

NON-PROLIFERATIVE LESIONS OF THE ALIMENTARY CANAL IN RATS

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INTRODUCTION

The alimentary canal (tractus alimentarius) serves as the entry point into the body of all orally administered compounds and consists of the oral cavity, esophagus, stomach, and intestines. This monograph focuses on the alimentary canal while accessory glands (liver, pancreas, and salivary glands) of the digestive system are discussed elsewhere.

Many compounds can have severe systemic toxicity but result in relatively limited damage to the alimentary canal. However, the alimentary canal cannot sustain widespread toxic insult without serious consequences to other organs or the animal's survival. When a compound is administered orally, the ultimate toxic effect manifested in the alimentary canal will be determined by interactions of the compound with luminal contents (inert materials and bacterial and mammalian enzymes), mucous blanket, and biotransforming enzymes of epithelial cells.

When considering non-proliferative lesions that may represent toxicologic processes, the basic structure and physiology of the alimentary canal should be considered. The normal luminal constituents are inherently toxic to the body, but are separated from the body by a thin (5-20 μm) mucus barrier. From the stomach to the rectum, the alimentary canal is composed of four basic layers: the mucosa, submucosa, muscular tunics,

and the one-cell serosal layer. The mucosa has a high proliferative and metabolic rate and is subjacent to a barrier that must allow passage of some materials but exclude others. The muscular tunics, which envelope the entire alimentary canal, are sensitive to toxic agents affecting smooth muscle and autonomic nerves; however, toxicologic alterations are less commonly observed in the muscular layers than in the mucosa.

The mucosal lining of the alimentary tract is highly sensitive to autolytic changes, frequently resulting in loss of epithelial cell lining. Many subtle toxicologic events will only be observed with careful and proper handling of these tissues. To avoid misinterpretation of potential ulcerative and erosive processes, evidence of a tissue reaction (e.g., shape changes in adjacent epithelial cells, inflammatory response, etc.) should be identified.

Non-proliferative lesions are often observed in the oral cavity. Such changes may represent an indication of local or systemic toxic injury or local trauma from foreign material (e.g., food). Ulceration and hemorrhage are common lesions and an inflammatory reaction is usually secondary to any breaks in the mucosal lining.

Esophageal damage is infrequent, although exposure to irritants and gastroesophageal reflux can lead to ulceration and stenosis (1,2). Perforation of the esophagus is commonly caused by gavage instruments, and is characterized by a variable but usually purulent inflammatory reaction that may have spread into surrounding fascial tissue or pleural or pericardial spaces. Immunosuppression or exposure to high doses of antibiotics can also lead to inflammatory reactions of the esophagus that

may be secondary to microbiological infection (1).

The rat stomach is divided into glandular and non-glandular components. The non-glandular portion occupies approximately two-thirds of the total surface area of the stomach. It is lined by stratified squamous epithelium and is distinctly separated from the glandular stomach by the limiting ridge. The non-glandular stomach serves as the site of short-term storage. Consequently, the duration of compound exposure may vary markedly.

The glandular stomach is divided into fundic and antral regions. The fundic glands are simple tubular structures with a base, neck, and isthmus that are continuous with the glandular gastric pit. The glands of the fundus contain mucous neck cells which produce mucus; parietal or oxyntic cells with a cellular product consisting of hydrochloric acid and intrinsic factor; chief or zymogen cells with a cellular product of pepsinogen; and argentaffin cells that produce a variety of endocrine and paracrine hormones. In the pyloric antrum, glands are lined by mucus containing pyloric glandular cells.

Unlike the rest of the alimentary canal, cellular proliferation in the fundic and antral mucosa occurs at the isthmus (3). Cells migrate basally to form cells of the gland (parietal and chief cells) and lumenally to form mucous cells.

Non-proliferative compound-induced changes in the stomach are usually erosive or ulcerative and potentially inflammatory in nature. The absence of an inflammatory reaction is not uncommon in toxic mucosal lesions (4). Hemorrhage associated with gastric ulcers may lead to anemia or changes in hematologic or hematopoietic parameters.

Since the small intestine is the primary site of compound absorption, this organ must be carefully evaluated in safety evaluations. Additionally, compounds can have an extended residence time in the small intestinal lumen. The large intestine has an ascending and descending segment, leading to the rectum. The cecum is large and has substantial fermentation potential. The intestinal mucosa is composed of villi in the small intestine and crypts in both the small and large intestine. The villi are lined by absorptive columnar epithelial cells and goblet cells. Paneth cells are also present in the small intestine. In the intestines, proliferation occurs in the basal region of the crypts and cells migrate toward the lumen as they differentiate. The very base of the crypts is composed of stem cells which have a low proliferation rate.

The primary toxicologically significant non-proliferative lesion of the intestines is ulceration and associated inflammation. Care must be taken to differentiate primary compound-related lesions from those that occur from spontaneous disease or are secondary to bacterial overgrowth.

MORPHOLOGY

ORAL CAVITY

Congenital Anomalies

Ectopic Sebaceous Gland

Sebaceous gland ectopia in the oral cavity may occur at the base of molar teeth in male rats and is usually found between the upper incisors. These glands are composed of normal secretory adenomeres, but can undergo cystic or hyperplastic changes.

Squamous Cysts

Squamous cysts may be found in the gingiva or associated with the teeth. These cysts are lined by keratinized squamous epithelium and the lumen usually contains keratinized material.

Degenerative Lesions

Mineralization of Muscle, Blood Vessels, and Stroma of Tongue

Mineralization of the muscle, blood vessels, and connective tissues of the tongue may occur secondarily to renal disease or disturbances in mineral metabolism.

Inflammatory and Ulcerative Lesions

Stomatitis, Gingivitis, Glossitis, Periodontitis, and Ulceration (Figure 1)

Inflammation of the oral cavity (stomatitis) may involve the gingiva (gingivitis), tongue (glossitis), and periodontal tissues (periodontitis). Stomatitis can be a manifestation of a direct irritant or systemic toxic effect. Anti-mitotic and anti-diuretic agents are particularly prone to induce stomatitis (5,6). Initial lesions consist of an acute neutrophilic exudative phase most pronounced in the venules lateral to the gingival sulcus (7,8). Early lesions are characterized by an infiltrate primarily composed of lymphocytes with fewer macrophages and plasma cells; an acute inflammatory reaction persists. Established lesions are primarily composed of plasma cells and advanced lesions result in alveolar bone loss. Bone loss is characteristic of periodontitis and is discussed in the monograph covering bone.

Glossitis can be the result of spontaneous disease or local or systemic toxic injury. Malocclusion with incisor overgrowth is a common cause of focal ulcerative glossitis. Ulceration and inflammation can also be secondary to uremia.

Type of diet and its consistency markedly influence the frequency and types of oral cavity lesions observed. Periodontitis and fistulas can occur following the feeding

of powdered diets that contain food fibers (9). The incidence of hair impaction also is influenced by diet consistency. Rats have keratinized epithelium in the gingival sulci with the gingival epithelium being apically oriented and joining the junctional epithelium on the side of the tooth. Although the gingival epithelium forms a stratum corneum, in which the most superficial cells are keratinized, it is the junctional epithelium that is the route of passage for foreign substances and inflammatory cell exudation (10).

Miscellaneous Lesions

Pigmentation of Oral Cavity

Pigmentary alterations of the oral mucosa are manifested only in pigmented rats (DA, Long-Evans rat). Pigmentary changes can be easily detected macroscopically and histologically in hyperpigmentary conditions. Melanocytes of treated rats enlarge with melanin (11) and in hypomelanosis, melanin content is reduced. The remaining anatomy of the oral mucosa is usually normal.

ESOPHAGUS

Congenital Anomalies

Squamous Cysts

These cysts are rarely observed congenital anomalies of the esophagus. They are characterized by keratinized stratified squamous epithelium, and extend into the submucosa/tunica muscularis. Mucous cells are occasionally present, and the lumen frequently contains keratinized material.

Megaesophagus

Although usually secondary to impaction (see below), megaesophagus may be congenital.

Degenerative Lesions

Hyperkeratosis/Parakeratosis

Hyperkeratosis/parakeratosis of the esophagus is a common alteration. Dietary composition is an important factor in controlling esophageal keratinization, with low fiber, low protein, or liquid diets leading to an increased thickness of the keratinized epithelial layer (12). In these situations, there will be no evidence of an increased proliferative response in the basal layer. Vitamin imbalance and zinc deficiency can cause hyperkeratosis/parakeratosis and associated squamous cell hyperplasia. Hyperkeratosis of the esophagus may also be induced by hydroxymethylglutaryl-CoA reductase inhibitors, by altering lipid composition of the epithelium, and by a reduction in the normal desquamation processes (13).

Inflammatory and Ulcerative Lesions

Esophagitis and Ulceration

Esophageal erosion, ulceration, and inflammation (esophagitis) are frequently the result of gavage accidents. Such trauma can lead to perforation, periesophageal abscesses, and fibrosis.

Miscellaneous Lesions

Esophageal Impaction

This lesion is characterized by dilatation of the esophagus with food (14). Muscle fibers of the muscular lining are fragmented, vacuolated, and may be mineralized.

Megaesophagus

Megaesophagus is characterized histologically by degeneration of muscle and nerve cells in the wall of the esophagus (15). This condition may occur spontaneously when rats are fed a powdered diet (16).

Stenosis

Stenosis is characterized histologically by a reduction of luminal diameter and moderate to severe fibrosis of the surrounding alimentary canal wall. Esophageal and intestinal stenosis are frequently the result of traumatic perforation, such as gavage trauma of the esophagus (17).

STOMACH

Congenital Anomalies

Squamous Cysts (Figure 2)

Squamous cysts usually occur in the non-glandular stomach near the limiting ridge and antral mucosa. Cysts of the non-glandular stomach are usually lined by keratinized stratified squamous epithelium and less frequently by mucous cells.

Glandular Cysts

Glandular cysts occur in the glandular stomach mucosa. These cystic glands may extend through the submucosa and tunica muscularis. Those of the antral mucosa have well-differentiated cuboidal or columnar epithelium. In the glandular stomach, cysts are usually found in the pyloric antrum, extend into the submucosa, and are lined by well-differentiated epithelial cells. Glandular cysts are frequently associated with mineralized deposits in aged rats. Cysts can also be associated with compound-induced neoplasms.

Ectopic Pancreas and Liver (Figure 3)

Ectopic tissue of accessory glands of the digestive

system can be present in the lamina propria (primarily) or submucosa of the stomach, and may be composed of ectopic hepatocytes or pancreatic epithelial cells.

Degenerative Lesions

Vacuolation of Squamous Epithelium (Figure 4)

This lesion is characterized by superficial epithelial cells with a pale staining and vacuolated cytoplasm. Associated mucosa may be ulcerated and epithelial cells may be degenerate or necrotic. Subjacent tissue is variably infiltrated by inflammatory cells. This change may represent a milder change than necrosis and can be observed in studies involving gavage methods. This lesion may also be due to ulcerogenic or anti-inflammatory compounds.

Mineralization of Gastric Mucosa and Blood Vessels (Figure 5)

Mineralization of the mucosa and blood vessels may occur secondarily to renal disease. This lesion in the gastric mucosa is found predominantly in the mid-gland region of the fundic mucosa and is frequently accompanied by mucous cell hyperplasia.

Mucosal Atrophy

Focal mucosal atrophy may result from ulceration, inflammation, mineralization, or infarction. Generalized mucosal atrophy is an age-related change with a diffuse decrease of mucosal height and increased mucosal fibrous connective tissue. In the aged rat, fundic glands may be diffusely atrophic and contain cysts. Inflammatory cells and fibrous connective tissue may be found in the lumen of ectatic glands and in the lamina propria around cystic glands.

Chief Cell Atrophy

This specific form of mucosal atrophy can be an age-related change. Chief cells are cuboidal and flattened, and remaining cells are decreased in size and number.

Parietal Cell Atrophy

This specific form of mucosal atrophy is rare and usually associated with erosion. Parietal cells can be decreased in size and number, and remaining cells will appear basophilic and undifferentiated. Reparative epithelial hyperplasia occurs in the foveolar region and may be observed if the lesion is associated with an ulcerative or erosive insult (18).

Mucus Depletion (Figure 6)

Mucus depletion of mucous epithelial cells is associated with ulcerogenic, anti-inflammatory com-

pounds and stress (19). The epithelial cell layer remains intact, but epithelial cells become basophilic and devoid of mucus. Mucous neck cells depleted of mucus may have brightly eosinophilic cytoplasmic mucus inclusions. The latter change may be spontaneous in aged animals or may be compound-induced.

Intestinal Metaplasia (Figures 7-9)

This lesion consists of areas of gastric mucosa morphologically and enzymatically similar to the intestine. The gastric mucosal lining may have crypts and variably developed villi. Goblet cells, paneth cells, and absorptive cells may be present.

Intestinal metaplasia may be classified as complete (having a small intestinal morphology) or incomplete (having a large intestinal morphology), depending on cell types present and tissue morphology. This lesion has been reported in rats treated with polychlorinated biphenols (20), ionizing radiation (21), or iodoacetamine (22). In some of these reports, the animals had intestinal metaplasia associated with gastric neoplasia (20).

Hyperkeratosis

This lesion is characterized by thickening of the keratinized layer of the mucosal epithelium. Epithelial cells are normally differentiated, and there is no cellular atypia. Hyperkeratosis of the non-glandular stomach, as a result of direct irritation, may occur with halogenated pyrroles (13).

Dysplasia

Dysplastic changes are found in the glandular stomach of rats treated with carcinogens (23). Atypical glands extend from the proliferating neck region into the muscularis mucosae. These changes have also been reported with an H₂ receptor antagonist (e.g., tiotidine) in which they were found primarily in the pyloric region and were associated with mucosal erosion (24). This lesion is frequently considered a reactive response to the inciting injurious agent.

Inflammatory and Ulcerative Lesions

Gastritis and Ulceration (Figures 10 & 11)

Inflammatory reactions of the stomach (gastritis) can be catarrhal, hemorrhagic, or purulent. Ulceration may or may not be associated with inflammation. Inflammation and ulceration of the non-glandular stomach and glandular stomach can be spontaneous, a result of gavage errors, or compound related. Age, dietary factors, feeding regimens, and stress are considered potential causes for spontaneously occurring ulcers of the non-glandular stomach (25). Protein restriction or starvation will produce non-glandular stomach ulcers and erosions, and ulcers of the glandular stomach can be induced by bile

acid reflux (26).

Determining the cause of gastric ulceration and inflammation must be done with understanding of the physical nature of the test material. Hyperosmolar solutions of innocuous agents, such as glucose, have been demonstrated to cause erosion and ulceration of the rat gastric mucosa (27). Additionally, synergism between stress and ulcerogenic drugs is established (28).

Miscellaneous Lesions

Eosinophilic Chief Cells (Figure 12)

With this lesion, the cytoplasm of affected cells stain intensely eosinophilic. The cells are distributed throughout the fundic mucosa. This is a species specific alteration that can spontaneously be associated with gastric neoplasia (e.g., lymphoma). It also can be induced by antisecretory compounds such as H₂ antagonists and is reversible (18).

SMALL AND LARGE INTESTINE

Congenital Anomalies

Ectopic Pancreas

In the intestine, ectopic pancreatic tissue is usually located on the mesenteric side of the gut. Typically, normally formed pancreatic acini and islets composed of well-differentiated epithelial or endocrine cells extend from the submucosa through the muscularis into the subserosa. Exocrine acini consist of eosinophilic and basophilic cells. The apices of exocrine cells contain zymogen granules. Islets of Langerhans are composed of pale staining endocrine cells (i.e., alpha cells, beta cells, etc.) on a delicate connective tissue stroma. Endocrine cells can be identified with special histochemical stains (e.g., Gomori's aldehyde fuchsin, Mallory-Azine stains).

Diverticula (Figure 13)

A diverticulum located on the antimesenteric side of the ileum represents a persistent yolk sac. This pouch-like structure in Sprague-Dawley rats corresponds to the Meckel's diverticulum of humans. Diverticula near the mesenteric attachment site found in older animals are a distinct entity. The diverticula of older animals likely represent regions of muscular wall weakness or discontinuity with subsequent herniation of the mucosa. Both types of diverticula are composed of regularly-sized glands and well-differentiated, normochromic cellular elements that help distinguish them from adenomas and well-differentiated adenocarcinomas, which tend to have irregular glands and hyperchromic cells. Histologically, the mucosal lining of diverticula resemble that of the normal intestine. Diver-

ticula may become impacted with intestinal contents, ulcerate, become locally inflamed, and eventually perforate leading to abscess formation and peritonitis.

Squamous Cysts

Inclusion cysts may occur in the large intestine, as in the oral cavity, esophagus, and stomach. They are rare and located in the serosal or subserosal layers.

Degenerative Lesions

Mucosal Mineralization (Figure 14)

Mucosal mineralization in the colon and rectum is usually diffuse and superficially located. Usually no inflammatory reaction is associated with the mineral deposition. The lesion is rare, but can be observed with compounds that decrease peristalsis or cause fecal retention (18).

A spontaneous, genetically-based change specific for some strains of rats is mineralization of the basement membrane. Basement membranes of the mucosa and blood vessels are duplicated, thickened, and mineralized (29).

Osseous Metaplasia (Figure 15)

Osseous metaplasia occurs in old rats in the submucosa or lamina propria and is associated with chronic inflammation, ulceration, and regenerative hyperplasia. These osseous spicules must be differentiated from osteoid formations in the stroma of intestinal neoplasms.

Villous/Mucosal Atrophy (Figure 16)

Villous atrophy is shortening of small intestinal villi with mucosal thinning and has been observed with a number of compounds and conditions that decrease cellular proliferation (30,31). Adhesions between adjacent villi result in markedly flattened, thick villi. Depending on the agent inducing the change, epithelial cells will vary morphologically from flattened cuboidal to vacuolated columnar. A decrease in the size and number of mucosal crypts of the large intestine occurs with ulcerogenic agents and chronic inflammation. Intestinal mucosal atrophy may also be induced by the anticholesterolemic agent triparanol (32). In the small intestine, paneth cell hypertrophy and hyperplasia may be present, while in the large intestine, cryptal depletion and loss are common.

Mucosal Hypertrophy

In the small intestinal mucosa, villous hypertrophy may be observed in lactating rats (33) or animals exposed to alloxan (34) or polychlorinated aromatics. Villous hypertrophy may also be induced by hyperthyroidism or thyromimetic drugs and conditions of thyroid hyperplasia

(35). Mucosal and submucosal thickness are increased, probably secondary to hyperthyroidism. Colonic epithelial cell hyperplasia is a rare sequela to ulcerative changes and is characterized by increased mitotic activity.

Paneth Cell Metaplasia

Metaplastic paneth cells can be found in the large intestine following epithelial damage and chronic inflammation.

Mucosal Lipidosis

Vacuolation of epithelial cells resulting from lipid accumulation has been observed with administration of puromycin, ethionine, tetracyclines, erythromycin esters, and glucose transport inhibitors (36,37). In the small intestine, lipid droplets are usually seen in the apical portion of epithelial cells of the upper third of the villus. Lipid material may be transported from the epithelial cells to the lamina propria and coalesce in macrophages or be free in the interstitial spaces.

Mucosal Phospholipidosis (Figure 17)

This is a specific form of mucosal lipidosis. Multilaminated lysosomes occur in mucosal epithelial cells and mesenteric lymph nodes after exposure to some amphiphilic drugs, such as amiodarone (38). The lamina propria contains foamy macrophages as well.

Inflammatory and Ulcerative Lesions

Enteritis, Colitis, Typhlitis, and Ulceration (Figures 18 & 19)

The histologic appearance of ulcerative and inflammatory lesions in the intestines (enteritis), colon (colitis), and cecum (typhlitis) are usually a mixture of necrosis with acute and chronic inflammation. With ulcerative lesions, pyogranulomatous inflammatory reactions are usual. In chronic enteritis and colitis, lymphoid hyperplasia may be accompanied by other inflammatory cell infiltration. Inflammation and ulceration of the intestine can be the direct effects of antimetabolic or radiomimetic agents. A synergistic effect can occur with compounds that depress the immune system and permit the infection of pathogenic microbes (39). Cellular debris, fibrin, bacteria, and/or food material can be trapped in the mucosal defect, enhancing the inflammatory response.

As a result of laboratory conditions, inflammatory lesions of the intestines resulting from infectious diseases are not frequently observed. Bacterial infections of the intestine include *Clostridium piliformis* (enteritis), *Salmonella* spp. (typhlitis and enteritis), and *Campylobacter*-like organisms (enteritis) (40). Protozoal agents may also be observed, but are not associated with

a primary intestinal disease. Similarly, nematodes (*Syphacia muris* and *Aspicularis tetraptera*) may be present in the large intestine without an accompanying inflammatory reaction.

Arteritis

Lesion of arteritis (formerly referred to as polyarteritis nodosa) can be present in the muscular arterioles of the tunica muscularis and the subserosa. The arteriole wall is thickened by acute or chronic inflammatory cells and the vascular lumen is compressed by fibrous tissue. The incidence of this lesion varies with season and strain of rat (for further discussion, refer to the monograph on the cardiovascular system).

Miscellaneous Lesions

Megaloileitis/Cecomegaly/Megacolon

Dilatation of specific segments of the alimentary canal is observed spontaneously or as a result of compound exposure (41). Megaloileitis may be observed with *C. piliformis* infection (42). Megacolon may be observed after large doses of chlorpromazine (41), in which there is no relationship to obstruction, or with calcium antagonist exposure, in which constipation may be the cause (43). Cecomegaly is observed in response to some antibiotics, starches, polyols, lactose, and some fibers (44).

DISCUSSION

The mucosal lining of the alimentary canal serves as a robust yet delicate boundary between the environment and internal tissues. When perturbed, this relatively thin (25–75 μm) barrier rapidly deteriorates, allowing the internal tissues to be exposed to foreign material and an ensuing inflammatory reaction. A unique feature of the alimentary canal is its ability to resist the toxic effect of some orally administered compounds that are highly toxic to other organ systems (e.g., CCl_4). Yet, damage to the alimentary canal mucosal lining occurs with a wide variety of compounds and circumstances and this damage can be influenced by the basal diet fed at the time of chemical exposure (45).

Adaptive cytoprotection is a phenomenon observed in rats exposed to mild gastric irritants (46). In such animals, minimal epithelial changes are induced in early exposure to the compound, but are replaced by normal epithelial cells that are resistant to subsequent and possibly more severe injury. Adaptive cytoprotection is mediated by a number of cytokines, blood flow, and other responsive elements of the alimentary canal (e.g., rapid cell proliferation) (4). This potent adaptive and regenerative potential can account for the

presence of alimentary canal damage being observed in short-term assays and interim sacrifices, but not in long-term studies (17).

Ulceration of the mucosa in the upper alimentary canal (proximal to the ileum) can occur with the administration of many compounds, including hyperosmolar liquids, acidic and alkaline solutions, bile salts, antihistamines (H₂ blockers), sulfites, surfactants, triparanol, BHA, and nonsteroidal anti-inflammatory compounds (4,27,31,32,46-51).

The distinction between erosion and ulcer is that in erosion, mucosal damage does not extend through the muscularis mucosa and in ulcer, it does. Erosions generally have less inflammatory reaction than do ulcers. Chronic ulcers are associated with substantial amounts of fibrous connective tissue deposition that can ultimately replace the normal mucosa. There are many morphological combinations of ulcerative and inflammatory lesions in both the stomach and intestines. In control animals, spontaneously occurring ulcerative and inflammatory lesions are more common in the stomach than intestines. Ulcerative inflammatory lesions of the large intestine, including cecum, are usually treatment related. In the absence of ulcers, the presence of acid hematin pigment in the mucosa is suggestive of an ulcerative or erosive process not in the plane of histologic section.

A primary concern when interpreting alterations in the alimentary canal is making a distinction between non-proliferative lesions that are compound-induced and those that are the result of spontaneous disease, secondary toxic effects, or poor tissue preparation. A number of normal luminal constituents (e.g., microorganisms and food material) and environmental agents (e.g., pathogenic microorganisms and contaminants in the feed or water) cause non-proliferative lesions similar to those associated with many alimentary canal toxicants. This similarity is not only the result of the limited number of responses observed in the alimentary canal, but also the synergism that exists between an ingested compound and the normal luminal constituents.

Differentiation between compound-related and spontaneous lesions of the alimentary canal can be done by evaluating anatomic location, incidence among treatment groups, and gross and microscopic morphology of observed lesions. Gavage accidents are usually recognized based on experimental design, number of animals involved, and characteristics of the lesion. Malocclusive disorders that result in alimentary lesions are readily visible at necropsy. Finally, there may be a limited inflammatory response associated with most compounds that cause damage in this region of the digestive tract. A minimal inflammatory response is the result of the limited number of bacteria in this area and the rapid transit of food material. If the inflammatory response is severe, a diligent search for food material

and pathogenic microorganisms should be done. Chemically-induced erosion, ulceration, and inflammation are less frequently encountered in the intestines than in the stomach. Nonsteroidal anti-inflammatory drugs can produce ulcerative changes in the small and large intestine.

The differentiation between compound-related spontaneous and secondary lesions in the distal small intestine and large intestine is more arduous. This difficulty is primarily the result of the high number of normal bacteria in the alimentary canal lumen and the similarity of the lesions induced by pathogenic bacteria and those caused by chemical injury. Distinguishing these lesions is best accomplished by routine diagnostic microbiology and the identification of the pathogen in the lesion site. If a chemically-induced lesion is infected by pathogenic bacteria, it may not be possible to distinguish between these two etiologies. However, tissue changes in other organs may aid in separating a spontaneous disease, such as Tyzzer's disease, from a toxicologic lesion.

Interpretation of alimentary canal alterations can be further confounded by failure to properly preserve the tissues, which undergo rapid autolysis. The differentiation of compound-induced erosions from artifacts resulting from poor fixation can present a significant diagnostic challenge. However, two key features of induced lesions that may aid the diagnostic process are the presence of an inflammatory response that occurs within a short time (minutes to hours) after the true erosive insult occurs and the rapid appearance (minutes) of flattened epithelial cells at the margin of the erosion or ulcer (52). These will be absent in autolyzed tissue.

Selection of the proper fixative is important for special stains commonly used to evaluate gastrointestinal pathology. Although 10% NB formalin can be used for Periodic Acid-Schiff's (PAS), Alcian Blue, and the high iron diamine stains, these stains for mucus also work well on tissues fixed in Carnoy's fixative or 10% NBF with 2% calcium acetate.

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

A. Congenital Ectopias

Ectopic Sebaceous Glands

1. Found in oral cavity
2. Composed of normal holocrine secretory adenomeres

3. Stem cells located near basement membrane
4. Differentiated cells accumulate lipid, become pyknotic, and die

Ectopic Pancreas

1. Found in the stomach
2. Composed of normal exocrine adenomeres
3. May have normal islets of Langerhans

Ectopic Liver

1. Generally found in small intestine or stomach
2. Composed of normal hepatocytes arranged in cords or nests
3. Cells are polyhedral, have distinct boundaries and centrally located vesiculated nuclei and large nucleoli
4. Binucleate cells may be observed
5. Located primarily in lamina propria or in submucosa

B. Diverticula

Congenital

1. Duct-like sacculated structure located on antimesenteric side of ileum
2. Mucosa is histologically similar to that of the adjacent intestine
3. Villi lined by normal columnar epithelium

Acquired

1. Found randomly throughout intestinal tract
2. Juxtaposed submucosa and muscular layer are thin or absent
3. May extend through muscular layers to serosa
4. Normal or thin mucosal lining

C. Cysts

Squamous Cysts

1. Keratinized stratified squamous epithelium
2. Mucous cells occasionally present
3. Extend into submucosa/tunica muscularis
4. Lumen frequently contains keratinized material

Glandular Cysts

1. Found in glandular mucosa of stomach and intestines
2. Lined by cuboidal to flattened epithelial cells
3. Chief, parietal, and mucous cells may line cysts in the stomach
4. May be surrounded by fibrosis and a chronic inflammatory cell infiltrate
5. Lumen may contain mucus

D. Atrophy

Mucosal Atrophy

1. Decreased mucosal thickness
2. The number and size of remaining epithelial cells may be decreased
3. Cysts in atrophic glands
4. Decreased villous length (small intestine)
5. Bridging or fusion of villi (villous atrophy)
6. Decreased crypt depth (small and large intestine)

Chief Cell Atrophy

1. Specific form of mucosal atrophy
2. Chief cells are cuboidal and flattened
3. Remaining cells are decreased in size and number

Parietal Cell Atrophy

1. Specific form of mucosal atrophy
2. Parietal cells can be decreased in size and number
3. Remaining parietal cells are basophilic and undifferentiated

E. Mucosal Hypertrophy

1. Mucosal thickness is increased
2. Epithelial lining is composed of normal cells
3. Mucosal glands and villi are increased in length
4. Villi may be wide
5. Submucosa and muscular layers are variably increased in thickness

F. Dysplasia

1. Distorted mucosal glands with arborescent and twisted shape
2. Epithelial cells may be basophilic and lack mucus
3. Goblet cells variably present
4. Frequently associated with an ulcerative and inflammatory process

G. Erosion

1. Loss of mucosal epithelial cells with intact muscularis mucosa
2. Inflammatory cells may be present in associated blood vessels, lamina propria, area of tissue loss, and in adjacent epithelial layer
3. Epithelial cells adjacent to area of tissue loss may be necrotic, cuboidal to flat, or basophilic

H. Mucus Depletion

1. Intact epithelial cell layer
2. Mucus containing epithelial cells have basophilic cytoplasm and have a cuboidal shape
3. Epithelial cells lack the normally clear apical cytoplasm (mucus)

I. Hyperkeratosis

1. Most commonly found in oral cavity, esophagus, and non-glandular stomach
2. Thickening of keratinized layer of mucosal epithelium

3. Epithelial cells are normally differentiated
4. No cellular atypia

J. Parakeratosis

1. Most commonly found in oral cavity, esophagus, and non-glandular stomach
2. Mucosal layer is thickened
3. Epithelial cells on mucosal surface retain nuclei

K. Vacuolation of Squamous Epithelium

1. Superficial epithelial cells have a pale staining, vacuolated cytoplasm
2. Associated mucosa may be ulcerated and epithelial cells may be degenerate or necrotic

L. Mineralization

1. Mineralization may be found in muscle layers, blood vessels, basement membrane, mucosa, or submucosa of the alimentary canal
2. Deposits of mineral (e.g., calcium) are focal aggregates or concretions that may stain intensely blue with H&E stains
3. Associated mucosal glands may be cystic
4. Lamina propria may contain edema and fibroplasia
5. Adjacent epithelial cells may be atrophic or degenerate

M. Osseous Metaplasia

1. Bone tissue in lamina propria or submucosa
2. No cellular atypia
3. Frequently associated with inflammatory process
4. Bone matrix is variably mineralized

N. Mucosal Lipidosis

1. Vacuolated enterocysts line the mucosa
2. Vacuoles are lipid containing, located in apical portions of the cells, and are clear multilocular or multilaminar
3. Lipid material may be found in cells of lamina propria and regional lymph nodes
4. A specific form of mucosal lipidosis is mucosal phospholipidosis, characterized by multilaminated lysosomes in mucosal epithelial cells and mesenteric lymph nodes

O. Ulceration

1. Extension of tissue loss through muscularis mucosa or into submucosa
2. Epithelial cells are necrotic, cuboidal, or flattened
3. Hemorrhage and edema in submucosa is common
4. Fibrosis frequently occurs at base of ulcer
5. Adjacent mucosa may be thickened and may be dysplastic with hyperplasia of adjacent epithelium

P. Intestinal Metaplasia

1. Occurs in gastric mucosa
2. Abundant mucin containing cells resembling intestinal epithelial cells
3. Gastric mucosal lining may have crypts and variably developed villi
4. Goblet cells, paneth cells, and absorptive cells may be present

Q. Inflammation

Acute

1. Inflammatory cellular accumulation in superficial mucosa, submucosa, or muscularis mucosa
2. Inflammatory cells include neutrophils, lymphocytes, and occasional macrophages
3. Epithelial cell degeneration or loss
4. Hemorrhage variably present in walls and on luminal surface

Chronic

1. Inflammatory cells are macrophages, plasma cells, lymphocytes, and fewer neutrophils
2. Adjacent mucosal tissue replaced with fibrous tissue and atrophic mucosal crypts/glands or regenerative/hyperplastic epithelium

Granulomatous

1. Macrophage replacement of resident lymphocytes in lamina propria
2. Macrophages may be foamy or vacuolated
3. Intact or ulcerated epithelial lining
4. Lamina propria fibrosis variably present
5. Atrophy of mucosa

R. Stenosis

1. Can occur at any location along the alimentary canal
2. Luminal diameter is reduced
3. Associated alimentary wall is fibrotic and may be chronically inflamed
4. Lumen proximal to stenosis may be ectatic

S. Megaesophagus/Megaloileitis/Megacolon/Cecomegaly

1. Tissue enlargement and luminal dilatation
2. Mucosa, submucosa, and tunica muscularis are thin
3. Degeneration of muscle fibers and ganglia cells in nerve plexus

T. Esophageal Impaction

1. Esophageal dilatation by food or bedding
2. Muscle layers of esophageal wall are thin
3. Myocyte vacuolation and swelling
4. Myofibril fragmentation

U. Eosinophilic Chief Cells

1. Eosinophilic chief cells are distributed throughout the fundic mucosa
2. Variable percentage of chief cells will be affected
3. Cytoplasm of affected cells is intensely eosinophilic

V. Pigmentation of Oral Cavity

1. Normal histologic character of oral tissues and cells
2. Increased numbers or size of normal melanocytes
3. Melanocytes located in mucosa and/or submucosa

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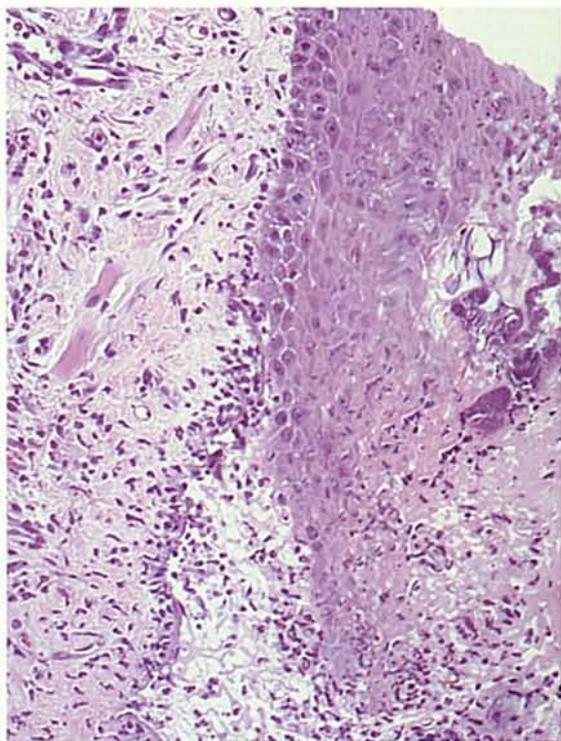


Fig. 1 – Acute inflammation, cleft formation adjacent to ulcer (not in photomicrograph); oral cavity (H&E).

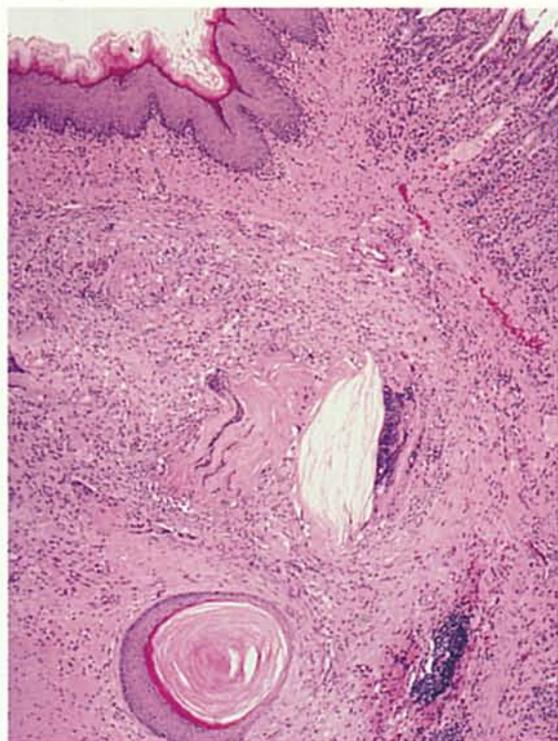


Fig. 2 – Squamous cyst; stomach (H&E).

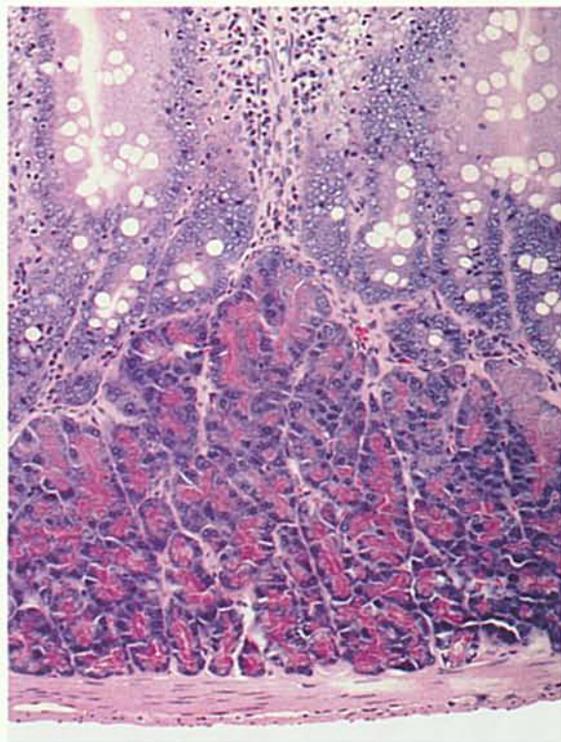


Fig. 3 – Ectopic pancreas; small intestine (H&E).

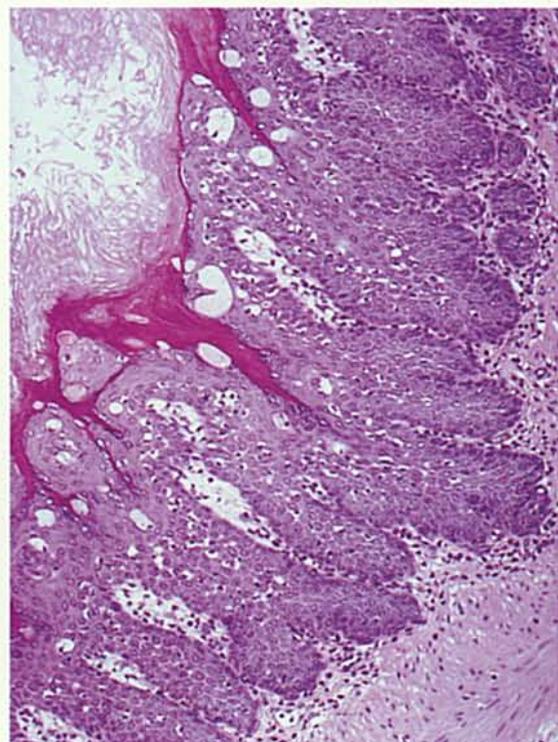


Fig. 4 – Vacuolation of squamous epithelium, hyperplasia, and hyperkeratosis; non-glandular stomach (H&E).

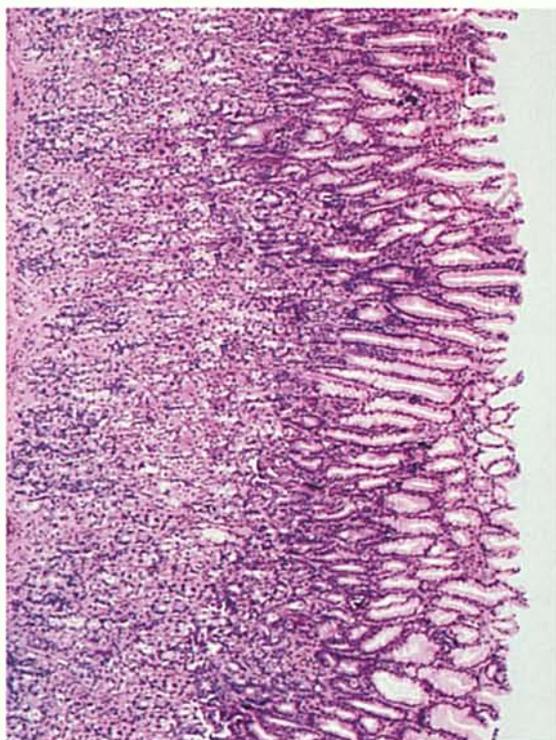


Fig. 5 – Mineralization of gastric mucosa (multiple foci); glandular stomach (H&E).



Fig. 6 – Mucus depletion in foveolar epithelial cells; glandular stomach (H&E).



Fig. 7 – Multiple foci of intestinal metaplasia; glandular stomach (H&E).

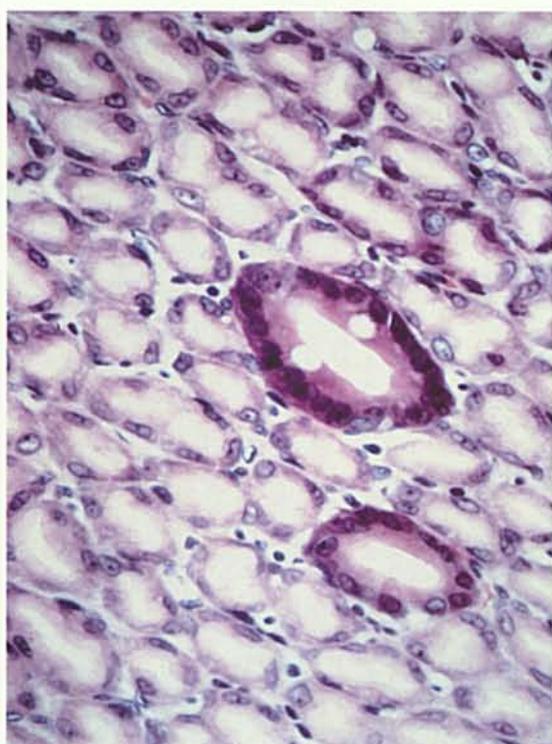


Fig. 8 – Intestinal metaplasia; glandular stomach (PAS).



Fig. 9 – Intestinal metaplasia; glandular stomach (Alcian Blue).



Fig. 10 – Ulcer, mucosal proliferation, and chronic inflammation; glandular stomach (H&E).

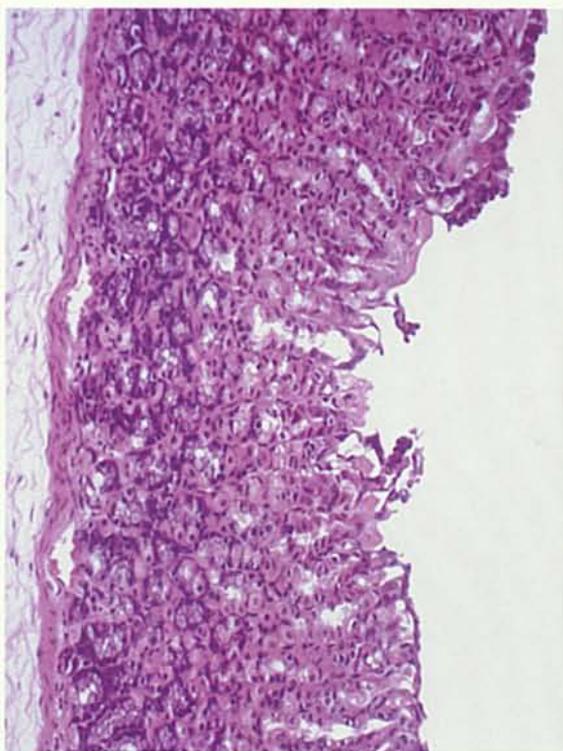


Fig. 11 – Erosion; glandular stomach (H&E).

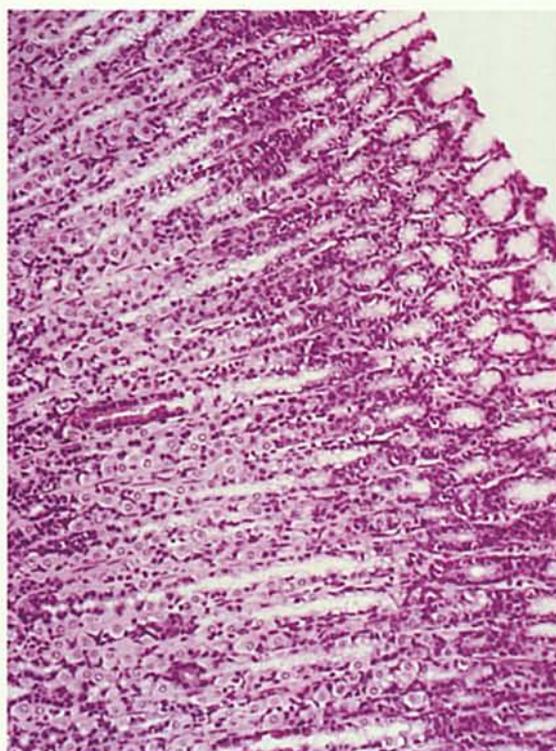


Fig. 12 – Eosinophilic chief cells in mucosal glands; glandular stomach (H&E).

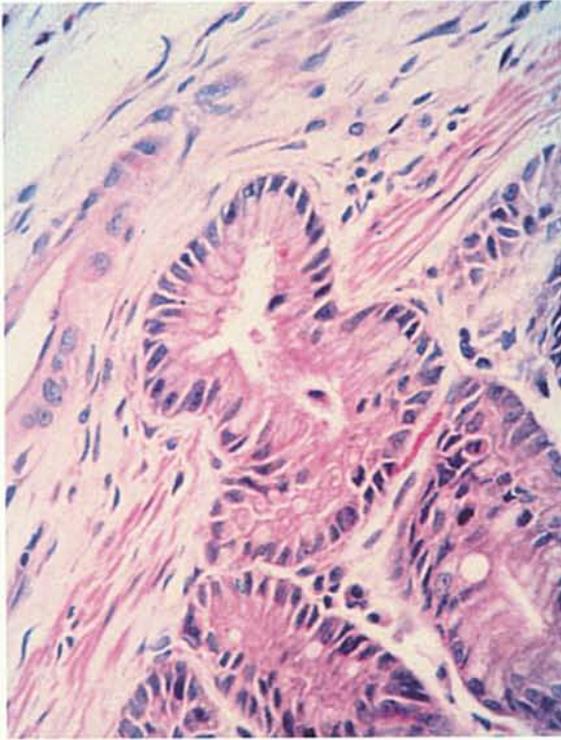


Fig. 13 – Diverticula with mucosal gland herniation; colon (H&E).

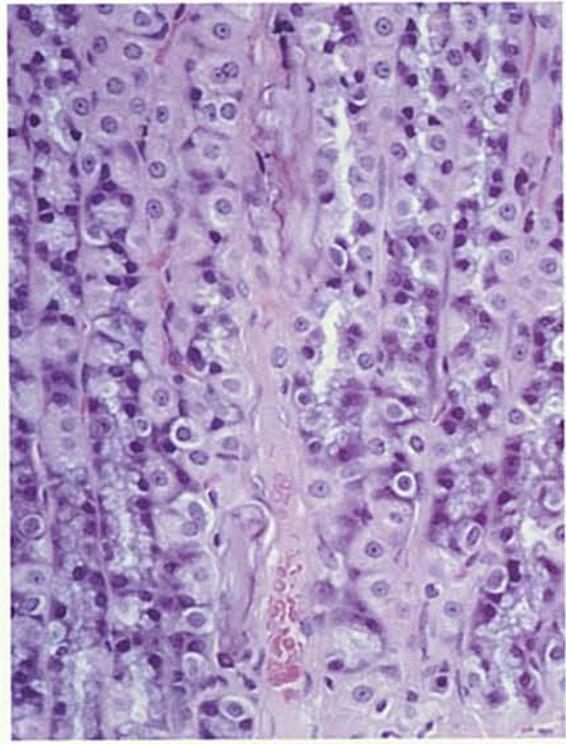


Fig. 14 – Basement membrane mineralization; glandular stomach (H&E).

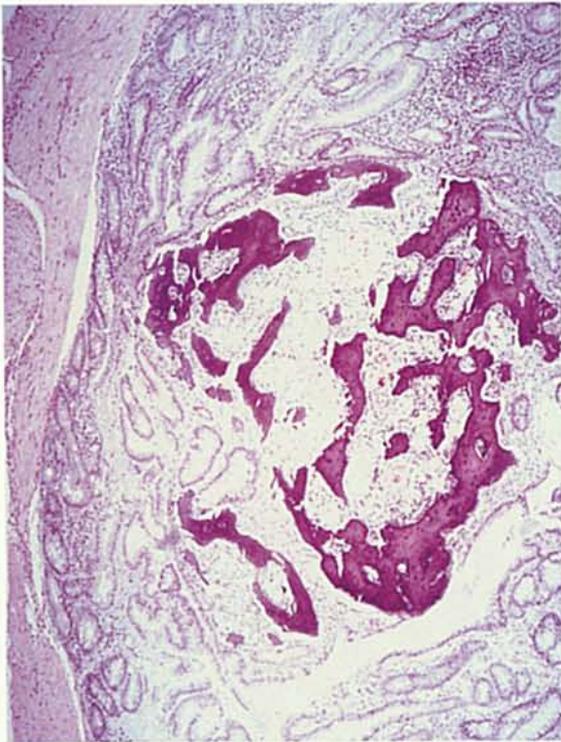


Fig. 15 – Osseous metaplasia; small intestine (H&E).

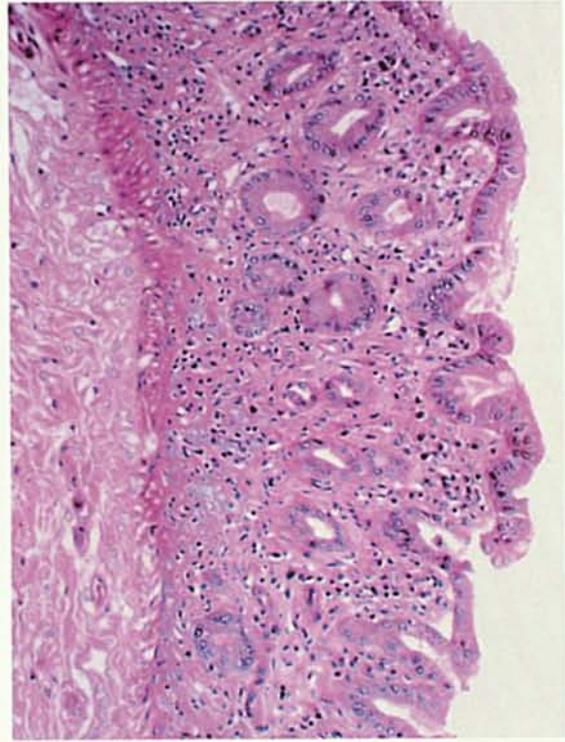


Fig. 16 – Chronic mucosal inflammation and atrophy; colon (H&E).

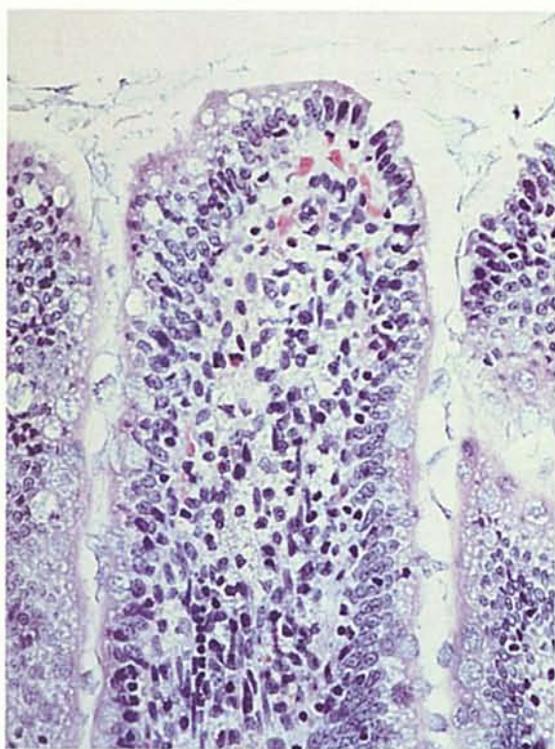


Fig. 17 – Phospholipidosis, a specific form of mucosal lipidosis; small intestine (H&E).

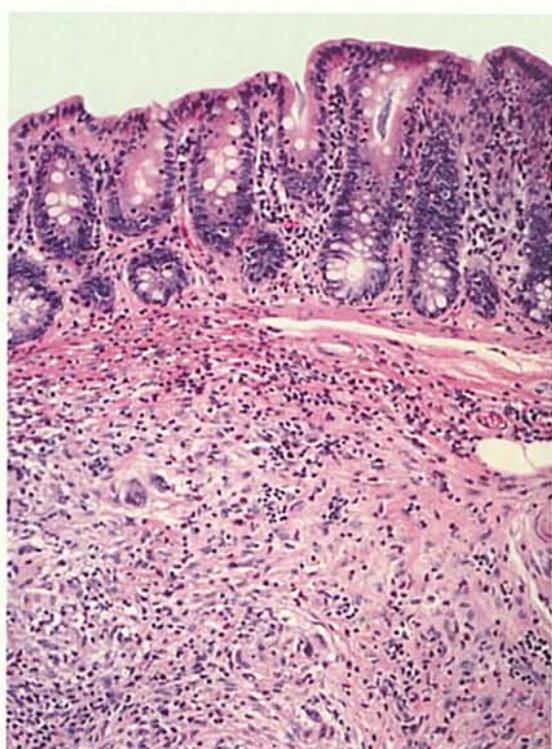


Fig. 18 – Chronic inflammation; colon (H&E).



Fig. 19 – Superficial mucosal necrosis with little inflammatory response; colon (H&E).