Proliferative Lesions of the Non-Glandular and Glandular Stomach in Rats

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INTRODUCTION

The rodent stomach is morphologically different from the stomach of other laboratory species and from that of man. (17, 24, 26) In the rat, the proximal portion, the non-glandular stomach (this anatomical term is preferred over “foregut”), is lined by stratified squamous epithelium and comprises approximately 60% of the total area of the stomach. It is separated from the distal portion, the glandular stomach, by the limiting ridge. Functionally, the non-glandular stomach serves as a storage organ, and, due to prolonged exposure, is potentially a major site of interaction between the rat and xenobiotics entering via the digestive system. (20) The glandular stomach of the rat is functionally similar to that of other laboratory animals.

In its natural configuration, the non-distended stomach has an irregularly folded mucosa and submucosa. It must be emphasized that proper opening and positioning during fixation and trimming is necessary to obtain sections with correct orientation of the muscularis, submucosa, and mucosa. Failure to process stomach tissues properly may produce diagnostic dilemmas that cannot be easily resolved.

Examination of the non-glandular and glandular mucosa at necropsy is accomplished by opening the stomach along the greater curvature into the duodenum, washing off ingesta with isotonic saline and pinning the stomach to a rigid surface. Pinning should be sufficient to obtain a flattened mucosa in the non-glandular and antral regions but the stomach should not be excessively stretched. The pinned stomach is more easily examined for any areas of thickening or depressions indicative of ulceration. Alternatively, the stomach may be inflated with fixative, then opened and examined at time of trimming in order to avoid fixation artifact.

If the stomach is a potential target organ, sections passing through representative areas should be utilized. A useful technique is depicted in Figure 1. The midline section includes the esophageal cardia, around which the squamous epithelial areas may normally appear somewhat thickened, the limiting ridge, the mucous cardiac glands and, if truly midline, antral mucosa, pylorus and duodenum with Brunner’s glands. The parasagittal section from the lesser and greater curvature regions provides non-glandular and oxyntic mucosa for examination. Ratios of parietal and chief cells in oxyntic glands may vary from lesser to greater curvature and, when taking longitudinal sections, one should be consistent in location to avoid inconsistent histology.

A variety of proliferative lesions may arise in the rat stomach, including epithelial (squamous and glandular), neuroendocrine, and stromal types. While spontaneous tumors of the rat stomach are rare, (21, 26)
proliferative lesions, especially of squamous epithelium (1, 4, 7, 12, 15, 18, 20, 25, 28, 36) and neuroendocrine cells (3, 5, 6, 8, 16, 21, 29, 30, 32) may be readily induced. Some common non-proliferative lesions, such as ulceration, will also be described for completeness, or because of their possible relationship to proliferative changes.

**Proliferative Lesions of the Non-Glandular Stomach**

**Hyperplasia** (Figures 2-4)

Hyperplasia is characterized by an increased number of one or more epithelial cell types (basal, spinous, or granulosum). Hyperplasia may be focal or diffuse and results in an increased thickness of the non-glandular stomach mucosa.

While several subcategories of hyperplasia may be suggested, it is recommended that all be included under the diagnostic term hyperplasia and that the pattern of the hyperplasia be described in whatever narrative accompanies a case or study report. Hyperplasia of the non-glandular stomach is often characterized as a uniform thickening of all layers of the epithelium without upward or downward projections. However, in more severe cases there are downward finger-like projections of rete peg-like structures with convolution of the germinal epithelium. (27) Projection of squamous epithelium through the muscularis mucosae may occur with severe hyperplasia, but the polarity of differentiation to keratinocytes is orderly and complete despite a high mitotic rate. (4) The term acanthosis is used by some when the latter pattern of hyperplasia (downward projections of rete peg-like structures) is present and when the proliferating cells are largely from the prickle cell layer. The term acanthosis is classically defined as a skin lesion and its use for describing hyperplasia of the non-glandular stomach is not appropriate. Focal upward proliferation into the lumen mimicking papilloma may be present in more severe cases of hyperplasia and may be categorized as papillary hyperplasia in the narrative. (9) The absence of a branching connective tissue core containing blood vessels and the presence of an intact muscularis mucosae distinguishes this form of hyperplasia from a true papilloma.

Erosion, ulceration, and attendant inflammation are frequently associated with epithelial hyperplasia. This is true whether the ulceration is a primary response to the treatment of the animal or if the ulceration is secondary. The implications of a proliferative response secondary to ulceration are different from those of a proliferative response that may be part of an early neoplastic process. (37) The absence of an ulcer or erosion in the plane of the section does not preclude the presence of such in adjacent unsectioned tissue. Recuts may be warranted to determine if an epithelial proliferative reaction is secondary to ulceration and inflammation. A careful gross examination in such cases will undoubtedly be helpful.

Caution should be exercised when examining lesions at the limiting ridge (along the junction of the non-glandular and glandular stomach). At this junction, the non-glandular stomach mucosa is generally thickened relative to adjacent squamous mucosa and there is a tendency for the mucosa to be sectioned obliquely at places along this junction.

**Hyperkeratosis**

Hyperkeratosis is characterized by an increased thickening of the superficial non-nucleated keratin layer. Hyperkeratosis frequently accompanies hyperplasia. Hyperkeratosis in the absence of hyperplasia is a feature commonly present in anorectic rodents and has different interpretative implications from hyperkeratosis occurring as part of the process of enhanced epithelial proliferation. In the anorectic rodent, the excess keratin is presumably the result of reduced mechanical removal by the passage of food. In cases of hyperkeratosis associated with anorexia, hyperkeratosis is usually also present in the esophagus.

**Parakeratosis**

Parakeratosis is characterized by the retention of nucleated keratinocytes in the superficial keratin layer. However, an occasional nucleated cell may normally be present in the keratin layer of the rodent non-glandular stomach and esophagus.

**Squamous Cell Papilloma** (Figure 5)

Papillomas are localized proliferations of the non-glandular stomach mucosa in which normal cellular differentiation is evident. (10) Papillomas are nearly always pedunculated, with fronds of epithelial tissue proliferating into the lumen of the stomach. The presence of a branching connective tissue core containing capillaries within these papillary fronds and disruption of the underlying muscularis mucosae allows distinction from focal hyperplasia. Papillomas may be single or multiple. Hyperkeratosis is usually prominent in papillomas and keratin pearls may be present, but these features may also be present in focal hyperplasia. The use of the diagnostic terms "sessile papilloma" or "inverted papilloma" should be discouraged, as differentiating this so-called lesion from focal hyperplasia is purely subjective.
SQUAMOUS CELL CARCINOMA (Figures 6-7)

Carcinoma of the non-glandular stomach is characterized by proliferation of the epithelium with loss of cellular differentiation, anaplasia, and evidence of localized invasion. Single cells or nests of neoplastic cells not circumscribed by PAS-positive basement membrane invade surrounding tissues. Sometimes sheets of neoplastic cells may form and can extend to the serosal surface. These neoplasms can range from well-differentiated to anaplastic; the latter sometimes have a spindle-cell or sarcomatous appearance. Localized extension (invasion) into surrounding tissue frequently causes inflammation and ulceration to which there may be a secondary hyperplastic epithelial response. Neoplastic cells in carcinomas are frequently larger than normal and mitotic figures may be numerous. Hyperkeratosis may be prominent, and numerous keratin pearl structures may be present. It is recommended that the single diagnostic category, squamous cell carcinoma, be used for malignant neoplasms of the non-glandular epithelium and that the degree of differentiation (i.e., well-differentiated, anaplastic) and the predominant cell type (e.g., basal cell, keratinized cell, spindle cell) be described in the narrative accompanying the case or study report.

Although carcinomas rarely arise in pre-existing papillomas, occasionally focal areas at the base of a well-defined papilloma may show evidence of invasion through the muscularis mucosae. In such cases, the neoplasm should be considered a squamous cell carcinoma.

In proliferative epithelial reactions, particularly when the non-glandular stomach is poorly oriented during fixation, nests of basal cells (stratum germinativum) and sometimes prickle cells may be found in the submucosa. This is caused when tips of curved finger-like downward projections of proliferative epithelium are sectioned transversely and the connection with the overlying epithelium is not present in the histologic section. Care must be exercised in not interpreting such nests of cells as evidence of invasive carcinoma. Such nests are typically well-differentiated and circumscribed by basement membrane. Serial sections may be necessary to determine the exact nature of such nests of cells.

Nests of growing epithelial cells, as well as keratinized cells, are sometimes mechanically translocated into the submucosa in ulcerative inflammatory reactions, as well as in some gavage studies. These nests may occur in the presence or absence of non-glandular stomach neoplasia. There may be an inflammatory reaction to these displaced epithelial cells. Caution and judgement must be exercised in differentiating such lesions from invasive carcinoma. Similarly, cysts lined by stratified squamous epithelium and filled with keratin may be seen.

LESIONS OF THE GLANDULAR STOMACH

EROSION

Erosions are focal or multifocal necrotic areas in the superficial mucosa that do not extend to the muscularis mucosae. In the acute stage, the necrotic tissue remains intact and hematin pigment may be present if there has been hemorrhage. Bile staining may occur on the surface. Repair of superficial erosions is by upward migration of foveolar cells. There may be reactive hyperplasia from the proliferative zones of oxyntic glands or from the base of antral glands adjacent to the erosion. A secondary inflammatory cell infiltrate is commonly found in the lamina propria, unless it is suppressed (e.g., with the use of non-steroidal anti-inflammatory drugs).

ULCERATION

Ulcers are focal or multifocal areas of full thickness necrosis of the mucosa that extend to or through the muscularis mucosae. Ulcers may extend through the serosa, leading to perforation. Repair is by hyperplasia of gastric glands at the ulcer’s margins. Often there is associated chronic inflammation and fibroplasia. Erosions and ulcerations of the glandular stomach are most common in the antrum and may be due to the effects of stress or the direct result of toxins.

GLANDULAR DILATATION (MICROCYST)

The basal portion of the gastric gland(s) becomes distended with clear fluid, secretion, or cellular debris. This usually occurs as a focal or multifocal event, and may be seen as an aging change in rats.

PARIETAL CELL VACUOLATION/DEGENERATION/NECROSIS (Figure 8)

Parietal cell vacuolation/degeneration/necrosis may consist of a spectrum of changes beginning with vacuolation and ending, in severe cases, with necrosis. The loss of parietal cells may be the result of a trophic effect from a potent antiserotery agent on the oxyntic mucosa. Parietal cell vacuolation/degeneration/necrosis may be observed in its mildest form as a spontaneous event and is considered to be associated with normal parietal cell turnover. Parietal cell vacuolation can be exacerbated by certain classes of drugs (e.g. protein pump inhibitors); this change is considered to be a reversible pharmacological effect.

EOSINOPHILIC CHIEF CELLS (Figure 9)
(Eosinophilic cytoplasmic granularity; hypertrophic hyperstaining cells with apical granularity; ‘Paneth cells’
Eosinophilic chief cells are intensely pink-red, pepsinogen-positive cells in single or multiple cell clusters in oxyntic glands; these cells are usually larger than surrounding normal cells. They occur infrequently as a spontaneous change, usually associated with another disease, such as a lymphomatous infiltrate of the gastric mucosa. They may be induced by antisecretory or other drug treatment, though the incidence is not proportional to neuroendocrine cell hyperplasia which may be seen concomitantly. They may also be noted in association with hyperplasia of the glandular epithelium, usually following ulcer or erosion repair. Eosinophilic chief cells are reversible and non-progressive, and generally occur focally or multifocally.

ECTOPIC PANCREAS

Groups of pancreatic acini and ducts may be present in submucosal or subserosal tissues of glandular or non-glandular stomach.

HYPERPLASIA

FOCAL HYPERPLASIA

(Adenomatous hyperplasia, adenomatous diverticulum)

This is the most common spontaneous type of hyperplasia involving the glandular stomach of the rat. It is considered to be a reactive change associated with erosion or ulceration of any part of the glandular stomach, although it is most common in the antrum. It may be due to the effect of stress or the direct result of toxins. There may be dysplastic changes in the affected glands. Chronic cases may be metaplastic with mucous epithelial differentiation. In severe cases, hyperplastic glands may extend through the muscularis mucosae where cystic structures with cuboidal epithelium, sometimes with papillary infolding, may persist. This type of lesion has been called "adenomatous diverticulum", but the use of this term should be avoided.

FUNDIC HYPERPLASIA (Figure 10) (Hypertrophic gastritis, mucosal hypertrophy, adenomatous hyperplasia)

This change may occur spontaneously, but is usually associated with antisecretory agents. It is thought to be due to stimulation by hypergastrinemia of the proliferative zone of oxyntic glands. Fundic hyperplasia is characterized by an increase in mucosal thickness involving all cell components. Affected glands become long and tortuous, and many are dilated at their base. A few glands may penetrate the muscularis mucosae, rarely the outer muscular layer, but not the serosa. Their well-differentiated nature distinguishes them from neoplasia. In the rat, the change tends to be generalized with increases in the foveolar:oxygen gland ratio in marked cases. However, increased foveolar: oxyntic glandular ratio, and convolution and infolding of the mucosa, is generally less marked in the rat than in the mouse or dog. Occasionally, a chronic inflammatory component may be present; this component may be described separately or described in the narrative.

NEUROENDOCRINE CELL HYPERPLASIA

(Figure 11)

Neuroendocrine cell hyperplasia is an increase in neuroendocrine cell numbers in gastric glands in response to general trophic effects or specific endocrine changes. In the oxyntic gland, the ECL-cell (enterochromaffin-like) is the main cell type responsive to hypergastrinemia.

The cytology of hyperplastic neuroendocrine cells is nearly normal. Nuclei are uniform and small, and mitotic figures are rare. The cytoplasm is pale and abundant. Cells are immunoreactive for neuron-specific enolase, chromogranin-A, histidine decarboxylase, and histamine, and are argyrophilic. The Grimelius and Sevier-Munger stains are most commonly used to demonstrate these cells. In diffuse neuroendocrine cell hyperplasia, scattered solitary ECL-cells are increased in number and small clusters of ECL cells may be seen. In focal neuroendocrine cell hyperplasia, there are larger discreet clusters of ECL-cells, up to three glands in diameter. They may be in solid clumps or pseudorosettes. There is a morphological continuum and a biological progression from focal hyperplasia to neoplasia. Solitary to a few ECL cells, without the characteristic cytological changes associated with neuroendocrine cell tumors, may be present in the submucosa; these errant cells are not considered to be evidence for neoplasia in these cases.

ADENOMA (Figure 12) (Adenomatous polyp, polyloid adenoma, polyx, exocrine adenoma)

Adenomas of the gastric epithelium are typically located in the antrum and composed of basophilic columnar exocrine epithelium in well-ordered glandular structures with only slight cellular atypia. They may be pedunculated with a connective tissue core. Submucosal cyst formation may occur, usually resulting from trapped hyperplastic antral glands, sometimes with infoldings lined by columnar mucous epithelial cells. There may be a slight to moderate increase in the number of mitotic figures. Adenomas may arise in areas of reactive hyperplasia.

ADENOCARCINOMA

Adenocarcinomas of the stomach are invasive into the submucosa as nests and cords of cells with loss of normal glandular organization. There is cytological dysplasia and anaplasia, nuclear pleomorphism, and a
moderate to marked increase in numbers of mitotic figures. The cytoplasm may be basophilic or mucinous. Well-differentiated tumors may include rare neuroendocrine cells. Additional descriptive terms, such as mucous, mucocystic, or signet-ring cell types, may be used in the narrative to characterize the lesions further.\(^{(31, 35)}\)

Poorly differentiated tumors generally still retain the tendency toward glandular formation, at least in some areas. Although fibropapilia is usually not a prominent feature, invasive anaplastic adenocarcinoma in the submucosa may induce a marked scirrhous reaction. Malignant behavior includes local invasion and metastasis.

**NEUROENDOCRINE CELL TUMOR** (Carcinoid, APUDoma, neuroendocrine carcinoma)

These are very rare as spontaneous tumors, but common and characteristic of potent gastric antisecretory agents causing sustained marked hypergastrinemia.\(^{(3, 16, 29, 30)}\) They arise in association with focal neuroendocrine cell hyperplasias in the oxyntic mucosa.

Neoplastic neuroendocrine cells are arranged in solid sheets, acinar structures, or small "oat cell" nests in excess of three glands in diameter. This size (three glands in diameter), which has been chosen as the arbitrary cut-off point between focal hyperplasia and neoplasia, is analogous to the situation with C-cell neoplasia in the thyroid and interstitial cell neoplasia in the testis. It must be emphasized that there is no definitive biological rationale for this arbitrary decision at this time. Clumps of tumor cells displace other cells in gastric glands. The cells are moderately pleomorphic, with eosinophilic cytoplasm, enlarged nuclei, and a variably increased number of mitotic figures. The cells are immunoreactive for non-specific enolase, chromogranin-A, and histamine, and are argyrophilic. These characteristic special stains show progressively weaker reactions in less-differentiated lesions in the neoplastic spectrum. Functional gastric neuroendocrine cell tumors have not been reported.

**BENIGN NEUROENDOCRINE CELL TUMOR** *(Figures 13, 14)* (Intramucosal neuroendocrine cell tumor)

Benign neuroendocrine tumors may be spherical, with clearly demarcated margins, or they may be infiltrative lesions merging with areas of focal neuroendocrine cell hyperplasia. These tumors lie wholly within the mucosa, and do not invade through the muscularis mucosae. Compression of surrounding glands is present and superficial necrosis of overlying foveolar or glandular epithelium is common. The potential for malignant behavior in these tumors is uncertain, but, in the absence of definitive data, intramucosal neuroendocrine tumors are considered to be benign.

**MALIGNANT NEUROENDOCRINE CELL TUMOR** *(Figures 15-16)* (Invasive neuroendocrine cell tumor)

Malignant neuroendocrine tumors show clearly malignant behavior with solid cords or nodular growths invading through the muscularis mucosae. The outer muscular layers may also be penetrated. Cells of invasive neuroendocrine tumors are often less differentiated than those of benign tumors. Metastasis to regional lymph nodes is seldom reported, but these lymph nodes are not routinely examined.

**PROLIFERATIVE LESIONS OF STROMAL TISSUES**

Epithelial and neuroendocrine tumors are the most commonly induced neoplasms of the rat stomach. Stromal tumors by comparison are rare, but may be induced by the oral administration of certain compounds.\(^{(26)}\) Three types are mentioned briefly below.

**LEIOMYOMA / LEIOMYOSARCOMA** *(Figure 17)*

Gastric leiomyomas and leiomyosarcomas are rare smooth muscle tumors that are usually well-demarcated, tan to red, firm nodules arising from the tunica muscularis. Leiomyomas are benign tumors composed of interlacing bundles of uniform, well-differentiated spindle cells that have long oval nuclei with blunt ends, a variable amount of eosinophilic cytoplasm, and few mitotic figures. In contrast, leiomyosarcomas are malignant smooth muscle tumors that have a greater cellularity, are more invasive to the serosa and submucosa, and are composed of disorganized bundles of anaplastic round to spindle cells that have oval to "cigar-shaped" central nuclei and many mitotic figures. Ulceration of the overlying mucosa frequently occurs with leiomyosarcomas.\(^{(34)}\)

**HISTIOCYTIC SARCOMA / LYMPHOMA / LYMPHOSARCOMA**

The criteria for classification are as for other organs.

**MESOTHELIOMA**

There may be serosal implantation following transcelomic spread.

**DISCUSSION**

The histological classification scheme that has been proposed is a relatively simple one. However, it is complicated, as in other organ systems, by the similarities between hyperplastic and neoplastic lesions, and between benign and malignant neoplasms.\(^{(26)}\)
Relatively little is known about the biological behavior of these entities in the rodent stomach.

While there is an apparent morphologic continuum from hyperplasia to benign neoplasia to malignant neoplasia, this does not necessarily mean that biological progression through such a continuum is an inevitable condition for the genesis of malignancy. Hyperplasia should not be considered a "preneoplastic" lesion a priori. Also, squamous cell carcinomas often arise in the absence of squamous cell papillomas. Chemically-induced squamous hyperplasia and papillomas have been shown to be reversible after withdrawal of treatment. It may be reasonable to consider hyperplasia, papilloma, and carcinoma as part of a biological progression when all are present in a group of similarly exposed rodents, and after careful examination, there is no alternative cause for the hyperplastic response. The occurrence of hyperplasia, benign neoplasia, and malignant neoplasia in a temporal sequence, or with a relationship to increasing dose, is also supportive of a true biological progression.

Although subcategories have been suggested or described for certain lesions, and diagnostic synonyms listed (in parentheses) whenever possible, it is strongly advised that the recommended nomenclature (in bold print for each entity) be used to include all variations of the diagnostic entity in question. Splitting the diagnosis into subcategories or using synonyms may lead to a loss of biological and/or statistical significance that might be detected with the use of a broader inclusive diagnostic term. Differences or variations in the patterns of the lesions should be described in the text that accompanies the animal or study, so that it can be retrieved at a later date, if necessary.

**Hyperkeratosis**
1. Increased thickening of keratin layer
2. Usually accompanies hyperplasia
3. May occur in anorectic rodents in the absence of hyperplasia

**Parakeratosis**
1. Nucleated keratinocytes in the keratin layer
2. An occasional nucleated keratinocyte is normal

**Squamous Cell Papilloma**
1. Single or multiple
2. Proliferating epithelial fronds with branching connective tissue cores containing capillaries; projects into lumen of stomach
3. Disruption of underlying muscularis mucosae
4. Hyperkeratosis usually prominent; may have keratin pearls

**Squamous Cell Carcinoma**
1. Cells are usually larger than normal and are anaplastic
2. Invasion by single or nests of neoplastic cells not circumscribed by basement membrane; may form sheets of neoplastic cells
3. May have basal cell, keratinized cell, or spindle cell types
4. May have many mitotic figures, hyperkeratosis, keratin pearls
5. Secondary inflammation and ulceration may be present

**GLANDULAR STOMACH**

**Erosion**
1. Focal or multifocal; most common in antrum
2. Superficial necrosis/loss of mucosa not involving the muscularis mucosae
3. May have hemorrhage, hematin pigment, and secondary inflammation
4. May have reactive hyperplasia of adjacent oxyntic or antral glands

**Ulceration**
1. Focal or multifocal; most common in antrum
2. Full thickness necrosis/loss of mucosa involving the muscularis mucosae
3. Often associated chronic inflammation and fibroplasia
4. May have reactive hyperplasia of surrounding gastric glands
Glandular Dilatation
1. Focal or multifocal
2. Distension of basal portion of gastric gland(s) with fluid or cellular debris

Parietal Cell Vacuolation/Degeneration/Necrosis
1. Diffuse vacuolation to necrosis/loss of parietal cells
2. Noted as spontaneous change in its mildest forms
3. Considered a reversible pharmacological effect of certain drugs

Eosinophilic Chief Cells
1. Focal or multifocal
2. Intensely pink-red, pepsinogen positive cells in glands
3. May be induced by antisecretory agents or associated with lymphomatous infiltrates

Ectopic Pancreas
1. Pancreatic acini and ducts in submucosa or subserosa

Focal Hyperplasia
1. Focal; most common in antrum
2. Reactive to erosions or ulcers
3. Dysplastic, cystic glands may extend through muscularis mucosae
4. Chronic lesions may show mucous epithelial differentiation

Fundic Hyperplasia
1. Usually generalized
2. Increase in mucosal thickness involving all cell components
3. Glands are long, tortuous; may be distorted at bases
4. Glands may penetrate muscularis mucosae
5. Increase in foveolar:oxygenic gland ratio in more severe cases
6. Associated with antisecretory agents due to hypergastrinemia

Neuroendocrine Cell Hyperplasia
1. Diffuse, with scattered solitary and small clusters of ECL cells; or focal, with larger discrete clusters of ECL-cells, up to three glands in diameter, in solid clumps or pseudorosettes
2. Cytology nearly normal; nuclei small and uniform with abundant, pale cytoplasm
3. Immunoreactive for neuron-specific enolase, chromogranin-A, histamine, and histidine decarboxylase
4. Argyrophilic cells
5. Trophic effect of hypergastrinemia

Adenoma
1. Usually located in antrum
2. Basophilic columnar exocrine epithelium in well-ordered glandular structures
3. Pedunculated with connective tissue core or endophytic with submucosal cyst(s)
4. May be slight to moderate increase in numbers of mitotic figures
5. May arise in areas of reactive hyperplasia

Adenocarcinoma
1. Basophilic or mucinous cytoplasm with nuclear pleomorphism
2. Moderate to marked increase in numbers of mitotic figures
3. Loss of normal glandular organization, but retains tendency toward glandular formation
4. Invasion into submucosa; may metastasize
5. May have mucous, mucocystic, or signet-ring cell types

Neuroendocrine Cell Tumor
1. Moderately pleomorphic, with eosinophilic cytoplasm, enlarged nuclei, and increased numbers of mitotic figures
2. Immunoreactive for neuron-specific enolase, chromogranin-A, and histamine, and argyrophilic
3. Arranged in solid sheets, acinar structures, or small 'oat cell' nests greater than three glands in diameter which displace other cells

Benign Neuroendocrine Cell Tumor
1. Spherical with clearly demarcated margins, or infiltrative within mucosa
2. Compression of surrounding glands
3. Superficial necrosis of overlying foveolar or glandular epithelium common

Malignant Neuroendocrine Cell Tumor
1. More anaplastic cells
2. Invasion through muscularis mucosae
3. May penetrate outer muscular layer
4. May rarely metastasize to local lymph nodes

STROMAL TISSUES

Leiomyoma / Leiomyosarcoma
1. Well demarcated
2. Benign tumors less cellular with few mitotic figures
3. Sarcomas more cellular, higher mitotic rate and infiltrative
REFERENCES


Fig. 1. Diagram of an opened stomach illustrating strips taken for histological sections.
Fig. 2. Hyperplasia, non-glandular mucosa, diffuse (H&E, 50x).

Fig. 3. Hyperplasia, non-glandular mucosa, focal with basal cell proliferation and keratin cysts (H&E, 94x).
Fig. 4. Hyperplasia and ulceration, non-glandular mucosa, focal (H&E, 31x).

Fig. 5. Squamous cell papilloma (H&E, 40x).
Fig. 6. Squamous cell carcinoma (H&E, 60x). Inset illustrates submucosal invasion (H&E, 480x).

Fig. 7. Squamous cell carcinoma (H&E, 60x). Inset illustrates serosal invasion (H&E, 250x).
Fig. 8. Vacuolation, parietal cell, diffuse (H&E, 156).
Fig. 9. Eosinophilic chief cells, focal (H&E, 117x).
Fig. 10. Hyperplasia, fundic, diffuse (H&E, 62x).
Fig. 11. Hyperplasia, neuroendocrine cell, multifocal (H&E, 235x).

Fig. 12. Adenoma (H&E, 39x).
Fig. 13. Benign neuroendocrine cell tumor (H&E, 63x).
Fig. 14. Benign neuroendocrine cell tumor with submucosal ECL cells (arrow) (H&E, 200x).

Fig. 15. Malignant neuroendocrine cell tumor with early submucosal invasion stained for neuron-specific enolase (H&E, 6.2x)
Fig. 16. Malignant neuroendocrine cell tumor (H&E, 94x).

Fig. 17. Leiomyosarcoma (H&E, 6.2x). Inset illustrates poorly differentiated spindle cells (H&E, 320x)