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## Chapter 5

# Salivary Glands

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## 1. INTRODUCTION

The salivary glands of the rat include three major paired and several minor glands. The major glands are the parotid, submaxillary (submandibular or mandibular), and major sublingual. The minor glands, which are not seen grossly, include the minor sublingual, buccal, palatine, and lingual glands. Both neoplastic and nonneoplastic lesions of the minor glands are rare in rats. Extensive physiologic, immunohistochemical, and ultrastructural studies of the acinar and ductular epithelium of the rat salivary glands have shown their importance in maturation and functional regulation of other tissues by the production and secretion of hormonal growth factors. Only the major salivary glands are routinely examined in standard toxicological studies.

## 2. NORMAL SALIVARY GLANDS

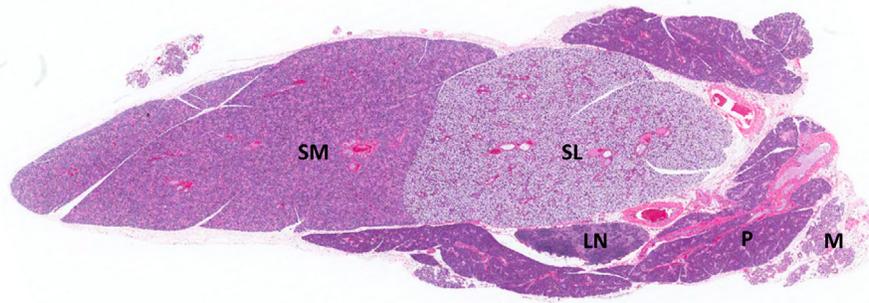
### 2.1. Embryology and Perinatal Development

The primordium of the major salivary glands is first seen by day 14 of gestation. These glands arise as paired outpocketings of the endodermal lining of the embryonic gut.

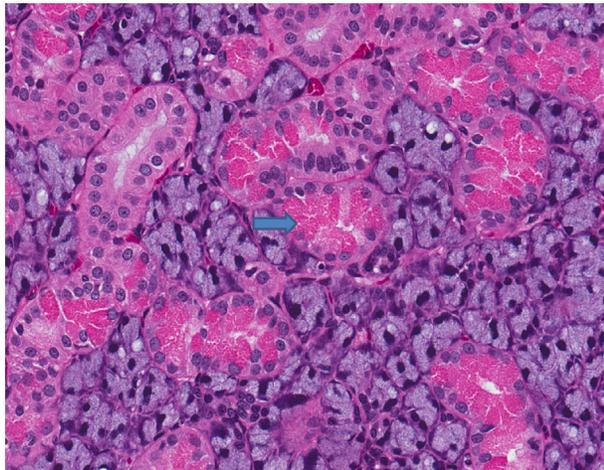
Among the major salivary glands of the rat, the postnatal development of the submaxillary gland has been studied most extensively. At birth, these glands are composed primarily of rudimentary lobules of mesenchyme with ductular structures lined by columnar to cuboidal epithelium. Acinar development begins at birth in rats and continues until about 6 weeks postnatally. Ductular development and maturation continue for over 4 months after birth. Sodium and potassium ATPase activities in the membrane fractions of this gland increase during the neonatal period until 21 days, when levels are similar to those of adults.

### 2.2. Anatomy and Histology

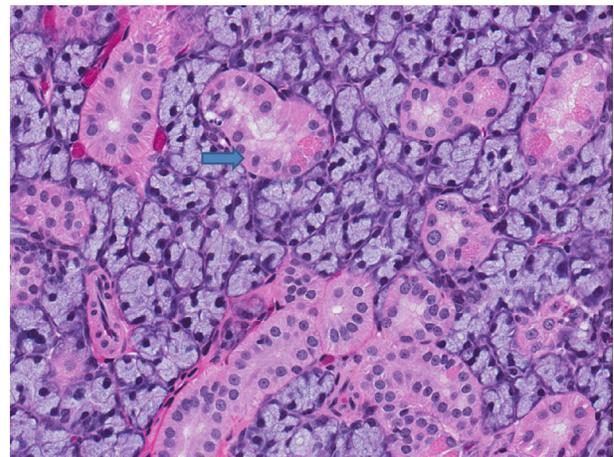
The extraorbital lacrimal gland must be distinguished from the major salivary glands both grossly and microscopically, since it is in close anatomic proximity to these structures. The major salivary glands are located along the ventral neck and extend upward to the base of the ear in close association with the mandibular lymph nodes and the extraorbitallacrimal gland rostrally. Careful dissection and orientation of these closely apposed structures in the paraffin block results in a portion of the lymph nodes and the three major salivary glands in a single section



**FIGURE 5.1** Salivary glands dissected with adjacent structures intact. Submandibular gland (SM), sublingual gland (SL), parotid gland (P), mandibular lymph node (LN), and mammary gland (M).



**FIGURE 5.2** Submandibular gland of male rat. Secretory granular ducts (arrow) are larger than those in the female rat (see Fig. 5.3).



**FIGURE 5.3** Submandibular gland of female rat at the same magnification for comparison with male in Fig. 5.2. Cuboidal epithelium forms smaller ducts (arrows) with fewer granules than in male gland.

(Fig. 5.1). A thin fibrous capsule covers each gland and blends into a common capsule. The connective tissue extends between lobes of individual glands to form a delicate stroma surrounding the lobules. White fat and brown fat are also associated with these glands.

### 2.2.1. Submandibular Salivary Gland (Submaxillary or Mandibular)

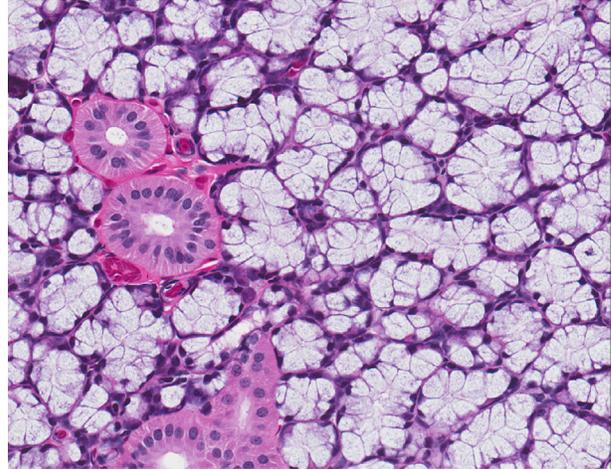
The submandibular gland is the largest salivary gland and lies adjacent to the ventral midline of the neck. It extends to the mandibular lymph nodes rostrally and nearly to the thoracic inlet caudally. It is bordered laterally by the more coarsely lobulated parotid gland. The smaller sublingual (major) gland is located at the rostralateral aspect of this gland just caudal to the mandibular lymph nodes. The submandibular gland is tan and has a smooth surface incompletely divided into rounded lobes of densely packed indistinct lobules. It is oval and compressed dorsoventrally with dimensions of approximately  $10 \times 15 \times 5$  mm.

Histologically, there are four components of the parenchyma of the submandibular gland: acini, intercalated ducts, convoluted (granular) ducts, and intralobular (striated) ducts (Figs. 5.2 and 5.3). The ductular system continues into the interlobular space and is composed of the excretory ducts which join to form the main excretory duct. Myoepithelial cells surround the acinar cells and intercalated ducts. They are located between the basal lamina and the epithelium and are attached by desmosomes to the epithelial cells. The acinar cells are mixtures of serous and mucous secretory cells. The cells are basophilic, with the strongest staining in the basilar portion of the cell near the nucleus. The apical area of the cell contains secretory granules. In mucous acinar cells, mucin droplets in the apical cytoplasm often appear as clear vacuoles. The ultrastructural features of the acinar cells include abundant rough endoplasmic reticulum (especially in the perinuclear region), Golgi complexes, and numerous mitochondria. Peroxisomes are also found in acinar cells of both the sublingual and submandibular glands. Groups of several acini join the ductular system by narrow intercalated

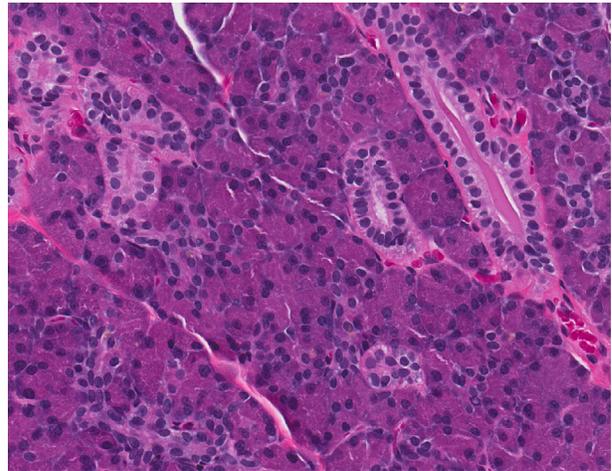
ducts, which are lined by low cuboidal to flattened epithelium. Oncocytes (characterized as cells with abundant granular eosinophilic cytoplasm, a central hyperchromatic nucleus, pleomorphic large mitochondria, and small apical secretory granules) have been reported in this portion of the submandibular gland ductular system in other strains of aged rats. The intercalated ducts join the secretory convoluted (granular) portion of the ductular system which is unique to the submandibular gland. The epithelium of this section of the duct is tall columnar. Sexual dimorphism becomes apparent in the submandibular gland by 7 weeks after birth and is characterized by a greater diameter of the secretory ducts in males. In the mature male these ducts constitute a larger percentage of the volume of the gland, have more eosinophilic secretory granules, are longer, and are lined by taller epithelium than in females. These cells are hormone dependent and testosterone-sensitive, which may account for the morphologic variations in this gland in rats (Figs. 5.2 and 5.3). The next segment of the ductular system is the intralobular or striated duct (so named because of prominent basilar striations). Cells are tall columnar with central or apically located nuclei. These ducts enter the excretory ducts which combine to form the main excretory duct. The excretory ducts have tall columnar epithelium with more apically located nuclei and prominent cytoplasmic striations. The main excretory duct of the submandibular gland is composed of several cell types based on ultrastructural features, including light (types I and II), dark, tuft, and basal cells. The most numerous cells in the lining of the main submandibular excretory duct are the light cells. Both light and dark cells have basal membrane infoldings. As the excretory duct nears the opening into the oral cavity it expands into a diverticulum, which is lined by simple columnar to squamous epithelium. The excretory duct segment and the intralobular or striated portion actively transport sodium and potassium to the saliva.

### 2.2.2. Sublingual Salivary Gland (Major)

The major sublingual salivary gland is closely adherent to the submandibular gland and is a darker tan-brown color. The discoid-shaped gland is approximately 5 mm in diameter with a thickness of 1–2 mm. The acini are mucous and the ductular system is less complex than that of the submandibular gland (Fig. 5.4). Intercalated ducts branch directly into the excretory portion of the ductular system. A nongranulated, flattened cuboidal epithelium forms the intercalated ducts, and in the excretory ducts the epithelium is cuboidal to columnar. Until they reach the level of the mandibular symphysis, the excretory ducts of the sublingual and submandibular glands course side by side and then diverge slightly as they curve toward their separate openings on the sublingual caruncle.



**FIGURE 5.4** Sublingual gland consisting of mucous acini and excretory ducts lined by cuboidal epithelium.



**FIGURE 5.5** Parotid gland with serous acini and excretory ducts lined by cuboidal epithelium.

### 2.2.3. Parotid Salivary Gland

Three or four well-delineated flattened lobes form the parotid salivary gland. It is pink to cream colored, which aids in distinguishing it from the tan-gray lacrimal gland located on its anterior dorsal border. The parotid gland is about equal in size to the submandibular gland. The intercalated ducts from each acinus join to form an excretory duct, which exits from each of the lobes. These excretory ducts join to become the main parotid duct, which is in close association with the mandibular and buccal branches of the facial nerve. The main parotid excretory duct crosses the masseter muscle laterally and enters the mouth near the rostral border of the masseter muscle. The parotid acini are serous and histologically similar to exocrine pancreas (Fig. 5.5). The lobes of the gland are divided into lobules by loose connective tissue septa, which extend between acini. Acinar cells are pyramidal

and columnar with basilar nuclei and indistinct cellular borders. The cytoplasm stains basophilic in basal and perinuclear areas due to the abundant rough endoplasmic reticulum, whereas it is more eosinophilic and granular in the apical region because of the zymogen granules. Argyrophilic cells located in the intercalated ducts are exocrine in function. The intercalated ducts of the parotid are important in secretion of electrolytes into the saliva. They are lined by a flattened cuboidal epithelium containing periodic acid-Schiff (PAS)-positive cytoplasmic granules. Ultrastructurally, a subsurface endoplasmic reticular cistern is present in parotid acinar cells where unmyelinated axons extend through the basement membrane of the acini. Axon terminals located at the basilar portion of the epithelial cells are enfolded by the cytoplasm of the acinar cells.

#### 2.2.4. Minor Salivary Glands

One of the four minor salivary glands is the minor sublingual, which is located at the level of the molars in the muscle along the floor of the mouth. The glandular epithelium consists entirely of mucous cells. There are two types of buccal glands. One is found in the mucosa near the angle of the mouth and has a mucous secretion. The anterior buccal glands, which are more serous, are present in the wall of the mouth anterior to the masseter muscle. Palatine glands in the soft palate consist of mucous acini. They are closely associated with the lingual glands to encircle the pharyngeal opening. Two layers of lingual glands are within muscle bundles near the root of the tongue. Their secretions are mucous at the caudal aspect of the tongue and serous at the rostral end. The serous portions have ducts leading to the vallate and foliate papillae and to the side of the tongue, while the mucous acini lubricate the mucosa around the epiglottis.

### 2.3. Physiology

The function of the salivary glands is to moisten food to begin the process of digestion. Salivation is a complex function regulated by the autonomic nervous system, the salivatory nuclei, the appetite area within the hypothalamus, and reflexes within the stomach and upper intestine initiated by nausea or ingested irritants. Saliva is a mixture of amylase, mucin, electrolytes, immunoglobulin, water, and other components. The saliva produced by the rat parotid gland is unique in that it has a protein concentration of about 2%. An extensive list of polypeptides have been identified in salivary glands of various species. A discussion of the importance of each is given by [Barka \(1980\)](#). Two hormonelike growth factors—nerve growth factor and epidermal growth factor (EGF)—have been the focus of interest and recent research efforts, especially in

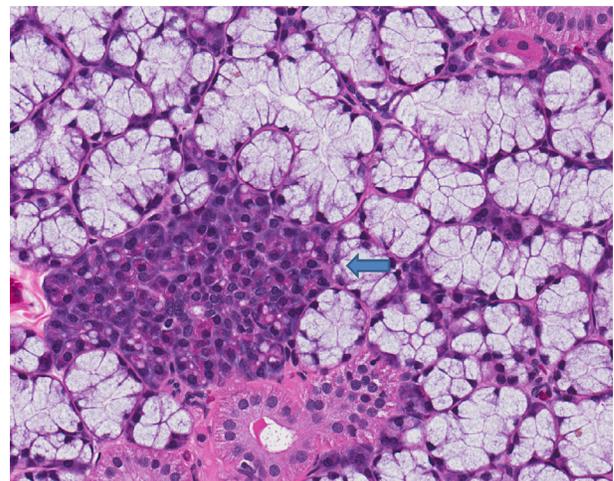
relation to development of neoplasia as well as normal organogenesis. Salivary gland extirpation or ductal ligation shows that these glands have broader influences on a wide range of endocrine and exocrine functions than was previously recognized. Extirpation of the major salivary glands of female rats results in fewer offspring (parotidectomized female rats eventually become infertile). Similar experimental procedures in male rats result in a decrease of plasma testosterone and total thyroxine. The parotid gland produces a hormone (designated parotid hormone) which stimulates dentinal fluid transport within the rat tooth and may prevent tooth decay. The acini and ductular epithelium have the capacity to regenerate. The regenerative acinar and striated duct epithelium of the parotid gland arises from the intercalated duct cells. The life spans of the various cells reported by [Glucksmann and Cherry \(1976\)](#) are as follows: secretory tubules of the submandibular gland, 95 days; submandibular acini, 65 days; sublingual acini, 60 days; and parotid acini, 41 days.

## 3. CONGENITAL LESIONS

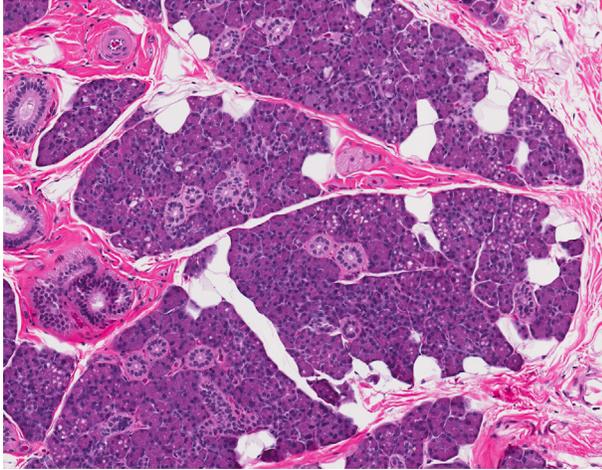
Congenital lesions of the salivary glands are rare in the rat. Ectopic foci of parotid acini occur in the sublingual gland: These foci consist of serous parotid acinar cells or acini between the pale-staining mucous acini of the sublingual gland ([Fig. 5.6](#)). The ectopic serous epithelial cells may be slightly smaller than those in the normal parotid gland ([Fig. 5.7](#)).

## 4. DEGENERATIVE LESIONS

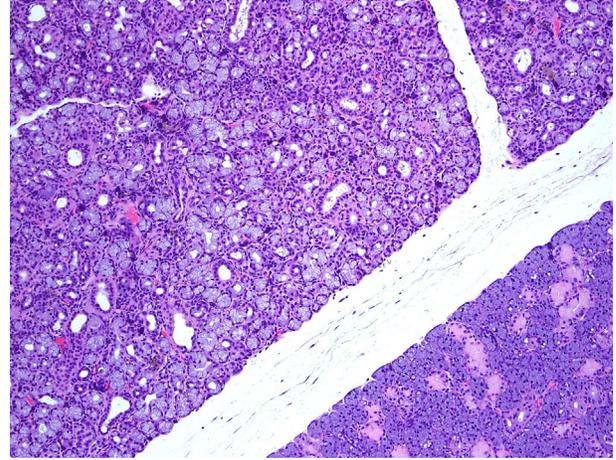
Atrophy of the salivary glands occurs commonly in older rats. Acini and acinar epithelial cells are decreased in both size and number. There may be a slight increase in



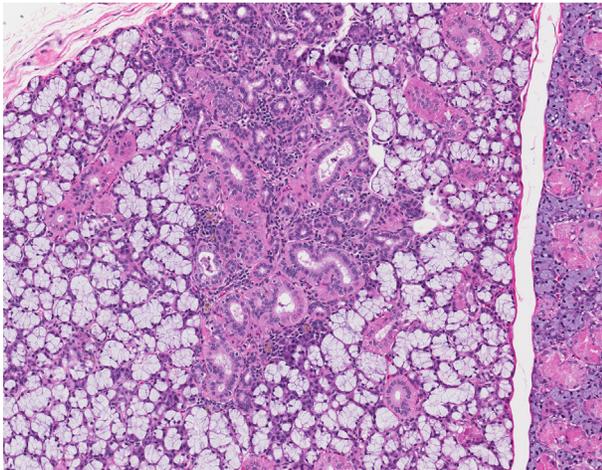
**FIGURE 5.6** Ectopic parotid gland (arrows) between mucous acini of sublingual gland.



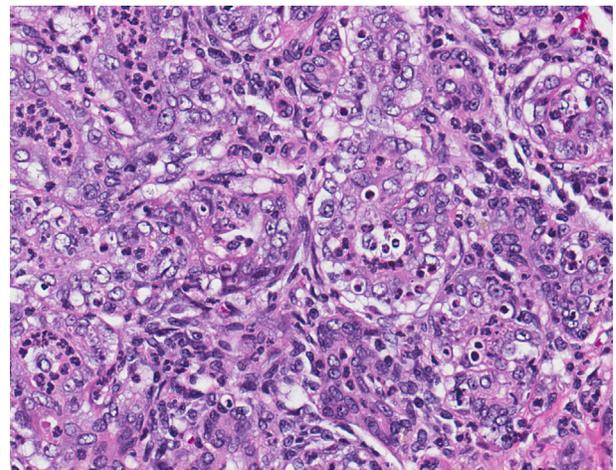
**FIGURE 5.7** Parotid gland with adipocytes in interlobular connective tissue and extending between acini.



**FIGURE 5.9** Diffuse atrophy of sublingual gland (top) with adjacent submandibular gland (lower right) unaffected. Acini are variably shrunken with ducts predominating.

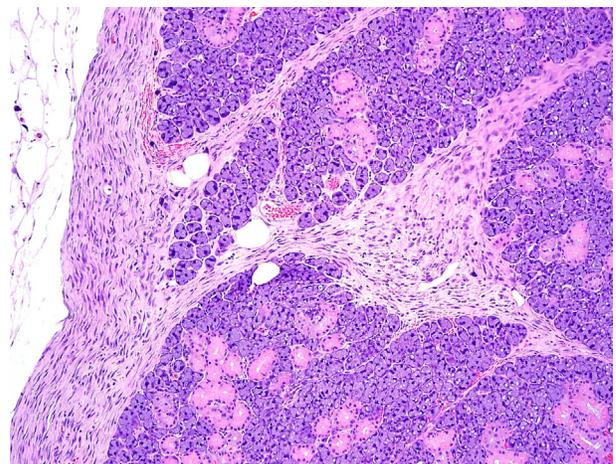


**FIGURE 5.8** Focal atrophy of parotid gland. Acini are not apparent with ducts predominating.



**FIGURE 5.10** Diffuse atrophy of submandibular gland. Acini and ducts are shrunken and disorganized and there is fibrosis and neutrophil infiltrates. Lesion was unilateral with contralateral gland unaffected.

stromal fibrous connective tissue, and focal aggregates of adipocytes are sometimes seen between lobules and acini, similar to involutional changes in the pancreas and thymus (Figs. 5.8–5.11). Atrophy may be the result of toxicity (see Section 7), but it is commonly seen in association with neoplasia or inflammatory lesions in the salivary gland. Necrosis of individual acinar cells and foci of lymphocytes or plasmacytes may be present. Atrophy, necrosis, and inflammation are typically seen with active sialodacryoadenitis virus infection. Atrophy is also seen with mononuclear cell leukemia infiltration of the salivary gland or local invasion by schwannoma arising in branches of the facial nerve. Mineralization of material in the ductular lumen occurs infrequently and may be seen with atrophy. Age-associated atrophic or degenerative changes similar to those in the F344 rat are seen in other strains of rats. Oncocytic cells are seen primarily in the



**FIGURE 5.11** Fibrosis of submandibular gland. Bands of fibrous tissue surround gland and separates lobules.

epithelium of the intercalated ducts and occasionally in the granular ducts of aged Sprague-Dawley and Wistar rats, but it is not known if they occur in F344 rats. By electron microscopy, cytoplasmic crystalloids resembling fused-unit membrane-bound secretory granules are also seen in the intercalated ducts of the parotid glands. Salivary mucocele, ranula, ductular cyst, or ductular dilation may occur secondary to trauma, salivary calculi, or ductular foreign bodies. These are rarely observed in F344 rats.

## 5. INFLAMMATORY AND VASCULAR LESIONS

Sialodacryoadenitis virus (SDA V, a coronavirus) is the most important infectious agent affecting the salivary glands because of its potential to compromise the interpretation of toxicological studies. Infection with this virus often produces gross enlargement of the salivary glands and mandibular lymph nodes (unilateral or bilateral) and an increase in secretion of tears, which stain the hair on the face and around the nose. The virus causes necrosis of both acinar and ductular epithelium in the submandibular and parotid salivary glands with marked inflammation. The mucous salivary glands (sublingual) are not affected. In the early phase of the infection a neutrophil infiltrate is associated with the necrosis, but later the infiltrates consist predominantly of mononuclear cells. In severely affected glands there is nearly complete replacement of the parenchyma by inflammatory infiltrates in the acinar connective tissue stroma, with only scattered ducts remaining. Ductular regeneration is accompanied by squamous metaplasia of the epithelium. Lymphoid hyperplasia in mandibular lymph nodes is usually seen with active SDA V infection. Susceptibility to experimental SDA V infection is similar in Wistar, Sprague-Dawley, Long-Evans, and F344 rats. A transient reduction in the amount of EGF in submandibular glands of Wistar rats occurs during experimental infection with SDA V. Intercurrent infection with SDA V during exposure to test chemicals in 2-year carcinogenicity studies conducted by the NTP had no effect on the incidences of salivary gland or other neoplasms. Another coronavirus, commonly referred to as "rat coronavirus," may affect the salivary glands minimally as well as the lung, although the infection is usually clinically inapparent. Current serologic tests do not discriminate between SDA V and rat coronavirus antibodies. Polyomavirus and cytomegalovirus infections may occur in the salivary glands, but no lesions have been reported in toxicological studies specifically attributed to these viral infections in F344 rats. Polyarteritis occurs rarely in the salivary glands compared with involvement of arteries at other sites, such as in the pancreas or mesentery. Other

vascular and inflammatory lesions are observed sporadically and are not unique in these glands.

## 6. HYPERPLASTIC AND NEOPLASTIC LESIONS

Hyperplastic or preneoplastic changes associated with spontaneously occurring neoplasms have not been identified in F344 rats. Spontaneous basophilic hypertrophic foci are observed in the parotid salivary gland of young adult and aged F344 rats, but it is not known if these are proliferative lesions or preneoplastic. They also occur in Sprague-Dawley rats at an incidence of 4.8%. The observed incidence of these foci increases with age, but the size and the number of foci per rat do not. Primary salivary gland neoplasms are rare; neoplasms of epithelial or mesenchymal origin in the cervical area arise more often from Zymbal's gland, mammary gland, the fibrous connective tissue of the stroma or adventitia, or peripheral nerves. In the F344 rat, infiltrates of neoplastic cells associated with mononuclear cell leukemia may efface an entire gland. These invasive and metastatic neoplasms must be considered in the evaluation of a salivary gland neoplasm.

### 6.1. Basophilic Hypertrophic Foci

Basophilic hypertrophic foci are not seen grossly and are characterized microscopically by focal enlargement of the acinar cells due mainly to an increase in cytoplasmic volume (Fig. 5.12). Fine vesiculation of the cytoplasm is a feature of the cells within the hypertrophic focus. The nucleus may be enlarged but is sometimes obscured by the basophilic basilar cytoplasm. A similar lesion is seen in the exocrine pancreas. A more diffuse change with hypertrophy of most acinar cells is also seen occasionally

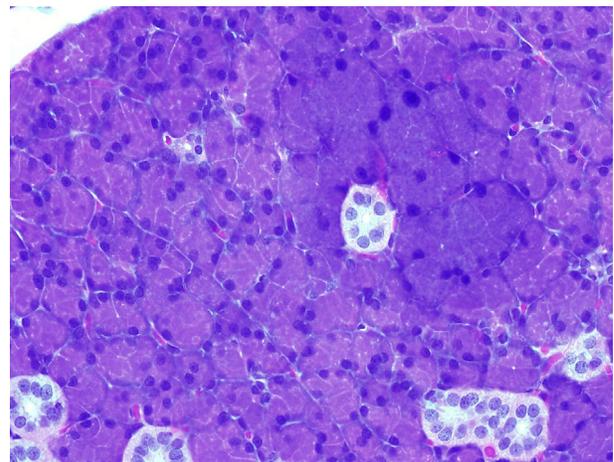
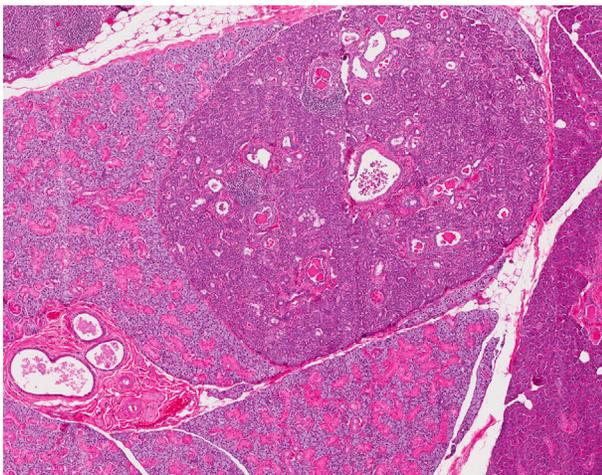


FIGURE 5.12 Basophilic hypertrophic foci within the parotid gland.

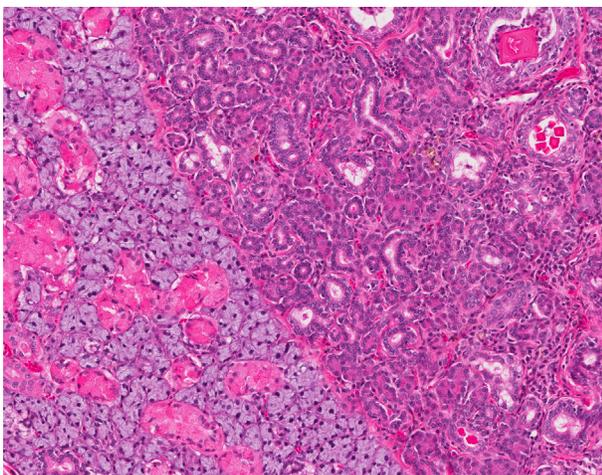
but individual cells are not as large as in the focal lesion. This may be seen occasionally in an untreated rat, but chemicals including doxylamine have produced this change in the parotid gland of F344 rats.

## 6.2. Adenoma

Adenomas of ductular or acinar cell origin are occasionally seen. The tubular form may arise from the intercalated or excretory duct and consists of expansile nodules of well-formed tubular structures separated by a variable amount of fibrous stroma (Figs. 5.13 and 5.14). Tubules have a single or stratified epithelium ranging from cuboidal to columnar to simple squamous in appearance. Mitotic figures are present in low numbers. Adenomas with an acinar pattern resemble the normal gland, except



**FIGURE 5.13** Adenoma of mandibular gland. Tumor is well-demarcated from normal gland.

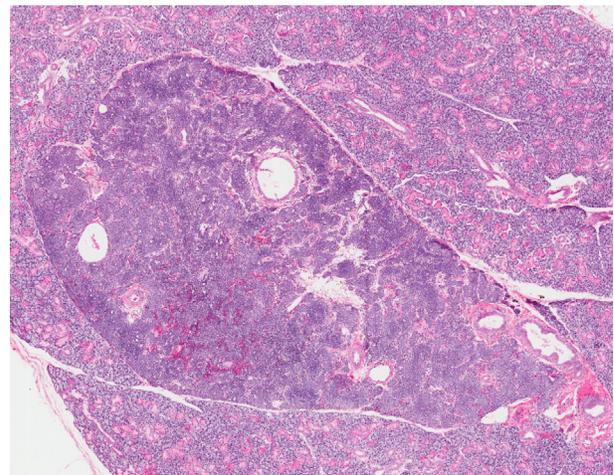


**FIGURE 5.14.** Higher magnification of adenoma in Fig. 5.13. Composed predominantly of well-formed tubules with occasional acini and minimal stroma.

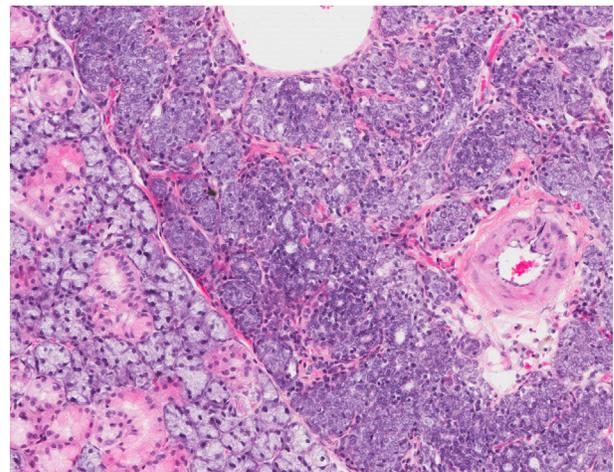
that the acini are often larger and ducts are absent. The acini are arranged in poorly formed expansile lobules which are irregular in size and compress normal lobules. Neoplastic cells have abundant cytoplasm and prominent nuclei; mitoses are present in variable number (Figs. 5.15–5.19).

## 6.3. Adenocarcinoma

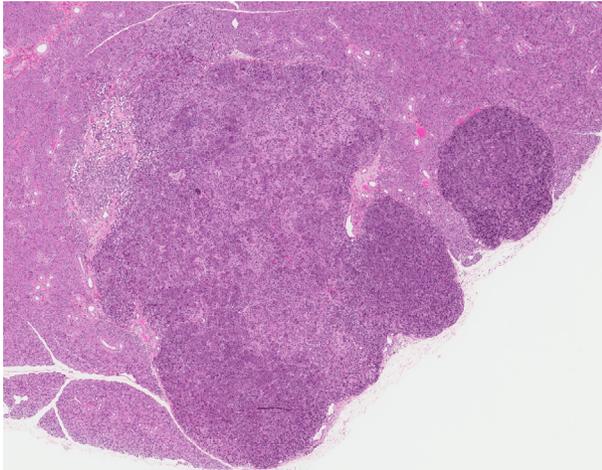
Adenocarcinoma occurs as a spectrum from the well-differentiated acinar or ductular pattern to the undifferentiated carcinoma. These are sometimes grossly apparent as an irregular nodular mass which distorts the normal contour of the salivary gland. Microscopic features vary with the cell type and the particular gland affected.



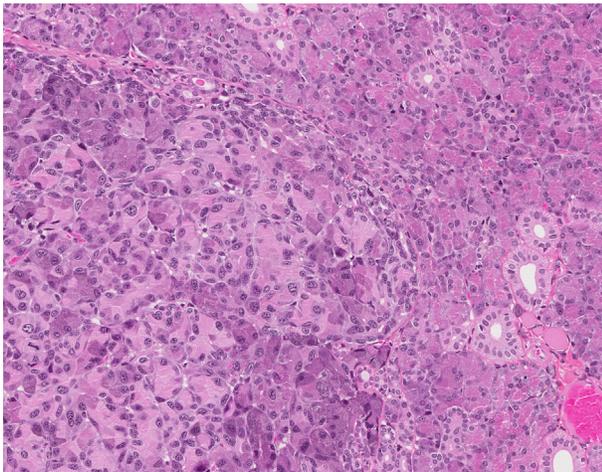
**FIGURE 5.15** Adenoma of mandibular gland.



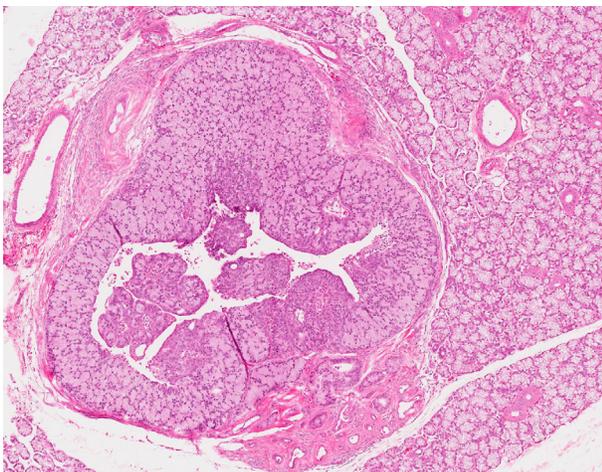
**FIGURE 5.16** Higher magnification of adenoma in Fig. 5.15. Tumor is well circumscribed within the mandibular gland but with less differentiated structure compared to tumor in Figs. 5.13 and 5.14. Solid bundles of epithelial cells with sparse cytoplasm approximating an acinar pattern and, in some areas forming duct-like structures.



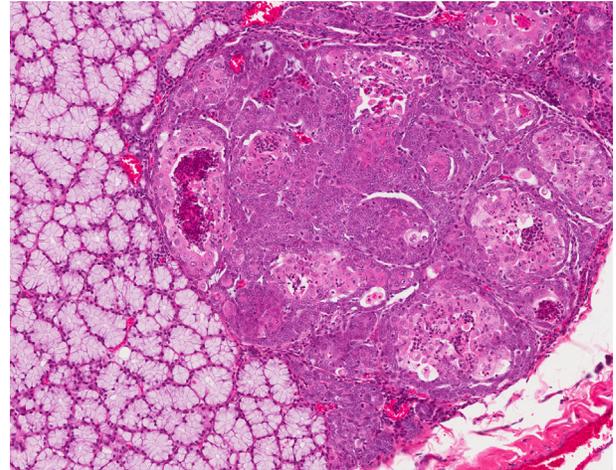
**FIGURE 5.17** Multilobulated adenoma of parotid gland.



**FIGURE 5.18** Higher magnification of adenoma in Fig 5.17. Acini are enlarged, frequently with multilayered epithelium which stains variable and does not have apparent cytoplasmic granules. Ducts are not apparent in tumor.



**FIGURE 5.19** Adenoma of the sublingual gland. An expansile, well-demarcated mass composed of thickened epithelium with reduced acinar structure.

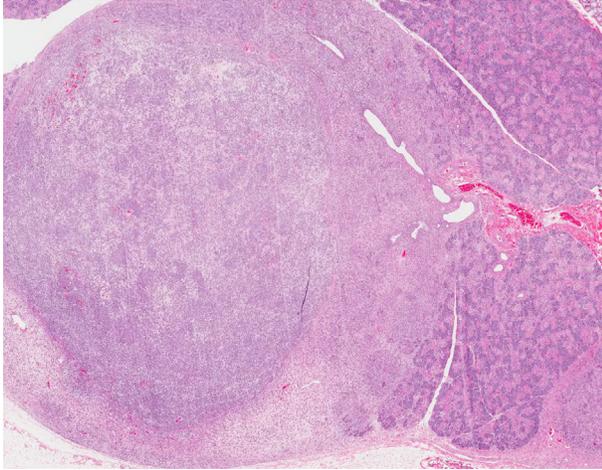


**FIGURE 5.20** Ductal adenocarcinoma of the sublingual gland. Solid lobules of neoplastic cells with variable formation of lumens which contain cell debris.

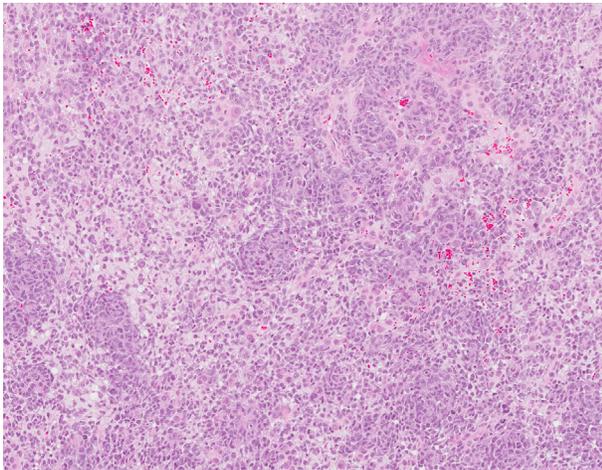
Features of salivary adenocarcinomas include a high mitotic index, invasion of adjacent tissues, and variable amounts of fibrosis, hemorrhage, or necrosis. Acinar adenocarcinomas have poorly delineated lobules with no ductular structures (Fig. 5.20). Compression and invasion of adjacent glandular parenchyma are characteristic features. In parotid gland acinar cell adenocarcinoma, secretory granules (zymogen) may be present, although in fewer numbers than in the normal acinar cell. Adenocarcinoma with a ductular pattern may consist of invasive well-formed tubular structures with slight cellular atypia, or poorly formed tubules and invasive nodular masses of anaplastic epithelial cells (Fig. 5.20). Poorly differentiated adenocarcinomas may incite adesmoplastic response in which only small acini of epithelial cells are present in rapidly expanding fibroblastic tissue resembling granulation tissue (Figs. 5.21 and 5.22). These have been designated carcinosarcomas or mixed tumors in some classification schemes. Whether the mesenchymal component as well as the epithelial portion is neoplastic is an unresolved controversy complicated by evidence that the myoepithelial cell may differentiate along several pathways in experimentally induced lesions. Fibrosarcomas of the adventitia or stroma which infiltrate the salivary gland may also isolate ducts and acini while compressing and obstructing ducts, with resulting epithelial degeneration and regeneration which may resemble the morphology of a mixed tumor. Exuberant reparative changes after extensive necrosis following SDA V infection also must be distinguished from adenocarcinomas.

#### 6.4. Squamous Cell Carcinoma

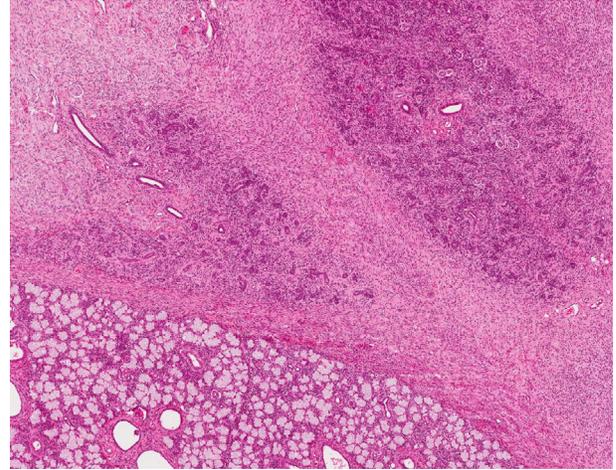
Spontaneous squamous cell carcinoma of the salivary gland occurs rarely in F344 rats, but it has been



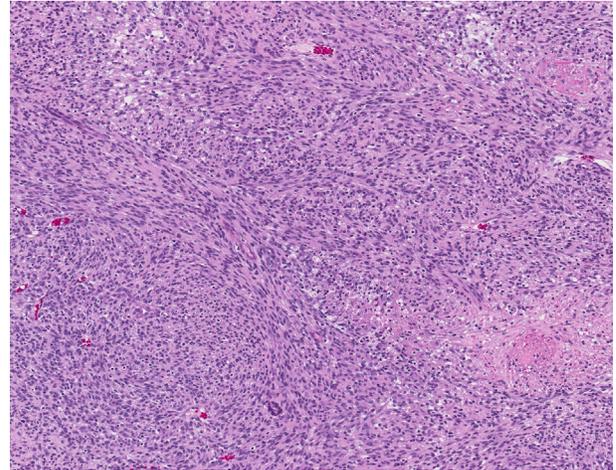
**FIGURE 5.21** Adenocarcinoma of mandibular gland. Tumor is poorly circumscribed from normal gland showing invasion at the border. Prominent fibrous tissue surround the tumor.



**FIGURE 5.22** Higher magnification of adenocarcinoma in Fig. 5.21. Thick nodules of epithelial cells resemble poorly-formed acina.



**FIGURE 5.23** Malignant schwannoma infiltrating and effacing the mandibular gland.



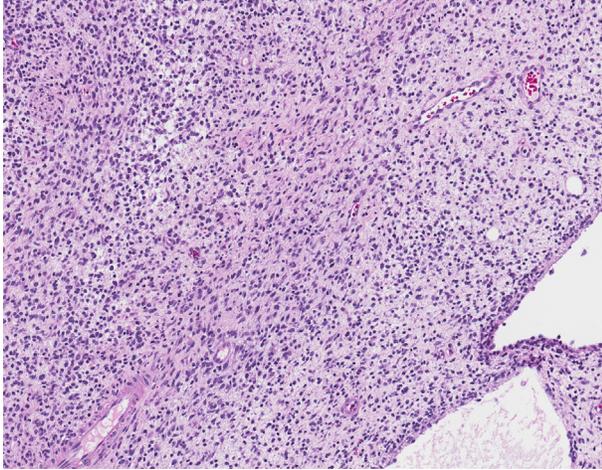
**FIGURE 5.24** Malignant schwannoma (different animal to Fig. 5.23). Mandibular and sublingual glands are almost completely effaced by densely packed bundles of fusiform cells (Antoni type A pattern).

chemically induced in other strains. Induced salivary gland neoplasms, especially in experiments using pellet implants or intraductal injections of 7,12-dimethylbenz[a]anthracene (DMBA), include both carcinomas and sarcomas or neoplasms with areas of poorly differentiated carcinoma or sarcoma admixed. Morphologic patterns in spontaneous tumors are those of the more typical squamous cell carcinomas with only the keratinized stratified squamous epithelial component. Some squamous cell carcinomas are markedly anaplastic and composed of fusiform cells with pleomorphic nuclei and numerous mitotic figures. Zymbal's gland neoplasms occur more frequently than salivary gland tumors and may be almost entirely squamous with little evidence of a sebaceous cell component. Zymbal's gland carcinomas may metastasize to the mandibular lymph node or extend into the salivary gland

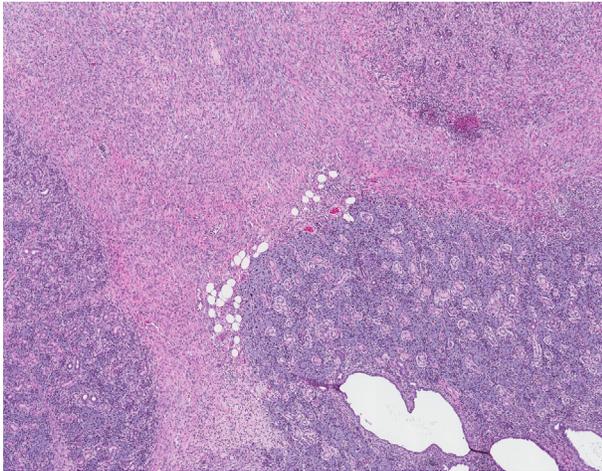
and should be distinguished from a squamous cell carcinoma of salivary gland or skin origin.

## 6.5. Mesenchymal Neoplasms

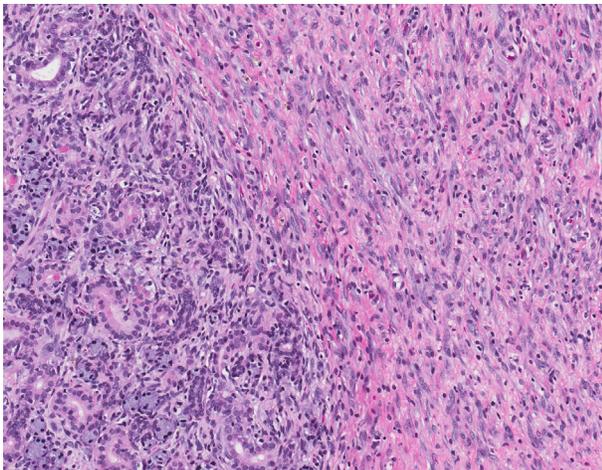
Mesenchymal neoplasms occurring most commonly within or near the salivary glands include malignant schwannoma (Figs. 5.23–5.25), fibrosarcoma (Figs. 5.26 and 5.27), undifferentiated sarcoma, and mononuclear cell leukemia. The histologic characteristics of schwannoma and fibrosarcoma are described in other chapters. The undifferentiated sarcomas infiltrate between acini and ducts, which then undergo atrophic, metaplastic, or reparative changes. Undifferentiated sarcomas have a pleomorphic cell type which ranges in appearance from fusiform



**FIGURE 5.25** Malignant schwannoma. Same animals as Fig. 5.24. This area of tumor consists of loosely arranged cells with abundant pale-staining cytoplasm with cystic spaces (Antoni type B pattern).



**FIGURE 5.26** Fibrosarcoma infiltrating mandibular gland.



**FIGURE 5.27** Higher magnification of fibrosarcoma in Fig. 5.26. Remaining mandibular gland tissue (left) is atrophied. Tumor (right) consists of fusiform cells with collagenous stroma and infiltrating multinucleate inflammatory cells.

to polygonal to giant multinucleated or straplike multinucleated cells. Undifferentiated sarcoma may be difficult to distinguish from an extremely anaplastic undifferentiated adenocarcinoma.

Similarly, fibrosarcoma and schwannoma have similar features and, if poorly differentiated, may not be easily categorized or distinguished from an undifferentiated sarcoma without special stains or immunohistochemistry. In mononuclear cell leukemia, infiltration of the salivary glands by neoplastic cells often occurs late in the course of the leukemia; atrophy is often associated with this neoplasm in the salivary gland.

## 7. TOXICOLOGIC LESIONS

Toxic changes in the salivary glands are often subtle and easily overlooked. Denervation,  $\alpha$ - and  $\beta$ -adrenergic antagonists, duct ligation, or liquid diet results in salivary gland atrophy. Neurotrophic effects are required to maintain functional and structural character of the salivary glands, and denervation results in atrophy. Since the sublingual gland lacks sympathetic innervation, it does not respond to these treatments in a similar manner.

A synthetic liquid dietary substitute or liquefied rat feed causes atrophy of the salivary glands characterized mainly by decreased acinar cell size, a slight decrease in ductular cell size, and an increase in connective tissue. Since denervation is not present, the reflex stimulation via mastication may also influence the maintenance of salivary gland structure and function. All the glands are affected by the liquid diet but the parotid gland is the most affected. Amputation of the lower incisor teeth once or repeatedly results in enlargement of the submandibular and sublingual salivary glands in rats. This enlargement is the result of hypertrophy and hyperplasia of acinar cells, which is associated with swollen nerve endings without vesicles. It has been suggested that this effect is mediated by neural regulation. A similar response is induced by sympathomimetic agonists in the submandibular and parotid glands, probably as an exaggerated physiologic response. Administration of furosemide in high doses causes atrophy of acinar cells of the salivary glands. Since hormonally induced sexual dimorphism is a normal feature of the submandibular gland, compounds which mimic or block the action of these hormones may enhance, induce, or reverse these effects, depending on their function. Apoptosis accompanied by small foci of acinar and ductular atrophy affecting both the parotid and submaxillary glands is observed with the administration of certain antihistamines. Doxylamine induces acinar cytomegaly with increased basophilic and coarsely granular or vacuolated cytoplasm within parotid gland acini. Reserpine administration results in a gradual change in submandibular acinar cells in which the mucus content is

increased. This compound also affects the size and structure of the zymogen granules within the parotid acinar cells. Squamous metaplasia of the salivary gland is seen with ionizing radiation and as a component of the regenerative process after infection with SDA V or rat coronavirus. Ionizing radiation induces fibrosis and atrophy as well as squamous cell carcinomas and undifferentiated sarcomas of the salivary gland. Squamous metaplasia may also be induced by certain chemicals, including iodinated glycerol and bromoform; salivary gland neoplasms did not occur in these studies. Hypovitaminosis A also can cause squamous metaplasia, although not as dramatically as in other organs. Experimental Vitamin A deficiency is associated with an increased incidence of salivary gland neoplasms induced by DMBA compared to that in DMBA-exposed rats given a nutritionally complete diet. Squamous metaplasia of the ductular epithelium has been considered as a preneoplastic condition progressing to squamous cell carcinoma induced by several compounds experimentally, as classically illustrated by DMBA in the submandibular salivary gland. Whether the initial target cell of the carcinogen is the striated or intercalated ductular epithelial cell or the acinar cell is a subject of controversy. Arterial ligation studies suggest that several cell types may be potential targets because of the presence of cytokeratins, which was demonstrated by immunohistochemistry in duct epithelium, acinar epithelium, and myoepithelium. Further evidence from electron microscopic studies indicates that squamous metaplasia occurs in both the duct and acinus and involves both the epithelial and myoepithelial cellular components.

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