

Proliferative Lesions of the Intestine, Salivary Glands, Oral Cavity, and Esophagus in Rats

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INTESTINE

Spontaneous benign or malignant neoplasms of the intestinal epithelium of the rat are rare (<0.5%) (15, 40, 64, 66). Spontaneous tumors occur more frequently in the small intestine compared to chemically-induced tumors which occur more often in the colon (10, 63). Several chemicals are known to induce neoplasia in the intestine (39). Tumors induced by dimethylhydrazine and its derivatives have been extensively studied as models for human colonic neoplasia and their morphology has been well-described. However, the terminology used to describe induced proliferative lesions in the intestine of rats is sometimes ambiguous and inconsistently applied, thus leading to difficulties in interpretation and comparison between studies. The classification system presented here is based on classification systems described previously by Pozharisski (48) and Elwell et al. (10) for rats and Fenoglio-Preiser (12) for humans. The morphology of proliferative lesions of the large and small intestine are similar and are discussed together.

MORPHOLOGY

Hyperplasia (Figures 1 & 2)

Hyperplasia of the large intestinal mucosa is characterized by an increase in crypt length (thickness of the mucosa) and/or an increase in cell density within the crypt which involves diffuse areas of the mucosa.

Epithelial cells may be enlarged. Polypoid structures may rarely occur. Goblet cell differentiation may be unchanged, increased, or reduced. Nuclei are basally located within the cell and are uniform in size and shape. The cytoplasmic tinctorial properties of epithelial cells in hyperplastic mucosa are normal. Cell division is restricted to the lower one-third to one-half of the crypt. Occasionally, the large intestinal mucosa will develop a villous-like architecture. There is slight variation in the diameter of crypts.

In the small intestine, hyperplasia is characterized by increased depth of the crypt and lengthening of the villi. Cell replication is usually confined to the lower two-thirds of the crypt, but may extend into the upper third. Alterations in cytologic characteristics are similar to the large intestine.

Reactive Hyperplasia (Figures 3 & 4)

In the large intestine, reactive hyperplasia is characterized by marked mucus depletion and is associated with injury and inflammation of the mucosa. The cytoplasm of epithelial cells has increased basophilia. Nuclei may be slightly elongated or vesicular with prominent nucleoli. As the reparative process progresses, goblet cell hyperplasia can occur. Extension of crypts into the submucosa (crypt herniation) may occur, particularly if the muscularis mucosae has been disrupted by the inflammatory process. In the small intestine, reactive hyperplasia can be accompanied by villous atrophy.

Focal Atypical Hyperplasia (Figures 5-9)

In the large intestine, focal atypical hyperplasia is

characterized by focal areas of one or more atypical crypts which are usually enlarged and have dilated lumens. The epithelium has varying degrees of abnormal differentiation, from nearly normal to severe dysplasia, which may involve the entire crypt epithelium or only a segment of it. In the large intestine, dysplastic epithelium can frequently be found as a focal segment on the mucosal surface or involve the superficial portion of one or more crypts. Dysplastic epithelium is characterized by varying degrees of nuclear elongation and pseudostratification with basophilic cytoplasm and nuclei. Goblet cell differentiation is usually decreased or absent. Cell proliferation may be increased in affected segments of epithelium and mitotic figures may be found throughout these areas. Occasionally, focal areas of one to two crypts may be found which have collapsed lumens, have the features of reactive hyperplasia without evidence of inflammation, and are surrounded by normal mucosa. The contour of the crypt basal border may be tortuous. However, the architecture of the adjacent mucosa and the arrangement of crypts is not markedly distorted by compression. In the small intestine, focal atypical hyperplasia is usually found in villous epithelium, but may also occur within crypts.

When severe inflammation is present, the reactive changes in the epithelium may have some of the characteristics of dysplastic epithelium, so a differential diagnosis of reactive hyperplasia must be considered. The most reliable differential characteristics that distinguish focal atypical hyperplasia from reactive hyperplasia are nuclear atypia and pseudostratification. If present, cell proliferation throughout areas of atypical hyperplasia may also aid in differentiation.

Squamous Metaplasia (Figure 2)

Squamous metaplasia is characterized by the replacement of colonic mucosa by a stratified keratinizing epithelium. It is associated with chronic severe inflammation and has been reported with the feeding of certain sulfated polysaccharides (26). Squamous metaplasia is found first in the distal colon and rectum and is usually confined to this region. It can progress to squamous cell carcinoma.

Adenoma (Figures 10-12)

Adenomas can be defined as well-demarcated and circumscribed areas of epithelial dysplasia that distort the adjacent mucosal architecture (30). The distinction between focal atypical hyperplasia and microscopic adenoma can be subjective because there is a continuum of morphologic changes between the two lesions. Adenomas are distinguished from focal atypical hyperplasia by the presence of compression of adjacent tissue and dysplasia throughout the affected epithelium. Adenomas in the large intestine can occur in single or multiple crypts. The neoplastic epithelium is confined by its basement

membrane and does not invade the lamina propria.

Microscopic adenomas may progress to form either large sessile adenomas with a broad epithelial base or pedunculated polypoid structures with a stalk containing submucosa and muscularis mucosae. Large intestinal tumors (adenomas and adenocarcinomas) usually have a tubular pattern, although a villous-like architecture can rarely be found. Paneth cells and endocrine cells can be found in large intestinal tumors (11, 48).

Adenomas of the small intestine exhibit exophytic growth that usually occurs over a diffuse area of the mucosa. These tumors form tubular or villous structures lined by dysplastic epithelium. Goblet cells and Paneth cells may be found within small intestinal adenomas.

Adenocarcinoma (Figures 13-18)

Adenocarcinomas have the features of dysplastic epithelium and have clear invasion of the epithelium into the lamina propria and/or submucosa. The term superficial adenocarcinoma indicates those tumors where invasion is confined to the lamina propria (12, 48). The invasive epithelium is usually more anaplastic than the majority of the epithelium in the tumor and does not have a clearly demarcated border. The invasive epithelium usually induces a scirrhous and inflammatory response. The invasive characteristics of adenocarcinomas must be differentiated from tangential cuts of glands in the lamina propria that may be found at the base of adenomas. Multiple step sections of a tumor may be needed to identify invasion of the muscularis mucosae. In some instances, extension of dysplastic epithelium into the submucosa appears to be confined by its basement membrane. In these cases, the presence of a scirrhous and inflammatory response is helpful in differentiating truly invasive epithelium from crypt herniation. In chronic inflammation with marked fibrosis, atypical glands may be found entrapped in the fibrous tissue. Care needs to be taken in differentiating this from carcinoma.

In the large intestine, adenocarcinomas may arise either *de novo* from flat mucosa which contains dysplastic epithelium or within an adenoma (38, 54-56, 61). Some tumors may have abundant goblet cell differentiation. Sessile tumors have a broad base and tend to be aggressive, invade extensively into the bowel wall, and metastasize more frequently than pedunculated tumors. Since the stalks of pedunculated adenocarcinomas are modifications of the large intestinal submucosa, the term polypoid adenocarcinoma should be used to describe these tumors. Tumors that have long stalks are frequently found to invade the stalk, but the invasive process rarely extends further into the bowel wall and metastases are rare.

Adenocarcinomas of the small intestine are more invasive and metastasize more frequently than those of the large intestine (25, 48, 61, 62). Small intestinal adenocarcinomas frequently have a diffuse growth pattern

within the mucosa. The cytologic features of dysplasia are present. Cystic distention of neoplastic glands is a frequent characteristic of these small intestinal tumors, and osseous metaplasia of the stroma may occur.

Mucinous Adenocarcinoma (Figures 19-21)

Mucinous adenocarcinomas in the large and small intestine are characterized by numerous signet ring cells that are distended with mucin and/or lakes of mucus surrounding clumps of anaplastic epithelial cells. The tumors are usually sessile. The earliest lesion that may be associated with mucinous adenocarcinoma is a focal aggregate of disorganized, anaplastic epithelial cells in the lamina propria. These neoplasms are highly invasive and metastasize early during their development. Glandular structures do not always form. These tumors are usually found in the proximal colon in association with pre-existing lymphoid follicles (36, 45, 59, 61) and in the small intestine. Osseous metaplasia may occur in association with these tumors.

Squamous Cell Carcinoma

Squamous cell carcinoma develops from squamous metaplasia and is diagnosed by the presence of atypical squamous epithelial cells invading into the adjacent stroma and bowel wall. Metastasis to the regional lymph nodes may occur. Squamous cell carcinoma is found in the large intestine of rats fed certain sulfated polysaccharides (26).

DISCUSSION

When evaluating the intestine for the extent and distribution of neoplastic lesions, it is important to examine the entire length of the intestinal mucosal surface because many lesions are evident only on close inspection during gross morphologic examination or are only detectable by microscopic examination. Thorough histologic examination for neoplastic lesions can be accomplished by the use of the "Swiss roll" methodology. Microscopic neoplastic and preneoplastic lesions can be identified in the large intestine before trimming by evaluating the mucosa for the presence of aberrant crypt foci (ACF). These types of foci have been described in the large intestine but not in the small intestine. ACF are found only in rats exposed to large intestinal carcinogens and their frequency increases in a dose-dependent manner (51, 52).

The term ACF should be used only for the evaluation of methylene blue stained whole mounts of large intestinal mucosa. ACF are easily recognized using a dissecting microscope when intact large intestinal mucosa has been stained with methylene blue before or after formalin fixation. In these preparations, aberrant crypts

are identified by increased size and staining intensity, thickened epithelial cell layer, slit-shaped (as opposed to round) lumen, and an increased amount of pericryptal lamina propria that separates them from the adjacent normal crypts. Foci may contain one to multiple crypts. ACF that are identified in whole mount preparations and marked with a permanent dye have variable morphologic features on H&E stained histologic sections. Their morphology can vary from near normal with slightly dilated lumens to those that have mild cellular atypia or show varying degrees of dysplasia and invasion. Many, but not all ACF, have increased PAS staining. However, all demonstrate decreased hexosaminidase activity.

Hyperplasia of the large intestinal mucosa is associated with diverse etiologies (18). Resection of part of the colon results in hyperplasia of the remaining segment of colon. Physical stimulation by increasing dietary bulk is associated with hyperplasia, including thickening of the muscularis mucosa and tunica muscularis. Mucosal hyperplasia is associated with the feeding of dextran sulfate with a molecular weight of 400,000, synthetic polydextrose, sugar alcohols, chemically-modified starches, caramels, and polyethylene glycols. Hyperplasia by itself may be an adaptive physiologic response to alterations in the large intestinal environment.

The interpretation of focal atypical hyperplasia is difficult. This diagnostic classification covers a range of morphologic abnormalities in crypt architecture and epithelial differentiation. This lesion consists of crypts which have mild to marked distortions of architecture and alterations in epithelial differentiation which vary from nearly normal to severe dysplasia. Focal atypical hyperplasia encompasses changes in the mucosa which others have referred to as dysplasia and has been reported primarily in rats treated with intestinal carcinogens. Some believe that severe dysplasia of the intestinal epithelium is the earliest neoplastic alteration (12, 31, 45, 53, 64). Epithelium that is confined by the basement membrane and is severely dysplastic has been referred to as carcinoma *in situ* (12, 43, 48). Others consider it to be a preneoplastic change (10). However, there is no definitive evidence which shows that this lesion invariably progresses to neoplasia in the rat.

As evidenced by the low incidence of spontaneous tumors and the comparatively few compounds that have been found to be intestinal carcinogens in bioassays (10), the intestinal mucosa of the rat is resistant to the neoplastic process. Neoplastic lesions of the large or small intestinal mucosa have been induced by a variety of compounds (10, 39, 48). Different investigators use different morphologic criteria to classify tumors induced by these agents as adenomas or adenocarcinomas. Some investigators require that there be extensive invasion into the submucosa before the term adenocarcinoma is used (13, 18, 36, 38, 43, 58, 60, 62, 65). Others will identify a

tumor as a carcinoma based on cytologic criteria (37, 49, 64) or if there is invasion of the lamina propria (4, 5, 8, 11, 12, 20, 32, 48, 54, 55). The classification presented here is consistent with those previously published for the rat and human, and uses invasion past the epithelial basement membrane as the minimum criterion for the diagnosis of carcinoma. To avoid confusion and to be precise in the morphologic description of a carcinoma, the term superficial adenocarcinoma should be used to identify those carcinomas where invasion is confined to the lamina propria. The use of the term superficial adenocarcinoma also recognizes that neoplasia and invasion is a multi-step process that is associated with the successive breakdown of host defense barriers (11). Electron microscopic (8, 54) and immunofluorescence studies (33) of rat colonic tumors have shown that the basement membrane is altered in adenocarcinomas and that there is extension of epithelial cell cytoplasm through the basement membrane. In humans, the extent to which the epithelial basement membrane is altered in colonic tumors correlates with the invasiveness of a tumor and clinical outcome (27).

SALIVARY GLANDS

In the rat, there are three pairs of major salivary glands located subcutaneously below the ear at the angle of the mandible in the cervical region. The parotid, submaxillary (mandibular or submandibular), and major sublingual are the major salivary glands routinely examined in toxicology studies. Several minor salivary glands located in the oral cavity, pharynx, and tongue are not visible grossly and are evaluated only incidentally during microscopic examination of other tissues. Primary neoplasms of the salivary glands are uncommon. The more frequently occurring neoplasms in this region originate from a mammary gland, Zymbal's gland, peripheral nerves, or the fibrous components of the stroma or adventitia. The extraorbital lacrimal gland is also located in close proximity and may very rarely have a neoplasm. The classification system presented here is based on ones previously described by Neuenschwander et al. (44) and Elwell et al. (9).

MORPHOLOGY

Basophilic Hypertrophic Foci (Figure 22)

Non-compressive basophilic hypertrophic foci are seen in very young or very old rats as a spontaneous lesion of the parotid gland and, less frequently, the submandibular gland (6, 9, 44). These are usually single foci and do not generally increase in size or number in individual animals. In this change, the finely vacuolated

cytoplasm of the acinar cells increases in volume, resulting in focal cellular enlargement. Nuclear enlargement is a variable feature. A more diffuse change may occur in which there is hypertrophy of the acinar cells within most of the gland; however, acinar cell size is not increased to the same extent as individual cells in the focal lesion. The cause of either of these lesions is not known.

Adenoma (Figures 23 & 24)

Adenomas may have a tubular or acinar pattern depending on the site of origin. Both are nodular and compressive. These neoplasms may be seen only microscopically or may be seen at necropsy if the salivary gland is enlarged or changed in shape. Depending on which portion of the ductular system from which they originate, neoplasms of the ductular epithelial components usually are characterized by lobules or aggregates of tubules lined by squamous to cuboidal or columnar epithelium. A fine fibrovascular stroma divides the mass into incomplete lobules. Usually the cells are well-differentiated and, while it may vary, the mitotic index is usually low. Adenomas of the acinar epithelial component often do not contain ducts. The acini are similar to but larger than those in the adjacent normal gland, and compression of adjacent acini is a feature of adenomas. Mitoses are variable in number. The neoplastic cells differ in staining and morphology from the normal acinar cells, but are well-differentiated, with basilar nuclei and apical secretory product near the center of the poorly formed acinus (9, 17, 41, 44).

Adenocarcinoma (Figures 25-27)

Adenocarcinomas, like adenomas, may be apparent grossly due to differences in coloration or enlargement and nodular changes in the normal smooth contour of the salivary gland. Depending on the type of salivary gland and the secretory product, cells may have serous, mucoid, or zymogen-type cytoplasmic product, or no product at all. Cellular morphology varies from well-differentiated ductular or acinar cells to such poorly differentiated cells that it is difficult to recognize the cell of origin to be epithelium. Ducts are usually absent in the acinar form, and the tumors consist of compressive lobules of acini ranging from well-organized, normal-sized acini to single, small acini widely scattered within a dense desmoplastic fibrous stroma. Tubular or ductular adenocarcinomas may be composed of clusters of well-differentiated tubules or very anaplastic, invasive, and poorly-delineated tubules. Cellular atypia varies widely. Adenocarcinomas are expansile and/or invasive and have a high mitotic index. Other features variably present include hemorrhage, fibrosis, and necrosis. Local invasion of nearby tissues and metastasis to regional lymph nodes is common, but distant metastasis is not. Myoepithelial cells may be present and may have the potential to differentiate along either a

mesenchymal or epithelial route, complicating the appearance of very poorly differentiated tumors and suggesting a mixed cell or carcinosarcoma designation (21).

Squamous Cell Carcinoma

Squamous cell carcinomas are typical of those described in other organ systems. The true nature of the origin of this lesion is controversial and unresolved. These neoplasms have a range of differentiation from well-differentiated islands and clusters of keratinized squamous epithelium to highly anaplastic fusiform cells that are difficult to recognize as epithelial in origin. Since the Zymbal's gland is located nearby and squamous cell carcinomas are seen in the salivary gland less frequently than in Zymbal's gland, the primary site must be established (9, 17, 44).

DISCUSSION

Induction of salivary gland neoplasia has been associated with the systemic or local application of irradiation, dimethylbenzanthracene, amino-p-nitrophenylthiazole, methylcholanthrene, and phosphorous-32 (9). Basophilic hypertrophic foci have been reported to occur spontaneously in Sprague-Dawley rats at an incidence of 4.8% (44). The incidence of these lesions is lower in older rats from chronic studies than in rats from subchronic studies. The incidence of basophilic hypertrophic foci can be increased by exposure to some compounds, such as certain antihistamines (44). These lesions do not demonstrate evidence of cell proliferation and it is unknown if these lesions are preneoplastic (44).

Squamous metaplasia of ductular epithelium can be induced by fibrosarcomas, poorly/undifferentiated sarcomas, adenocarcinomas, sialodacryadenovirus infection secondary to ductular obstruction, or repair of necrosis (7, 9, 28, 41, 44, 46). In some cases, squamous metaplasia associated with sarcomas may resemble a mixed neoplasm of both epithelial and mesenchymal origin because of the vigorous metaplastic response of the ductular epithelium. There is no definitive evidence that squamous metaplasia is a prerequisite for progression to squamous cell carcinoma. In metaplasia, the normal cuboidal to columnar ductular epithelium is flattened and becomes stratified or simple squamous. In exuberant repair of necrosis or inflammation, as with sialodacryadenitis virus, keratinization and small foci of necrotic epithelial cells may be present.

The categories for different salivary neoplasms are limited because other neoplasms, not unique to the salivary gland, have been classified under other organ systems. Mesenchymal tumors found within the salivary glands include undifferentiated sarcoma, fibrosarcoma,

rhabdomyosarcoma, hemangiosarcoma, and schwannoma (9). The malignant schwannoma merits special consideration because it can be easily mistaken for fibrosis in the early stages of development. The schwannoma is more frequently seen in this region because branches of the facial nerves course through the salivary gland region. In the Fischer 344 rat, mononuclear cell leukemia may be found in the salivary gland. However, it is not often found in other strains of rats (9, 17, 44).

ORAL CAVITY AND ESOPHAGUS

Spontaneous neoplasms of the oral cavity epithelium occur with low incidence (range 0.1-1.1%) and spontaneous neoplasms of the esophagus are rare (3, 16, 23, 35, 57). Proliferative lesions of the oral cavity and esophagus arise principally from the stratified squamous epithelium, with the tongue and palate being the sites most commonly involved. Hyperplasias may arise from the gingiva. Neoplasms arising from connective tissues have been reported only rarely. Fibrosis and/or muscle regeneration may occur in the esophagus following gavage trauma and must be distinguished from neoplasms. Furthermore, neoplasms arising in other sites such as the Zymbal's gland, nasal passage, and skin may invade the oral cavity or esophagus and must be differentiated from primary neoplasms. The proliferative lesions of the stratified squamous epithelium in the oral cavity and esophagus have a similar appearance and are morphologically similar to those seen in stratified squamous epithelium at other sites. Proliferative lesions of the teeth are described in the *Guide for Bone, Cartilage, Tooth, and Synovium* (34).

MORPHOLOGY

Hyperplasia (Figure 28)

Microscopically, hyperplasias are broad areas of thickened, well-differentiated squamous epithelium consisting of an increased number of epithelial cell layers that is usually accompanied by increased thickness of the keratin layer. In milder cases of hyperplasia, the thickened hyperplastic epithelium may be smooth and plaque-like. As hyperplasia becomes more severe, the epithelium may form a series of folds or, in marked hyperplasia, may form a series of prominent papillary projections. Some hyperplasias may be predominantly made up of basal cell types, with an endophytic growth pattern. Hyperplasias in the oral cavity occur most commonly on the tongue and palate, but can be found on the gingiva in some circumstances. Gingival hyperplasia occurs at the base of teeth and is characterized by

proliferation of both the epithelium and the underlying connective tissue. It is recommended that a single category, *hyperplasia*, be used to describe squamous cell, basal cell, and gingival lesions; the cell types, growth pattern, and location should be described in the pathology narrative.

Squamous Cell Papilloma (Figures 29 & 30)

Microscopically, squamous cell papillomas are pedunculated masses with a complex arboriform structure. They contain a highly-branched fibrovascular core, consisting of multiple radiating finger-like projections that is connected to the mucosal surface by a fibrous stalk. The fibrovascular core is covered by a thickened, well-differentiated, and often heavily keratinized stratified squamous epithelium that resembles the epithelium seen in hyperplasias. Papillomas can be distinguished from marked hyperplasias by their narrow base and complex branching structure, as opposed to the broad base and simple non-branching structure of hyperplasias.

Squamous Cell Carcinoma (Figures 31 & 32)

Squamous cell carcinomas may arise directly from the epithelium or within a papilloma. Carcinomas arising directly within the epithelium appear microscopically as thickened and disorganized areas of epithelium with varying degrees of invasion of the underlying connective tissue. Some of these carcinomas may have an exophytic component projecting into the lumen, while others have little of the neoplasm projecting above the normal level of the epithelial surface. Carcinomas consist of large pleomorphic cells, with large nuclei and moderately abundant cytoplasm, that are arranged in a disorganized fashion. Some carcinomas may become undifferentiated and contain anaplastic cells or may be predominantly composed of basal cells. Mitotic figures may be common. Some neoplastic cells may show varying degrees of keratinization, and keratin pearls or cyst-like structures filled with keratin and cell debris are sometimes seen.

Invasion is the most important characteristic of squamous cell carcinoma. Some carcinomas are highly invasive with multiple broad bands and variable-sized sheets and clusters of neoplastic cells extending deep into the underlying connective tissue. This invasion sometimes incites varying degrees of fibrosis around the neoplastic cells. Alternatively, the invasion may be less obvious and consist of thin cords, small clusters, or even individual neoplastic cells within the connective tissue underlying the epithelium. This less obvious invasion can be recognized by the apparent lack of confinement of the cells by a basement membrane and by the abnormal morphology of the cells. The degree of invasion in many carcinomas lies between these two extremes.

Squamous cell carcinomas occasionally arise within papillomas; these usually are distinguished by observing

invasion of the fibrovascular core by malignant epithelial cells. Due to the highly branched structure of some papillomas, however, it may be possible to find apparently isolated clusters of epithelial cells within the connective tissue core as a result of a sectioning artifact. These clusters of cells have clear, well-defined borders, indicating they are still contained within a basement membrane, and maintain a well-differentiated appearance and a normally ordered growth pattern.

DISCUSSION

Proliferative epithelial lesions of the oral cavity or esophagus have been induced in rats by various chemicals. Squamous cell papillomas and carcinomas of the oral cavity epithelium have been produced by benzene and 1,2-dibromo-3-chloropropane (22), benzidine and benzidine congeners (42), quinoline derivatives (29, 47), and 3-diazotyramine (14). Some of these also produced epithelial hyperplasias. Nitrosamines also can induce squamous cell neoplasms of the oral cavity (24). However, some nitrosamines exert a strong carcinogenic effect in the esophagus, in some cases producing multiple esophageal neoplasms in a single animal and having less effect in the oral cavity (1, 19). Chemical-related hyperplasia of the gingiva has been associated with the administration of certain anticonvulsant drugs and calcium channel blockers, and has occurred secondary to tooth malformation induced by high doses of sodium fluoride (2).

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

INTESTINE

Hyperplasia

1. Increase in crypt length and/or an increase in the number of cells per crypt; in the small intestine, the villi may also be lengthened
2. Normal differentiation and goblet cell formation (goblet cells may increase in number)
3. Nuclear morphology is indistinguishable from normal mucosa
4. In the large intestine, polypoid structures may occur
5. Cell division is confined to the lower one-third to one-half of the crypt in the large intestine
6. In the small intestine, cell division is confined to the crypt and does not extend up the villus
7. There is slight variation in the diameter of crypts and crypt duplication is rarely present

Reactive Hyperplasia

1. Associated with inflammation
2. Increased length of the crypt and/or increased density of cells per crypt
3. Loss of or decreased goblet cell formation
4. Basophilic cytoplasm
5. Nuclei are uniform in size, oval to elongated, basally located, and may be vesicular with a prominent nucleolus
6. In the small intestine, villous atrophy may occur
7. Cell proliferation confined to the basal half of the crypt

Focal Atypical Hyperplasia

1. Single to multiple abnormally-formed crypts without distortion of adjacent mucosal architecture
2. Irregular crypt branching or distortion of crypt architecture is frequently present
3. Altered epithelial differentiation ranging from nearly normal to severe dysplasia
4. Epithelial cell nuclei of dysplastic epithelium have varying degrees of elongation, loss of basal orientation, and pseudostratification
5. Nuclear density within the affected epithelium is increased and there is mild to marked nuclear pleomorphism
6. Segments of dysplastic epithelium are frequently found at the surface of the mucosa in the large intestine or along villi in the small intestine
7. Usually has decreased goblet cell differentiation
8. Increased basophilia of the cytoplasm and nuclei
9. Cell division may occur throughout affected segments of epithelium

Squamous Metaplasia

1. Replacement of colonic mucosal crypts with stratified squamous keratinizing epithelium

Adenoma

1. Circumscribed area of dysplastic epithelium that distorts the adjacent normal mucosal architecture
2. May be sessile with a wide base or form pedunculated polypoid structures that have a thin stalk
3. The epithelium is confined by the basement membrane

Adenocarcinoma

1. Have the features of atypical hyperplasia with the invasion of epithelium through the basement membrane into the lamina propria or submucosa
2. Superficial adenocarcinomas are confined to the lamina propria
3. Adenocarcinomas may arise within an adenoma or within areas of atypical hyperplasia

Mucinous Adenocarcinoma

1. Usually sessile with production of intracellular and/or extracellular mucin
2. Focal disorganization of anaplastic cells in the lamina propria can be the earliest lesion
3. Glands do not necessarily form
4. Mucin-filled signet ring cells are usually present
5. Invade into the submucosa early and metastasize readily
6. There can be abundant extracellular mucin
7. Tumors usually occur in the proximal colon in association with lymphoid follicles and in the small intestine
8. Osseous metaplasia may occur in the tumor stroma

Squamous Cell Carcinoma

1. Develops from squamous metaplasia of colonic mucosa
2. Invasion of atypical squamous epithelial cells into the bowel wall

SALIVARY GLANDS**Basophilic Hypertrophic Foci**

1. Non-compressive, focal enlargement of acinar cells
2. Increase in cytoplasmic volume
3. Cytoplasm of cells within foci is finely vacuolated
4. Parotid gland primarily affected
5. May be a diffuse change (diffuse hypertrophy) but acinar cell enlargement is not as great as seen in focal hypertrophy

Adenoma

1. Ductular (tubular) or acinar
2. Compressive or expansile
3. Well-differentiated cells with abundant cytoplasm and prominent nuclei
4. Low mitotic index
5. Ductular adenomas have lobules or aggregates of tubules lined by squamous to cuboidal or columnar epithelium
6. Acini within adenomas are similar to normal but are larger without the presence of ducts

Adenocarcinoma

1. Cellular morphology varies from well-differentiated acinar or ductular cells to undifferentiated cells
2. Irregular nodular surface of salivary gland with gross enlargement of the gland
3. High mitotic index
4. Invasion of adjacent tissues including regional lymph nodes but wide metastasis is unusual
5. Compression

6. Variable necrosis, hemorrhage, and fibrosis
7. Acinar adenocarcinomas consist of irregularly arranged lobules without ducts
8. High nuclear to cytoplasmic ratio
9. Parotid acinar adenocarcinomas may have a few zymogen cytoplasmic granules
10. Ductular adenocarcinomas may be well-organized tubules within an expansile mass or consist of very invasive nodules of poorly arranged tubules with clusters of highly anaplastic epithelial cells
11. Extensive desmoplasia may occur with poorly differentiated adenocarcinomas in which only widely-scattered, small foci of bizarre neoplastic epithelial cells are present

Squamous Cell Carcinoma

1. Ranges from well-differentiated islands and clusters of keratinized squamous epithelium to highly anaplastic carcinoma with fusiform cells, or a mixture of both
2. Invasion of adjacent tissues and wide metastasis
3. Variable mitotic index
4. Necrosis

ORAL CAVITY AND ESOPHAGUS

Hyperplasia

1. Broad-based lesion with a simple non-branching structure
2. Squamous epithelium is thickened and well-differentiated
3. Epithelium may be flat or folded, or may form a series of papillary projections
4. Some lesions are predominantly composed of basal cells and may have an endophytic growth pattern
5. Hyperplasia of the gingival epithelium is accompanied by stromal hyperplasia

Papilloma

1. Narrow-based lesion attached by a narrow stalk
2. Complex structure with highly-branched fibrovascular core covered by epithelium
3. Epithelium is thickened, well-differentiated, and resembles that seen in hyperplasia of squamous cells

Squamous Cell Carcinoma

1. Broad-based lesion composed of disordered pleomorphic cells
2. Invasion of adjacent tissues is principal distinguishing feature
3. May arise within a papilloma; invasion of the connective tissue core is the definitive criterion for malignancy
4. Basal cells or keratinized cells may predominate

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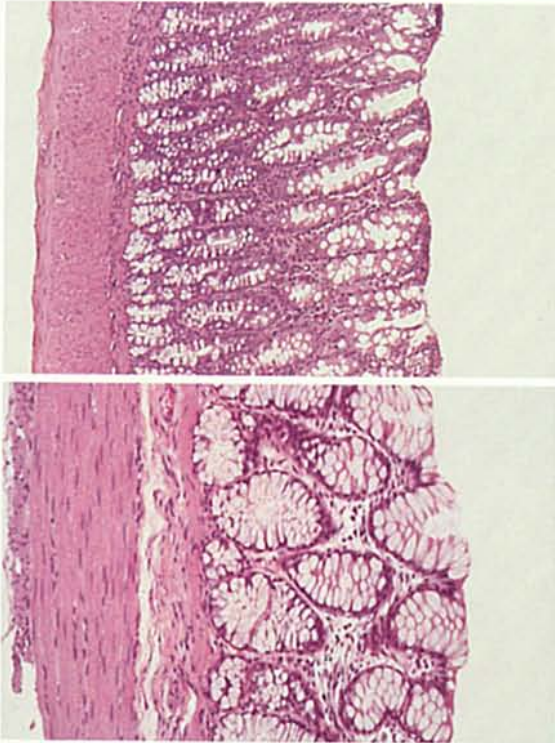


Fig. 1 – Top: hyperplasia, colon; Bottom: goblet cell hyperplasia, colon (H&E).



Fig. 2 – Goblet cell hyperplasia with crypt herniation, colon; squamous metaplasia also present (H&E).



Fig. 3 – Reactive hyperplasia, colon (H&E).



Fig. 4 – Reactive hyperplasia with villous atrophy, small intestine (H&E).



Fig. 5 – Focal atypical hyperplasia, colon (H&E).



Fig. 6 – Focal atypical hyperplasia, colon. The yellow dye on the mucosal surface was applied at time of trimming to mark lesion (H&E).



Fig. 7 – Herniated crypt, colon (H&E).

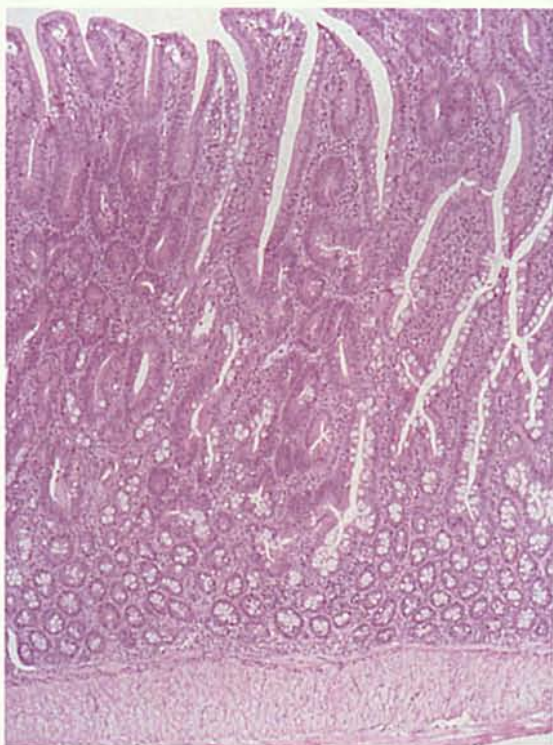


Fig. 8 – Focal atypical hyperplasia, small intestine (H&E).

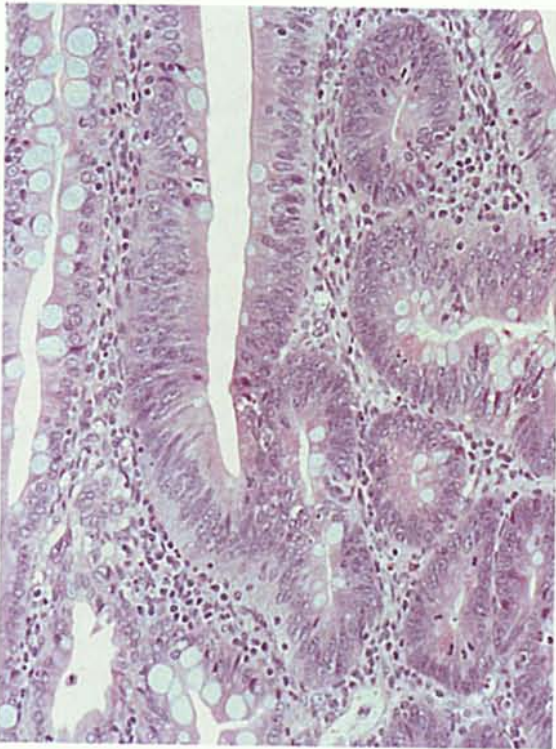


Fig. 9 – Higher magnification of atypical epithelium in Fig. 8 (H&E).



Fig. 10 - Adenoma, colon. Compression of adjacent crypts distinguishes adenoma from atypical hyperplasia. Note mitotic figures within the dysplastic epithelium (H&E).



Fig. 11 – Adenoma, colon (H&E).

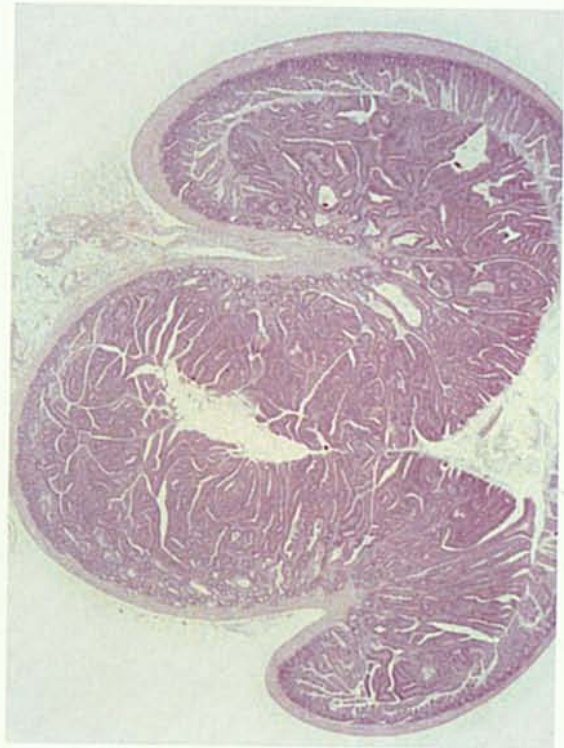


Fig. 12 – Adenoma, small intestine (H&E).



Fig. 13 – Sessile adenocarcinoma with scirrhous response to invading epithelium, colon (H&E).



Fig. 14 – Polypoid adenocarcinoma, colon. There is invasion of well-defined stalk (H&E).

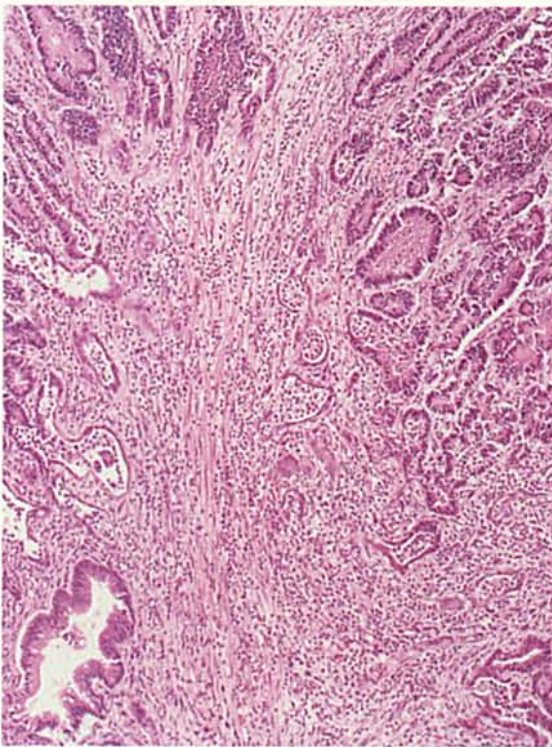


Fig. 15 – Higher magnification of Fig. 14 demonstrating invasion of stalk (H&E).



Fig. 16 - Polypoid adenocarcinoma with early invasion of lamina propria and submucosa, colon (H&E).

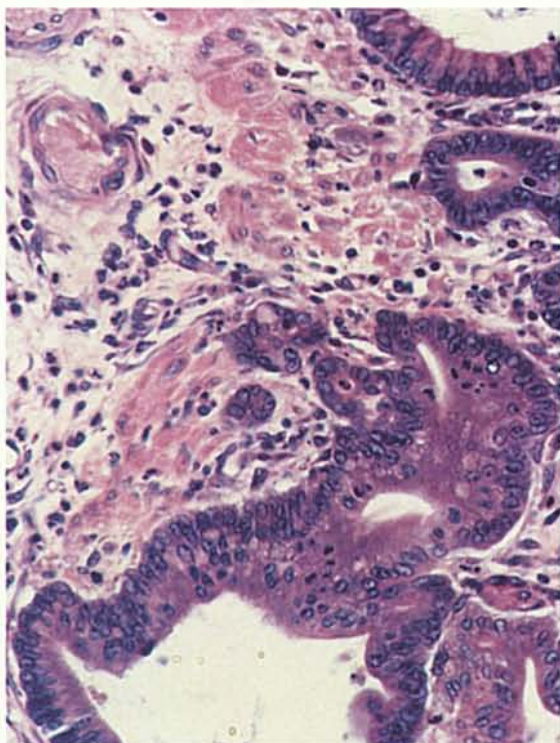


Fig. 17 – Higher magnification of Fig. 16 demonstrating invasion (H&E).

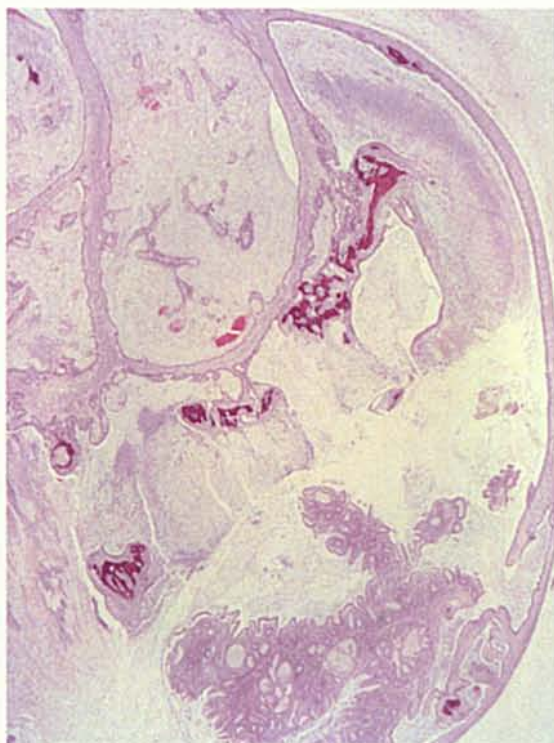


Fig. 18 – Cyst adenocarcinoma with osseous metaplasia, small intestine (H&E).



Fig. 19 – Mucinous adenocarcinoma, colon (H&E).

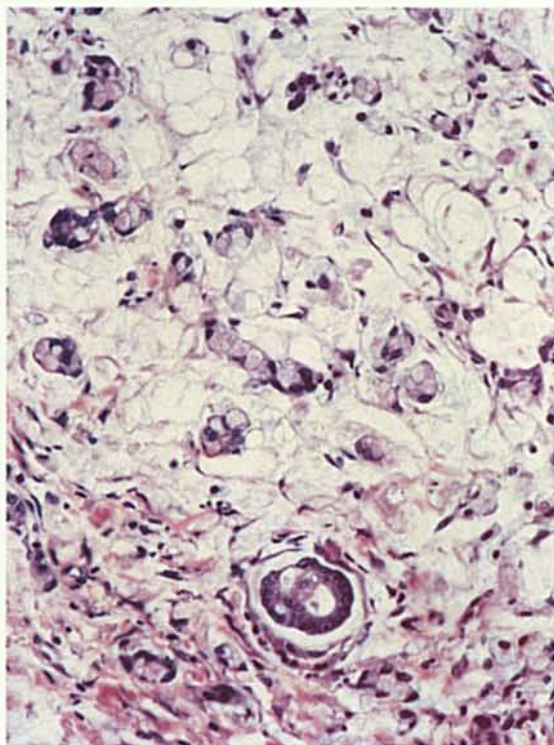


Fig. 20 – Higher magnification of Fig. 19 demonstrating signet ring cells and extracellular mucin in the submucosa (H&E).

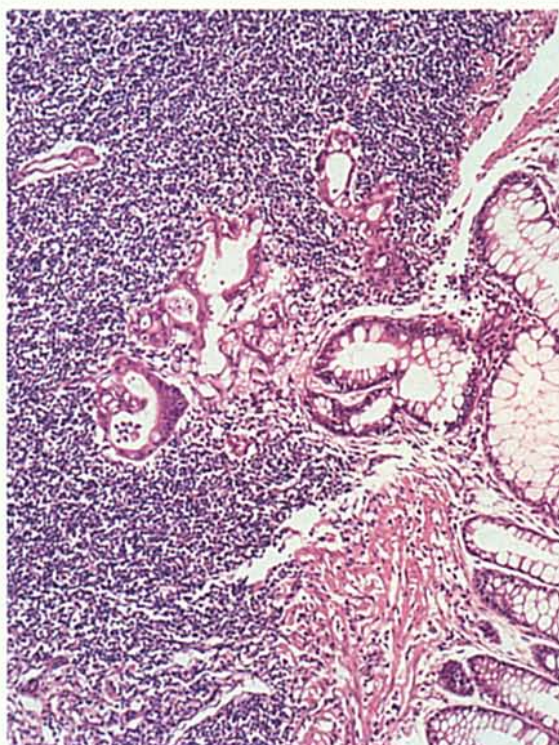


Fig. 21 – Mucinous adenocarcinoma with early invasion of submucosal lymphoid follicle, colon (H&E).

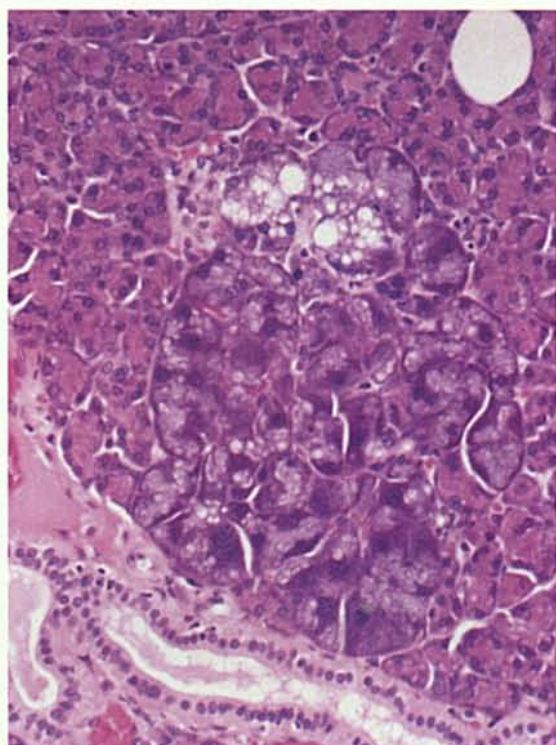


Fig. 22 – Basophilic hypertrophic focus, salivary gland (H&E).

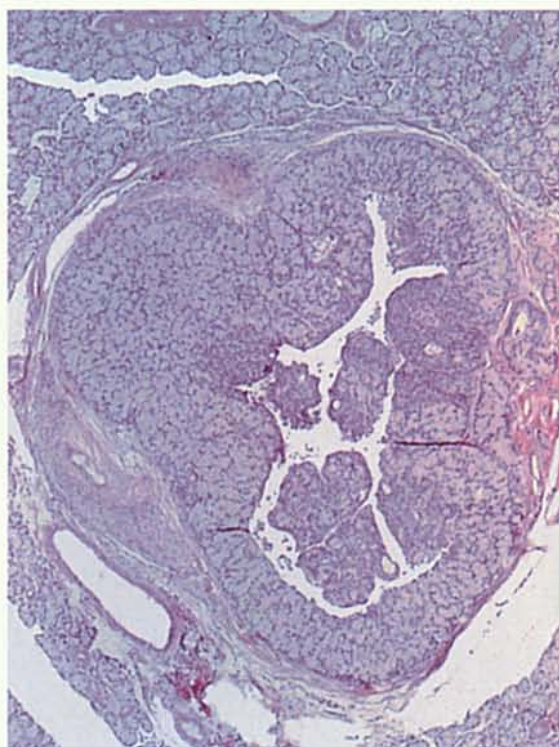


Fig. 23 – Acinar adenoma, salivary gland (H&E).

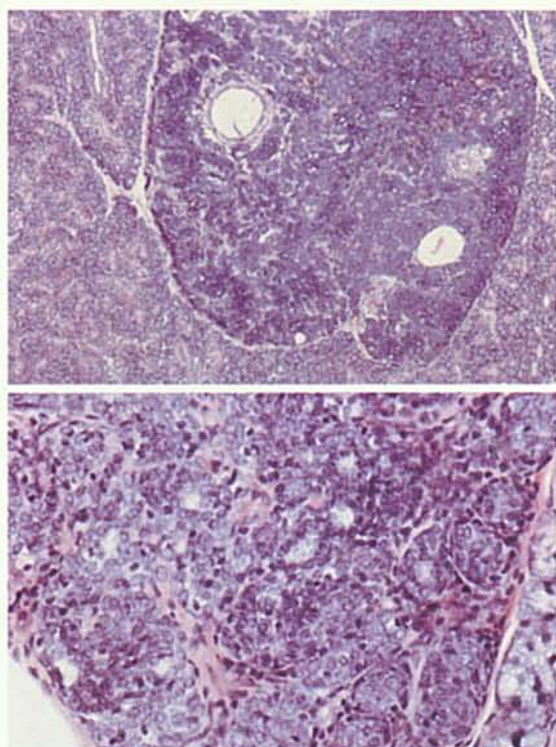


Fig. 24 – Top: mixed ductal and acinar adenoma, salivary gland; Bottom: higher magnification (H&E).

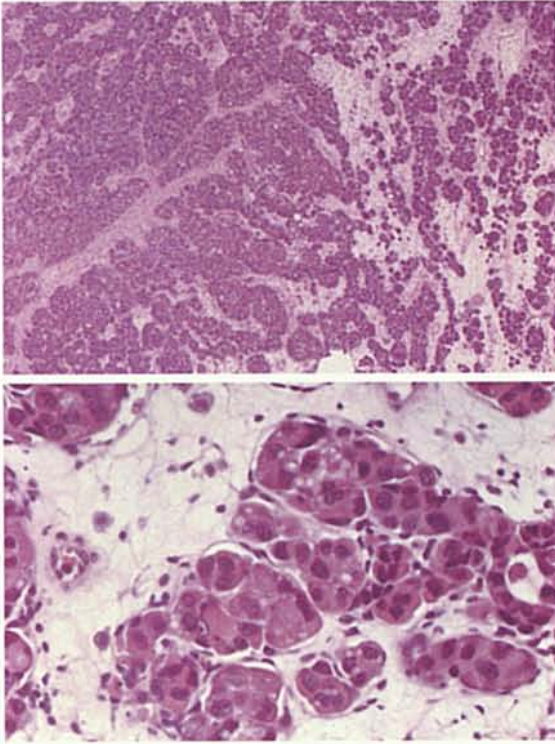


Fig. 25 – Top: acinar adenocarcinoma, salivary gland; Bottom: higher magnification (H&E).

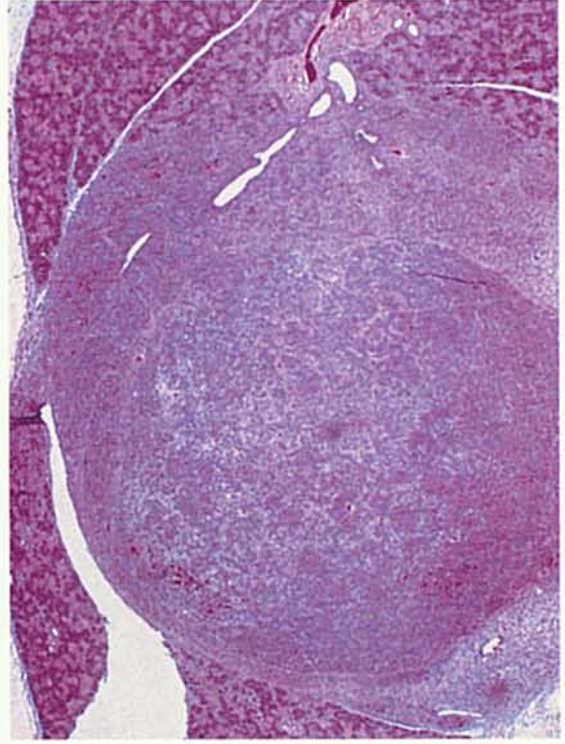


Fig. 26 – Adenocarcinoma, salivary gland (H&E).

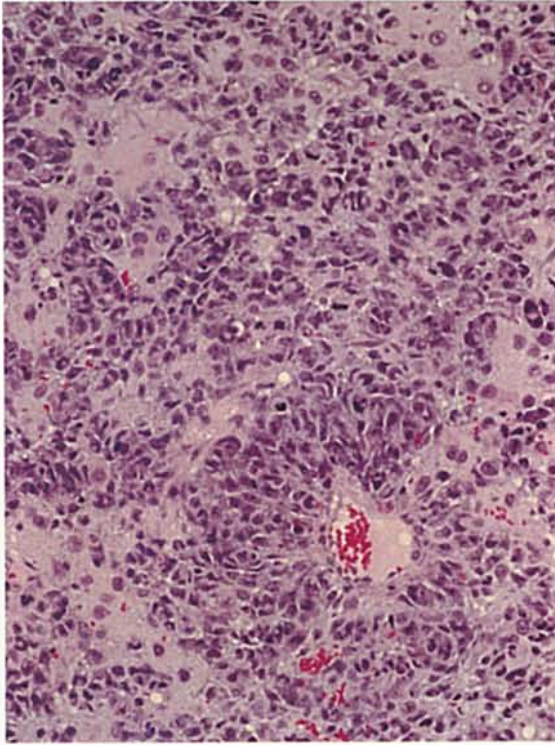


Fig. 27 – Higher magnification of Fig. 26 (H&E).

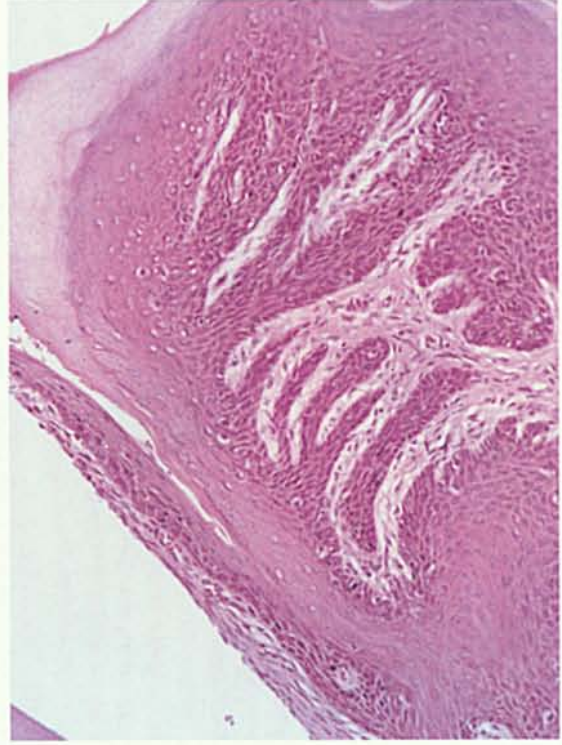


Fig. 28 – Hyperplasia of gingiva, oral cavity (H&E).



Fig. 29 – Squamous cell papilloma, esophagus (H&E).



Fig. 30 – Squamous cell papilloma, tongue (H&E).

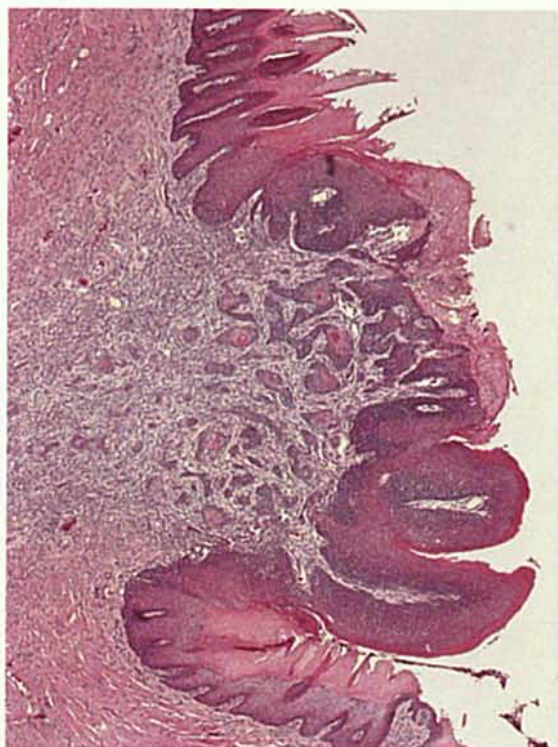


Fig. 31 – Squamous cell carcinoma, tongue (H&E).

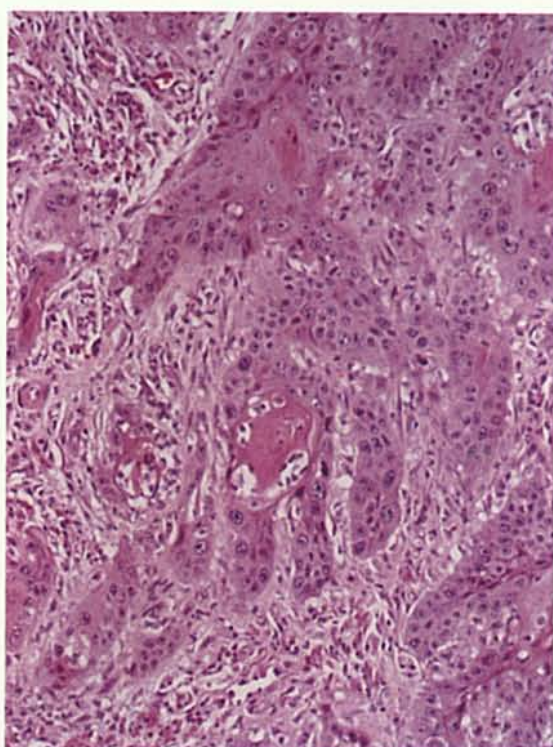


Fig. 32 – Higher magnification of invasive epithelium in Fig. 31 (H&E).