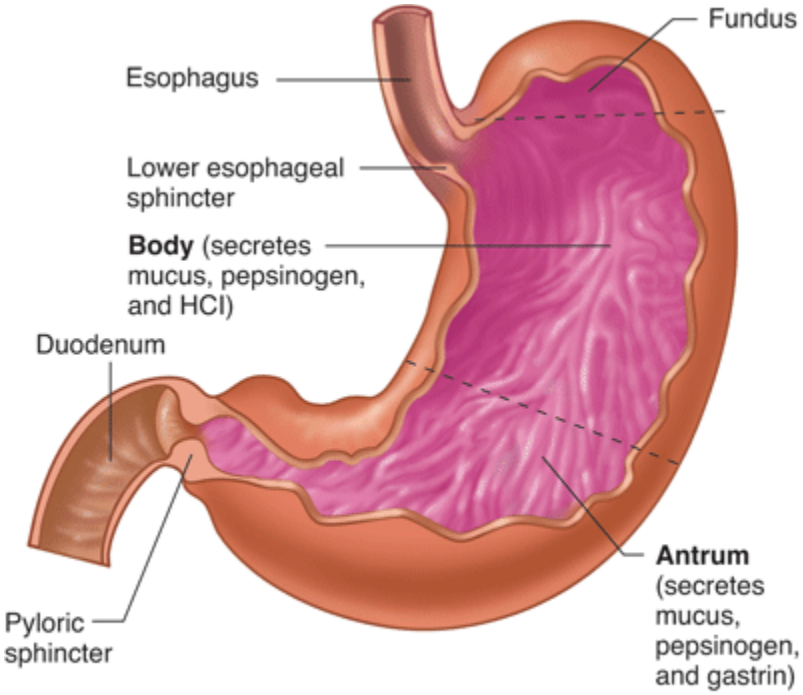
DISORDERS OF THE STOMACH

Kenneth Alonso, MD, FACP

Anatomy

- The pancreas, spleen, diaphragm, left adrenal (suprarenal) gland and the left kidney form the stomach bed and lie posterior to the stomach.
- The transverse colon lies inferior to the stomach.
- The first portion of the duodenum alone is covered by peritoneum.
- The 2nd portion of the duodenum receives the bile duct and pancreatic duct.
- The stomach, 1st and 2nd portions of the duodenum, pancreas, and liver receive their innervation from T6-T9; the spleen, T6-T8.

Anatomy



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

The principal secretions of the body and antrum are listed in parentheses.

(Reproduced with permission from Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology: The Mechanisms of Body Function*, 11th ed. McGraw-Hill, 2008.)

Fig. 26-4 Accessed 08/01/2010

Anatomy

- The ligament of Treitz is the suspensory muscle of the duodenum. Skeletal muscle from diaphragm and smooth muscle from duodenum.
- Contraction widens angle of the duodenal jejunal flexure.
- Divides the upper GI tract from the lower GI tract.
- The 3rd portion of the duodenum courses posterior to the superior mesenteric vessels. The 4th part ascends.

Anatomy

- The epiploic foramen is a space that communicates between the peritoneal cavity and the omental bursa.
- It is bounded by the caudate lobe of the liver and the first part of the duodenum.
- Posteriorly the inferior vena cava bounds the space.
- Anteriorly, the hepatoduodenal ligament (containing bile duct, hepatic artery, and portal vein) bounds the space. The ligament is derived from the lesser omentum.

Anatomy

- The celiac artery is the first unpaired visceral branch of the abdominal aorta. Gives rise to the left gastric, common hepatic, and splenic arteries.
- The left gastric artery supplies the left half of the lesser curvature of the stomach.
- The right gastric artery arises from the hepatic artery and supplies the right half of the lesser curvature of the stomach.

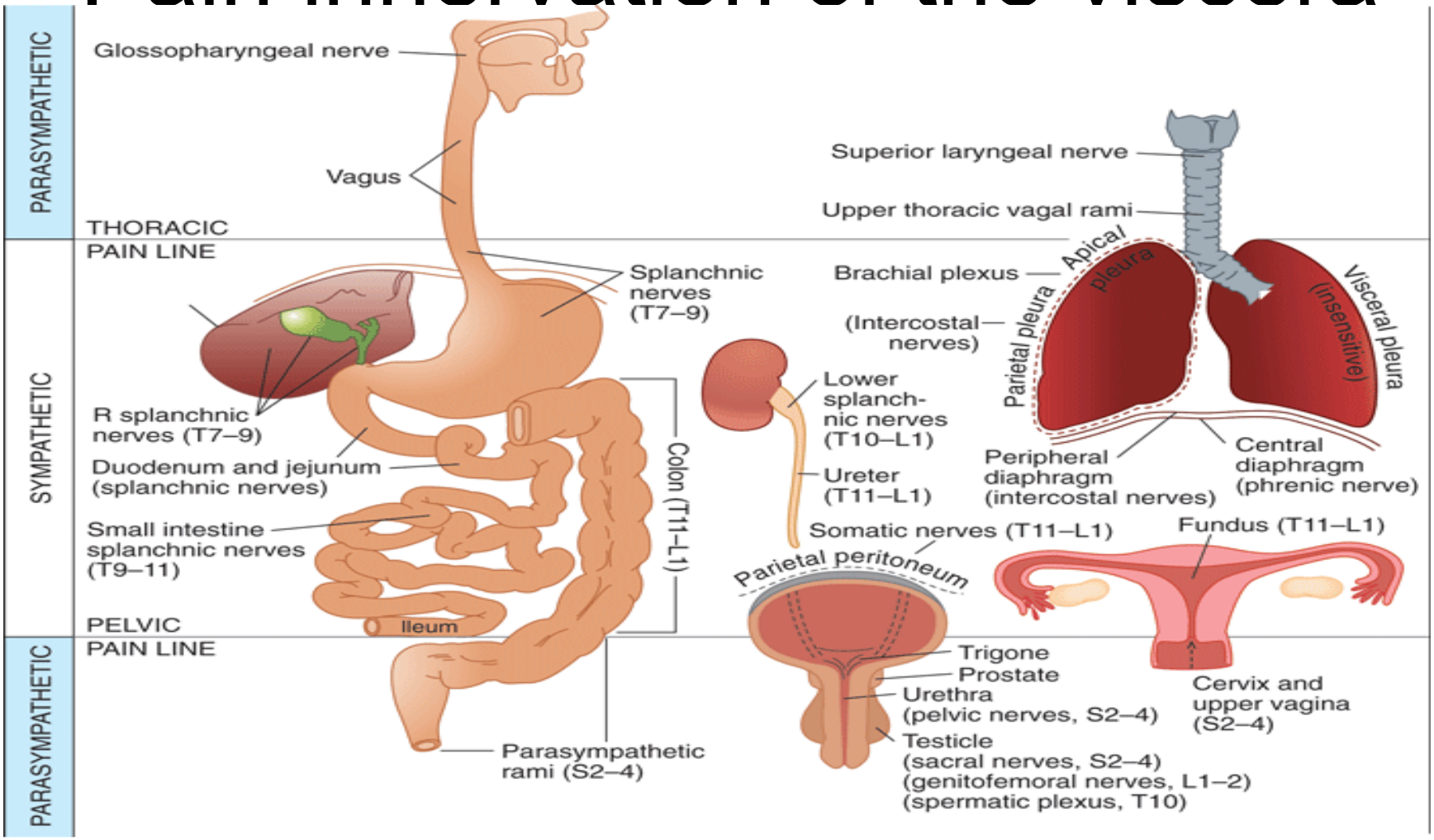
Anatomy

- The left gastro-epiploic artery arises from the splenic artery and supplies the left half of the greater curvature of the stomach.
- The right gastro-epiploic artery arises off the gastroduodenal artery and supplies the right half of the greater curvature of the stomach.
- The short gastric arteries arise from the splenic artery and supply the fundus of the stomach.
- Venous drainage directly to portal vein.

Anatomy

- Pain afferents (general visceral afferent) travel with sympathetic to the level of preganglionic origin.
- Referred pain is perceived at the level of preganglionics.
- The stomach, 1st and 2nd portions of the duodenum, pancreas, and liver receive their innervation from T6-T9; the spleen, T6-T8.
- The 3rd and 4th portions of the duodenum and the small intestine receive their innervation from T8-T12.
- Kidneys and adrenal are innervated from T10-L1.

Pain innervation of the viscera



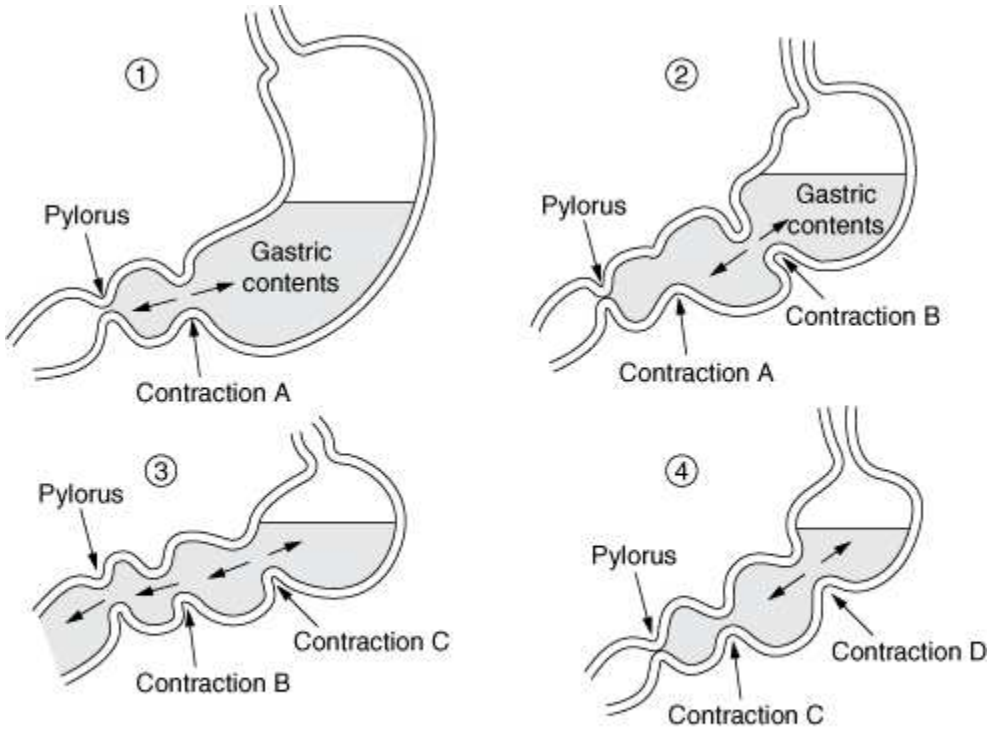
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(After White JC. Reproduced with permission from Ruch TC: In *Physiology and Biophysics,* 19th ed. Ruch TC, Patton HD (editors). Saunders, 1965.) Fig. 10-2 Accessed 07/01/2010

Chapman's reflex points

- Smooth, firm, discretely palpable nodules 2-3mm in diameter located within deep fascia or on the periosteum of a bone.
- May represent viscerosomatic reflexes (empirical evidence only)
- T4 to the base and left of the spinous process is associated with hyperacidity of the stomach
- T5 to the base and left of the spinous process is associated with peristalsis abnormality
- T8 to the base and right of the transverse process is associated with somatic dysfunction of the pylorus

Gastric motility



Source: Barrett KE: *Gastrointestinal Physiology*:
http://www.accessmedicine.com

Fig. 8-5 Accessed 02/01/2010

Gastric pacemaker at midpoint of wall of greater curvature

Circular muscle bands are not well developed until the antrum is approached.

Gastric emptying

- Peristalsis directs food from the esophagous to the stomach.
- The lower esophageal sphincter relaxes (resting pressure, 20 mmHg). Proximal stomach receptively relaxes.
- The stomach contracts 3-5/minute.
- Vagal stimulation increases frequency
- Sympathetic stimulation (celiac plexus) decreases frequency
- Every 90-120 minutes while fasting, the stomach and small intestine contract in sequence (migrating motility complex, mediated by motilin, produced by enterochromaffin cells).

Gastric emptying

- Delay gastric emptying
- Hypotonic or hypertonic food
- Low duodenal pH
- Release of cholecystokinin in response to a lipid meal.
- Gastrin is released in response to stomach distention.
- Later, to presence of protein in the duodenum.

Gastric emptying

- Inhibit gastric secretion as food passes into intestine:
- Secretin
- Somatostatin
- Gastric inhibitory peptide
- Vasoactive intestinal peptide

Gastric emptying

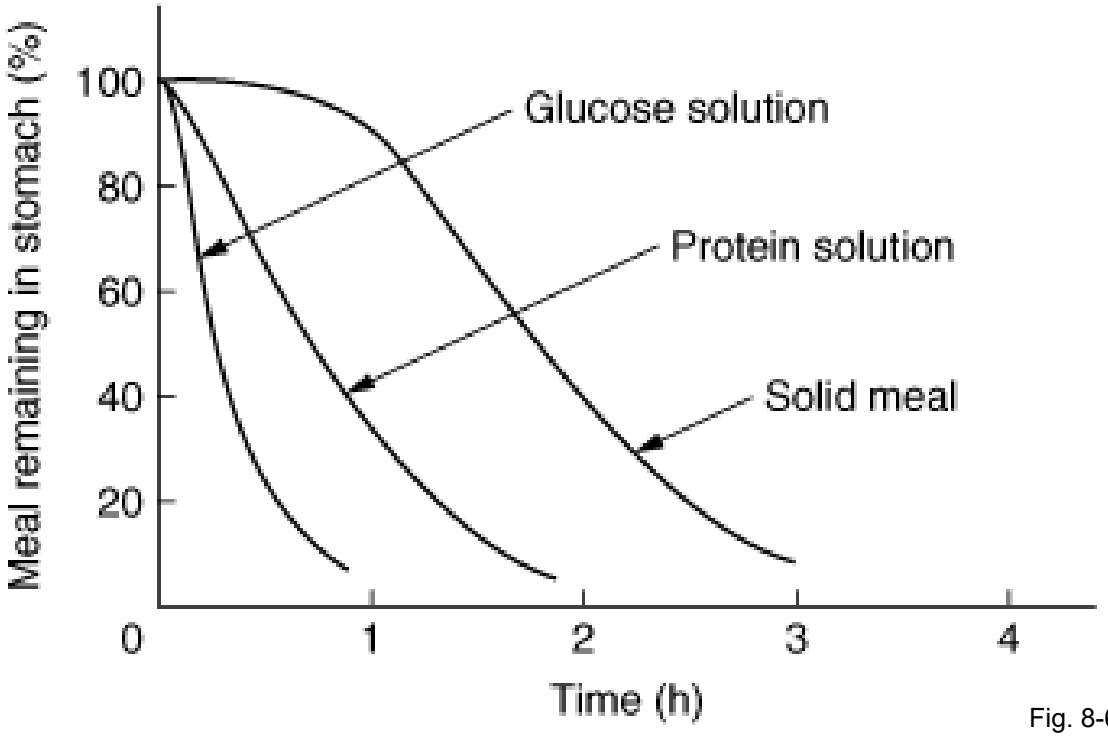
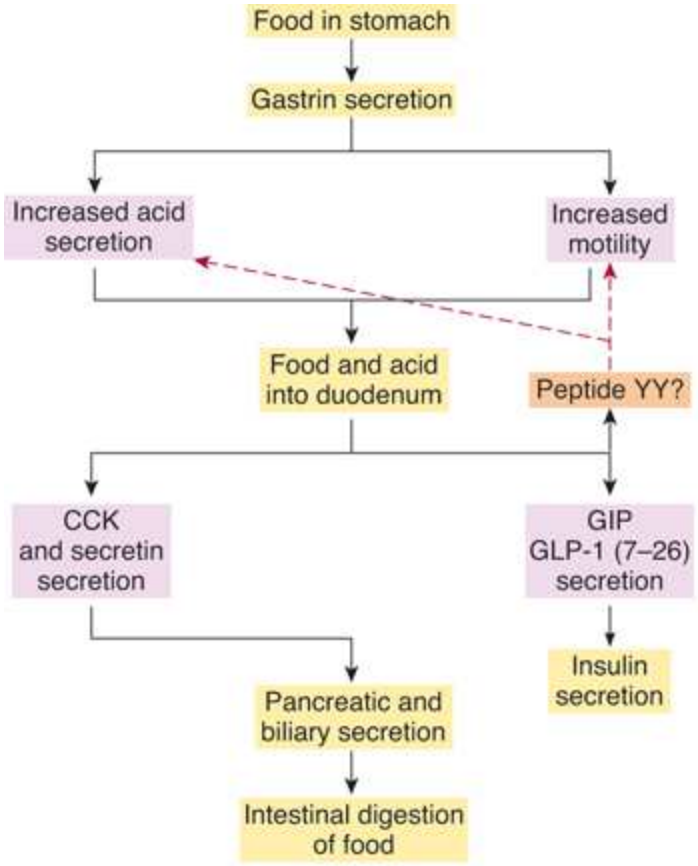


Fig. 8-6 Accessed 02/01/2010

Neurohormonal control of digestion

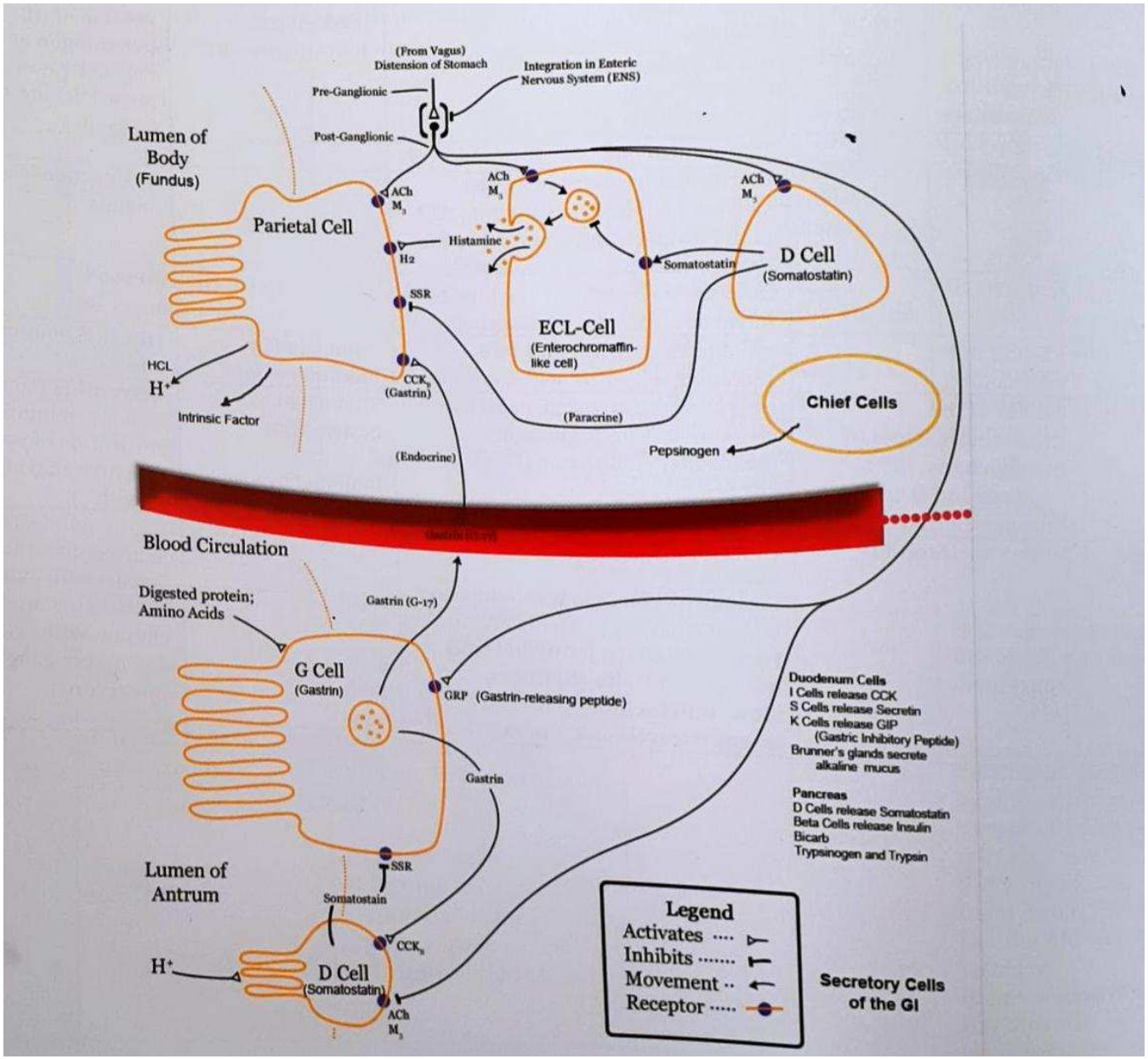


Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 26-23 Accessed 02/01/2010

Gastroparesis

- Manifests as diminished motility with early satiety and bloating after feeding.
- Autonomic neuropathy
- Diabetes mellitus
- Responds to metoclopramide (prokinetic agent).


(From Vagus)
Distension of Stomach
Integration in Enteric
Nervous System (ENS)
Pre-Ganglionic
Post-Ganglionic
Lumen of
Body
(Fundus)
Parietal Cell
ACh
M3
Histamine
H2
SSR
HCL
H+
Intrinsic Factor
CCK2
(Gastrin)
ECL-Cell
(Enterochromaffin-
like cell)
Somatostatin
D Cell
(Somatostatin)
(Paracrine)
Chief Cells
Pepsinogen
(Endocrine)
Blood Circulation
Digested protein;
Amino Acids
Gastrin (G-17)
G Cell
(Gastrin)
GRP (Gastrin-releasing peptide)
Gastrin
Lumen of
Antrum
Somatostain
CCK2
D Cell
(Somatostatin)
Duodenum Cells
I Cells release CCK
S Cells release Secretin
K Cells release GIP
(Gastric Inhibitory Peptide)
Brunner's glands secrete
alkaline mucus
Pancreas
D Cells release Somatostatin
Beta Cells release Insulin
Bicarb
Trypsinogen and Trypsin
Legend
Activates ....
Inhibits .....
Movement ..
Receptor .....
Secretory Cells
of the GI

Gastrin

- Produced by G cells in the antrum of the stomach as well as in pancreatic islets.
- Stimulates enterochromaffin-like cells to secrete histamine
- Stimulates chief cells to produce pepsinogen
- Stimulates parietal cells to produce acid.

Cholecystokinin

- Produced by I cells in the duodenum and jejunum.
- Stimulates pancreatic enzyme secretion
- Gallbladder contraction
- Relaxation of the sphincter of Oddi
- Cholecystokinin serves to coordinate nutrient delivery to match intestinal capacity.
- Secretin inhibits cholecystokinin.

Somatostatin

- Produced by D cells in the duodenum and intestinal mucosa as well as in pancreatic islets (δ cells).
- Inhibits
- Gastric acid and pepsinogen secretion
- Pancreatic and small intestine fluid secretion
- Gallbladder contraction
- Insulin and glucagon release.
- Inhibited by vagal action.

Gastric inhibitory peptide

- Produced by K cells of the duodenum and jejunum.
- Stimulates insulin release
- Inhibits gastric acid secretion.

Secretin

- Produced by S cells in the crypts of Lieberkühn.
- Stimulates pancreatic bicarbonate secretion
- Stimulates production of bile by the liver.
- Inhibits cholecystokinin

Vasoactive intestinal peptide

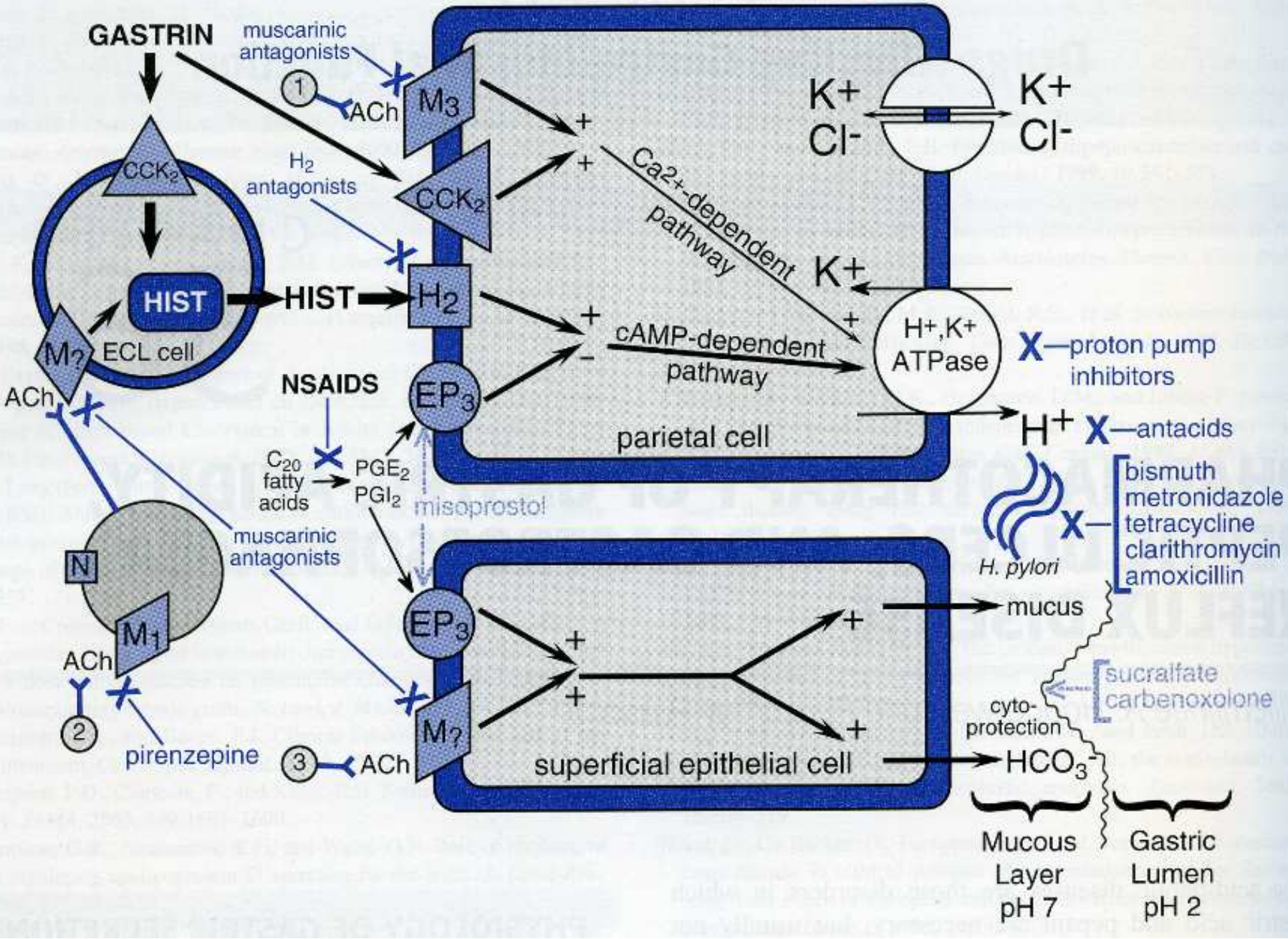
- Produced by enteric neurons and in the pancreas.
- Vagal activation.
- Stimulates smooth muscle relaxation
- Stimulates intestinal water and pancreatic bicarbonate secretion.
- G-protein coupled adenyl cyclase activation.

Pancreatic polypeptide

- Produced by F cells in the small intestine as well as in pancreatic islets.
- Inhibits the release of pancreatic secretions.

Acid production

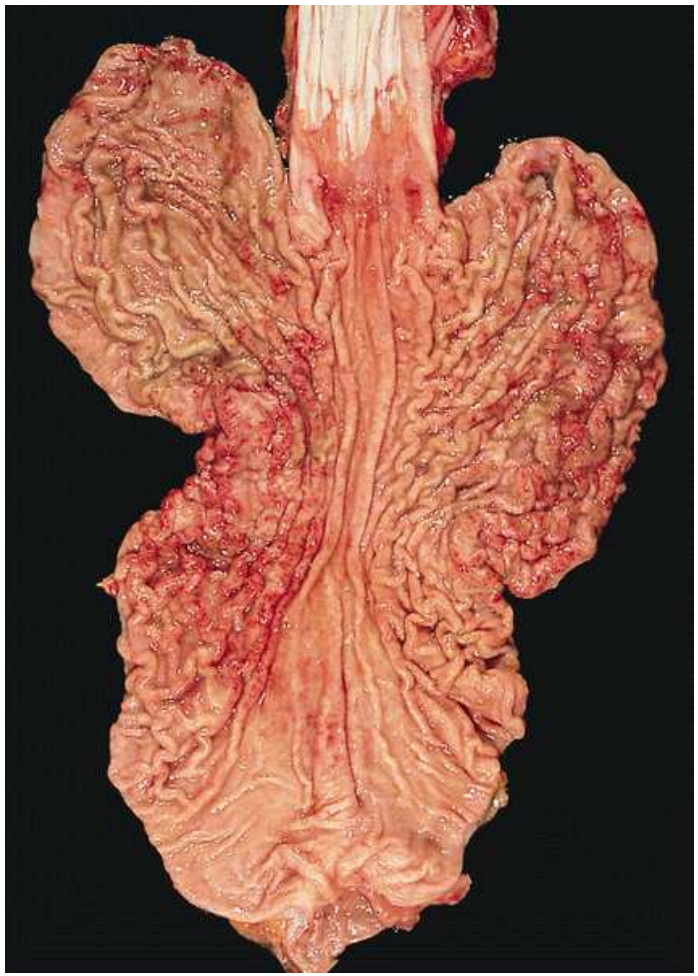
- Gastrin (via cholecystokinin B receptor) increases adenyl cyclase to stimulate H^+ production by parietal cells.
- Vagal stimulation leads to acetylcholine release (muscarinic 3 receptor) and increases adenyl cyclase to stimulate H^+ production by parietal cells.
- Histamine (histamine 2 receptor) increases cAMP, stimulating H^+ production by parietal cells.
- Secretion of hydrochloric acid by the parietal cells is an active process that uses ATP and takes place against a steep concentration gradient.


GASTRIN
muscarinic antagonists
1
ACh
M3
CCK2
H2 antagonists
CCK2
HIST
HIST
H2
M? ECL cell
ACh
NSAIDS
EP3
C20 fatty acids
PGE2
PGI2
misoprostol
parietal cell
K+
Cl-
K+
Cl-
Ca2+-dependent pathway
K+
cAMP-dependent pathway
H+,K+ ATPase
X—proton pump inhibitors
H+
X—antacids
H. pylori
X—
bismuth
metronidazole
tetracycline
clarithromycin
amoxicillin
mucus
sucralfate
carbenoxolone
cyto-protection
HCO3-
N
M1
ACh
2
pirenzepine
muscarinic antagonists
EP3
M?
3
ACh
superficial epithelial cell
Mucous Layer pH 7
Gastric Lumen pH 2

Digestion

- Hydrochloric acid activates pepsinogen and provides a pH for optimal enzyme function.
- Bile acids emulsify ingested water insoluble neutral fats, preventing coalescence in the bowel lumen, permitting hydrolysis by lipases.

Stomach



Mucosal view of a whole stomach opened along the greater curvature with the esophagus at the top.

The parallel folds in the middle of the specimen run along the lesser curvature.

The two wings at either side are the fundus. The entire fundus and body are covered by thick, often serpentine, folds or rugae. They flatten distally in the antrum.

The bulge at the bottom is the pyloric sphincter.

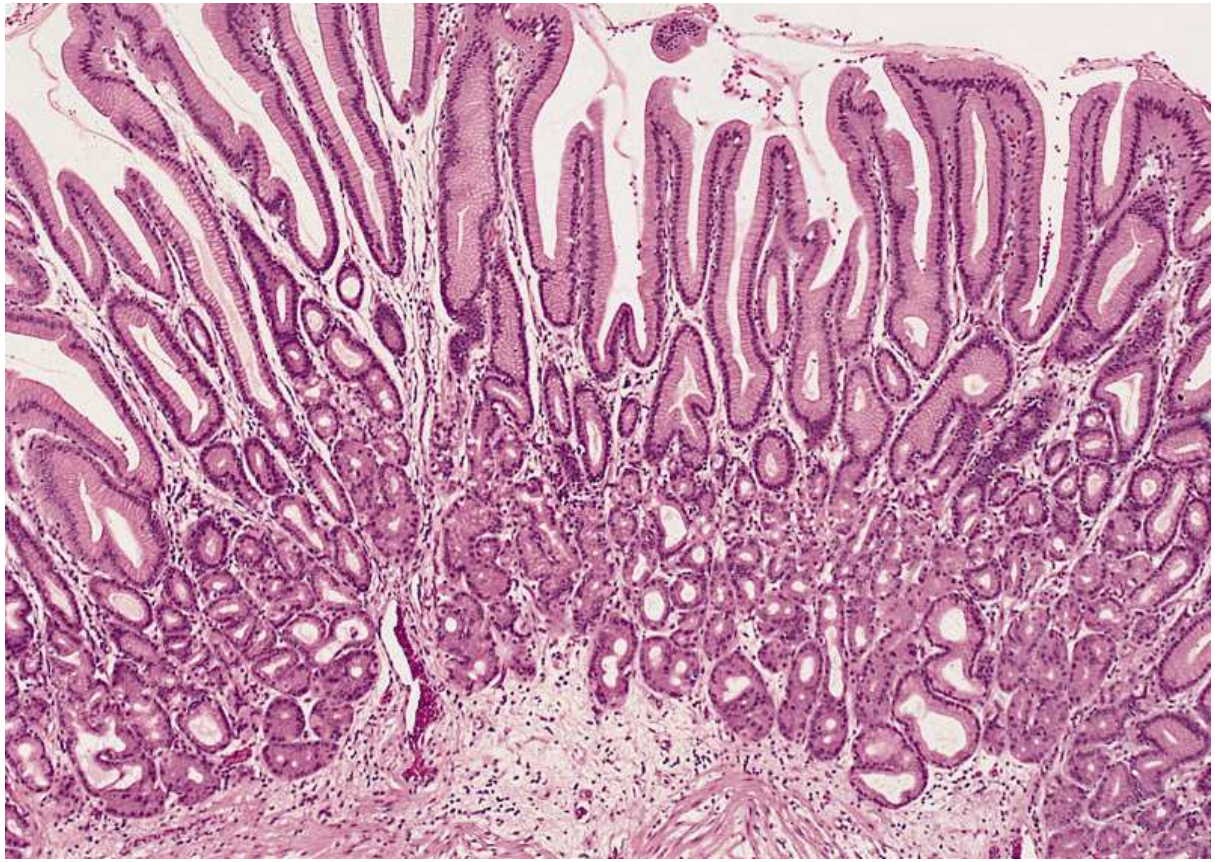
Fig. 8-2

Lewin, KJ, Appelman, HD., "Tumors of the esophagus and stomach." Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Stomach

- Mucosal surface totally replaced every 2-6 days.
- Only mucous glands are found in the cardia.
- Mucous cells populate the glands of the cardia and antral regions and secrete mucus and pepsinogen II.
- The mucous neck cells in the glands of the body and fundus secrete mucus as well as group I and II pepsinogens.
- Antral or pyloric glands contain mucus-secreting cells and endocrine cells.

Stomach (cardia)

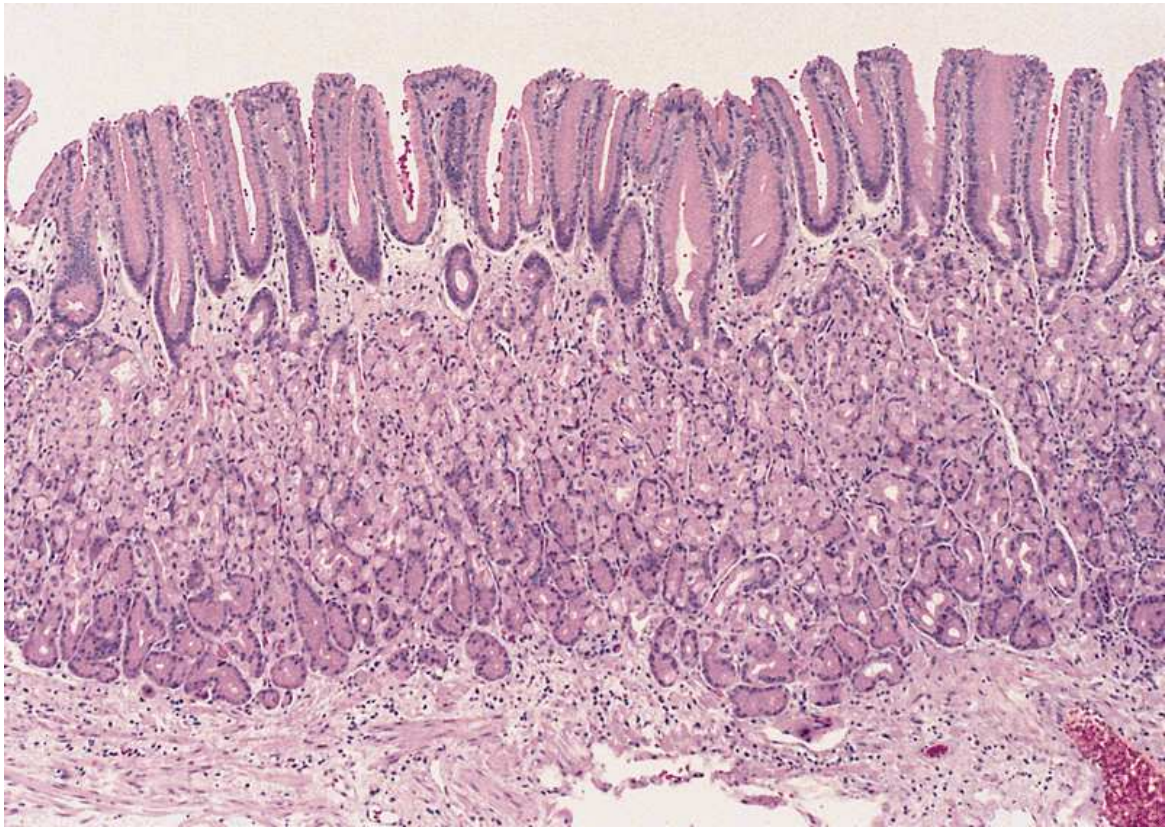


The pit and the glandular compartments in cardiac mucosa are approximately equal in height. Scattered glands are dilated.

Fig. 8-4

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Stomach (fundus)

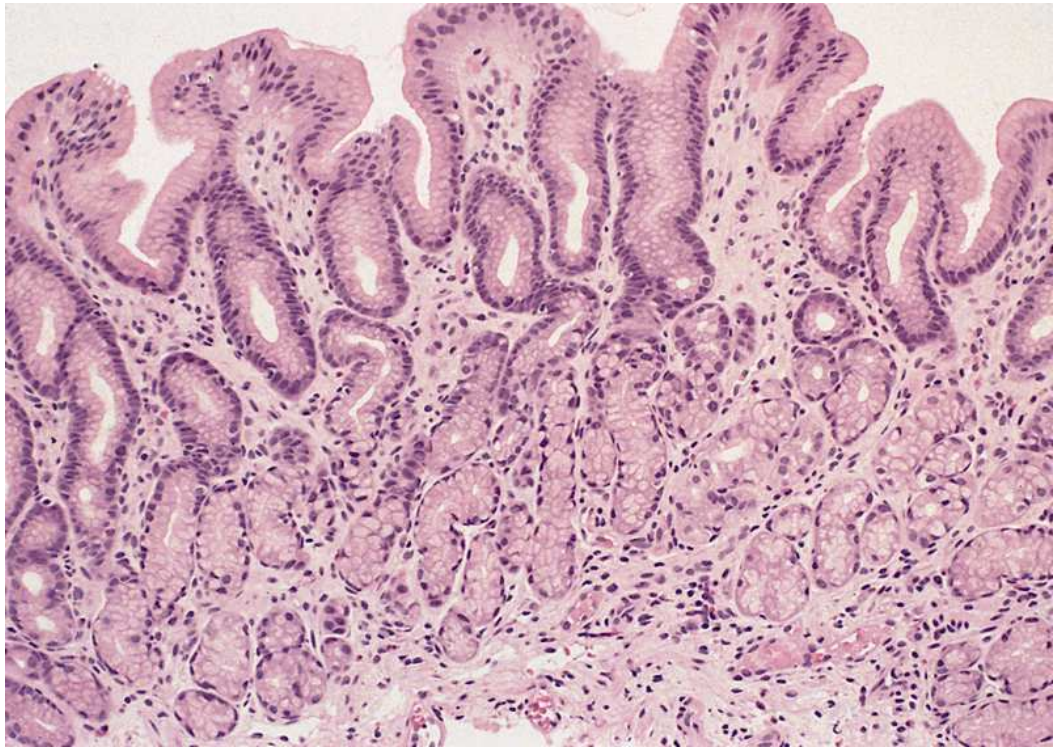


The pit compartment is about one fourth of the entire mucosal thickness in the fundus (body), resulting in a pit to gland ratio of 1 to 3. The glands are tightly clustered. The superficial lamina propria has few cells.

Fig. 8-5

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Stomach (antrum)



The pit and glandular compartments are about the same height in the antrum. The glands are clustered and less densely packed than are the body glands.

Fig. 8-6

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Stomach

- Oxyntic (acid producing) glands
- Found in the fundus and body
- Contain parietal cells, chief cells, and scattered endocrine cells.
- Parietal cells line predominantly the upper half of the oxyntic glands in the fundus and body.
- Stain eosinophilic attributable to their abundant mitochondria.
- The apical membrane of the parietal cell is invaginated, forming an extensive intracellular canalicular system complete with microvilli.

Stomach

- In the resting state, vesicles that contain the proton pump (H^+-K^+-ATPase) lie in close approximation to the canalicular system.
- Within minutes of parietal cell stimulation, the vesicles fuse with the canalicular system, creating an apically directed acid-secreting membrane of enormous surface area.
- Parietal cells also secrete intrinsic factor, which binds luminal vitamin B_{12} in the duodenum and permits its absorption in the ileum.

Stomach

- Chief cells
- Concentrated more at the base of gastric glands
- Responsible for the secretion of the proteolytic proenzymes pepsinogen I and II.
- Released by exocytosis
- Chief cells are notable for their basophilic cytoplasm.
- Possess an extensive rough endoplasmic reticulum, a prominent supranuclear Golgi apparatus, and numerous apical secretory granules.
- Pepsinogens are activated to pepsin by acid pH (and deactivated by a pH>6.0).

Stomach

- Endocrine or entero-endocrine cells are scattered among the epithelial cells of gastric and antral glands.
- Cytoplasm contain brightly eosinophilic granules concentrated on the basal aspect of the cell.
- Can act in an endocrine mode, releasing their products into the circulation,
- Can act in a paracrine mode, via secretion into the local tissue.
- In the antral mucosa, most of the endocrine cells are the gastrin-producing cells, or G cells.
- Other enterochromaffin-like cells in the gastric mucosa include X cells.

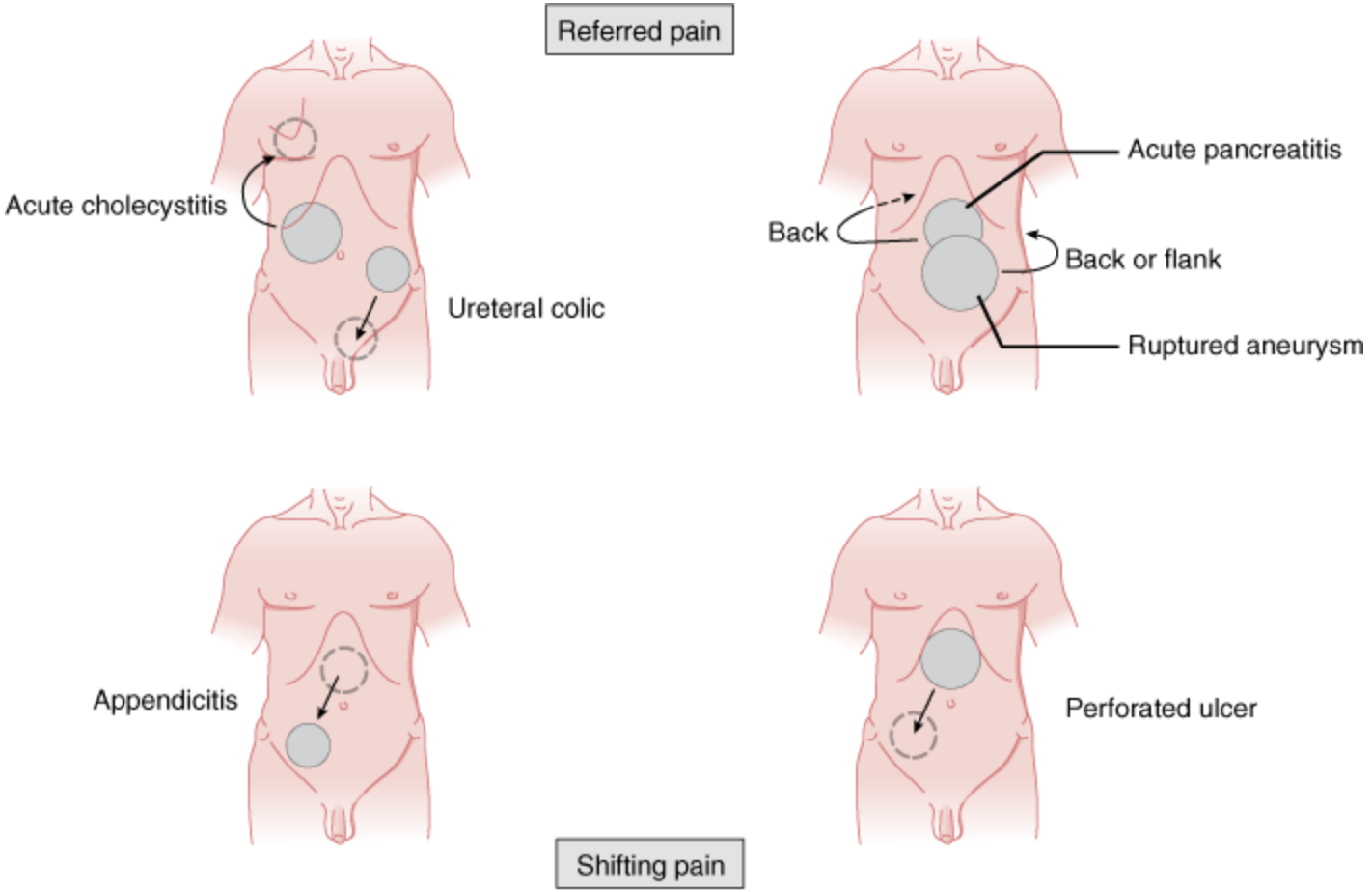
Dieulafoy lesion

- Caused by a submucosal artery that does not branch properly within the wall of the stomach.
- This results in a mucosal artery with a diameter of up to 3 mm, or 10 times the size of mucosal capillaries.
- Dieulafoy lesions are most commonly found along the lesser curvature, near the gastroesophageal junction.
- Erosion of the overlying epithelium can cause gastric bleeding that, while usually self-limited, can be copious.

Gastric antral vascular ectasia

- GAVE is responsible for 4% of non-variceal upper gastrointestinal bleeding.
- It can be recognized endoscopically as longitudinal stripes of edematous erythematous mucosa that alternate with less severely injured, paler mucosa
- Watermelon stomach
- Histologically, the antral mucosa shows reactive gastropathy with dilated capillaries containing fibrin thrombi.

Referred abdominal pain



Source: Gerard M. Doherty: *CURRENT Diagnosis & Treatment: Surgery, 13th Edition*: http://www.accessmedicine.com

Fig. 21-2
Accessed 07/30/2010

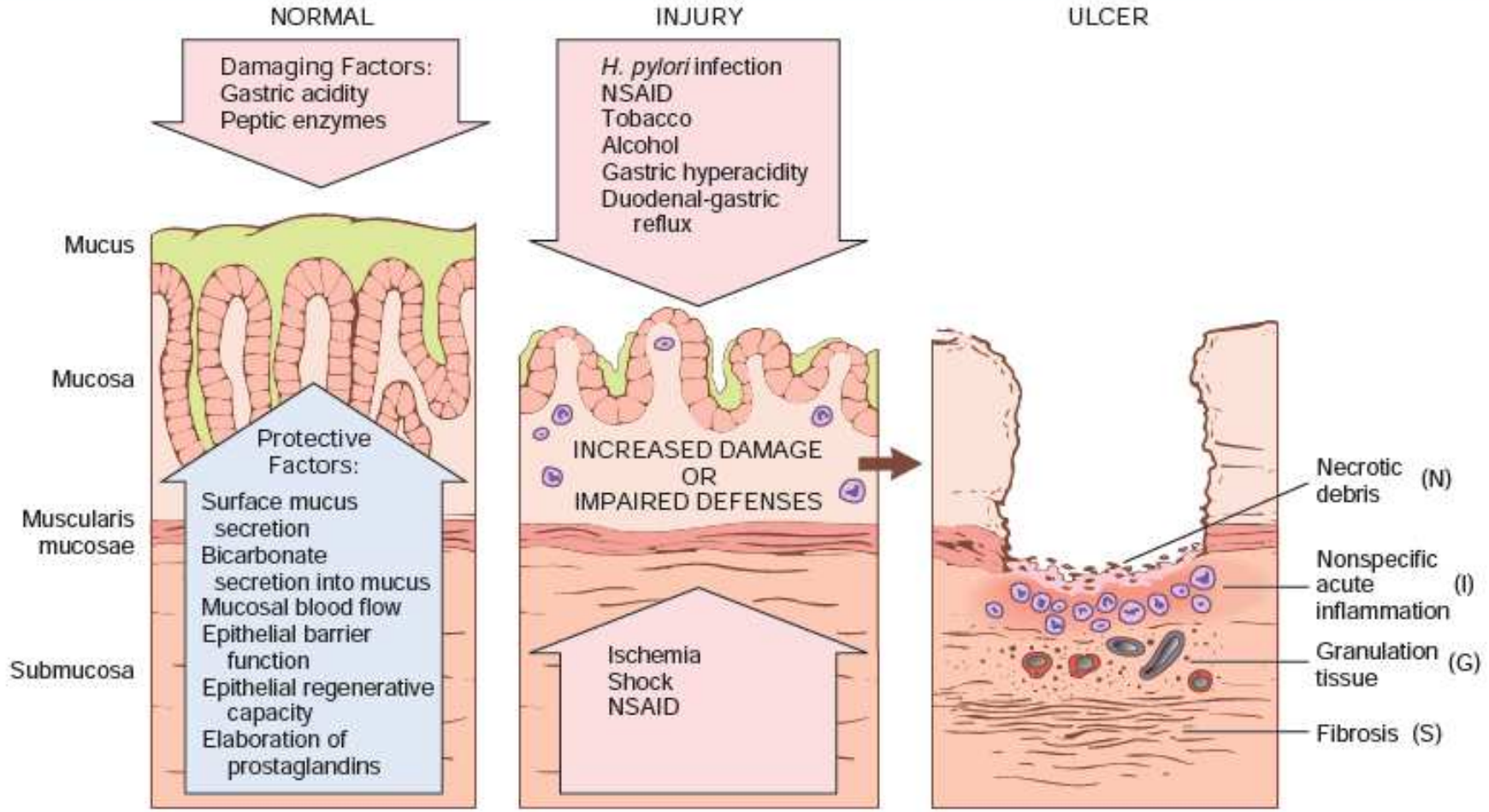


Figure 17-11 Mechanisms of gastric injury and protection. This diagram illustrates the progression from more mild forms of injury to ulceration that may occur with acute or chronic gastritis. Ulcers include layers of necrosis (N), inflammation (I), and granulation tissue (G), but a fibrotic scar (S), which takes time to develop, is only present in chronic lesions.

Mucosal barrier

- The thin layer of surface mucus in the stomach and duodenum exhibits a diffusion coefficient for H^+ that is one quarter that of water.
- Acid and pepsin-containing fluid exits the gastric glands as "jets" passing through the surface mucus layer
- Enter the lumen directly without contacting surface epithelial cells.
- Surface epithelial cells in both the stomach and duodenum secrete bicarbonate into the boundary zone of adherent mucus, creating an essentially pH-neutral microenvironment immediately adjacent to the cell surface.

Mucosal barrier

- Intercellular tight junctions provide a barrier to the back-diffusion of H^+.
- Epithelial disruption is followed rapidly by migration of existing cells along the exposed basement membrane to fill in the defects and restore epithelial barrier integrity. (restitution)
- The rich mucosal blood supply provides removes back-diffused acid.

Mucosal barrier

- Complete replacement of the surface foveolar cells every 3 to 7 days is essential for both the maintenance of the epithelial layer and the secretion of mucus and bicarbonate from these cells.
- In acid-secreting parts of the stomach, a capillary “alkaline tide” is generated as parietal cells secrete hydrochloric acid into the gastric lumen and bicarbonate into the vessels.

Mucosal barrier

- Prostaglandins are produced by mucous cells.
- They favor production of mucus and HCO_3^-, and they inhibit acid secretion by parietal cells.
- Prostaglandins E and I improve mucosal blood flow through promotion of vasodilatation.
- Drugs that block prostaglandin synthesis reduce this cytoprotection and thus promote gastric mucosal injury and ulceration.

Acute gastritis

- The surface epithelium is intact, and scattered neutrophils are present among the surface epithelial cells or within the epithelial layer and lumen of mucosal glands.
- Foveolar cell hyperplasia, with characteristic corkscrew profiles and epithelial proliferation are typically present.
- Lamina propria exhibits only moderate edema and slight vascular congestion.

Acute gastritis

- The presence of neutrophils above the basement membrane within the epithelial space is abnormal and signifies active inflammation.
- With more severe mucosal damage, loss of the superficial epithelium and punctate mucosal hemorrhage develop.
- It is accompanied by a pronounced mucosal neutrophilic infiltrate and a fibrin-containing purulent exudate in the lumen.
- The mucosal defect (erosion) does not cross the muscularis mucosa.
- Concurrent erosion and hemorrhage is termed acute erosive hemorrhagic gastritis

Stress ulcers

- More than 75% of critically ill patients develop endoscopically visible gastric lesions during the first 3 days of their illness.
- Curling ulcers are stress ulcers occurring in the proximal duodenum and associated with severe burns or trauma.
- Cushing ulcers are stress ulcers of esophagous, stomach, or duodenum associated with increased intracranial pressure.
- Prone to perforation.

Stress ulcers

- Unlike peptic ulcers, which arise in the setting of chronic injury, acute stress ulcers are found anywhere in the stomach and are most often multiple.
- Microscopically, acute stress ulcers are sharply demarcated, with essentially normal adjacent mucosa. There may be a suffusion of blood into the mucosa and submucosa and an associated inflammatory reaction.
- Conspicuously absent are the scarring and blood vessel thickenings that characterize chronic peptic ulcers.
- Heal spontaneously.

Pathogenesis

- The pathogenesis of stress-related gastric mucosal injury is most often related to local ischemia.
- May be due to systemic hypotension or reduced blood flow caused by stress-induced splanchnic vasoconstriction.
- Upregulation of inducible NO synthase and increased release of the vasoconstrictor endothelin-1 also contribute to ischemic gastric mucosal injury
- Lesions associated with intracranial injury are thought to be caused by direct stimulation of vagal nuclei, which causes hypersecretion of gastric acid.

Table 17-2 Characteristics of *Helicobacter pylori*–Associated and Autoimmune Gastritis

	H. pylori–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to decreased	Increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, MALToma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease

Chronic gastritis

- Type A involves body and fundus.
- Spares the antrum and pylorus.
- 10% of cases
- 80% demonstrate autoantibodies to components of gastric gland parietal cells (including antibodies against the acid-producing enzyme H^+,K^+-ATPase, gastrin receptor, and intrinsic factor).
- Loss of acid production.
- Neuroendocrine hyperplasia.
- Cannot activate pepsinogen to release Vitamin B_{12} (pernicious anemia)

Chronic gastritis

- Increased gastrin production.
- Chronic mucosal inflammatory changes leading eventually to mucosal atrophy and intestinal metaplasia, usually in the absence of erosions.
- Significant risk for developing gastric carcinoma and endocrine tumors (carcinoid tumor).
- 45% have Celiac disease (lymphomatous gastritis)

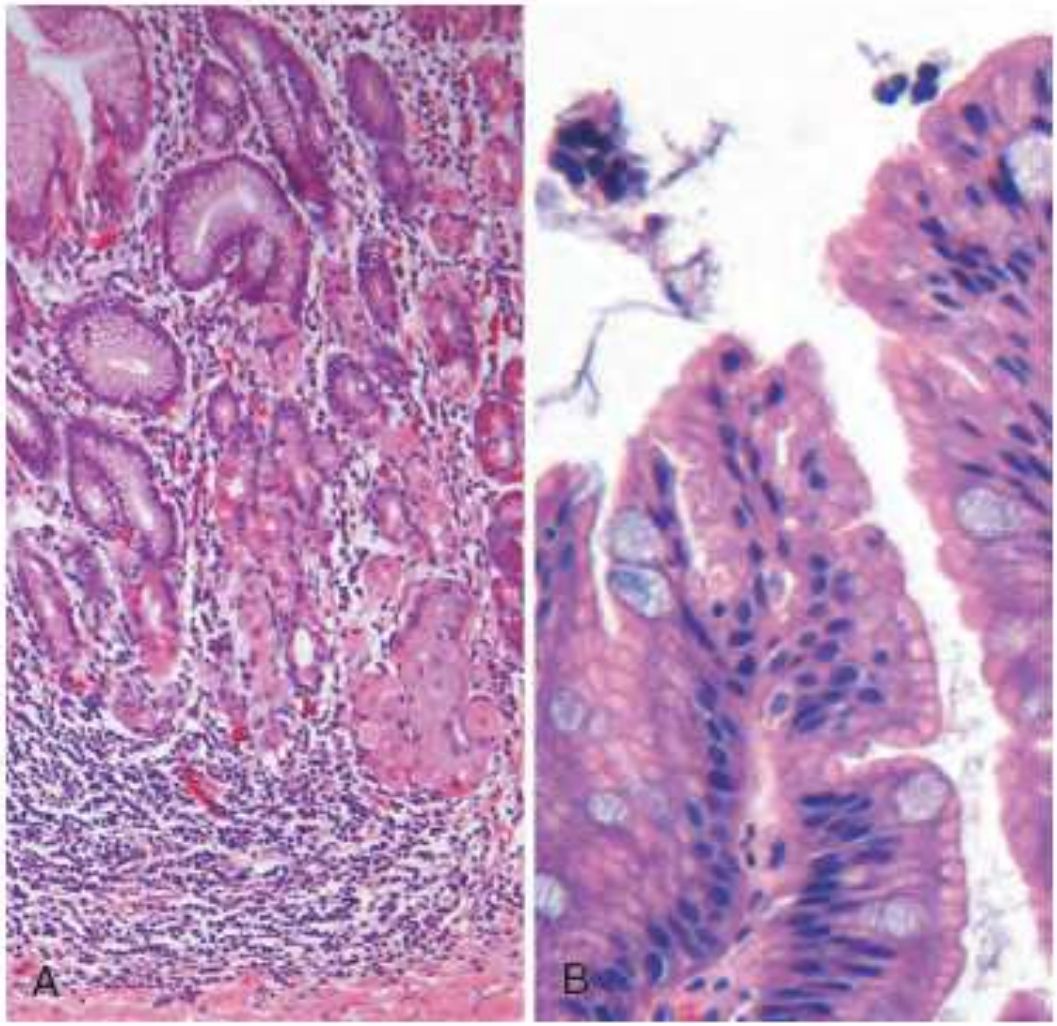


Figure 17-13 Autoimmune gastritis. **A,** Low-magnification image of gastric body demonstrating deep inflammatory infiltrates, primarily composed of lymphocytes, and glandular atrophy. **B,** Intestinal metaplasia, recognizable as the presence of goblet cells admixed with gastric foveolar epithelium.

Chronic gastritis

- Type B involves antrum and pylorus.
- Helicobacter pylori related.
- The organism is concentrated within the superficial mucus overlying epithelial cells in the surface and neck regions.
- The distribution can be irregular, with areas of heavy colonization adjacent to those with few organisms.
- Adheres to sialic acid and blood group antigen 0 of the parietal cells of the stomach.
- Local erosion (Vac A gene).

Chronic gastritis

- High urease activity triggers local ammonia production
- (CagA gene).
- This damages the ion pump, leads to neutrophil chemotaxis and epithelial damage of gastric pits.
- Intraepithelial neutrophils and subepithelial plasma cells are characteristic of H. pylori gastritis.
- Lymphoid aggregates, some with germinal centers, are frequently present

Chronic gastritis

- May promote gastric cancer.
- Stimulate mucosal associated lymphoid tissue.
- May lead to MALT lymphoma.

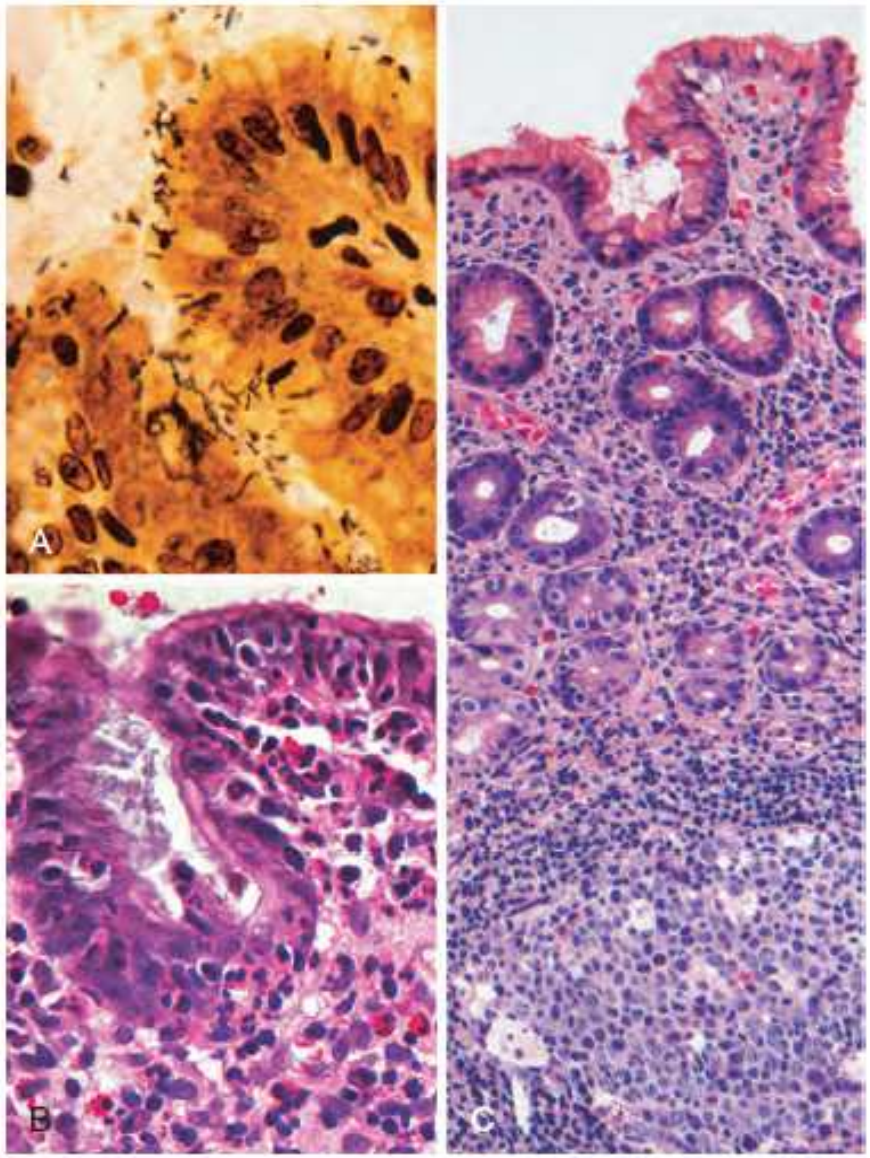


Figure 17-12 *Helicobacter pylori* gastritis. **A,** Spiral-shaped *H. pylori* are highlighted in this Warthin-Starry silver stain. Organisms are abundant within surface mucus. **B,** Intraepithelial and lamina propria neutrophils are prominent. **C,** Lymphoid aggregates with germinal centers and abundant subepithelial plasma cells within the superficial lamina propria are characteristic of *H. pylori* gastritis.

Chronic gastritis

- Urea breath test documents active infection.
- Stool antigen negative when infection cleared.
- Biopsy demonstrates the presence of organisms in the superficial mucus.
- Principally found in the antrum.
- Therapy with proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole for 7-14 days eliminates infection in 70% of patients.

Eosinophilic gastritis

- Eosinophilic gastritis
- Occurs with polymyositis and systemic sclerosis
- Occurs with exposure to cow's milk or soy protein.
- IgE levels elevated in serum; peripheral eosinophillia is also present.

Lymphocytic gastritis

- This disease preferentially affects women
- Approximately 40% of cases are associated with celiac disease, suggesting an immune-mediated pathogenesis.
- Lymphocytic gastritis typically affects the entire stomach (varioliform)
- Thickened folds covered by small nodules with central aphthous ulceration.
- Histologically there is a marked increase in the number of intraepithelial T lymphocytes.

Granulomatous gastritis

- Many cases are idiopathic.
- Gastric involvement by Crohn disease is the most common specific cause of granulomatous gastritis.
- Followed by sarcoidosis and infections (including mycobacteria, fungi, CMV, and H. pylori).
- In addition to the presence of histologically evident granulomas, narrowing and rigidity of the gastric antrum may occur secondary to transmural granulomatous inflammation.

Reactive gastropathy

- Reactive gastropathy will also show glandular regenerative changes in addition to foveolar hyperplasia.
- Reactive gastropathy is present following gastric antral trauma or gastric surgery that bypasses the pylorus.
- Hyperplastic polyp a common sequel to chronic gastritis and achlorhydria
- Adenomatous polyps uncommon

Complications of chronic gastritis

- Peptic ulcer disease usually presents with pain.
- The pain tends to occur 1 to 3 hours after meals during the day, is worse at night (usually between 11 PM and 2 AM), and is relieved by alkali or food.
- Nausea, vomiting, bloating, belching, and significant weight loss are additional manifestations.
- With penetrating ulcers (to the pancreas) the pain is occasionally referred to the back, the left upper quadrant, or the chest.
- Perforation is a medical emergency.
- Free air is noted under the diaphragm on x-ray.

Table 17-3 Risk factors for Peptic Ulcer Disease

- *H. pylori* infection
- Cigarette use (synergizes with *H. pylori* for gastric PUD)
- Chronic obstructive pulmonary disease
- Illicit drugs, e.g. cocaine, that reduce mucosal blood flow
- NSAIDs (potentiated by corticosteroids)
- Alcoholic cirrhosis (primarily duodenal PUD)
- Psychological stress (can increase gastric acid secretion)
- Endocrine cell hyperplasia (can stimulate parietal cell growth and gastric acid secretion)
- Zollinger-Ellison Syndrome (PUD of stomach, duodenum, and jejunum)
- Viral infection (CMV, herpes simplex virus)

Peptic ulcers

- Most common cause of upper gastrointestinal bleed.
- 50% have no prior symptoms.
- Most cases are self-limited.
- Chronic, most often solitary, punched-out lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acid/peptic juices:
- Duodenum, first portion
- Stomach, usually antrum
- At the gastroesophageal junction, in the setting of gastroesophageal reflux or Barrett esophagus

Peptic ulcers

- Within the margins of a gastrojejunostomy
- In the duodenum, stomach, and/or jejunum of patients with Zollinger-Ellison syndrome
- Within or adjacent to an ileal Meckel diverticulum that contains ectopic gastric mucosa.
- An ulcerative lesion on the greater curvature is more likely to be malignant.

Peptic ulcer disease

- Peptic ulcers are solitary in more than 80% of patients.
- Lesions less than 0.3 cm in diameter tend to be shallow while those greater than 0.6 cm are likely to be deeper.
- The classic peptic ulcer is a round to oval, sharply punched-out defect.
- The base of peptic ulcers is smooth and clean as a result of peptic digestion of exudate.

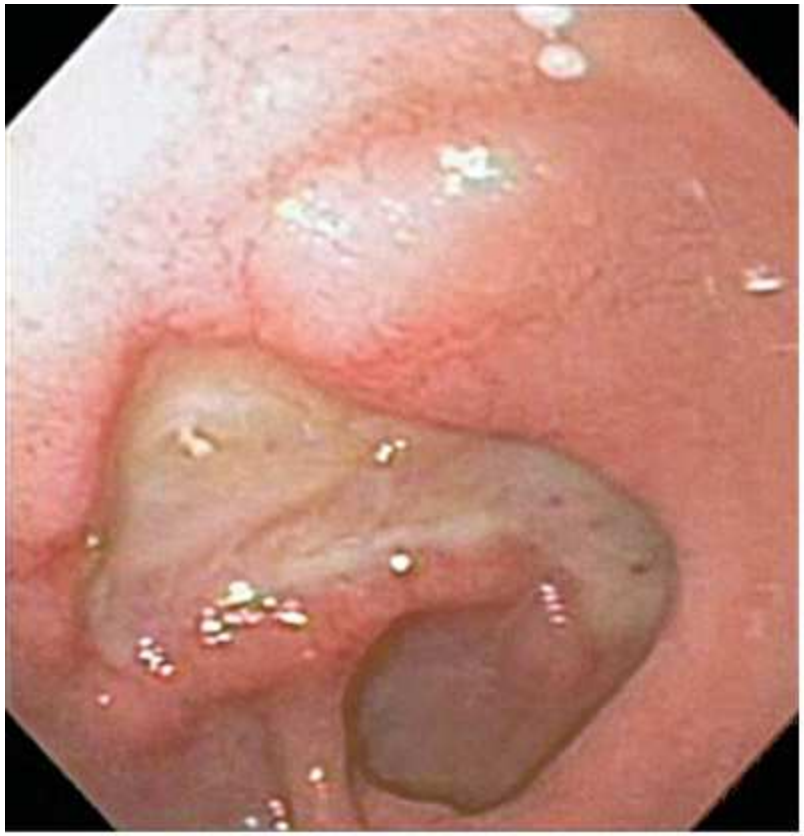
Peptic ulcer disease

- The mucosal margin may overhang the base slightly, particularly on the upstream side, but is usually level with the surrounding mucosa.
- In contrast, heaped-up margins are more characteristic of cancers.
- The depth of ulcers may be limited by the thick gastric muscularis propria or by adherent pancreas, omental fat, or the liver.
- Hemorrhage and fibrin deposition are often present on the gastric serosa.

Peptic ulcer disease

- Active ulcers may be lined by a thin layer of fibrinoid debris underlaid by a predominantly neutrophilic inflammatory infiltrate.
- Beneath this, granulation tissue infiltrated with mononuclear leukocytes and a fibrous or collagenous scar forms the ulcer base.
- Vessel walls within the scarred area are typically thickened and are occasionally thrombosed.
- Scarring may involve the entire thickness of the wall and pucker the surrounding mucosa into folds that radiate outward.

Duodenal ulcer



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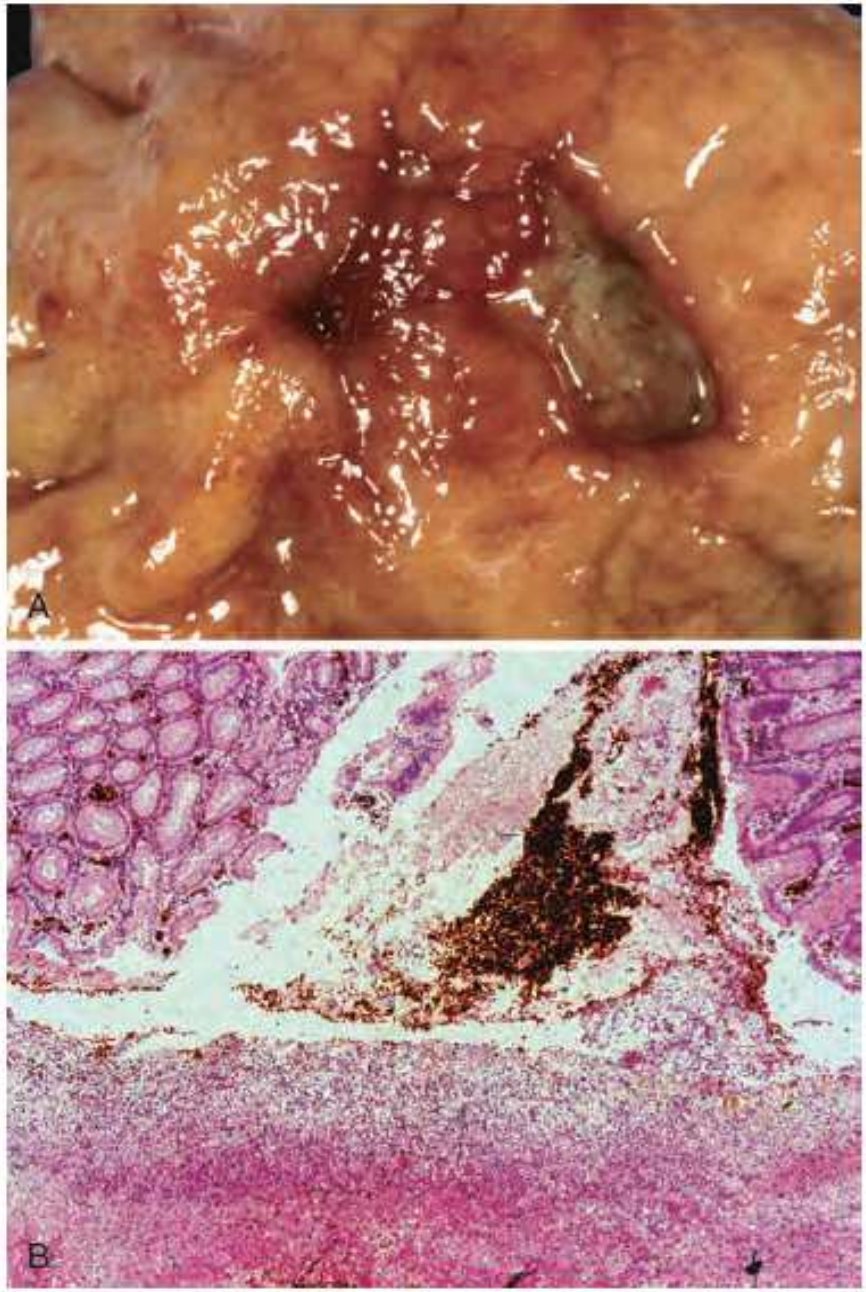


Figure 17-14 Acute gastric perforation in a patient presenting with free air under the diaphragm. **A,** Mucosal defect with clean edges. **B,** The necrotic ulcer base is composed of granulation tissue.

Table 17-4 Complications of Peptic Ulcer Disease

Bleeding
Occurs in 15% to 20% of patients
Most frequent complication
May be life-threatening
Accounts for 25% of ulcer deaths
May be the first indication of an ulcer
Perforation
Occurs in up to 5% of patients
Accounts for two thirds of ulcer deaths
Is rarely first indication of an ulcer
Obstruction
Mostly in chronic ulcers
Secondary to edema or scarring
Occurs in about 2% of patients
Most often associated with pyloric channel ulcers
May occur with duodenal ulcers
Causes incapacitating, crampy abdominal pain
Can rarely cause total obstruction and intractable vomiting

Complications of proton pump inhibition

- A pure form of parietal cell hypertrophy, without hyperacidity, may occur in long-term takers of acid secretion inhibitors.
- Cessation of therapy may cause a transient rebound of excess acid secretion.

Surgical therapy for peptic ulcer

- Visualization of a vessel in the ulcer crater is associated with a 90% re-bleed rate following therapy.
- Electrocautery and topical epinephrine may be used to stop bleeding in an active ulcer.
- Intractable pain or bleeding, outlet obstruction, or anterior perforation are indications for surgical intervention, usually a vagotomy and pyloroplasty.
- A posterior perforation generally penetrates the pancreas and does not necessarily require surgical intervention.

Ménetriér's disease

- Chronic gastritis (hypoproteineimic hypertrophic gastropathy)
- Most often encountered in males 30-50 years of age, but occasionally is seen in children.
- It often produces epigastric discomfort, diarrhea with protein loss, weight loss, and sometimes bleeding related to superficial rugal erosions.
- The etiology of this disease is unknown, but a role has been suggested for TGF-α over-expression in superficial gastric epithelium.

Ménetriér's disease

- Giant "cerebriform" enlargement of the rugal folds due to epithelial hyperplasia without inflammation.
- Found in body and fundus. Antrum is spared.
- Microscopic:
- Hyperplasia of foveolar mucous cells.
- The glands are elongated, dilated cystically, and have a "cork-screw" appearance.
- Patchy or diffuse glandular atrophy
- Causes protein loss.
- Achlorhydria as a result of parietal cell loss.

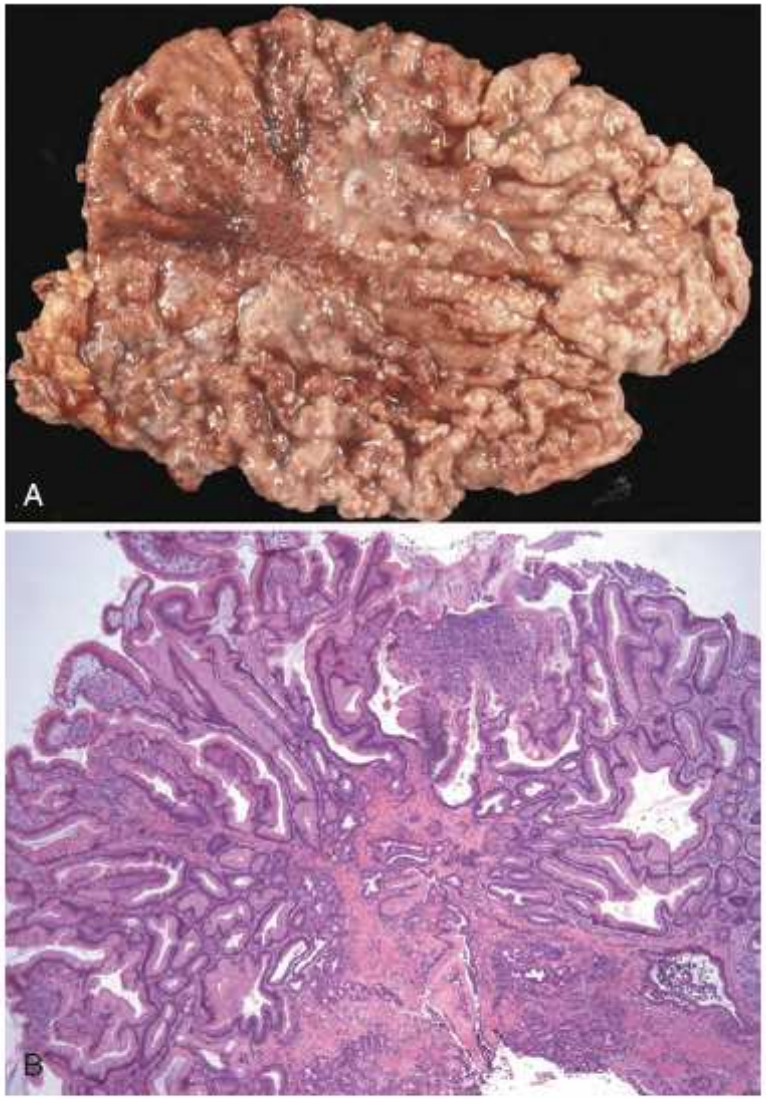


Figure 17-15 Ménétrier disease. **A,** Marked hypertrophy of rugal folds. **B,** Foveolar hyperplasia with elongated and focally dilated glands. (Courtesy Dr. M. Kay Washington, Vanderbilt University, Nashville, Tenn.)

Zollinger-Ellison syndrome

- Patients at risk for peptic ulceration because of excessive gastrin production leading to hyperacidity.
- Usually solitary duodenal ulcer,
- But multiple ulcers may be seen as well
- Distal duodenum, stomach, jejunum
- There is a doubling of oxyntic mucosal thickness due to a five-fold increase in the number of parietal cells as well as hyperplasia of mucous neck cells, mucin hyperproduction, and proliferation of gastrin producing cells.
- Gastrin producing cells may also be found and form small dysplastic nodules.
-

Zollinger-Ellison syndrome

- 60% are malignant tumors of the pancreatic islet.
- A variant may also present with diarrhea (production of vasoactive intestinal peptide as well).
- Elevated gastrin levels diagnostic
- 25% of patients have MEN
- Control with proton pump and H_2 inhibitors.
- Resect pancreatic tumor.

Table 17-5 Hypertrophic Gastropathies and Gastric Polyps

Parameter	Ménétrier Disease (adult)	Zollinger-Ellison Syndrome	Inflammatory and Hyperplastic Polyps	Gastritis Cystica	Fundic Gland Polyps	Gastric Adenomas
Mean patient age (yr)	30-60	50	50-60	Variable	50	50-60
Location	Body and fundus	Fundus	Antrum > body	Body	Body and fundus	Antrum > body
Predominant cell type	Mucous	Parietal > mucous, endocrine	Mucous	Mucous, cyst-lining	Parietal and chief	Dysplastic, intestinal
Inflammatory infiltrate	Limited, lymphocytes	Neutrophils	Neutrophils and lymphocytes	Neutrophils and lymphocytes	None	Variable
Symptoms	Hypoproteinemia, weight loss, diarrhea	Peptic ulcers	Similar to chronic gastritis	Similar to chronic gastritis	None, nausea	Similar to chronic gastritis
Risk factors	None	Multiple endocrine neoplasia	Chronic gastritis, *H. pylori*	Trauma, prior surgery	PPIs, FAP	Chronic gastritis, atrophy, intestinal metaplasia
Association with adenocarcinoma	Yes	No	Occasional	No	Syndromic (FAP) only	Frequent

FAP, Familial adenomatous polyposis; PPIs, proton pump inhibitors.

Gastric polyps

- 75% of gastric polyps are inflammatory or hyperplastic.
- Usually associated with chronic gastritis.
- Foveolar hyperplasia.
- Commonly present between 50-60 years of age
- May regress with H. pylori therapy.

Gastric polyps

- Fundic gland polyp
- Prevalence has increased with use of proton pump inhibitors.
- Women more likely affected.
- Single or multiple and composed of cystically dilated, irregular glands lined by flattened parietal and chief cells.
- No inflammation.
- May be present in those with familial adenomatous polyposis

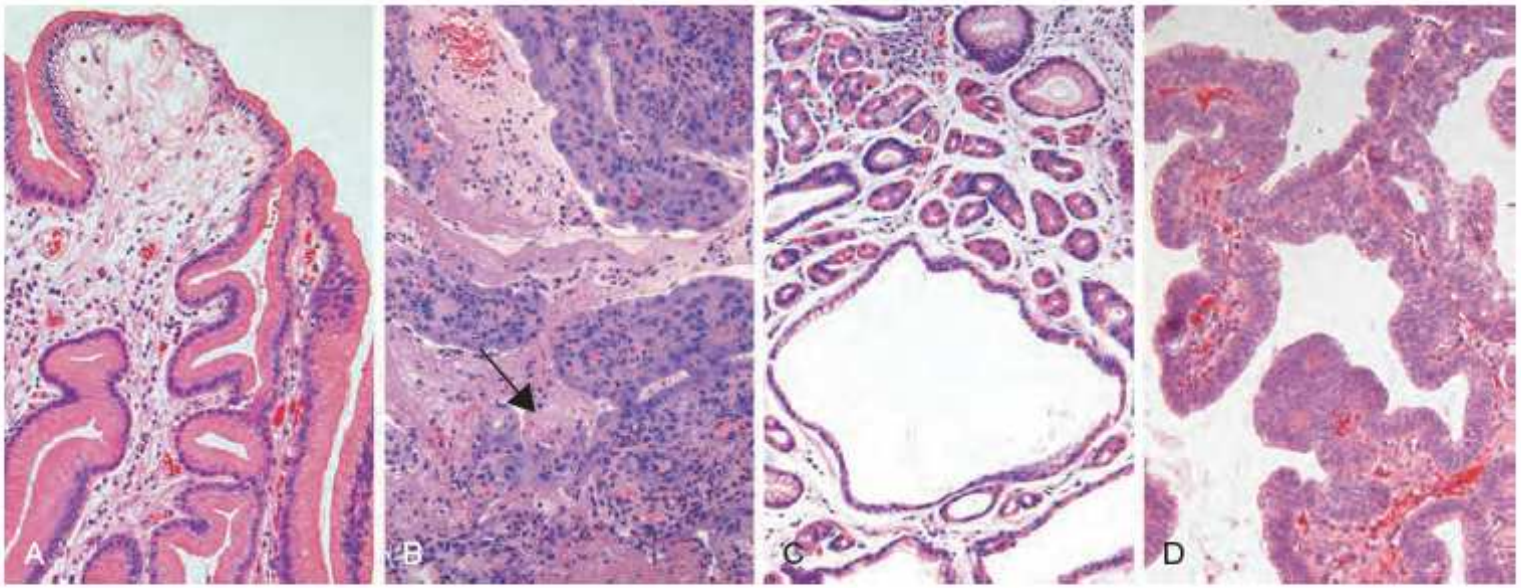


Figure 17-16 Gastric polyps. **A,** Hyperplastic polyp containing corkscrew-shaped foveolar glands. **B,** Hyperplastic polyp with ulceration *(arrow)*. **C,** Fundic gland polyp composed of cystically dilated glands lined by parietal, chief, and foveolar cells. **D,** Gastric adenoma recognized by the presence of epithelial dysplasia.

Mucosal atrophy and intestinal metaplasia

- Long-standing chronic gastritis that involves the body and fundus may ultimately lead to significant loss of parietal cell mass.
- This oxyntic atrophy may be associated with intestinal metaplasia, recognized by the presence of goblet cells.
- Achlorhydria of gastric mucosal atrophy permits overgrowth of bacteria that produce carcinogenic nitrosamines
- Strongly associated with increased risk of gastric adenocarcinoma

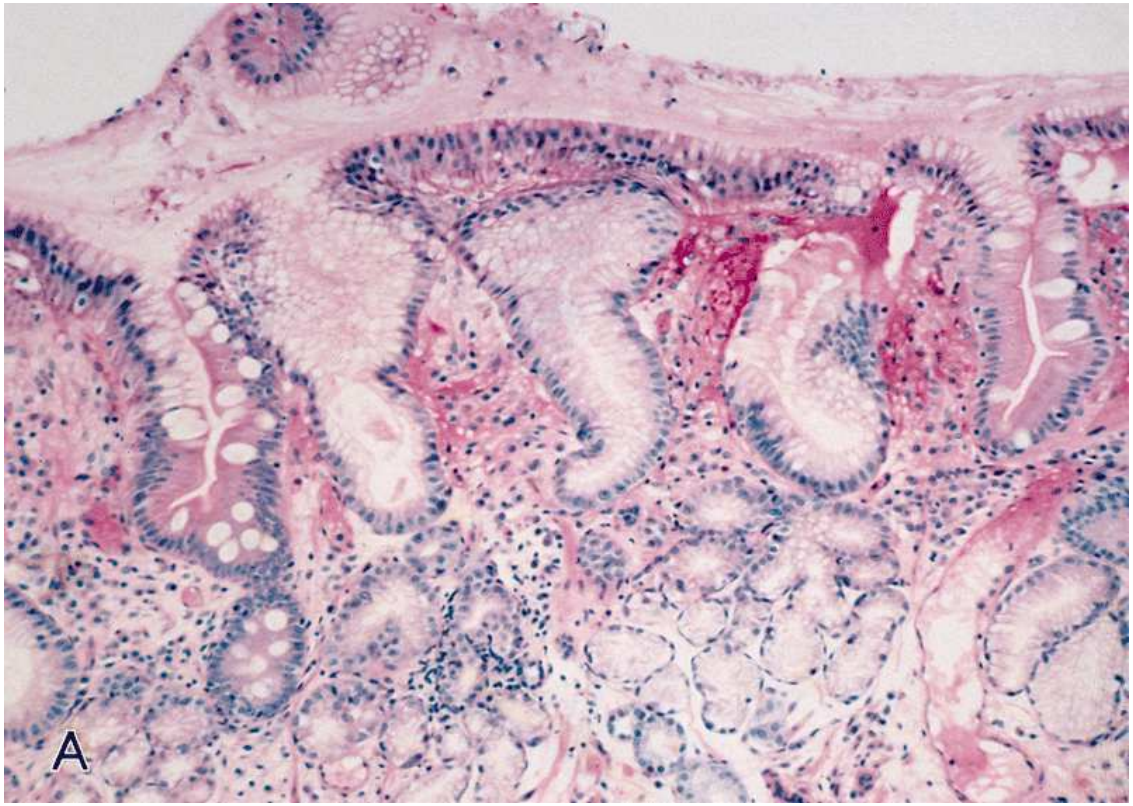
Mucosal reparative change

- Chronic gastritis exposes the epithelium to inflammation related free radical damage and proliferative stimuli.
- Gastritis cystica is an exuberant reactive epithelial proliferation associated with entrapment of epithelial-lined cysts.
- These may be found within the submucosa (gastritis cystica polyposa) or deeper layers of the gastric wall (gastritis cystica profunda).
- Increased epithelial proliferation and mitotic figures may be prominent in both repair and dysplasia.
- However, reactive epithelial cells mature as they reach the mucosal surface.

Mucosal dysplasia

- There are two separate types of dysplastic epithelial changes identified. Both may be found.
- Intestinal type,
- Most common
- The cells and their nuclei are elongated.
- The nuclei are stratified, but the stratification is mostly confined to the basal half of the cells.
- Little pleomorphism.
- This epithelium is indistinguishable from that which occurs in colorectal adenomas.

Intestinal metaplasia



This epithelium is identical to that in many colorectal adenomas.

Small mucus vacuoles within dysplastic goblet cells are present in the luminal cytoplasm of many cells.

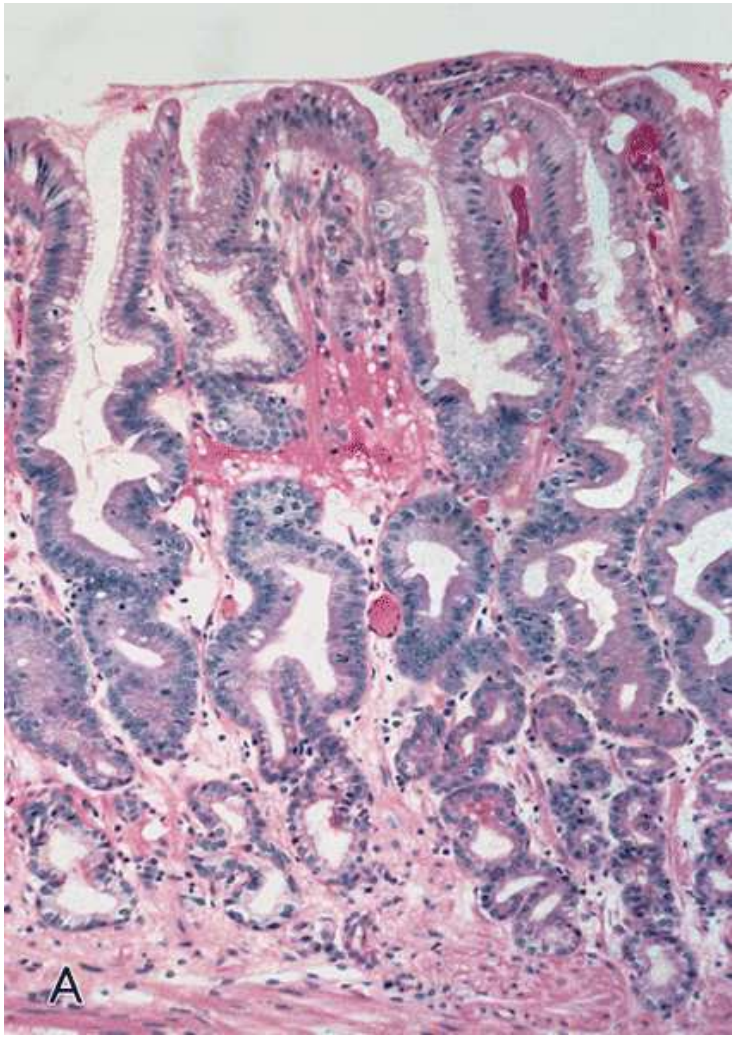
Fig. 11-1A

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Mucosal dysplasia

- Gastric type
- Foveolar metaplasia.
- Dysplastic cells resemble gastric foveolar and surface cells with apical neutral mucin vacuoles.

Foveolar metaplasia



The cells are columnar. Many cells contain apical mucin vacuoles that stain red with periodic acid- Schiff, but not with Alcian blue. The nuclei are oval to round, and many have small nuclei. Nuclear stratification is limited to the basal half of the epithelium. (Hematoxylin and eosin stain)

Fig. 11-2A

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Gastric polyps

- 75% of gastric polyps are inflammatory or hyperplastic. Usually associated with chronic gastritis. Foveolar hyperplasia.
- Commonly present between 50-60 years of age
- May regress with H. pylori therapy.
- Fundic gland polyp prevalence has increased with use of proton pump inhibitors. Women more likely affected.
- Single or multiple and composed of cystically dilated, irregular glands lined by flattened parietal and chief cells. No inflammation.

Gastric adenoma

- Gastric adenomas account for 10% of polyps.
- Men.
- Present between 50-60 years of age.
- Intestinal-type columnar epithelium comprise the adenoma.
- A background of chronic gastritis is present.
- Dysplastic change noted.
- May be present in those with familial adenomatous hyperplasia.
- >2cm size usually associated with malignancy.

Environmental, dietary and lifestyle factors that are or may be associated with gastric cancer risk		
FACTORS	DECREASES RISK	INCREASES RISK
Infectious factors		*H. pylori* (non-cardia) (virulence factors: *CagA, VacA s1, VacA m1, babA2, CagA Epiya-C*)
Tobacco		Smoking
Dietary factors	Green-yellow vegetables Allium vegetables Fruits and citrus fruits Flavonoid Green tea	Salt and salty foods Smoked foods Pickled foods Nitrosamines and nitroso-compounds Alcohol (heavy intake) Red and processed meat Haem iron (from red meat)
Body mass index		Obesity (cardia)
Hormones	Oestrogens	
Anti-inflammatory drugs	Aspirin use	

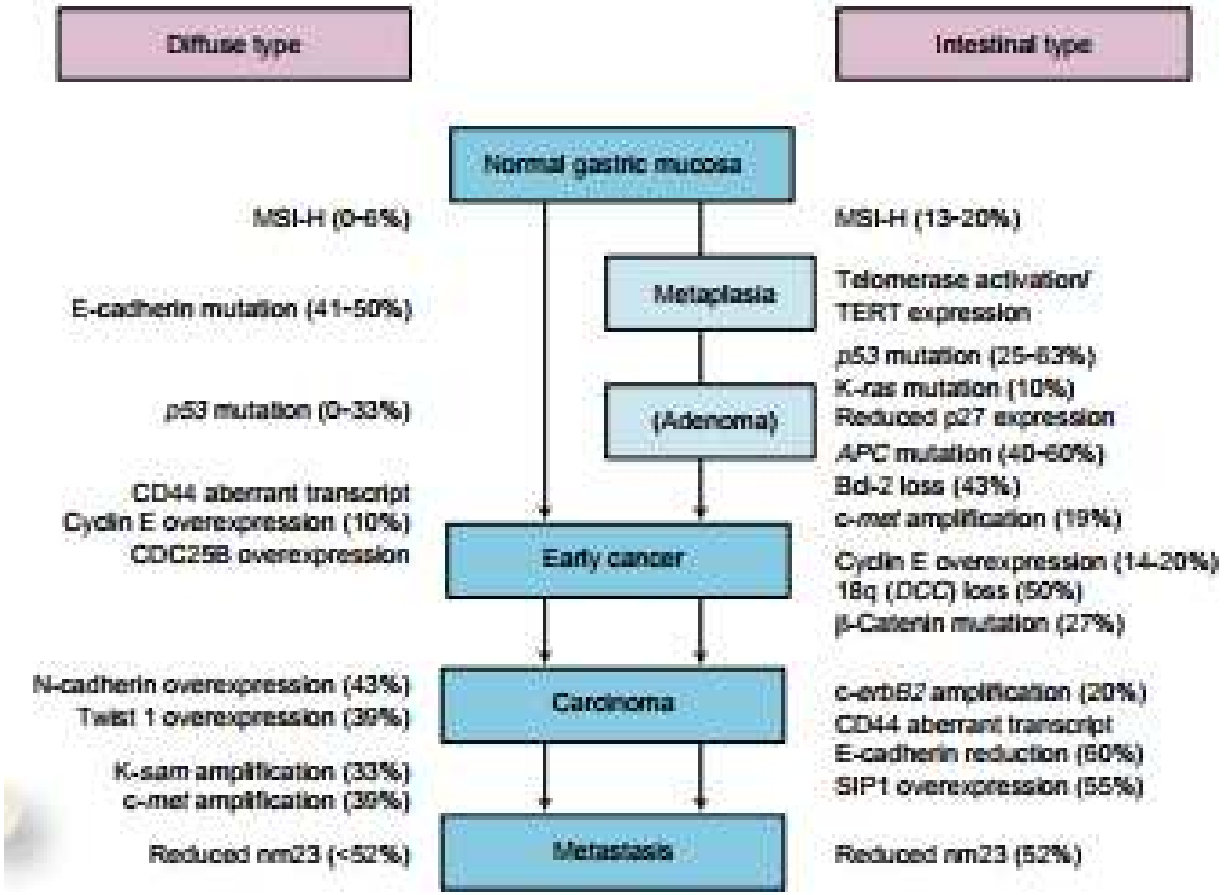
Gastric cancer

- The majority of gastric cancers are adenocarcinomas.
- Most gastric cancers are associated with infectious agents, including Helicobacter pylori and Epstein–Barr virus (EBV).
- A minority are associated with germline mutation in E-cadherin (CDH1) or MMR genes
- Sporadic MMR-deficient gastric cancers have epigenetic silencing of MLH1 in the context of CIMP.
- Mutations in the ubiquitin ligases RNF43 and ZNRF3 or fusions of RSPO2/3 genes are alterations that activate WNT/β-catenin oncogenic signaling.

Gastric cancer

- Gastric carcinomas of the pylorus and antrum account for 50-60% of cases
- Cardia, 25%
- With the remainder divided equally between the body and fundus.
- The lesser curvature is involved in about 40%
- The greater curvature, in 12%.
- Metastases are often detected at time of diagnosis.

Genetic alterations in gastric cancer



Genetic variation and gastric cancer risk in GWAS studies	
GENES	GASTRIC SUBGROUPS
MUC1 rs2070803 (1q22)	*Diffuse carcinoma*
MTX1 rs2075570 (1q22)	*Diffuse carcinoma*
PSCA rs2294008 (8q24.2)	*Non-cardia*
PRKAA1 rs13361707 (5p13)	*Non-cardia*
PLCE1 rs2274223 (10q23)	*Cardia*
TGFBR2 rs3087465 (3p22)	*Asian*
PKLR rs3762272 (1q22)	*Diffuse*
PSCA rs297392 (8q24.2)	*Intestinal*
GSTP1 rs1695 (11q13)	*Asian*
CASP8 rs3834129 (2q33)	*Mixed*
TNF (rs1799724 (6p21.3)	*Mixed*

GWAS, Genome wide association studies.

Single nucleotide polymorphisms (SNPs) in a wide variety of genes may modify the effect of environmental exposure, and this could explain the high variation in GC incidence worldwide

A germline mutation in CDH1 causes the rare familial form of diffuse gastric carcinoma

Gastric cancer

- There are four molecular subtypes
- (1) Tumors positive for Epstein–Barr virus
- EBV-positive tumors display CDKN2A ($p16^{INK4A}$) promoter hypermethylation
- No MLH1 hypermethylation
- >80% have PIK3CA mutations
- 55% have ARID1A mutations (helicase and ATPase functions)
- Amplification of JAK2, PD-L1 and PD-L2

Gastric cancer

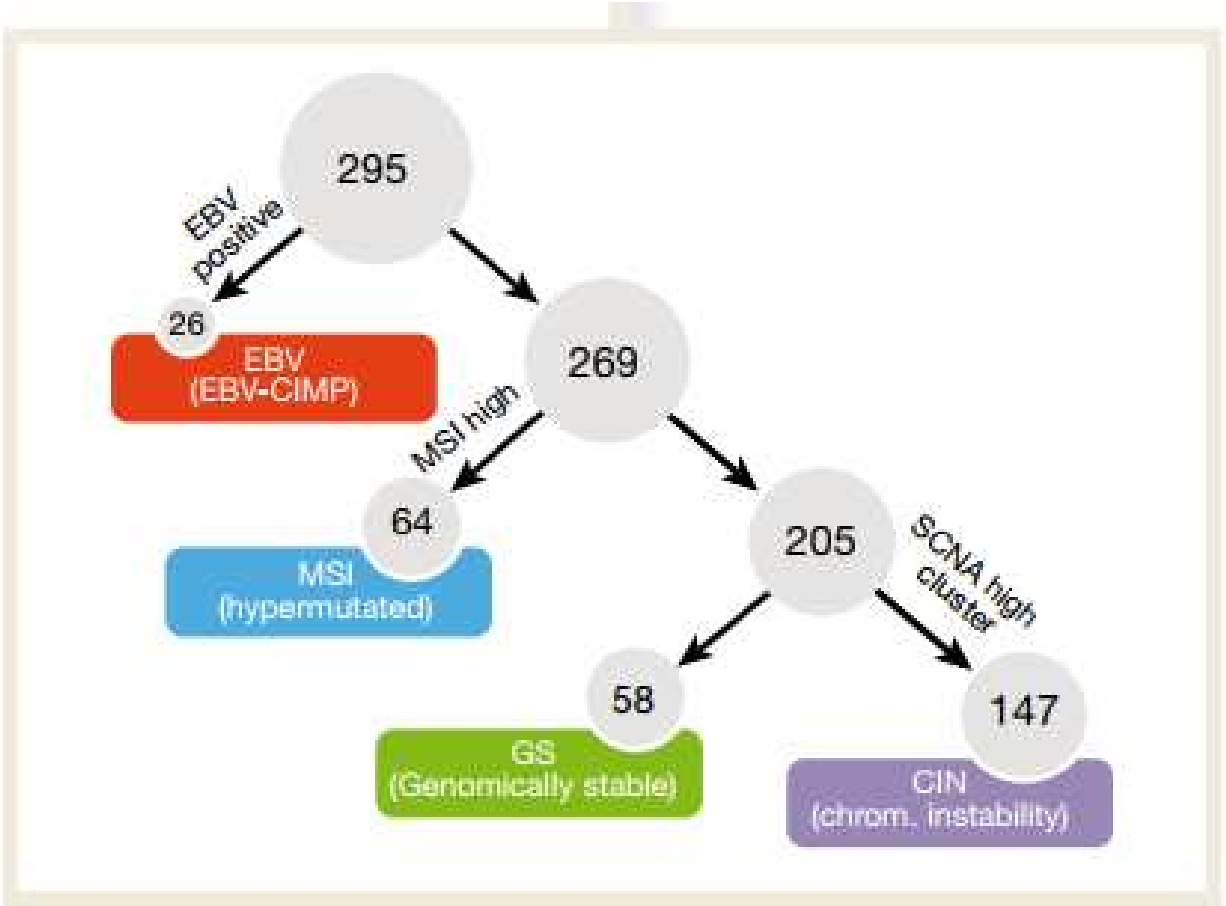
- (2) Microsatellite unstable tumors
- Elevated mutation rates
- MLH1 hypermethylation characteristic
- TP53, KRAS, ARID1A, PIK3CA, ERBB3, PTEN and HLA-B commonly mutated
- HLA-B mutation associated with diminished presentation of tumor antigen
- More common in distal stomach

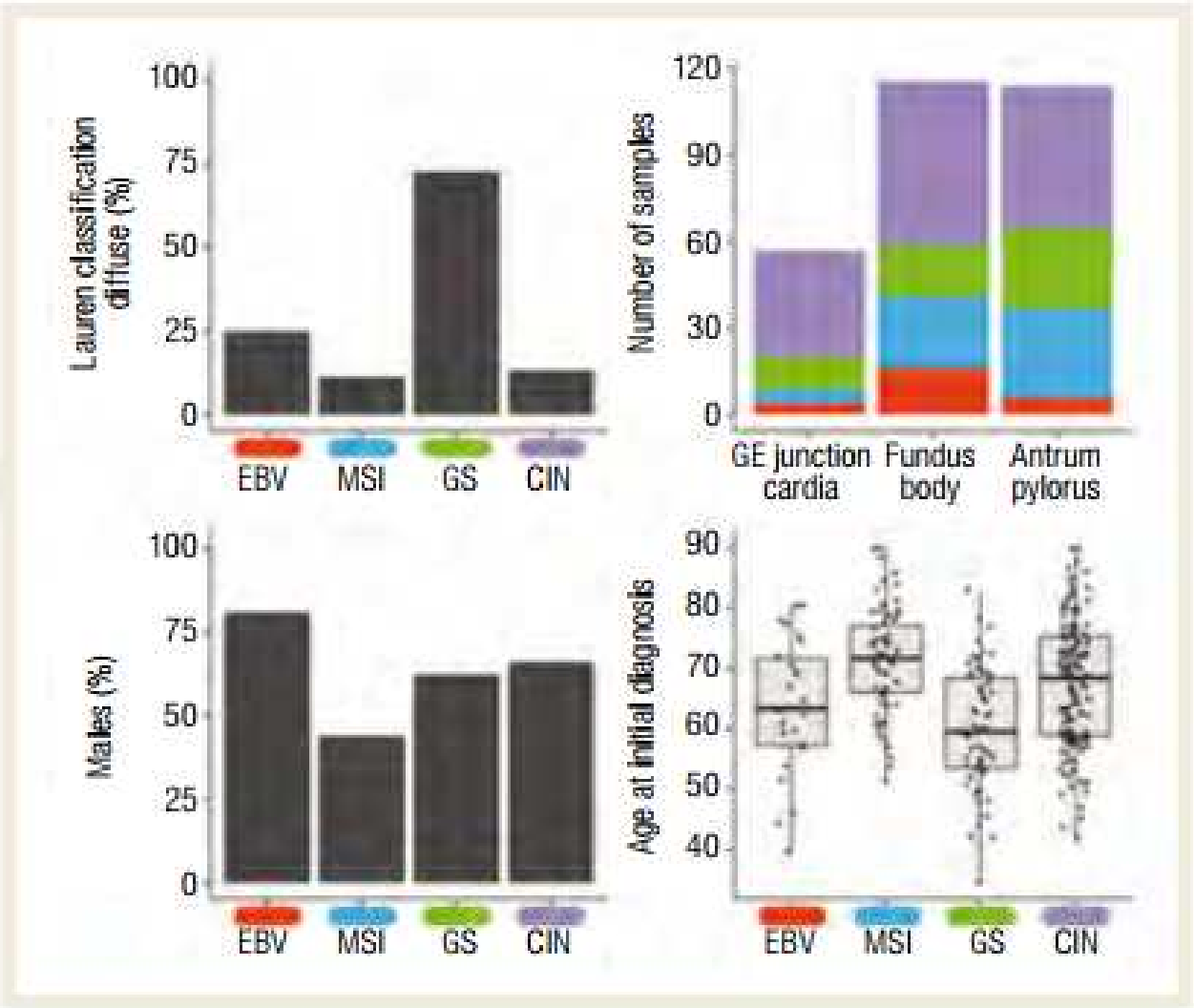
Gastric cancer

- (3) Genomically stable tumours
- The diffuse histological variant
- Mutations of RHOA or fusions involving RHO-family GTPase-activating proteins
- Actin-myosin dependent cell contractility and cell motility
- STAT kinase
- ARID1A mutations common
- 50%, loss-of-function mutations in CDH1 in sporadic diffuse gastric tumors
- E-cadherin expression is drastically decreased
- Hyper-methylation and silencing of the CDH1 promoter.

Gastric cancer

- (4) Tumors with chromosomal instability, which show marked aneuploidy and focal amplification of receptor tyrosine kinases.
- EGFR amplified or mutated
- 32%, gastroesophageal junction
- 26%, distal stomach
- CDH1/TP53 are the most frequent driver mutations
- Elevated expression of p53


295
EBV positive
26
EBV
(EBV-CIMP)
269
MSI high
64
MSI
(hypermutated)
205
SCNA high cluster
58
GS
(Genomically stable)
147
CIN
(chrom. instability)


Lauren classification diffuse (%)
100
75
50
25
0
EBV
MSI
GS
CIN
Number of samples
120
90
60
30
0
GE junction cardia
Fundus body
Antrum pylorus
Males (%)
100
75
50
25
0
EBV
MSI
GS
CIN
Age at initial diagnosis
90
80
70
60
50
40
EBV
MSI
GS
CIN

Gastric cancer

- The intestinal and diffuse histologic sub-types appear to have a different pathogenetic basis.
- The intestinal type predominates in high-risk areas, and develops from precursor lesions.
- The intestinal type exhibits a mean age of incidence of 55 years and predominantly involves men.
- 40% occur in the body of the stomach.
- Bulky.

Gastric cancer

- Associated with H. pylori.
- Loss of function mutations in the APC gene as well as gain of function mutation in β-catenin (binds to E-cadherin and APC)
- CIMP associated with poor response, young age.

Gastric cancer

- The incidence of the diffuse type is relatively constant, and the tumors have no identifiable precursor lesions.
- Diffuse gastric cancer occurs at a mean age of 48 years with no sex predominance.
- No peristalsis.
- Tumor cells infiltrate stomach wall. Marked desmoplastic reaction. (Linitis plastica)
- Undifferentiated signet-ring histology.

Gastric cancer

- BRCA2 mutations predispose
- Associated with Helicobacter pylori infection but no mechanism of carcinogenesis proposed.
- Involve the body 25% of the time
- Cardia and fundus, each 35%.

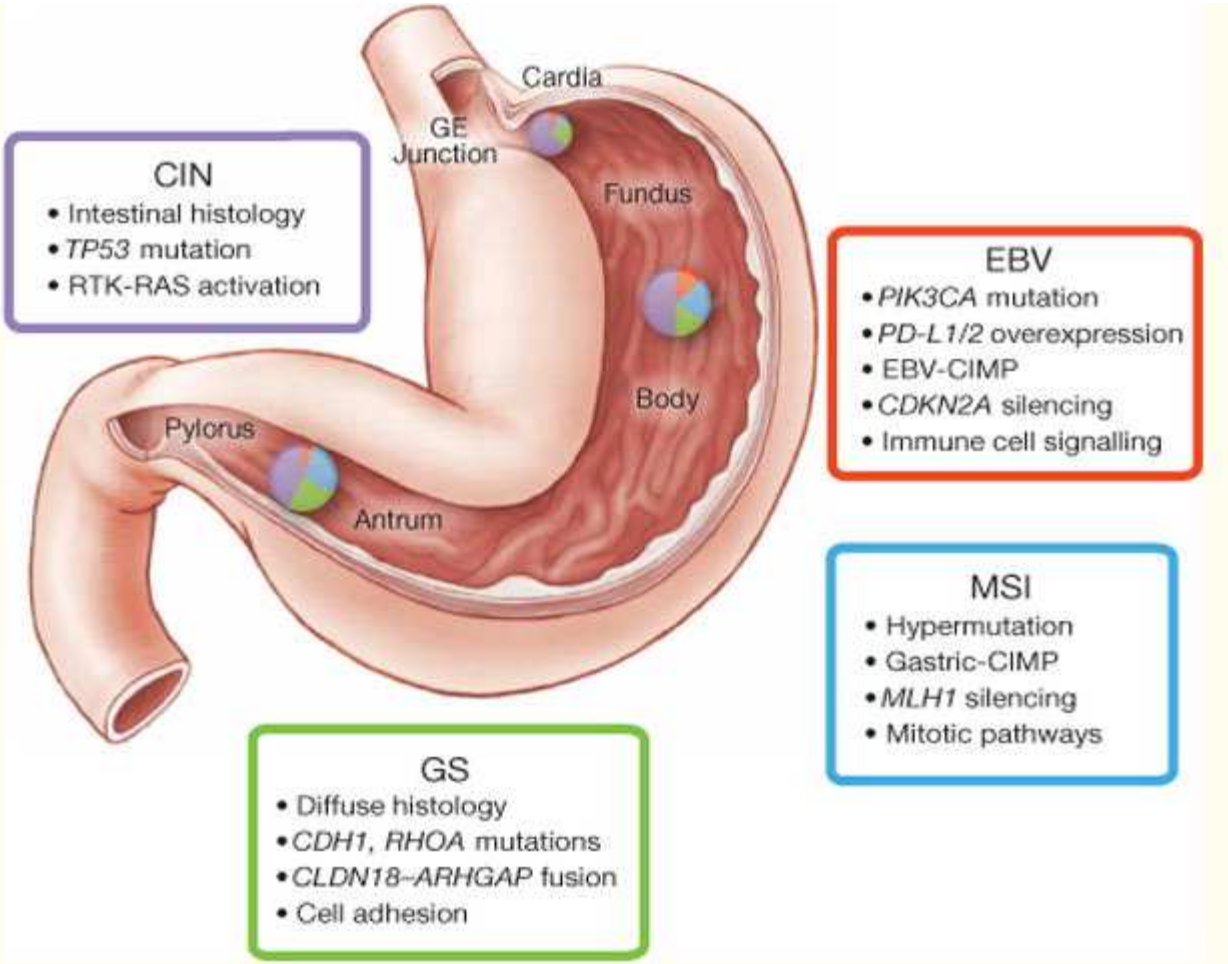


Figure 6

Key features of gastric cancer subtypes

This schematic lists some of the salient features associated with each of the four molecular subtypes of gastric cancer. Distribution of molecular subtypes in tumours obtained from distinct regions of the stomach is represented by inset charts.

doi: 10.1038/nature13480

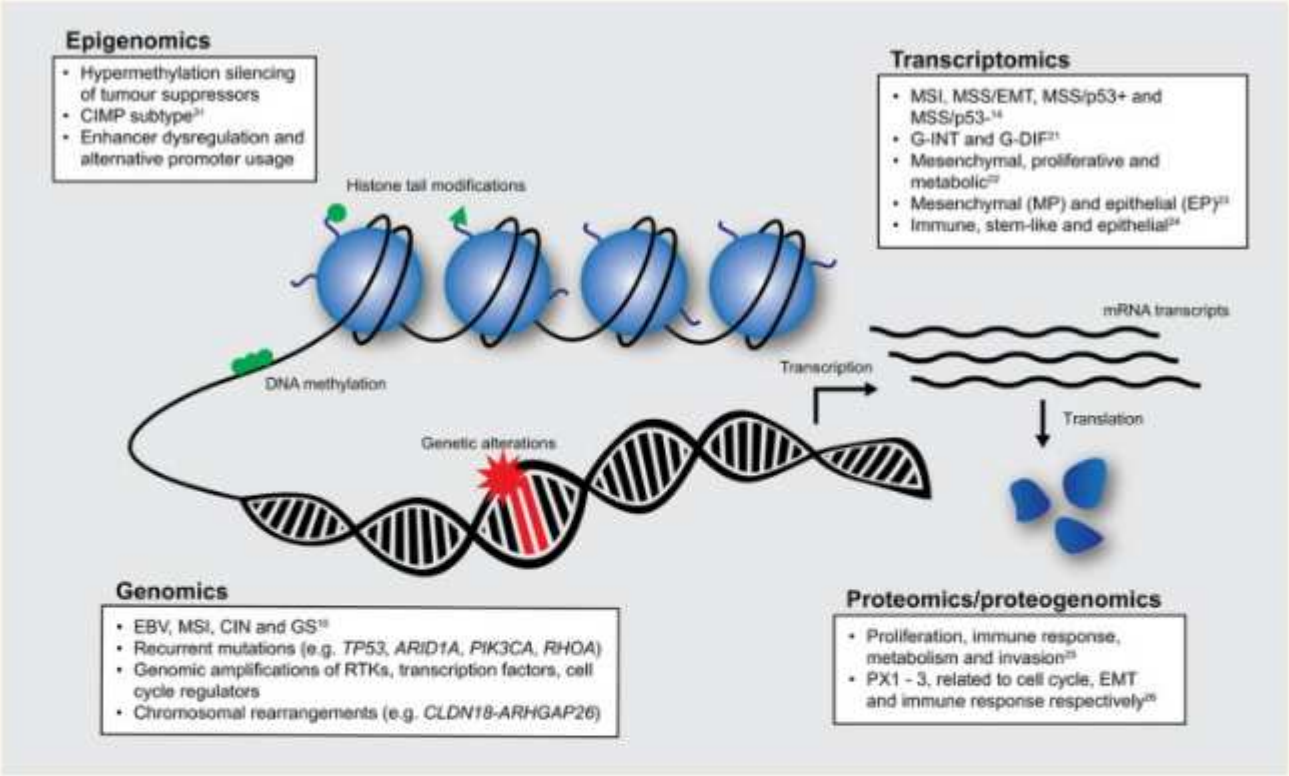


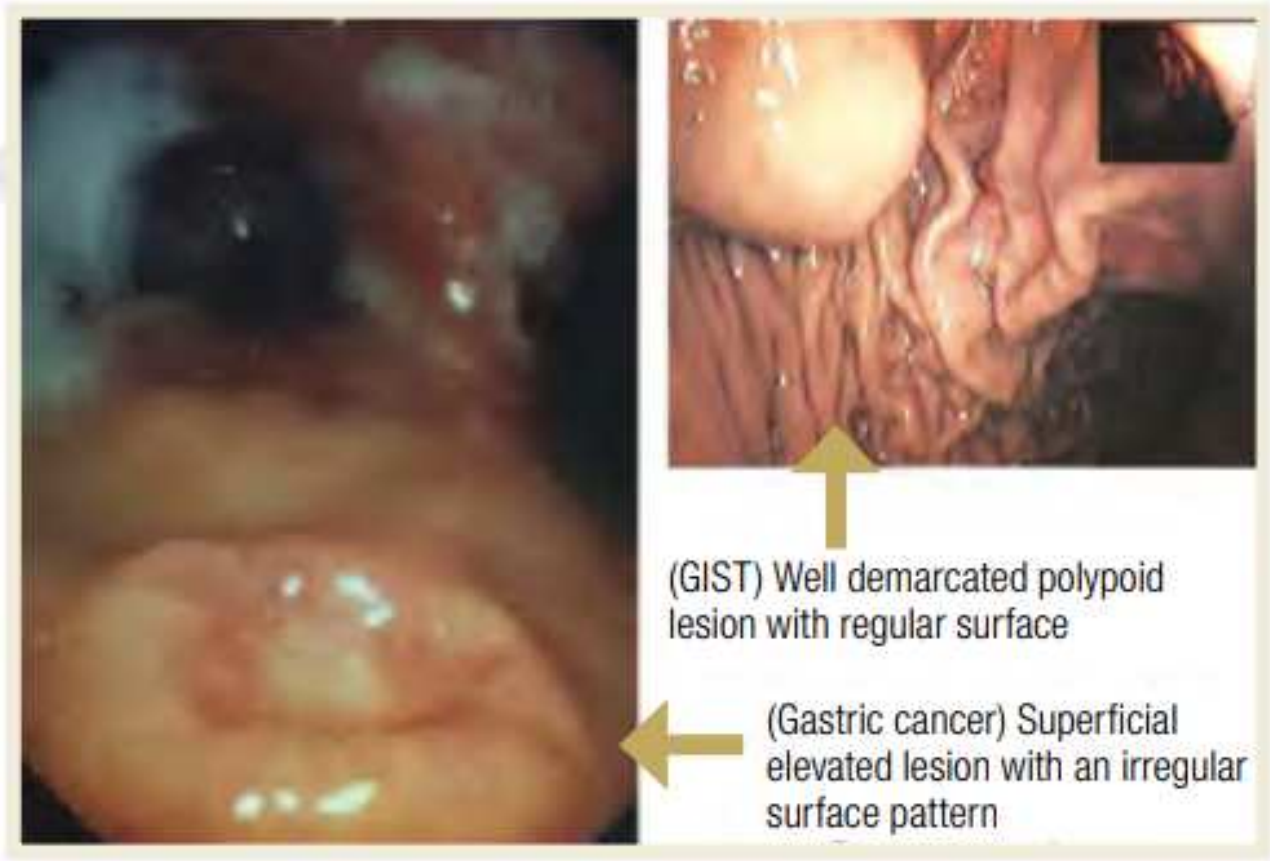
Figure 1

Overview of current molecular classifications in gastric cancer including epigenomic, genomic, transcriptomic and proteomic alterations. Key relevant papers are referenced. CIMP, CpG island methylator phenotype; CIN, chromosomal instability; EBV, Epstein-Barr virus; EMT, epithelial-mesenchymal transition; G-DIF, genomic diffuse; G-INT, genomic intestinal; GS, genomically stable; MSI, microsatellite instability; MSS/EMT, microsatellite stable with EMT phenotype; RTK, receptor tyrosine kinase

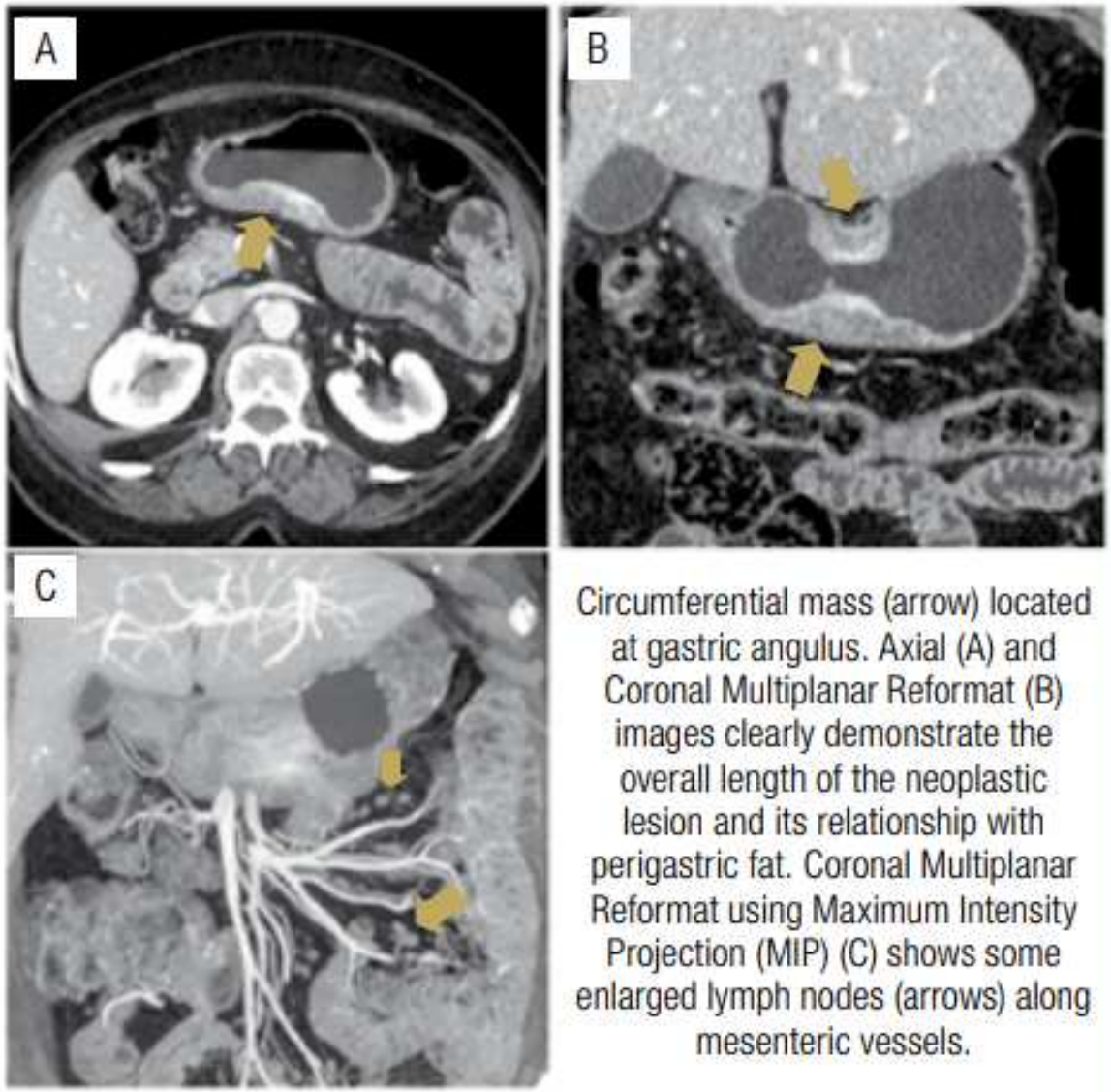
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6825006/

Gastric cancer

- Endoscopy with biopsy is the most sensitive and specific test to detect gastric cancer.
- EUS is important in the initial staging
- Pneumo/hydro-CT has proved to be a useful, safe and accurate technique to identify gastric wall thickening and to stage gastric cancer.
- In diffuse or mucinous tumours, 18 FDG-PET/CT can be inconclusive.

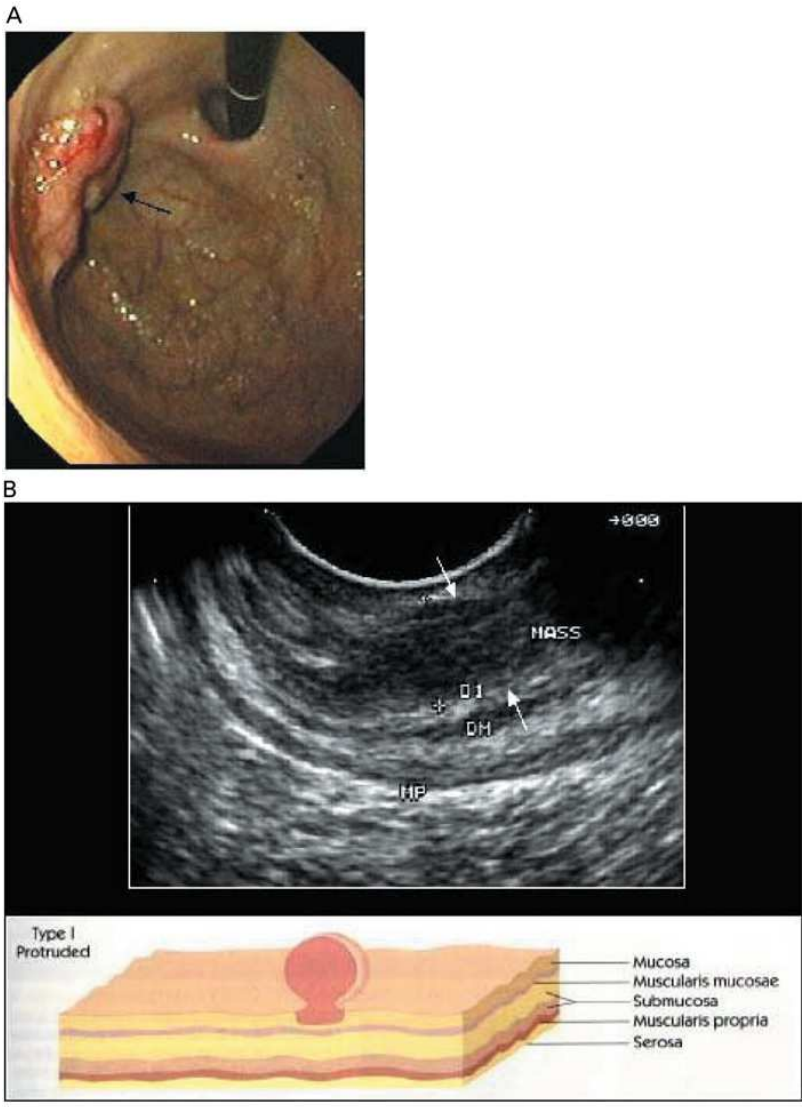


GIST, Gastrointestinal stromal tumour.



Circumferential mass (arrow) located at gastric angulus. Axial (A) and Coronal Multiplanar Reformat (B) images clearly demonstrate the overall length of the neoplastic lesion and its relationship with perigastric fat. Coronal Multiplanar Reformat using Maximum Intensity Projection (MIP) (C) shows some enlarged lymph nodes (arrows) along mesenteric vessels.

Gastric cancer



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

T1 lesion.
A. Endoscopic view.
B. Ultrasound.

(*Reproduced with permission from* http://www.massgeneral.org/gastro/endo_homepage.htm .)

Fig.14-10 Accessed 04/01/2010

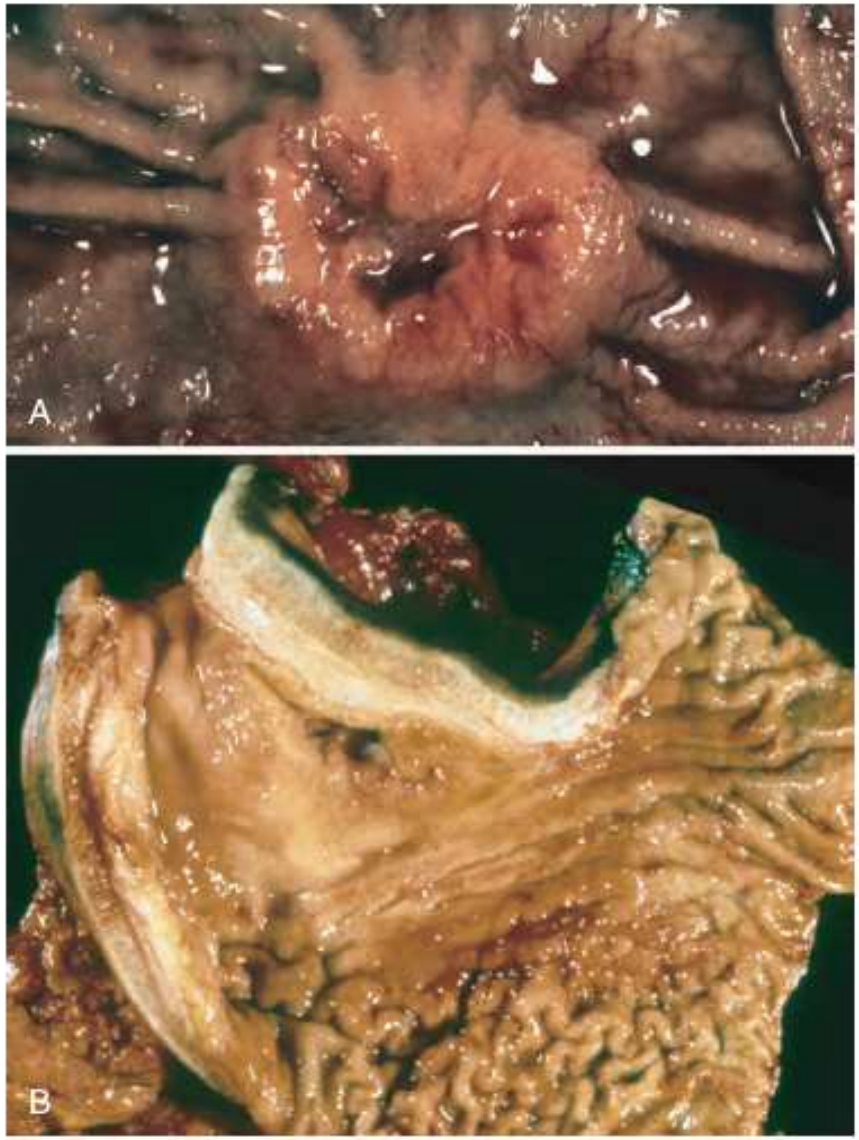


Figure 17-17 Gastric adenocarcinoma. **A,** Intestinal-type adenocarcinoma consisting of an elevated mass with heaped-up borders and central ulceration. Compare to the peptic ulcer in Figure 17-14*A*. **B,** Linitis plastica. The gastric wall is markedly thickened and rugal folds are partially lost.

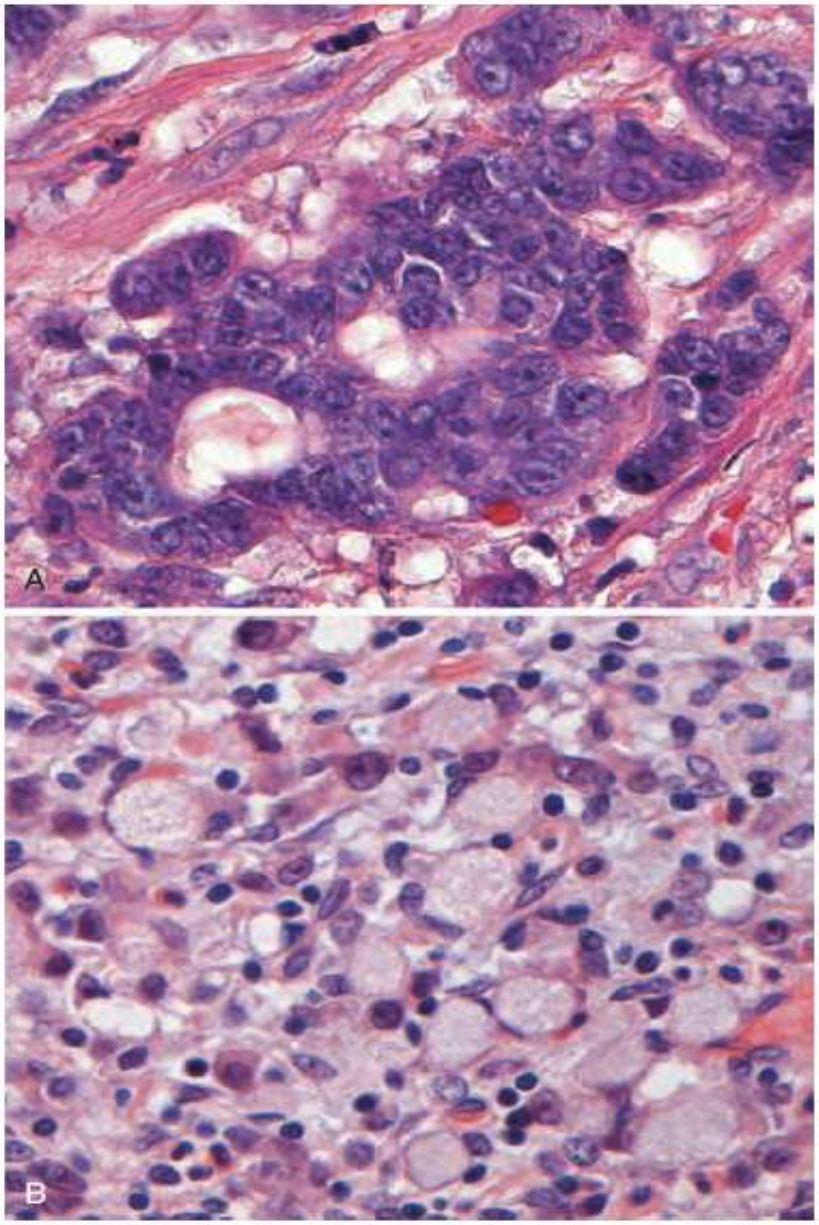
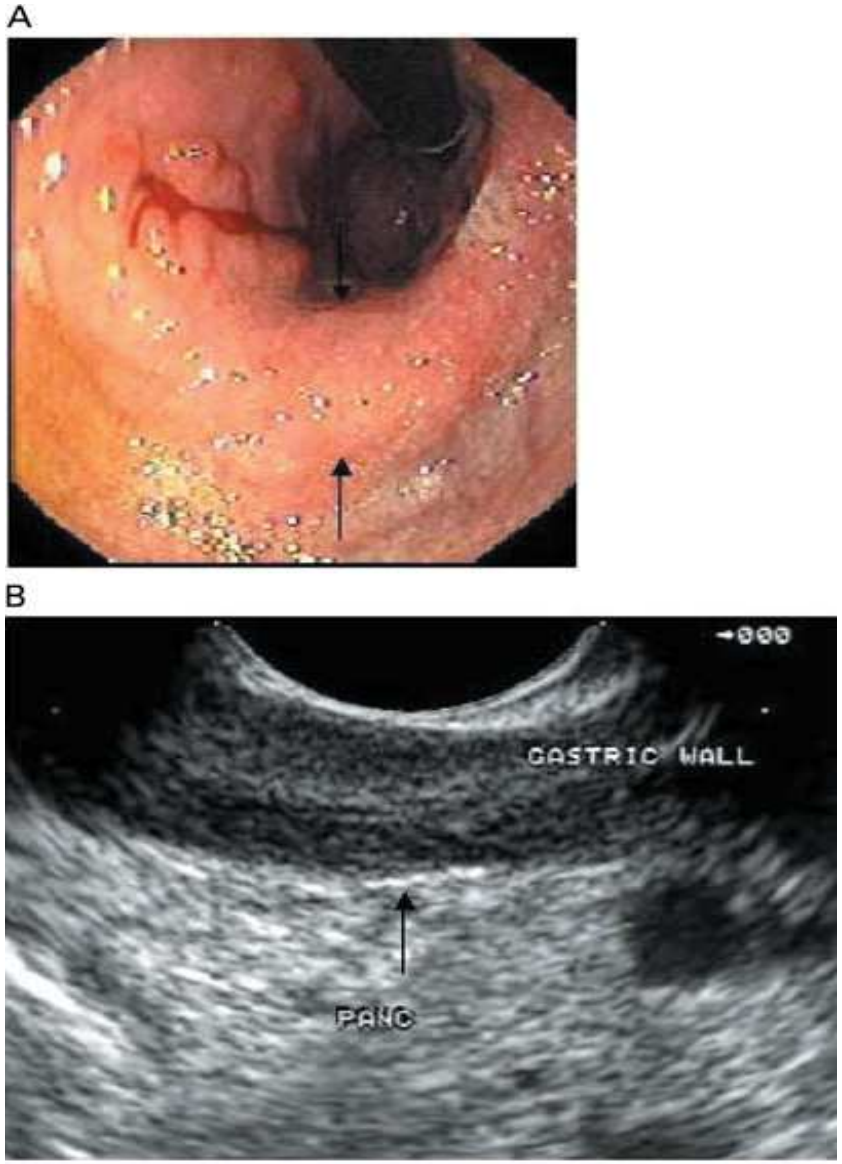


Figure 17-18 Gastric adenocarcinoma. **A,** Intestinal-type adenocarcinoma composed of columnar, gland-forming cells infiltrating through desmoplastic stroma. **B,** Signet-ring cells can be recognized by their large cytoplasmic mucin vacuoles and peripherally displaced, crescent-shaped nuclei.

Linitis plastica



Diffuse submucosal infiltration by cancer.

Fig.14-12 Accessed 04/01/2010

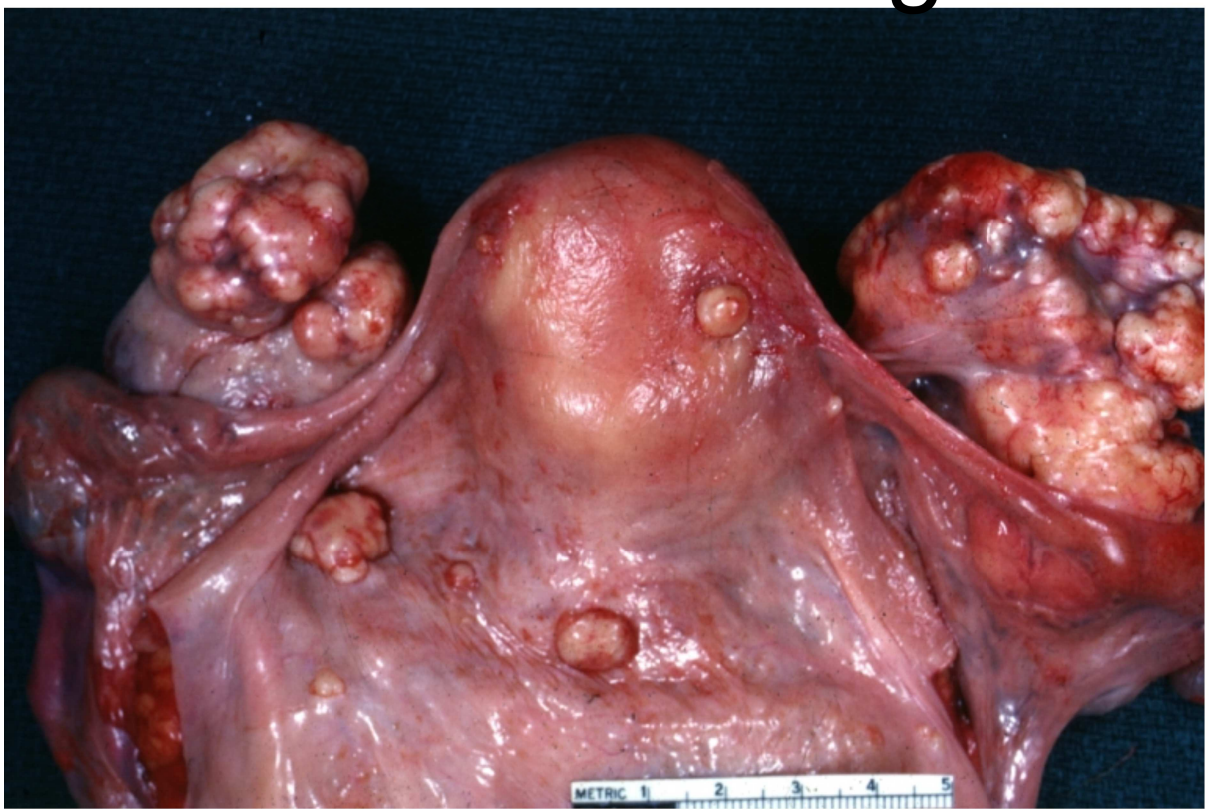
Gastric cancer

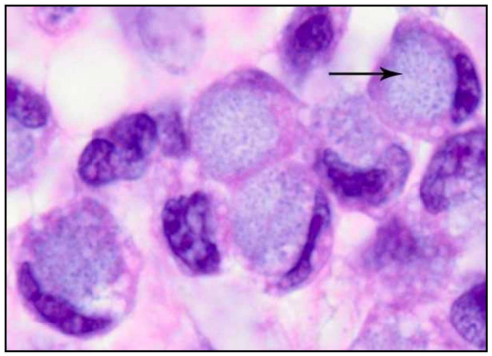
- Local invasion of gastric carcinoma into the duodenum, pancreas, and retroperitoneum.
- At the time of death, widespread peritoneal seeding and metastases to the liver and lungs are common.

Gastric cancer

- Sister Mary Joseph nodule.
- Metastasis to the periumbilical region to form a subcutaneous nodule.
- Virchow node (left supraclavicular node).
- The left axillary lymph node (Irish node)
- The pouch of Douglas (Blumer shelf)
- A notable site of visceral metastasis is to one or both ovaries.
- Although uncommon, metastatic adenocarcinoma to the ovaries (from stomach, breast, pancreas, and even gallbladder) is so distinctive as to be called Krukenberg tumor.

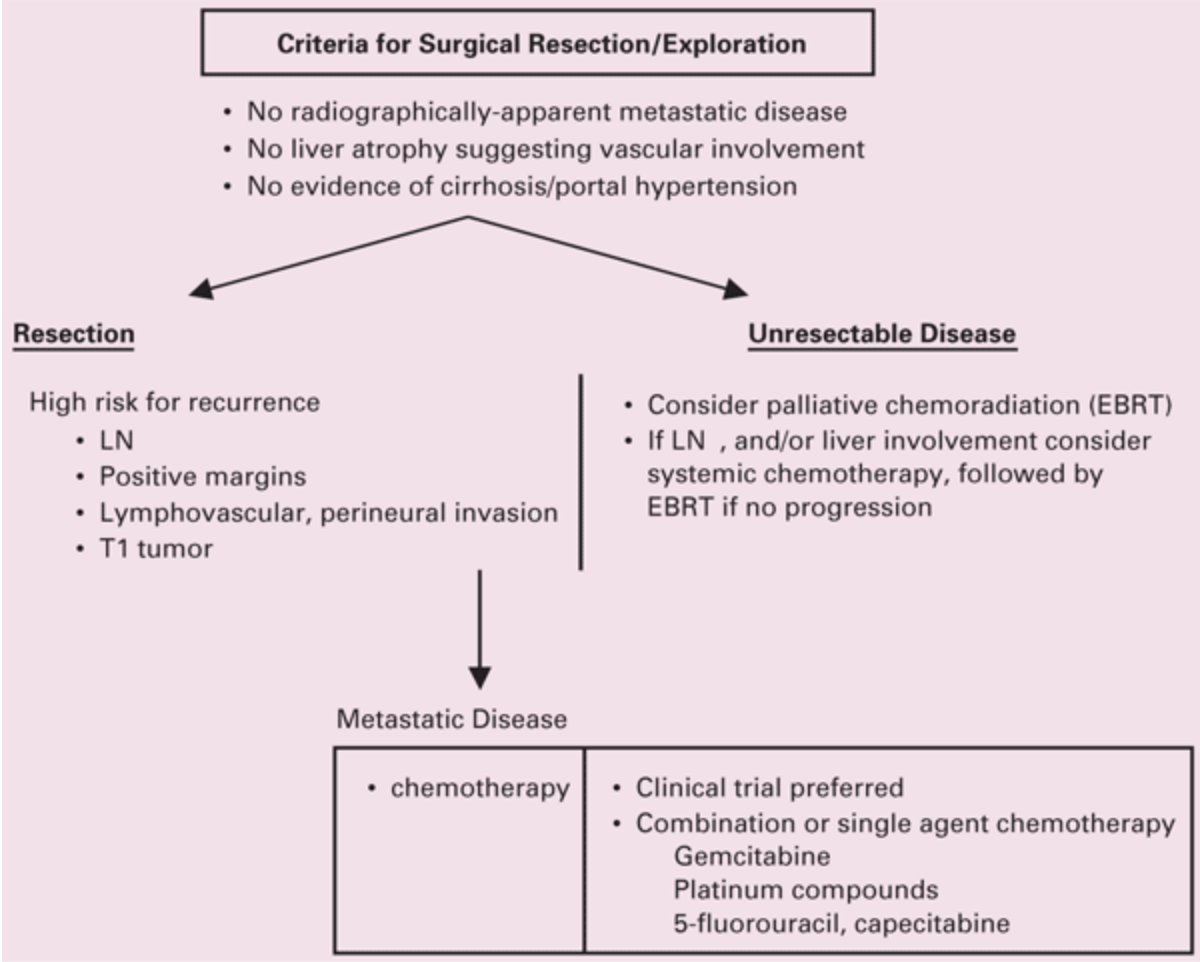
Krukenberg tumor





Retrograde lymphatic spread of mucin producing gastric carcinoma in peritoneal cavity. Nodules on surface of ovaries.
At right are signet ring cells characteristic of gastric adenocarcinoma. Lobular carcinoma of the breast may also metastasize in the same fashion.

Gastric cancer



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Trastuzumab-deruxtecan only if EGFR mutated

Fig. 15-4 Accessed 04/01/2010

Treatment strategy

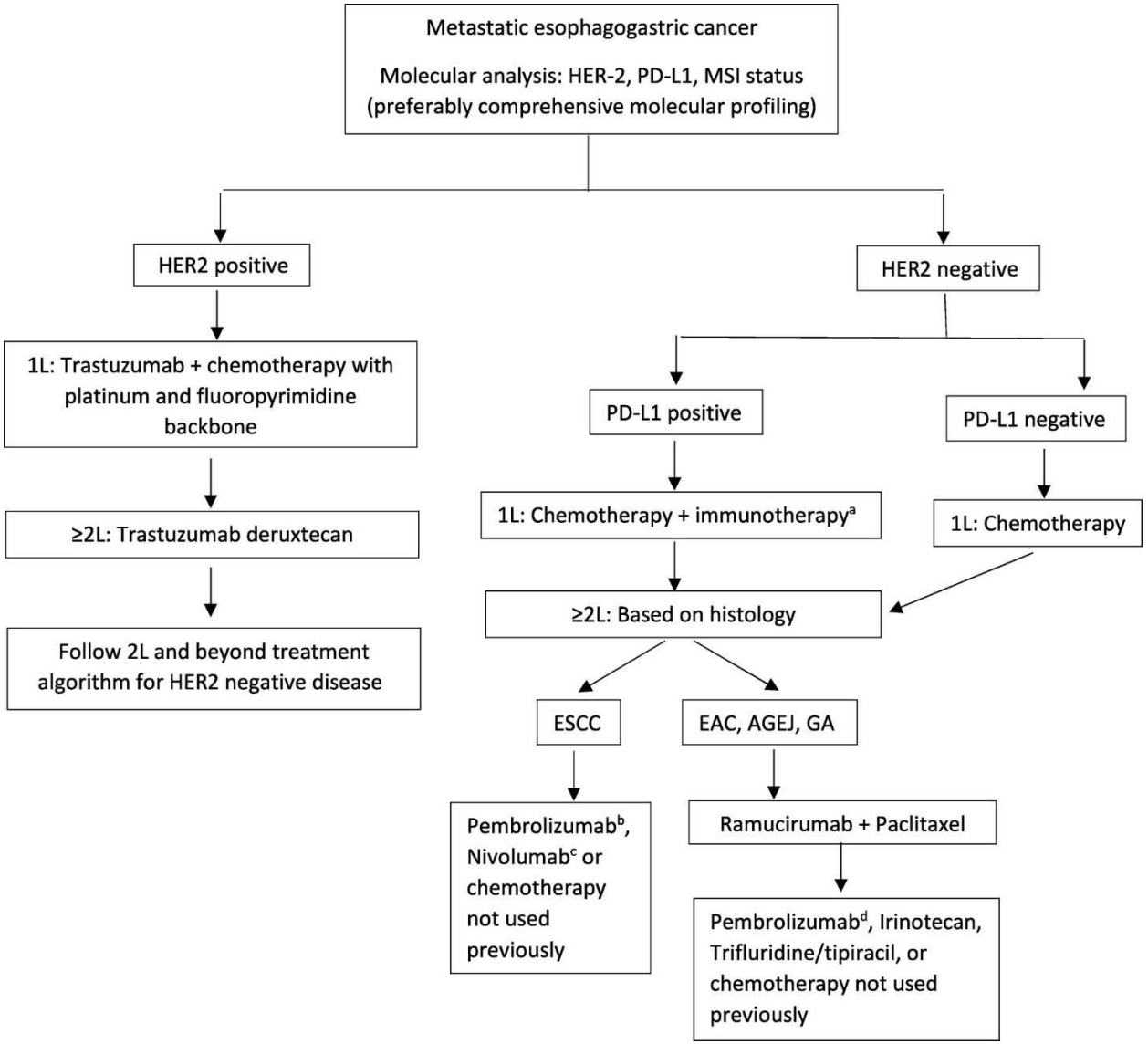
- Resection is indicated in patients with stage I-III disease with minimal lymph node involvement.
- Subtotal gastrectomy in the case of proximal cardia or distal lesions provided the fundus or gastroesophageal junction is not involved.
- Total gastrectomy in the case of diffuse tumors arising in the body and extending to within 6cm of the cardia.

Treatment strategy

- Lymphadenectomy of perigastric, left gastric, common hepatic, splenic, and celiac axis nodes (D2) may be curative
- No need for adjuvant radiation therapy
- 50% recur locally or intraperitoneally if less than D2 resection.
- Nivolumab (PDL1 target)and FOLFOX chemotherapy.
- Oxaliplatin induces immunogenic death of tumor cells, which activates antigen processing cells via calreticulin 1, HMGB 1, and other damage associated molecular patterns.

Treatment strategy

- Percutaneous gastrostomy/jejunostomy and endoscopic placement of self-expandable metallic stents are safe, effective and minimally invasive palliative treatments for patients with luminal obstruction.



Mamdani, H, and Jalal, SL, "Where to Start and What to Do Next: The Sequencing of Treatments in Metastatic Esophagogastric Cancer," American Society of Clinical Oncology Educational Book 41 (March 25, 2021) 170-185. DOI: 10.1200/EDBK_321243 Figure 1

MALT lymphoma

- Extranodal marginal zone (MALT) lymphoma.
- Stomach is most common extranodal site.
- 5% of gastric tumors
- 50% of gastric lymphomas.
- Associated with H. pylori infection.
- In the stomach, MALT is induced, typically as a result of chronic gastritis.

MALT lymphoma

- Low grade tumors that do not regress with treatment of Helicobacter pylori usually contain genetic abnormalities
- t(11,18)(q21;q21)
- t(1;14)(p22;q32)
- t(14;18)(q23;q21)
- Trisomy 3
- t(11,18) brings together the API2 (apoptosis-inhibitor 2) gene on chromosome 11 with the MLT (mutated in MALT lymphoma) gene on chromosome 18. The fusion protein is thought to inhibit apoptosis.

MALT lymphoma

- t(1;14) and t(14;18) translocations increase expression of BCL10 and MLT proteins respectively.
- Antigen dependent activation of NF-κB in normal lymphocytes requires BCL10 and MLT.
- Constitutively expressed in t(1;14) and t(14;18) lesions.
- p53 and p16 mutations may lead to transformation to diffuse large B-cell lymphoma.

MALT lymphoma

- The neoplastic lymphocytes infiltrate the gastric glands focally to create lymphoepithelial lesions.
- This is diagnostic.
- Reactive-appearing B-cell follicles may be present, and, in about 40% of tumors, plasmacytic differentiation is observed.
- At other sites GI lymphomas may disseminate as discrete small nodules or infiltrate the wall diffusely.
- Like other tumors of mature B cells, MALTomas express the B-cell markers CD19 and CD20.
- They do not express CD5 or CD10, but are positive for CD43 in about 25% of cases

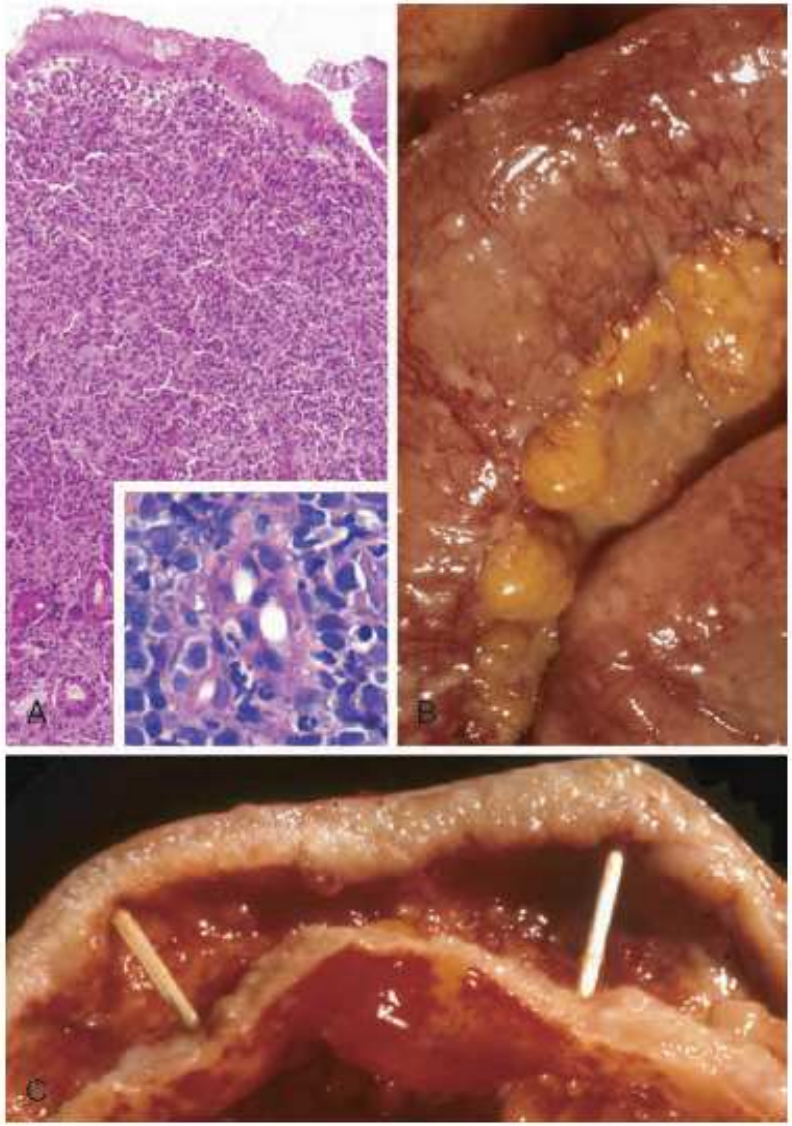


Figure 17-19 Lymphoma. **A,** Gastric MALT lymphoma replacing much of the gastric epithelium. Inset shows lymphoepithelial lesions with neoplastic lymphocytes surrounding and infiltrating gastric glands. **B,** Disseminated lymphoma within the small intestine with numerous small serosal nodules. **C,** Large B-cell lymphoma infiltrating the small intestinal wall and producing diffuse thickening.

Treatment of MALT not responsive to H. pylori therapy

- Cyclophosphamide, doxorubicin, vinblastine, prednisone, etoposide regimen followed by antibody to CD-20 is the treatment regimen for high grade lymphoma.

Carcinoid tumor

- Gastric carcinoid tumors may be associated with endocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN-I, and Zollinger-Ellison syndrome.
- Grossly, carcinoids are intramural or submucosal masses that create small polypoid lesions.
- In the stomach they typically arise within oxyntic mucosa.
- The overlying mucosa may be intact or ulcerated
- Carcinoids tend to be yellow or tan in color and are very firm as a consequence of an intense desmoplastic reaction.

Carcinoid tumor

- Histologically, carcinoids are composed of islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and a round to oval stippled nucleus.
- There is minimal pleomorphism.

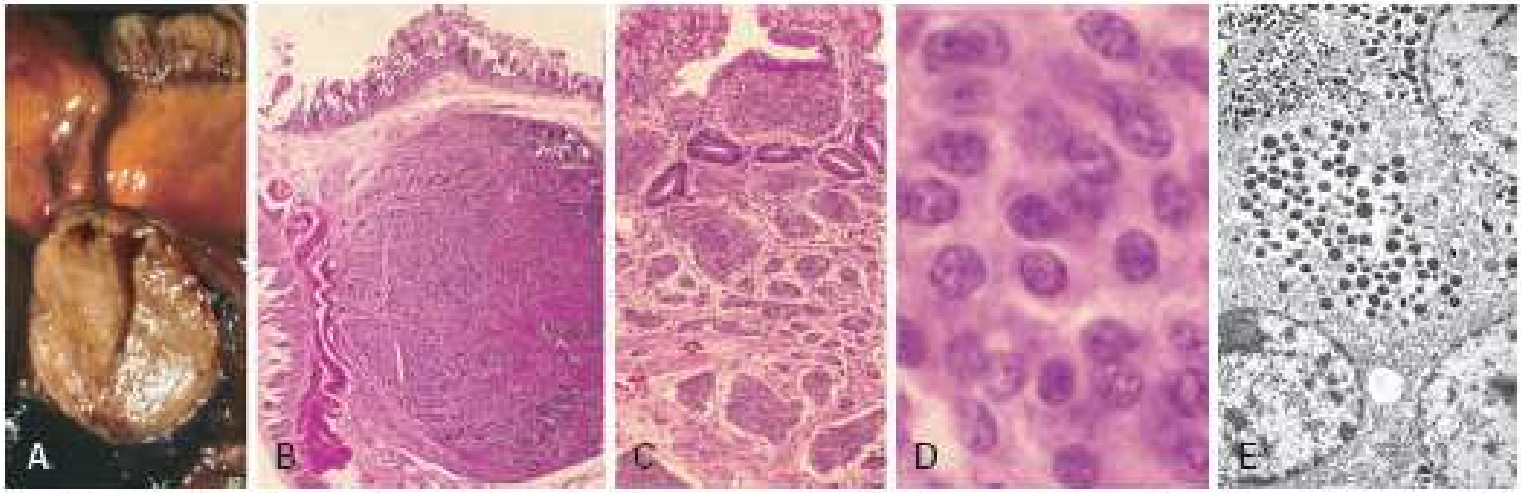


Figure 17-20 GI carcinoid tumor (neuroendocrine carcinoma). **A,** Gross cross-section of a submucosal tumor nodule. **B,** Microscopically the nodule is composed of tumor cells embedded in dense fibrous tissue. **C,** In other areas, the tumor has spread extensively within mucosal lymphatic channels. **D,** High magnification shows the bland cytology of carcinoid tumors. The chromatin texture, with fine and coarse clumps, is frequently described as a "salt and pepper" pattern. Despite their innocuous appearance, carcinoids can be clinically aggressive. **E,** Electron microscopy reveals cytoplasmic dense core neurosecretory granules.

Gastrointestinal stromal cell tumor

- Most common mesenchymal tumor in gastrointestinal tract
- Stomach (60%) and jejunum and ileum (30%)
- Arise from interstitial cells of Cajal.
- 25% metastasize (gastric)
- 35-40% metastasize (small intestine)
- Mean age 60-65 years old

Gastrointestinal stromal cell tumor

- Familial:
- Germline mutations in C-KIT or PDGFRα
- Autosomal dominant
- Immunopositive for SDHB
- Neurofibromatosis:
- 7% of patients with NF1 develop one or more GIST, usually in small bowel
- Both C-KIT (75% of cases) and PDGFR (10% of cases) mutations lead to constitutive phosphorylation of tyrosine kinases (75% of cases)
- C-KIT and PDGFR mutations are mutually exclusive

Gastrointestinal stromal tumor

- Succinate dehydrogenase (SDH) deficient
- Young adults (before age 40)
- 1 - 2% of all GIST in pediatric patients
- Female preponderance (> 2:1)
- Almost exclusively in stomach (predilection for distal stomach and antrum)
- Minimal nuclear pleomorphism

Gastrointestinal stromal tumor

- Succinate dehydrogenase (SDH) deficient:
- Carney triad:
- GIST, pulmonary chondroma, paraganglioma
- Nonhereditary
- SDHC promoter hypermethylation
- Small percentage have germline SDH mutations
- Carney-Stratakis syndrome:
- GIST and paraganglioma
- Autosomal dominant
- Germline mutations in SDHB, SDHC or SDHD subunit

Gastrointestinal stromal cell tumor

- GIST is CD117+
- 82% of gastric tumors are CD34+, but only 40% of small intestinal tumors
- SMA+ in 18% of gastric tumors, but 34% of small intestinal tumors
- Tumors that show features of enteric plexus (spindle cell) differentiation are often classified among GISTs.
- Gastrointestinal autonomic tumor (GIST)
- Vimentin, S100, and NSE+.

Gastrointestinal stromal cell tumor

- Well circumscribed, intramural lesion, centered within the muscularis propria
- Fleshy, tan-pink cut surfaces, which may show hemorrhage or cystic degeneration
- Size >5cm associated with poor prognosis
- 3 morphologic types:
- Spindle (70%),
- Epithelioid (20%)
- Mixed (10%)

Gastrointestinal stromal cell tumor

- Epithelioid:
- Round cells with clear to eosinophilic cytoplasm in sheets or nests; increased tendency for pleomorphism versus spindle type
- Subtypes: sclerosing, discohesive, hypercellular, sarcomatous with significant atypia and mitotic activity
- Mixed:
- Tumor is composed of cells with spindle and epithelioid morphology

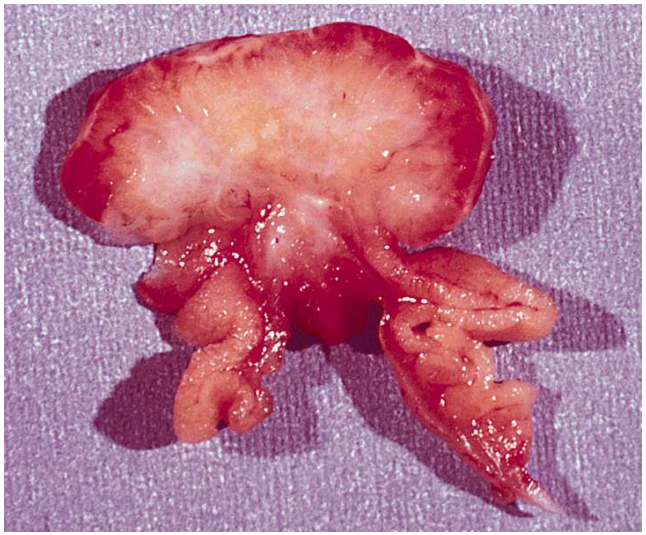
Gastrointestinal stromal cell tumor

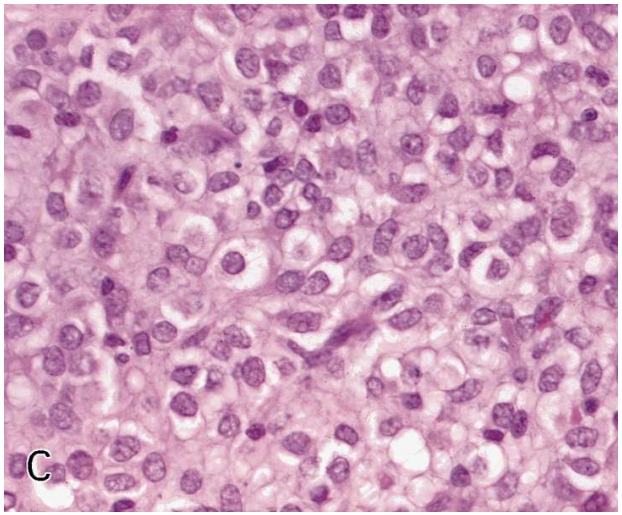
- Spindle:
- Bland spindle cells with faintly eosinophilic cytoplasm in a syncytial pattern; elongated nuclei with inconspicuous nucleoli;
- Subtypes: sclerosing, palisaded, vacuolated, diffuse hypercellular, sarcomatoid features with significant nuclear atypia and mitotic activity

Gastrointestinal stromal tumor

- Dedifferentiated:
- Anaplastic appearance with an unusual phenotype (may lose expression of KIT or may aberrantly express other markers such as cytokeratin)

Gastrointestinal stromal tumor





Gross appearance of primarily submucosal tumor. Typical central nuclei and partially retracted cytoplasm are seen. Tumors vary in cellularity: those that are the most cellular tend to have smaller cells and larger nuclei. These are the areas where mitoses are most likely to be found.

Figs. 7-01R and 07-08C

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

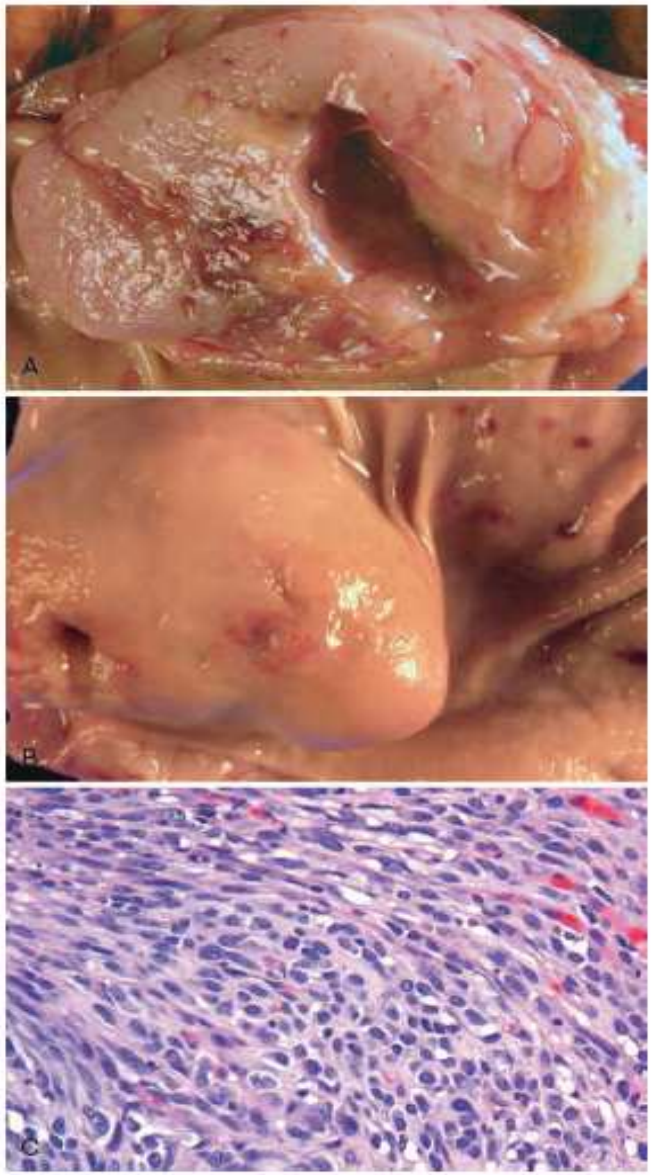
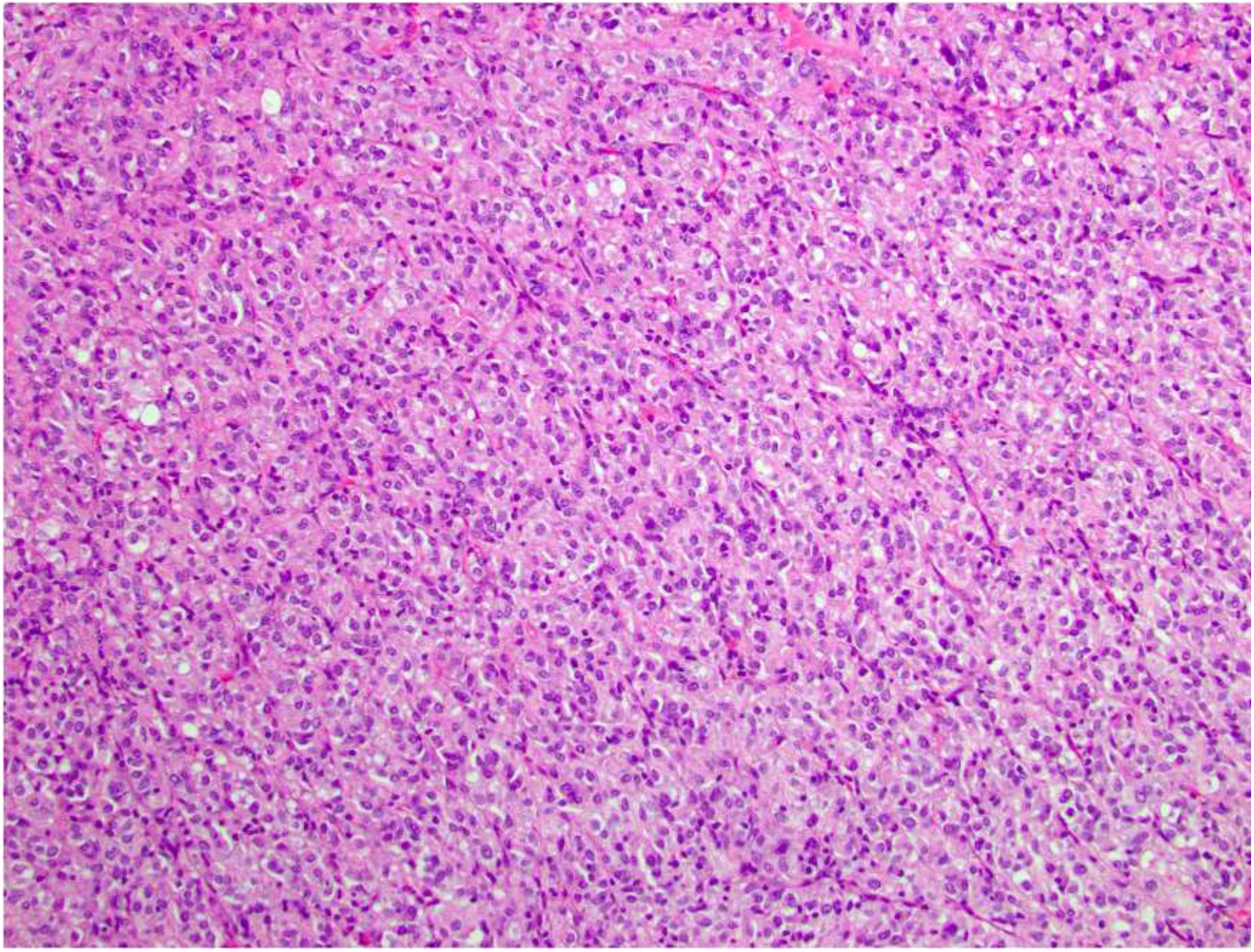
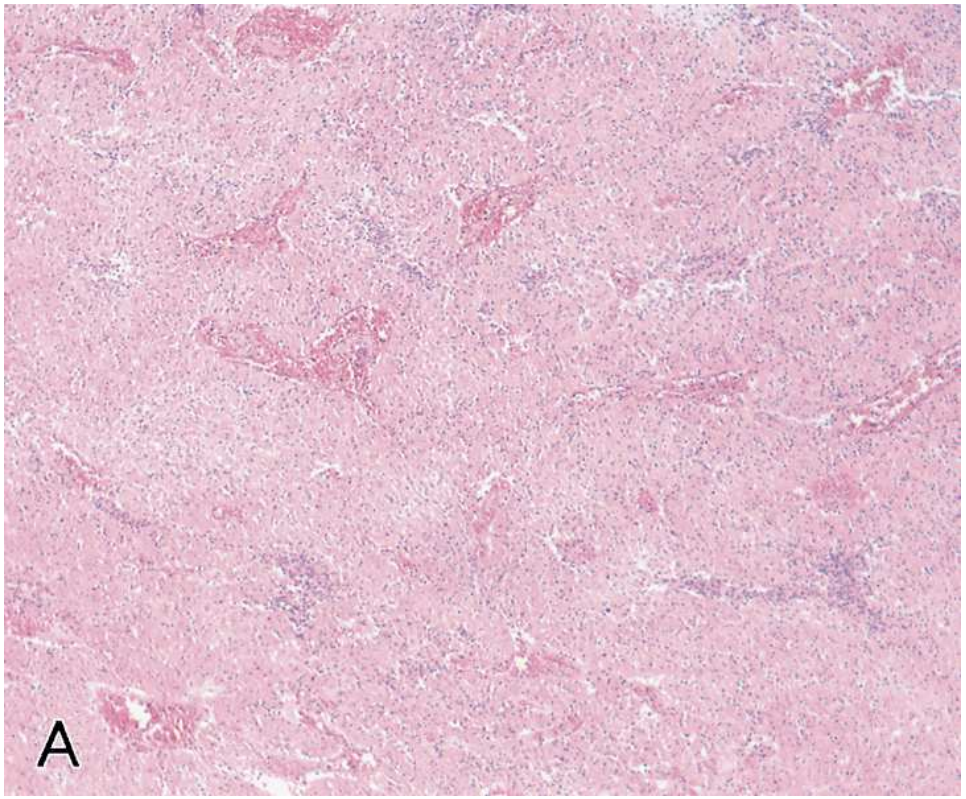


Figure 17-21 GI stromal tumor. **A,** On cross-section a whorled texture is evident within the white, fleshy tumor. **B,** The mass is covered by intact mucosa. **C,** Histologically the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)



Gastrointestinal stromal tumor



The more intact parts of the tumor are composed of uniform eosinophilic cells in which are seen occasional lymphoid aggregates. Resemble enteric plexus.

Fig. 7-11A

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

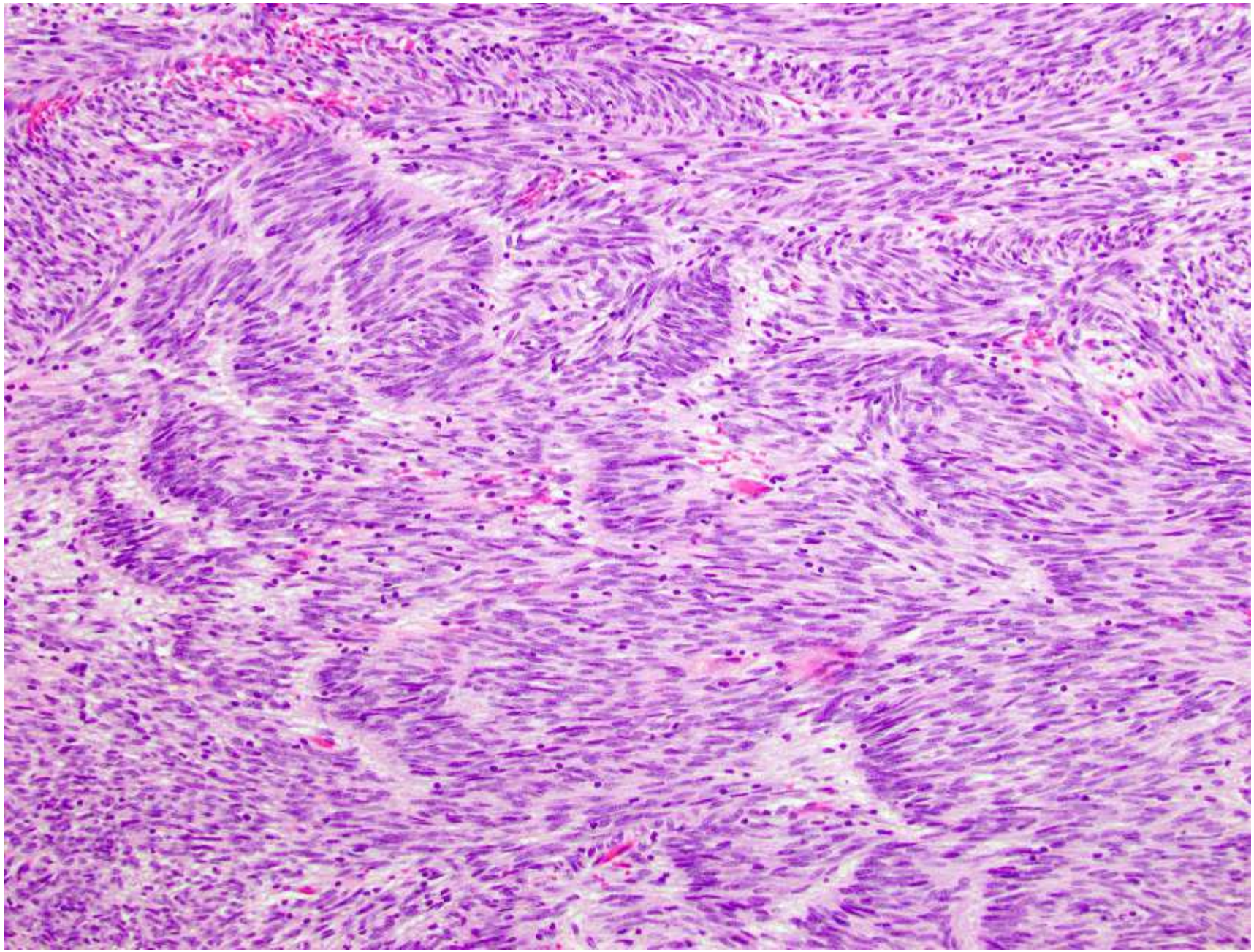


Table 17-6 Features of Gastrointestinal Carcinoid Tumors

Feature	Esophagus	Stomach	Proximal Duodenum	Jejunum and Ileum	Appendix	Colorectum
Fraction of GI carcinoids	<1%	<10%	<10%	>40%	<25%	<25%
Mean patient age (yr)	Rare	55	50	65	All ages	60
Location	Distal	Body and fundus	Proximal third, peri-ampullary	Throughout	Tip	Rectum > cecum
Size	Limited data	1-2 cm, multiple; >2 cm, solitary	0.5-2 cm	<3.5 cm	0.2-1 cm	>5 cm (cecum); <1 cm (rectum)
Secretory product(s)	Limited data	Histamine, somatostatin, serotonin	Gastrin, somatostatin, cholecystokinin	Serotonin, substance P, polypeptide YY	Serotonin, polypeptide YY	Serotonin, polypeptide YY
Symptoms	Dysphagia, weight loss, reflux	Gastritis, ulcer, incidental	Peptic ulcer, biliary obstruction, abdominal pain	Asymptomatic, obstruction, metastatic disease	Asymptomatic, incidental	Abdominal pain, weight loss, incidental
Behavior	Limited data	Variable	Variable	Aggressive	Benign	Variable
Disease associations	None	Atrophic gastritis, MEN-I	Zollinger-Ellison syndrome, NF-1, sporadic	None	None	None

MEN-I, Multiple endocrine neoplasia type I; NF-1, neurofibromatosis type I.