pleura, or vessels. They occasionally metastasize to regional lymph nodes, liver, kidney, heart, or other organs.

The bronchiolo-alveolar carcinoma has three histologic patterns—papillary, glandular, or solid—just as seen with the bronchiolo-alveolar adenomas. The neoplastic epithelial cells are cuboidal or columnar and fill the normal alveoli, ultimately destroying the normal alveolar structure. With the papillary pattern, the neoplastic cells grow on a fine fibrovascular stroma. In the glandular pattern, the neoplastic epithelium forms nests or acini. These acini are frequently enmeshed in a thick

fibrous stroma. The solid pattern has little stroma, and the epithelial cells are usually more cuboidal or round, not columnar.

The cytologic features of the neoplastic epithelium are important in determining malignant tumors. Tumors that show dysplasia or anaplasia frequently invade vessels, but metastases are not common.

Neoplastic cells of a carcinoma may be quite pleomorphic and anaplastic spindle-shaped cells. Even when the neoplasms have a prominent spindle-cell component and appear sarcomatous, the term carcinosarcoma is not warranted because these spindle cells simply represent anaplastic epithelium. Focal squamous metaplasia is occasionally observed and may be quite prominent; however, the diagnosis of squamous cell carcinoma should be restricted to neoplasms that consist predominantly of squamous epithelial cells.

Bronchiolo-alveolar carcinomas appear to arise from the progenitor epithelium of the bronchiolo-alveolar region, as the name implies. Ultrastructural features of chemically induced neoplasms of this type include features of both type II alveolar pneumocytes and nonciliated bronchiolar epithelial cells. These neoplasms are infrequent in the rat as spontaneous tumors and do not commonly metastasize. Experimentally induced tumors have been observed to metastasize, and the metastatic lesions tend to exhibit papillary or glandular patterns of growth. 2, 5, 11, 34, 38, 41

Squamous Cell Carcinoma (Figure 49)

In the rat squamous cell carcinomas are solid lesions containing islands of necrotic and keratinized epithelium. Spontaneous squamous cell carcinomas are rare in the rat. The chemically induced neoplasms tend to occur at the site of carcinogen deposition. Radiation induced squamous cell carcinomas are generally located within the parenchyma and rarely oriented around major airways.¹⁸ Both spontaneous and experimentally induced squamous cell carcinomas generally consist of well-differentiated squamous epithelial cells with abundant keratin. Squamous cell carcinomas obliterate the normal architecture of the lung, are locally invasive and may induce a marked scirrhous response. Although metastases are rare, the predominance of squamous epithelial cells, abundant keratin, and a marked fibroblastic response usually allows separation of this malignancy from bronchiolo-alveolar carcinomas, which may contain small areas of squamous metaplasia. Squamous cell carcinomas must also be differentiated from benign squamous (epidermal) cysts, which may be induced by prolonged inhalation exposure to toxicants or inert particles. The epithelial lining of a squamous cyst is well differentiated and shows no atypia, dysplasia, or invasive growth. The site of origin of pulmonary squamous cell carcinomas in the rat is uncertain. They

may arise from the bronchial, bronchiolar, or alveolar epithelium or occasionally from benign keratinizing squamous cysts. 2, 7, 18, 34, 38, 41

Pleural Mesothelioma (Figures 50–52)

Pleural mesotheliomas are very rare in rats and tend to occur more often in males than females. Morphologic descriptions of pleural mesotheliomas are based on a few reported spontaneous cases and reports of induced pleural mesotheliomas by intrapleurally injected asbestos or other fibrous dusts or by inhalation of radioactive materials. The distribution of pleural mesotheliomas may be either focal or diffuse within the pleural cavity. On occasion, invasion of the mediastinum, diaphragm, or thoracic wall may occur.

Pleural mesotheliomas may have histologic features of either epithelial or mesenchymal components or a mixture of both. An epithelial pattern is most frequent and is usually papillary. The individual cells are monomorphic, usually cuboidal, and grow on a delicate stroma that may be extensive. Hemorrhage and focal calcifications in the interstices of the tumor are common. The mesenchymal type consists of spindle-shaped cells that resemble fibroblasts. Malignant forms resemble fibrosarcomas. The mixed tumor has morphologic expression of both epithelial and mesenchymal components.

The pleural mesotheliomas must be differentiated from several other neoplasms of the thorax. Metastatic peritoneal mesotheliomas must not be mistaken for primary pleural mesothelioma, since the two are morphologically similar. Peritoneal mesothelioma is more common and frequently arises from the tunics of the testicle. Primary carcinomas of the lung may invade the pleura and extend along pleural surfaces or follow lymphatics into the mediastinum. The papillary pattern of bronchiolo-alveolar carcinoma of the lung is similar in appearance to the epithelial pattern of mesothelioma. The possibility of an invasive pulmonary carcinoma or an atrio-caval tumor must be ruled out before the diagnosis of pleural mesothelioma is made. Atrio-caval tumors are characteristically found in NZR/Gd rats, but have been reported in F-344 rats. As the name suggests, these tumors originate in the wall of the right atrium or in the post vena cava and are generally more glandular than the papillary, epithelial pleural mesothelioma.

Mesenchymal Neoplasia

Primary mesenchymal neoplasms of the rat lung are extremely rare. The absence of glandular or epithelial components is essential to fully support the diagnosis of a primary mesenchymal neoplasm, since some carcinomas may be associated with extensive fibroplasia or have a spindle-cell component. The types of mesenchymal tumors reported in the rat include fibrosarcoma,

hemangiosarcoma, leiomyoma and leiomyosarcoma, and anaplastic sarcomas of uncertain histogenesis. In the Fischer 344 rat, mononuclear cell leukemia frequently involves the lung but cannot be considered a primary lung neoplasm.² In the Sprague-Dawley rat and the Wistar rat, histiocytic sarcoma is well recognized as a mesenchymal lesion involving the lung, but not as a primary tumor at that site.^{1, 41} A similar, but distinct neoplasm, malignant fibrous histiocytoma is also a recognized metastatic tumor of the lung in the Fischer 344 and the Sprague-Dawley rat. It appears to originate in the skin or peritoneum.⁵⁰

DISCUSSION

The respiratory tract is not a common site for carcinogenic responses. Published historical data on the incidence of spontaneous tumors of the respiratory tract are available for both the Fischer 344 rat and Sprague-Dawley rat.^{2, 3, 22, 31, 43, 46} Solleveld and co-workers reported the incidence of neoplastic lesions in 529 male and 529 female F-344 rats from a life-span study and within this report included historical control data from 2,320 male and 2,370 female rats from the NTP historical control data base. From this total of 2,849 male and 2,899 female F-344 rats, nasal tumors were observed in 4 male and 3 female rats. A tracheal tumor was observed in 1 male rat. Primary lung tumors were observed in 75 males and 35 females, and pleural tumors occurred in 2 male rats. Historical data from control F-344 rats have also been summarized by Haseman *et al.*²¹ and by Schuller *et al.*⁴¹ In recently published data from NTP carcinogenicity studies in control F-344 rats, out of 3,877 male rats, 70 had adenomas, 45 had adenocarcinomas, and 4 had squamous cell carcinomas. Out of 3,919 female F-344 rats, 32 had adenomas, 13 had adenocarcinomas, and 1 had a squamous cell carcinoma.²¹ These summaries again document the paucity of neoplastic respiratory tract lesions in the rat.

There are also historical data from the Sprague-Dawley rat.^{10, 33, 47} Stula reported from 365 male and 365 female Sprague-Dawley rats that 4 pulmonary adenomas were observed.⁴⁷ MacKenzie *et al.* summarized observations from several laboratories; from a total of 2,082 rats, 12 had primary lung tumors.³¹ Spontaneous neoplastic lesions in the Sprague-Dawley rat reported by Charles River include 3 adenomas and 2 bronchiolo-alveolar carcinomas from 880 male rats and no primary pulmonary tumors from 877 female rats.²⁶ Chandra and coworkers reported the incidence of spontaneous neoplasms in 1,340 male and 1,329 female Sprague-Dawley rats. They observed 1 neoplasm in the trachea and 5 in the lung of male Sprague-Dawley rats

and 3 neoplasms in the lung of females.¹⁰ In unpublished data from Merck, Sharp and Dohme Research Laboratories, out of 10,302 control Sprague-Dawley rats, there was the following incidence of primary lung tumors: 21 adenomas, 8 adenocarcinomas, and 1 squamous cell carcinoma. Collectively, these and other data emphasize the sparsity of spontaneous proliferative respiratory tract lesions in the rat, in obvious contrast to the incidence of respiratory neoplasia in humans. This also contrasts with the apparent susceptibility of the rat to respiratory tract infections and to the rat's rapid pulmonary response with regenerative and/or proliferative lesions after infectious or toxicological insults to the lung. Considering the closely controlled environmental conditions to which laboratory rats are exposed, this contrast between the incidence of respiratory tract neoplasia in rats and humans may reflect differences in exposure and local reactivity to inhaled carcinogens.

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RECOMMENDED NOMENCLATURE WITH DIAGNOSTIC CRITERIA

NASAL CAVITY

Mucous (Goblet) Cell Hypertrophy/Hyperplasia

1. Respiratory epithelium thickened, undulating rugose surface
2. Mucous (goblet) cells taller, apical mucus goblets, basal nuclei
3. Ciliated cells crowded and/or less evident
4. Clusters of goblet cells may form intraepithelial crypts or cysts
5. Associated frequently with degeneration and inflammation

Squamous Cell Hyperplasia

1. Focal increase to three or more layers of epithelial cells
2. Normal differentiation
3. Occasional mitoses
4. Cells with larger nuclei, more prominent nucleoli, more abundant cytoplasm

Squamous Metaplasia

1. Three or more layers of epithelial cells with prominent cell boundaries and abundant eosinophilic cytoplasm
2. Normal differentiation
3. Advanced lesions showing intercellular bridges, keratinization, and occasional mitoses

Respiratory Epithelial Metaplasia

1. Present in olfactory epithelium
2. Loss of sensory and sustentacular cells
3. Simple columnar epithelium with or without cilia resembling respiratory epithelium

Epithelial Hyperplasia with Atypia (Atypical Hyperplasia, Basal Cell Hyperplasia, Dysplasia)

1. These responses occur in respiratory, transitional, and olfactory epithelium
2. Increased thickness and disorganized structure of epithelium
3. Proliferation of basal or undifferentiated cells is present
4. Atypia and pleomorphism of undifferentiated polyhedral cells are present with other epithelial cell types

Adenoma (Polypoid or Villous Adenoma, Adenomatous Polyp, Papilloma)

1. Anterior portion of the nasal cavity
2. Sessile and broad based or attached by a small stalk

3. Nonciliated, pseudostratified epithelium in villous or tubular structures
4. Scant fibrovascular stroma
5. Well-differentiated epithelium with occasional ciliated and/or secretory cells
6. No evidence of malignancy (well circumscribed, minimal pleomorphism or atypia)
7. Adenomas of nasal glands are usually circumscribed areas of epithelium with acinar arrangement; acini may be smaller or larger than normal; occasionally solid; low mitotic rate

Squamous Cell Papilloma

1. Exophytic or endophytic papillary projection of squamous epithelium
2. Thin connective tissue stroma
3. Well-differentiated squamous epithelial cells

Squamous Cell Carcinoma (Epidermoid Carcinoma)

1. Large, invasive, destructive tumor
2. Well-differentiated squamous epithelial cells with cellular atypia and dysplasia
3. Extensive keratinization
4. Scirrhous response

Adenocarcinoma

1. Occurs in respiratory, transitional, olfactory, or nasal glandular epithelium
2. Exophytic well-differentiated cells in a villous or polypoid growth pattern
3. Cellular pleomorphism, atypia, and/or prominent stratification of cells with solid growth pattern
4. Moderate amounts of loose stroma
5. Glandular epithelium with secretory material (PAS-positive material)
6. Poorly differentiated carcinomas may have round to polyhedral, pleomorphic epithelial cells in sheets and cords
7. Endophytic growth with invasion of adjacent nasal tissues is more common with poorly differentiated adenocarcinomas

Olfactory Neuroblastoma

1. Origin from olfactory epithelium
2. Neoplastic cells in lobules or solid sheets with a scant fibrovascular stroma
3. Neoplastic cells are usually uniform with scant cytoplasm, round to oval hyperchromatic nuclei
4. True rosettes or pseudorosettes may be present
5. Evidence of neurogenic features (ultrastructural or immunohistochemical stains)

Mesenchymal Tumors

1. Morphologic features of similar neoplasms at other sites

LARYNX, TRACHEA, AND BRONCHI

Squamous Cell Hyperplasia/Metaplasia

1. Associated with epithelial degeneration and inflammation
2. Loss of mucocilliary differentiation, hyperchromatic nuclei, occasional mitoses, basophilic to eosinophilic cytoplasm, multiple layers, and no atypia
3. One or two layers of cuboidal epithelium with occasional mitoses (hyperplasia)
4. Three or four layers of stratified squamous epithelium, normal differentiation (metaplasia)

Mucous (Goblet) Cell Hypertrophy/Hyperplasia

1. Respiratory epithelium thickened, undulating rugose surface
2. Mucous (goblet) cells taller, apical mucus goblets, basal nuclei
3. Ciliated cells crowded and/or less evident
4. Clusters of goblet cells may form intraepithelial crypts or cysts
5. Associated frequently with degeneration and inflammation

Papilloma (Papillary Adenoma, Papillary Polyp)

1. Exophytic papillary or polyplike projections into the airway
2. Stratified squamous epithelium or a cuboidal or columnar respiratory epithelium
3. Thin connective tissue stroma
4. Squamous hyperplasia/metaplasia
5. No atypia or pleomorphism

Bronchial Carcinoma

1. Exophytic papillary or glandular growth pattern that may obstruct the airway
2. May invade bronchial wall
3. Cytologic features of anaplasia and invasion are usually present

LUNG

Hyperplasia, Bronchiolo-alveolar (Type II Cell Hyperplasia)

1. Peripheral location most common
2. Increased number of type II pneumocytes lining the alveoli
3. Alveolar architecture is maintained
4. No cellular atypia
5. No or limited disruption of adjacent tissues
6. Associated with inflammatory cell responses

Squamous Metaplasia

1. Associated with chronic inflammation or focal scarring

2. Several layers of stratified squamous epithelium, normal differentiation
3. May be associated with excessive keratin

Squamous Cyst

1. Cystic structure with well-differentiated stratified epithelial lining
2. Abundant keratin
3. May be incidental finding
4. May be associated with inflammation and scarring
5. Must differentiate from squamous cell carcinoma

Adenoma, Bronchiolo-alveolar

1. Alveolar architecture is distorted with compression
2. Simple cuboidal or columnar epithelium, arranged in papillary or glandular patterns
3. Epithelium is relatively uniform with little pleomorphism or atypia
4. Peripheral location with sharp demarcation of adjacent tissues
5. Limited fibrovascular stroma

Carcinoma, Bronchiolo-alveolar

1. Disrupts normal alveolar architecture
2. Poorly demarcated, may be in peripheral location
3. Epithelium may be multilayered or growing in solid clusters
4. Cellular anaplasia with pleomorphism, atypia, and spindle-shaped sarcomatous epithelial cells
5. Squamous metaplasia may occur
6. Scirrhous response to anaplastic cells may be seen
7. Invasion of vessels, pleura and metastases may occur

Squamous Cell Carcinoma

1. Generally a large tumor, disrupting the normal architecture
2. Well-differentiated squamous epithelial cells with atypia
3. Abundant keratin is present or individual cell keratinization
4. Locally invasive, metastasis rare
5. May induce marked scirrhous response

Pleura, Mesothelioma

1. Primarily growth along pleural surfaces
2. May invade mediastinum, thoracic wall, or less commonly, the lung
3. Epithelial, mesenchymal, or mixed histologic patterns
4. Focal or diffuse forms

Mesenchymal Tumors

1. Absence of glandular or epithelial components
2. Typical mesenchymal tumor appearance
3. Rare as primary lung tumors

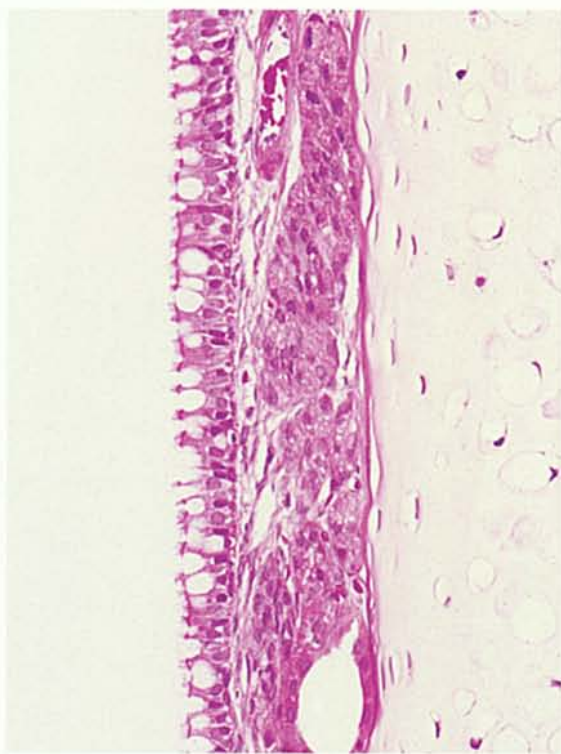


Fig. 1 – Normal respiratory epithelium. Ciliated and goblet cells along the nasal septum. H&E.

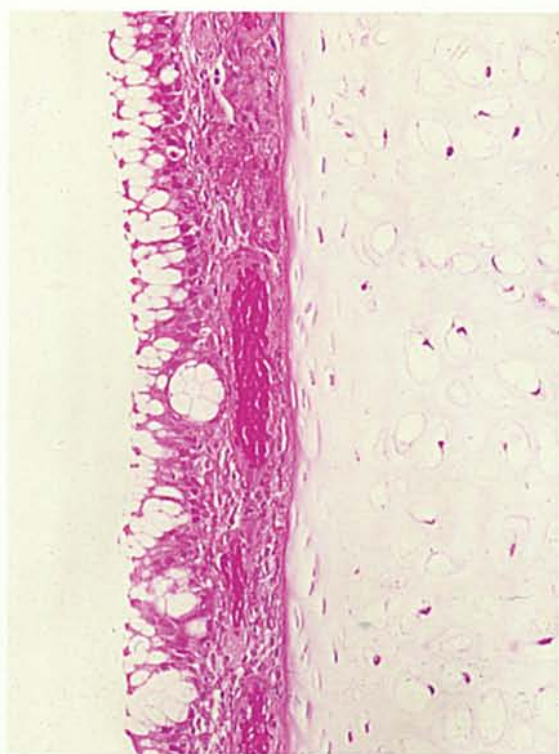


Fig. 2 – Mucous cell hyperplasia. H&E.



Fig. 3 – Mucous cell hyperplasia. H&E.



Fig. 4 – Squamous metaplasia of respiratory epithelium. H&E.

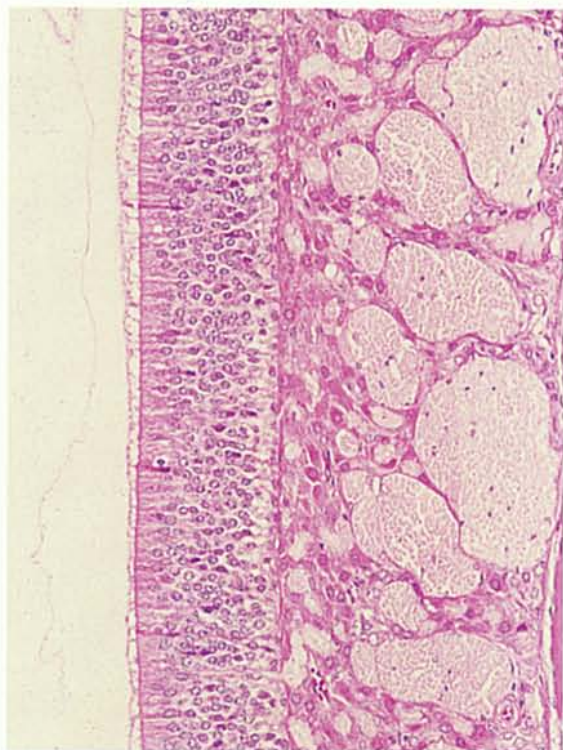


Fig. 5 – Normal olfactory epithelium. H&E.

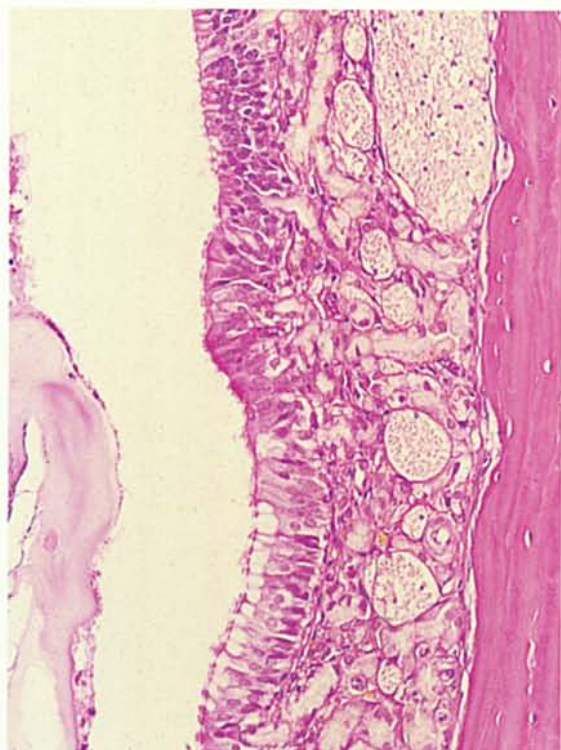


Fig. 6 – Respiratory metaplasia of olfactory epithelium. Note transition with normal olfactory epithelium. H&E.

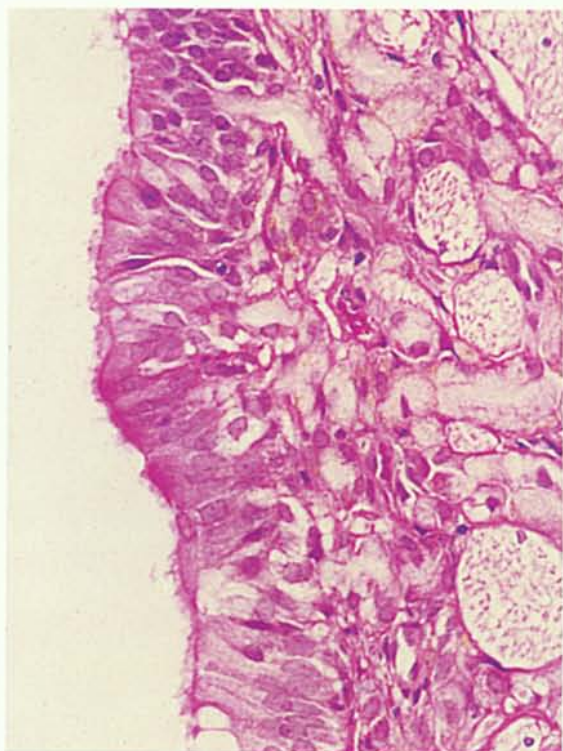


Fig. 7 – Higher magnification of Figure 6. H&E.



Fig. 8 – Respiratory metaplasia of olfactory epithelium. H&E.

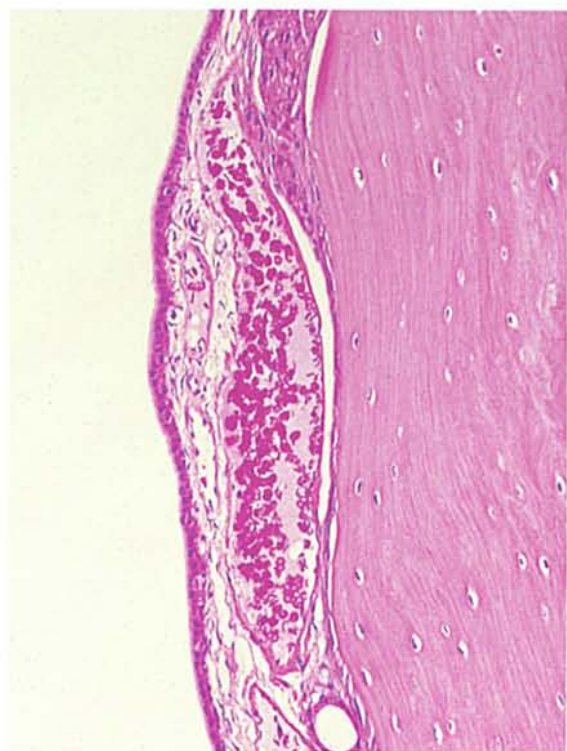


Fig. 9 – Normal respiratory epithelium. Cuboidal transitional epithelium of the lateral wall. H&E.

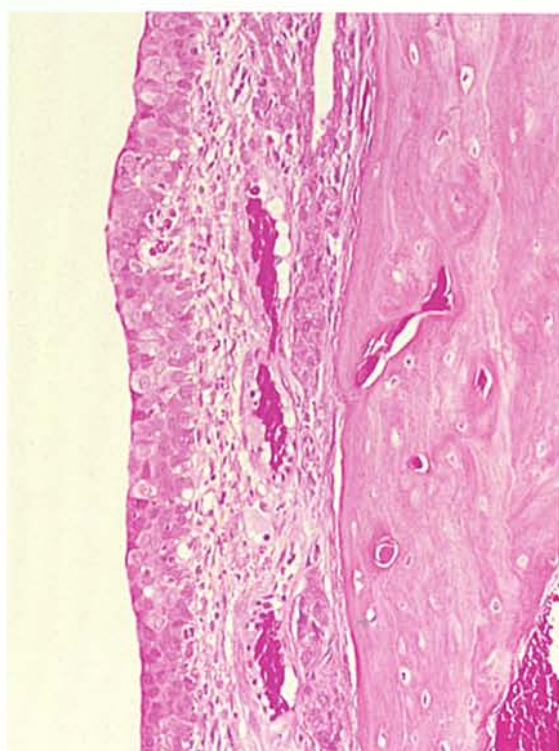


Fig. 10 – Transitional epithelial hyperplasia. H&E



Fig. 11 – Higher magnification of Figure 10. H&E.

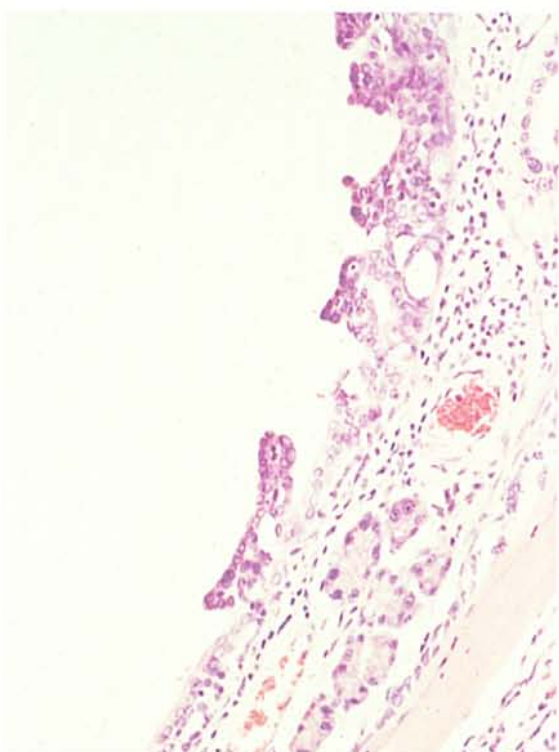


Fig. 12 – Papillary hyperplasia and atypia of transitional epithelium lining the anterior dorsal region of the lateral wall. H&E

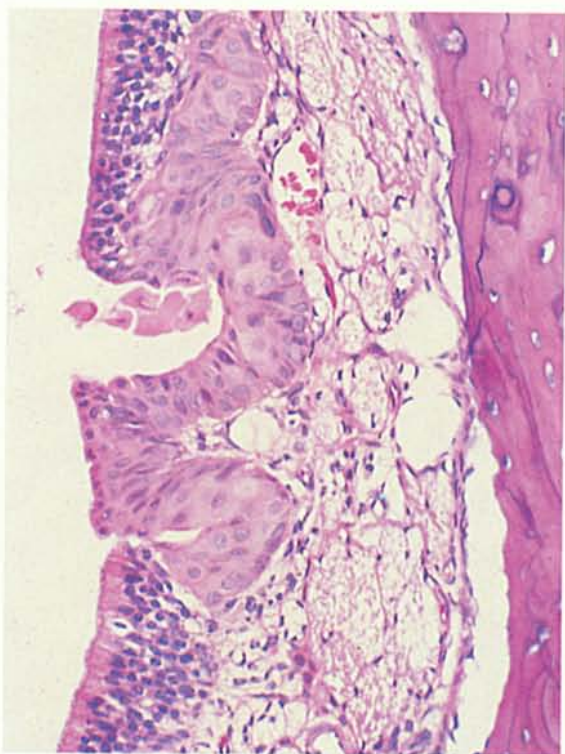


Fig. 13 – Basal cell hyperplasia of olfactory epithelium. H&E.

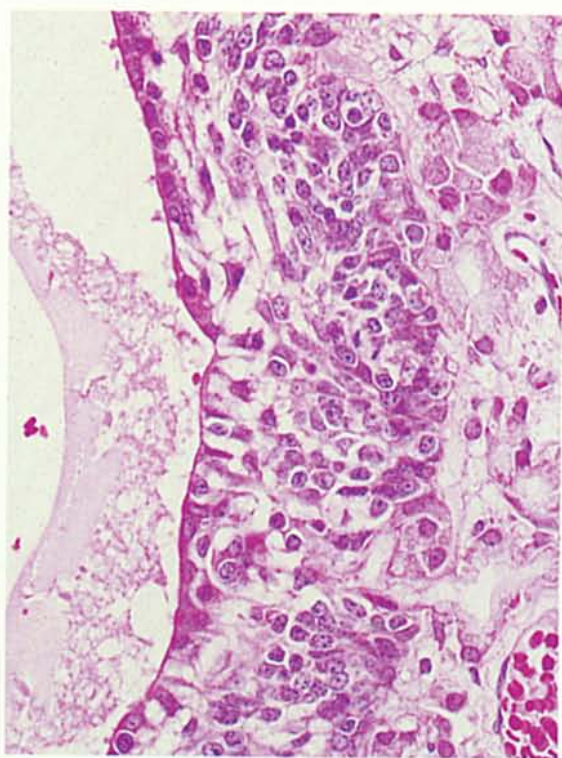


Fig. 14 – Olfactory epithelial hyperplasia with irregular arrangement of sensory cells. H&E.



Fig. 15 – Papillary adenoma of respiratory epithelium. H&E.

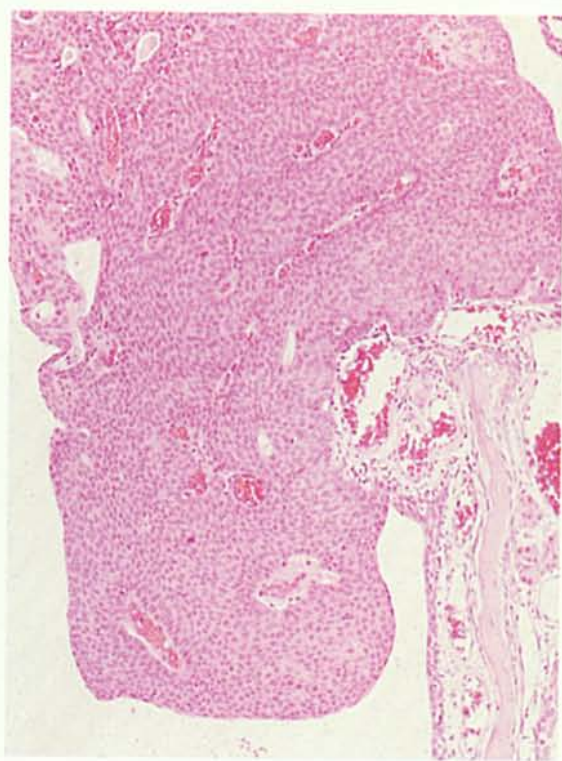


Fig. 16 – Adenoma of transitional epithelium arising from the lateral surface of the anterior nasal turbinate. H&E.

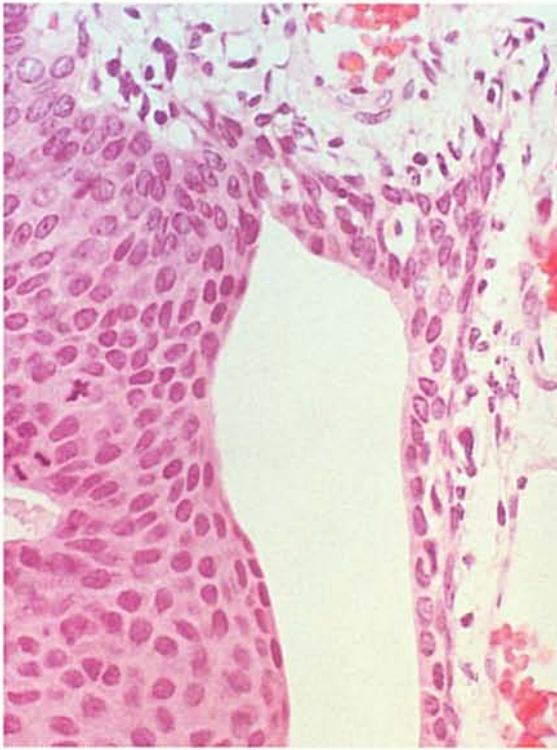


Fig. 17 – Higher magnification of the above lesion showing continuity with normal transitional epithelium. H&E.

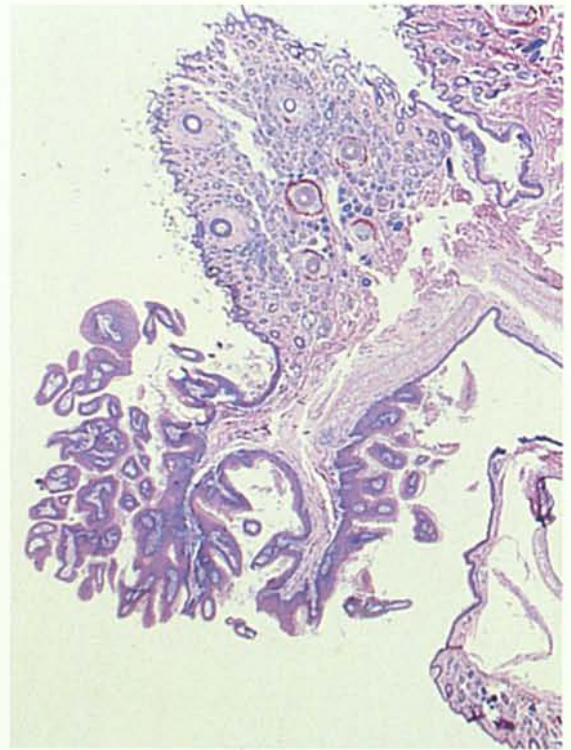


Fig. 18 – Squamous cell papilloma arising from the nares and extending into the nasal vestibule. H&E.

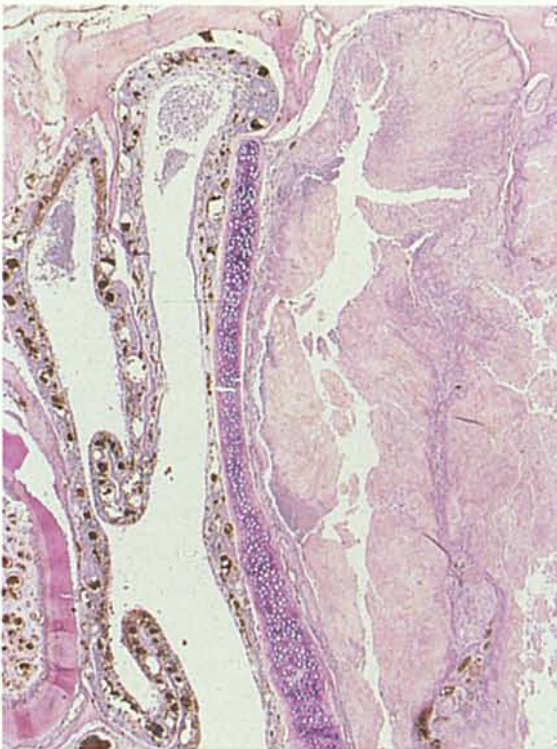


Fig. 19 – Squamous cell carcinoma arising from respiratory epithelium of the dorsal meatus and nasal turbinate. H&E.

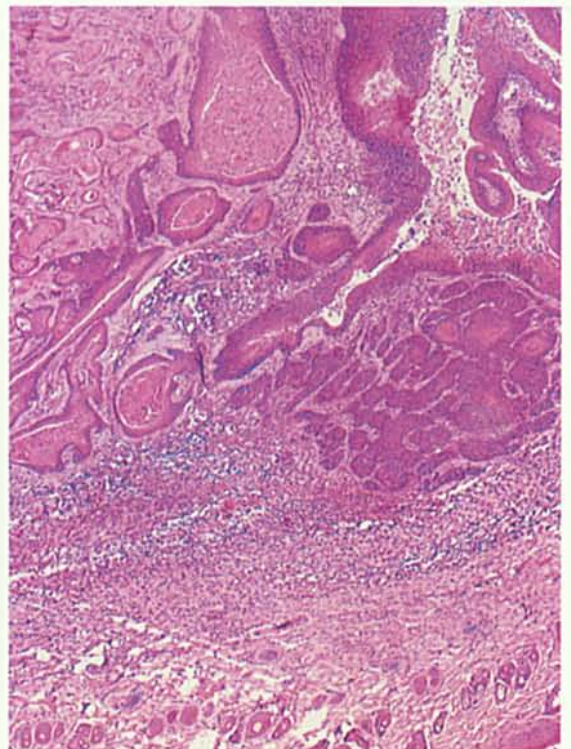


Fig. 20 – Squamous cell carcinoma. H&E.



Fig. 21 – Adenocarcinoma of respiratory epithelium. H&E.

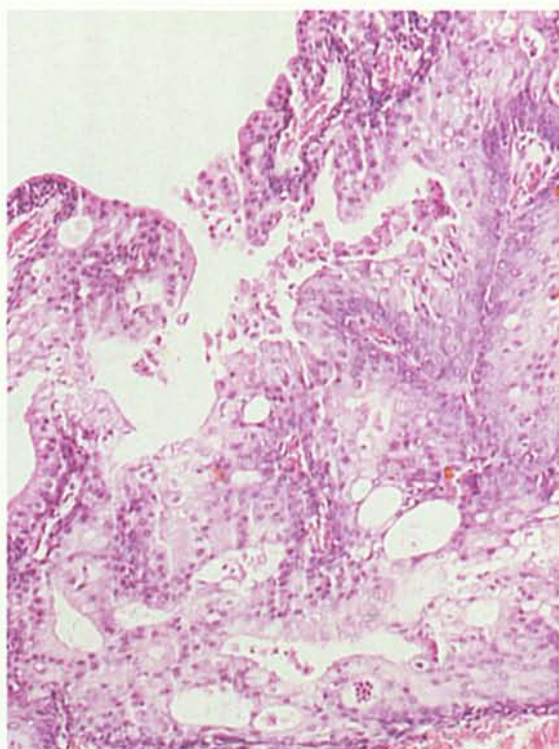


Fig. 22 – Adenocarcinoma of transitional epithelium. H&E.

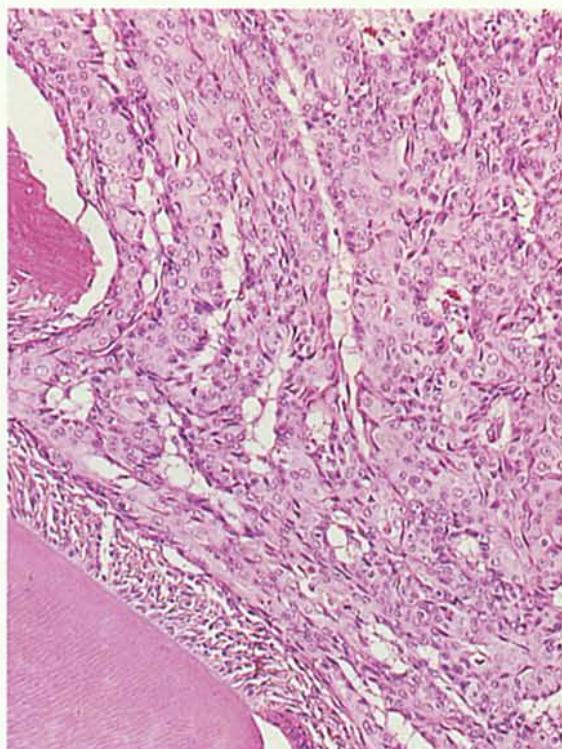


Fig. 23 – Invasion of the above tumor into the periodontal ligament. H&E.

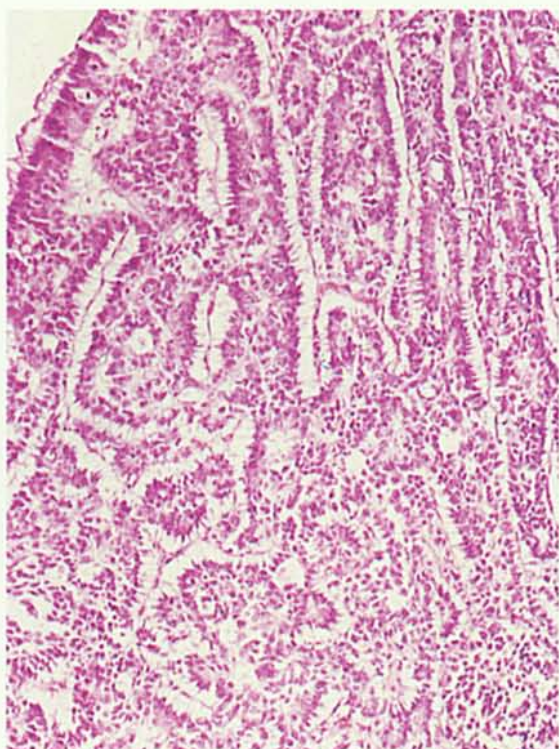


Fig. 24 – Olfactory neuroblastoma with sustentacular-like cells arranged in rows or columns. H&E.

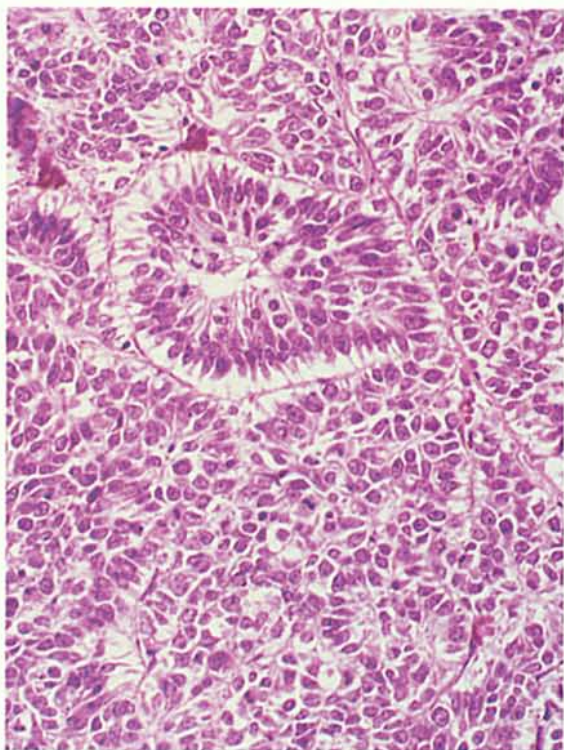


Fig. 25 – Olfactory neuroblastoma with rosette formation and sustentacular-like cells with vacuolated cytoplasm. H&E.

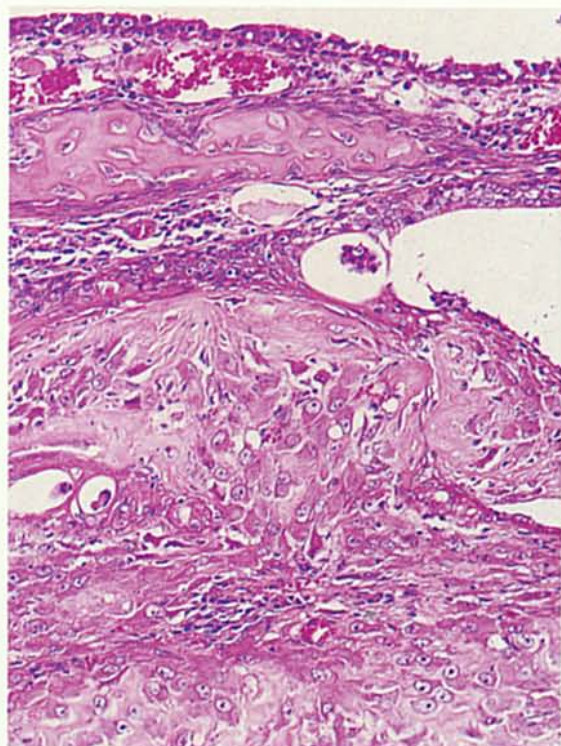


Fig. 26 – Osteosarcoma involving the lateral wall. H&E.

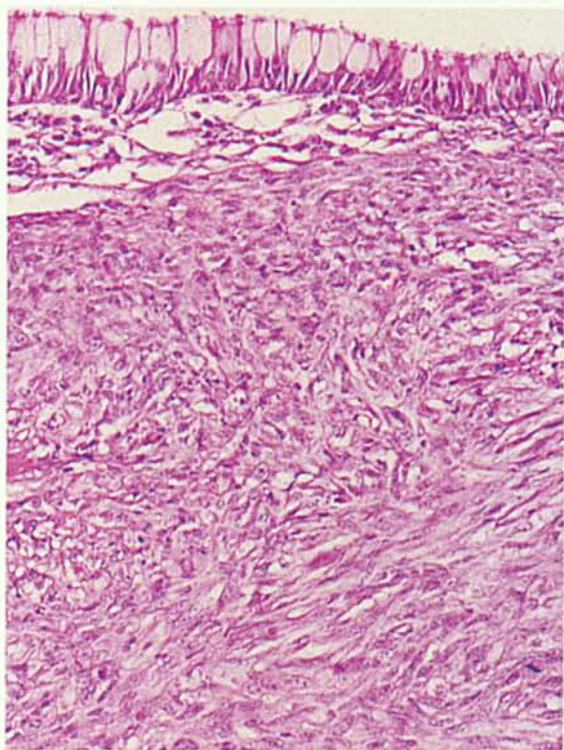


Fig. 27 – Malignant Schwannoma involving the lateral wall. H&E.

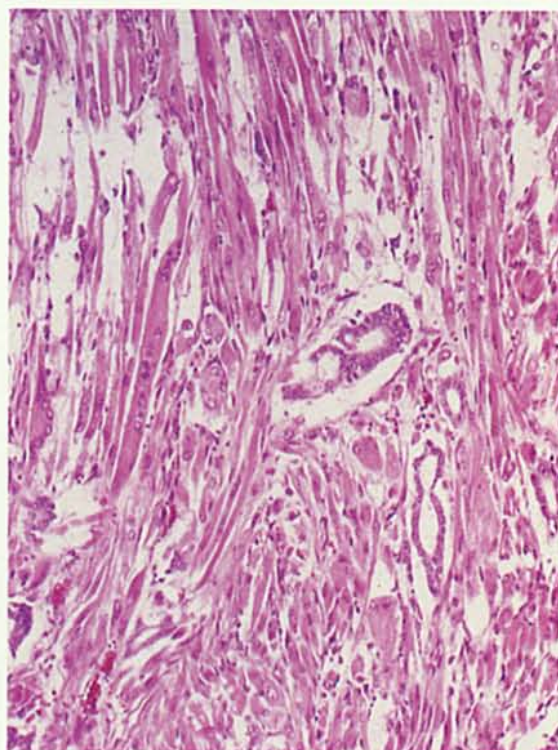


Fig. 28 – Rhabdomyosarcoma. H&E.



Fig. 29 – Normal larynx. H&E.

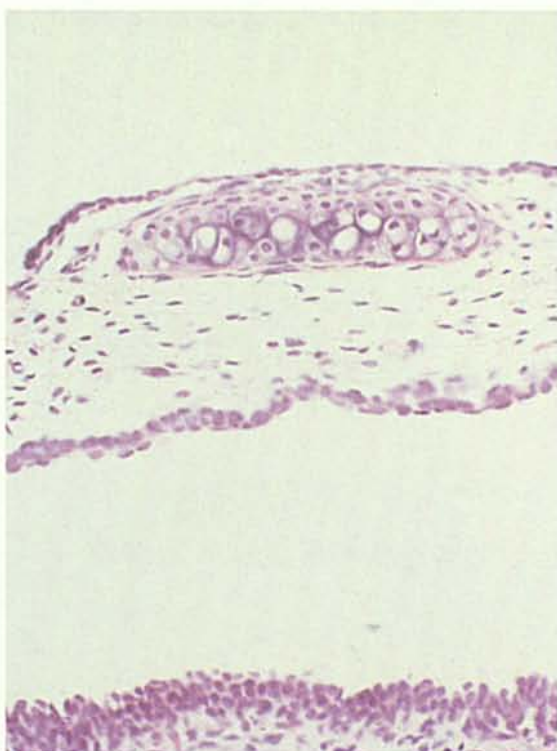


Fig. 30 – Normal larynx, ventral pouch. H&E.

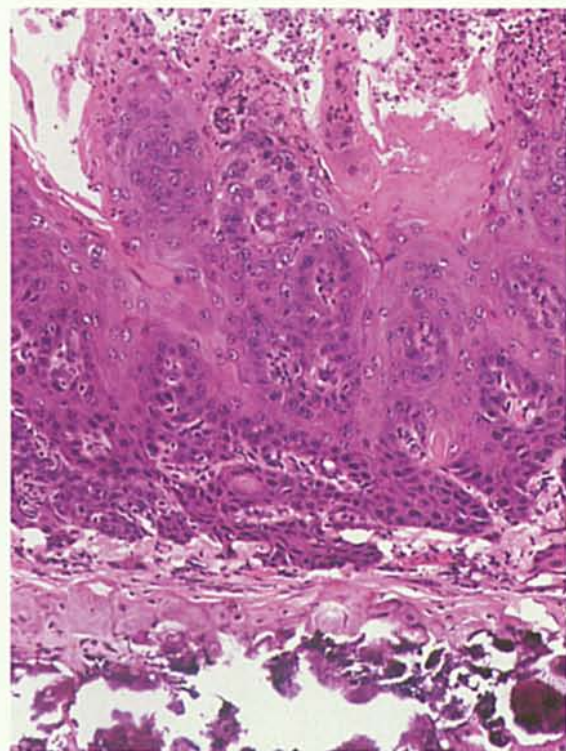


Fig. 31 – Squamous metaplasia of the larynx. H&E.

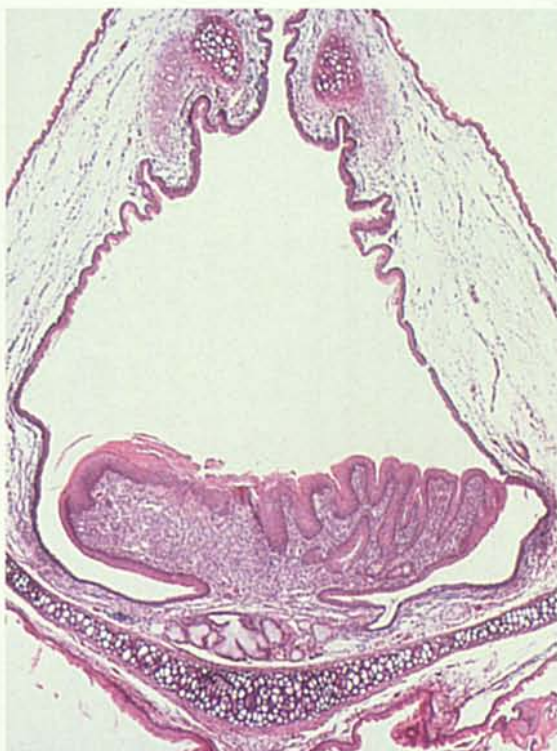


Fig. 32 – Polyp (inflammatory). H&E.

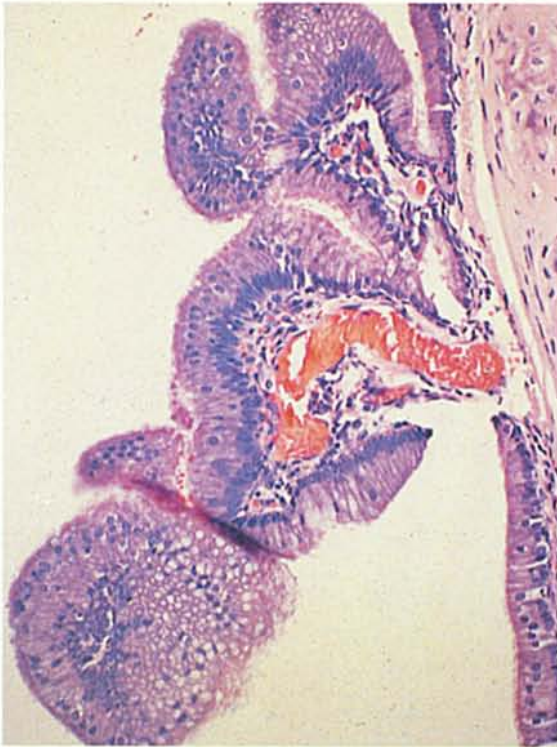


Fig. 33 – Papilloma of the larynx. H&E.



Fig. 34 – Papilloma of the trachea. H&E.



Fig. 35 – Papilloma of the bronchus. H&E.



Fig. 36 – Granular cell tumor of the larynx. H&E.



Fig. 29 – Normal larynx. H&E.

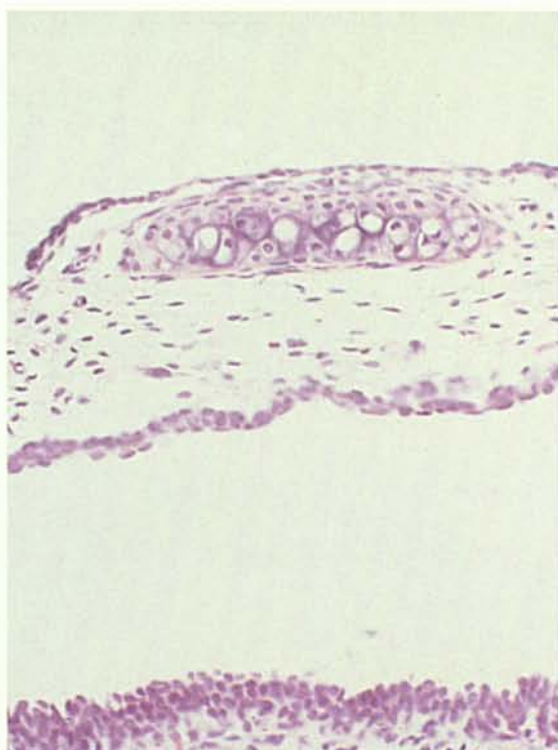


Fig. 30 – Normal larynx, ventral pouch. H&E.

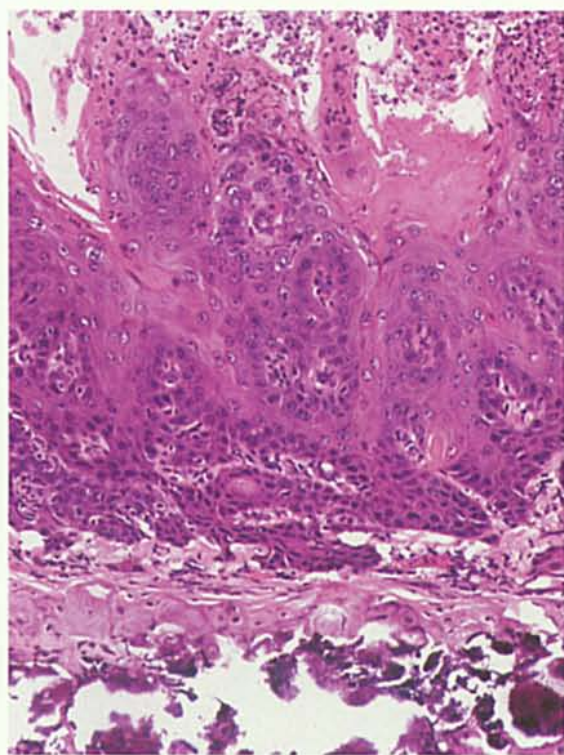


Fig. 31 – Squamous metaplasia of the larynx. H&E.



Fig. 32 – Polyp (inflammatory). H&E.

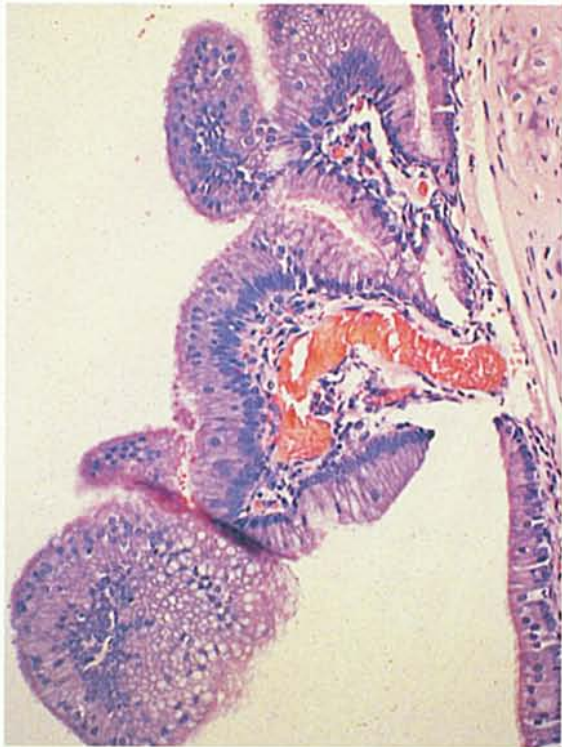


Fig. 33 – Papilloma of the larynx. H&E.



Fig. 34 – Papilloma of the trachea. H&E.

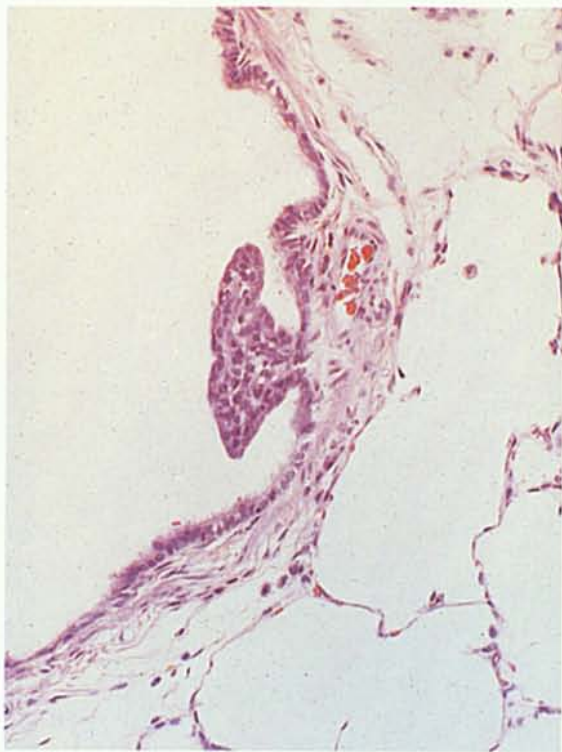


Fig. 35 – Papilloma of the bronchus. H&E.



Fig. 36 – Granular cell tumor of the larynx. H&E.

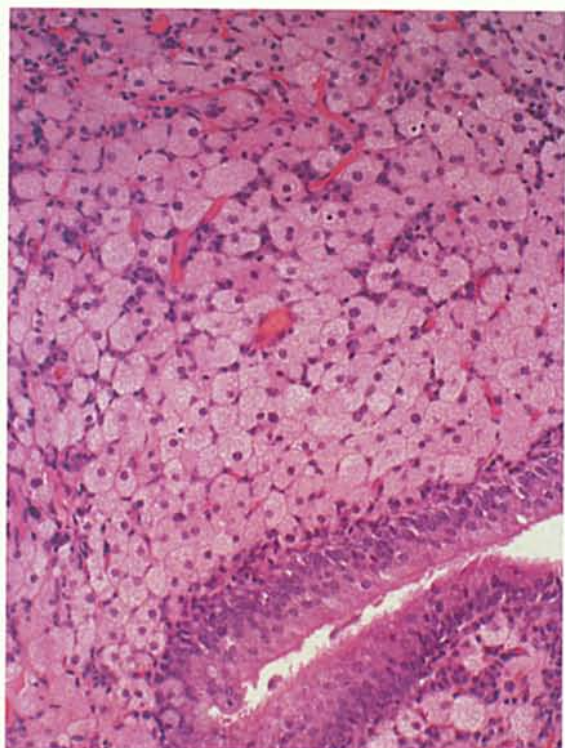


Fig. 37 – Higher magnification of the preceding tumor. H&E.



Fig. 38 – Bronchiolo-alveolar hyperplasia. H&E.

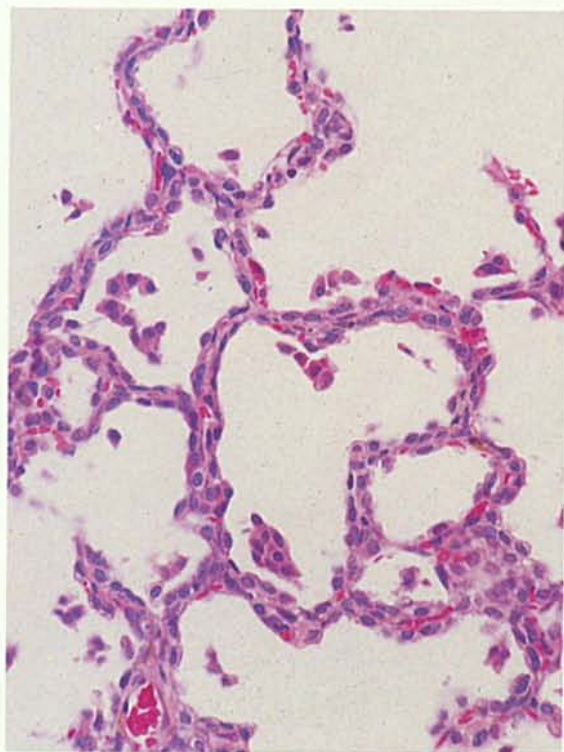


Fig. 39 – Higher magnification of Figure 38. H&E.

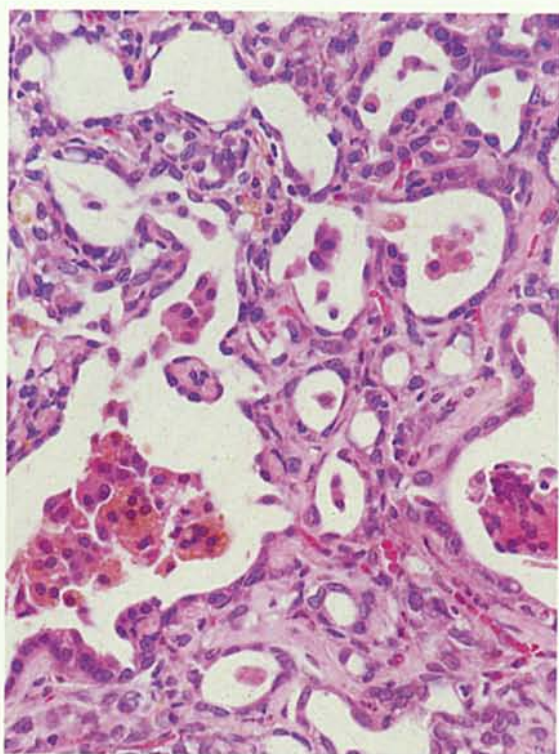


Fig. 40 – Bronchiolo-alveolar hyperplasia with pulmonary fibrosis. H&E.

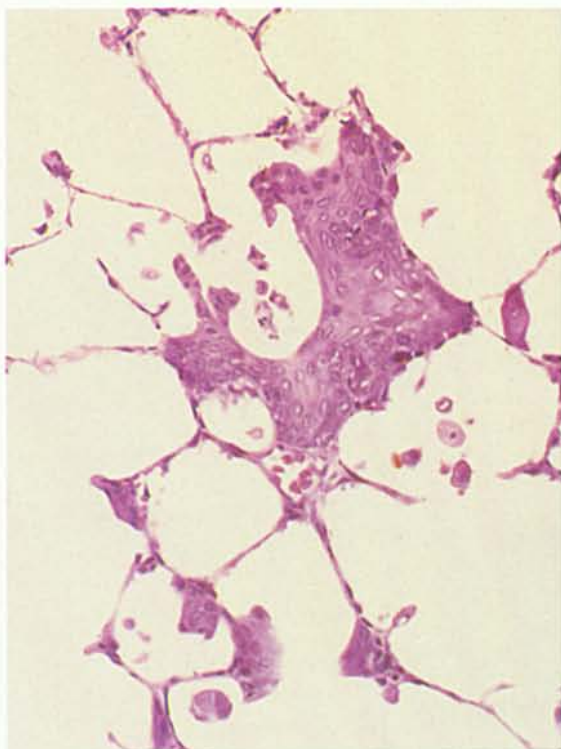


Fig. 41 – Squamous metaplasia of the alveolus. H&E.

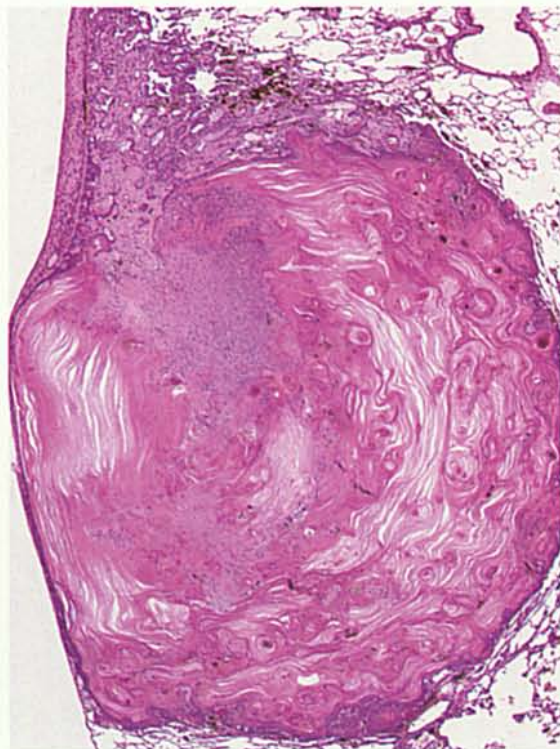


Fig. 42 – Squamous cyst. H&E.

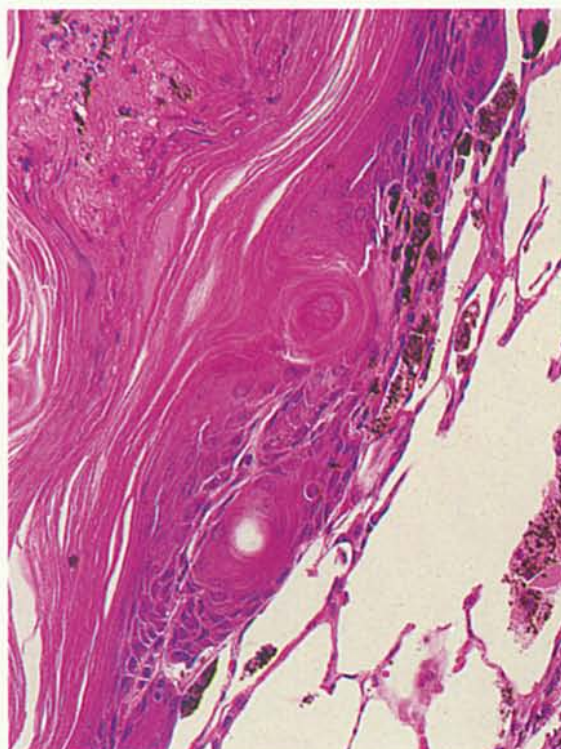


Fig. 43 – Cyst wall showing normal differentiation with abundant keratin. H&E.

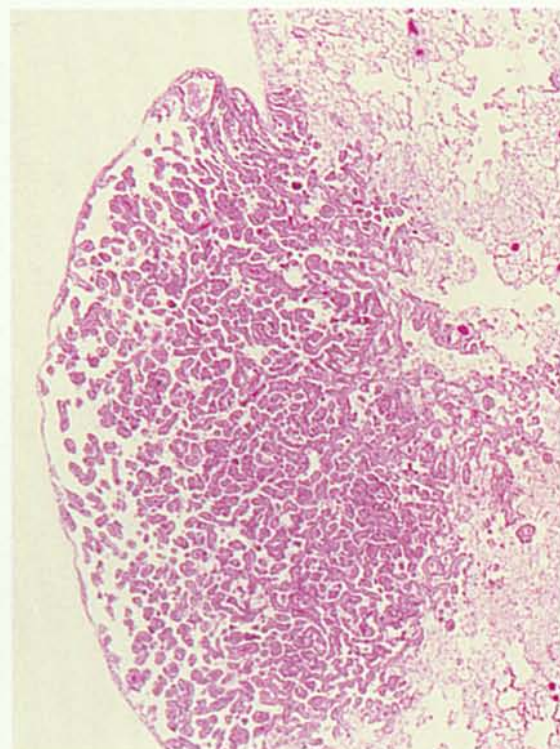


Fig. 44 – Bronchiolo-alveolar adenoma. H&E.

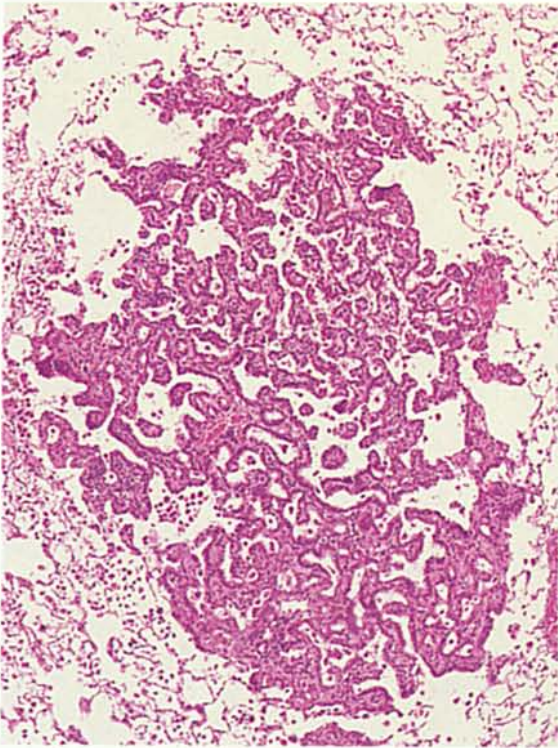


Fig. 45 – Bronchiolo-alveolar adenoma. H&E.

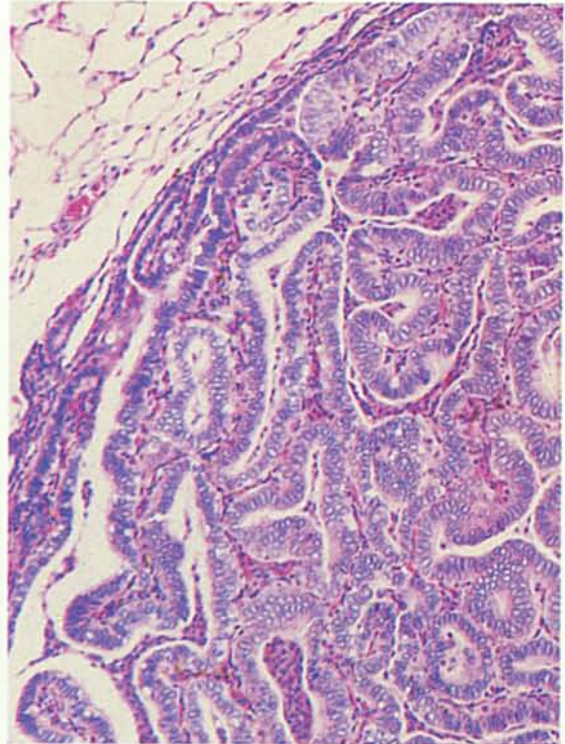


Fig. 46 – Bronchiolo-alveolar adenoma, papillary. H&E.

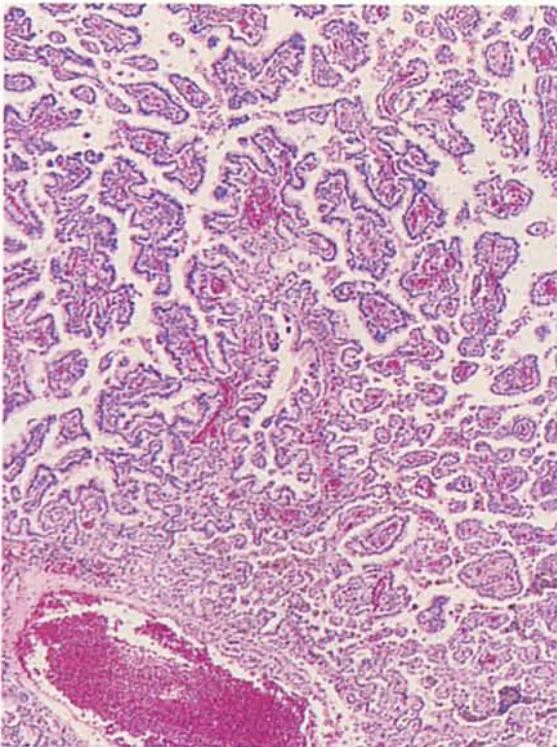


Fig. 47 – Bronchiolo-alveolar carcinoma with large cuboidal to columnar cells in a papillary pattern. H&E.

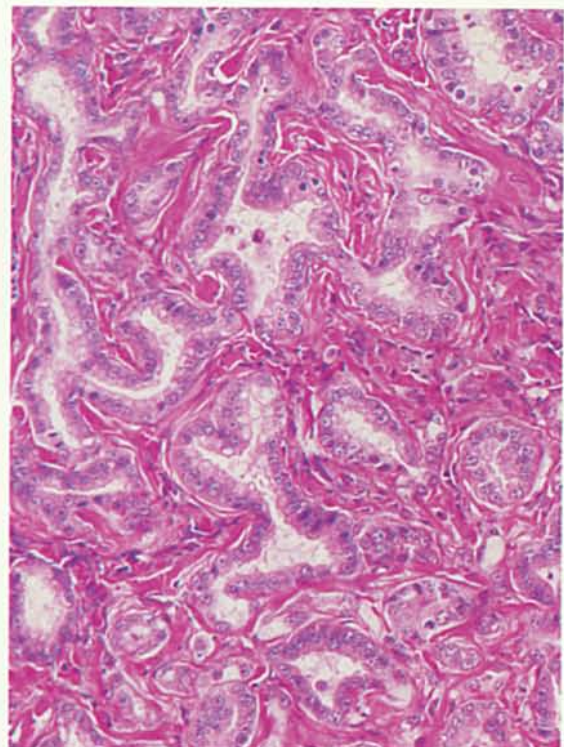


Fig. 48 – Bronchiolo-alveolar carcinoma with large cuboidal anaplastic cells in a tubular pattern. H&E.

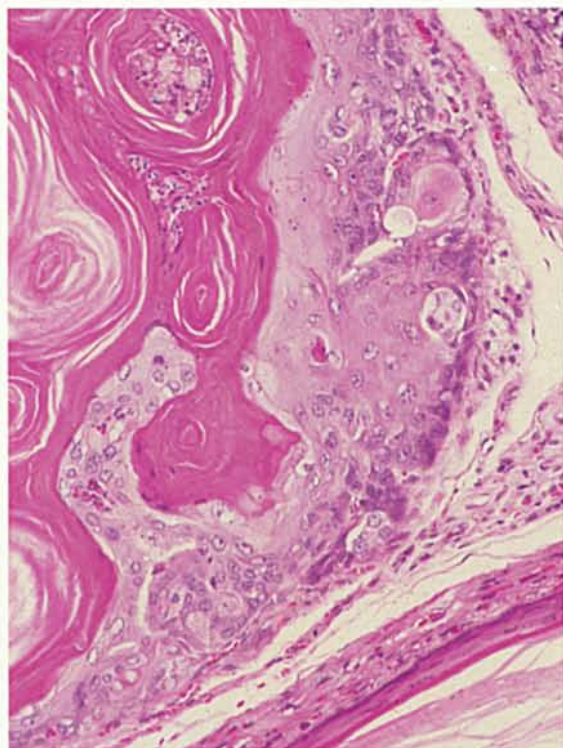


Fig. 49 – Squamous cell carcinoma. H&E.

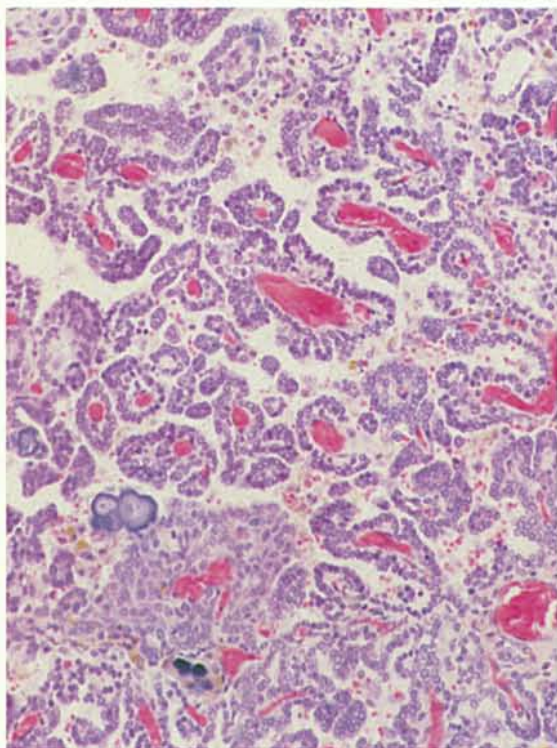


Fig. 50 – Papillary mesothelioma. H&E.

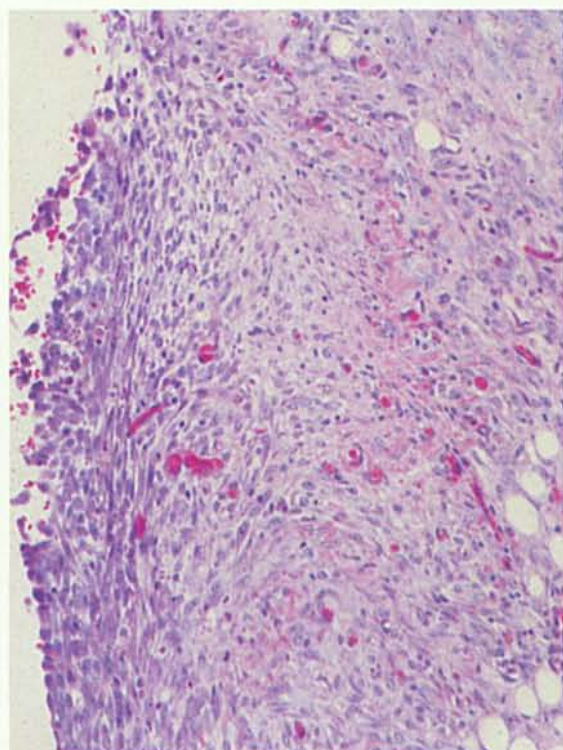


Fig. 51 – Fibrous mesothelioma. H&E.

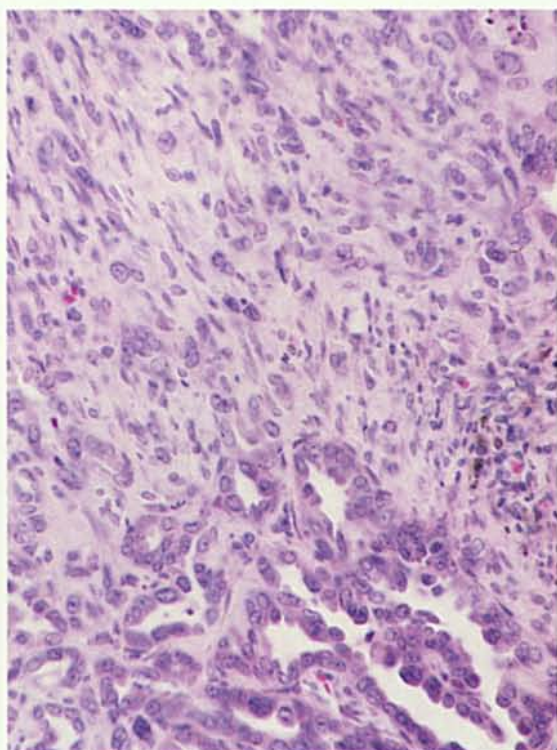


Fig. 52 – Mixed mesothelioma. H&E.