DISORDERS OF THE SMALL BOWEL

Kenneth Alonso, MD, FACP

Anatomy

- The ileum and jejunum are suspended by mesentery. The root of the mesentery is attached to the posterior body wall from the left side of L2 to the right sacro-iliac joint.
- The cecum does not have a mesentery.
- The root of the appendix attaches where the three tenia coli unite.
- The cecum and appendix are supplied by the ileocolic artery from the superior mesenteric artery.

Anatomy

- The superior mesenteric artery supplies the entire small bowel, cecum, appendix, ascending colon, the right two-thirds of the transverse colon and pancreas.
- Arises at L1.
- Overlies 3rd portion of duodenum, the uncinate process of the pancreas, and the left renal vein.
- An aneurysm at this site may block the duodenum as well as the left renal vein (as well as the infraphrenic, suprarenal and gonadal vein that drain into the left renal vein).

Anatomy

- 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.
- The greater splanchnic nerve (T5-T9) synapses at the celiac ganglion and suprarenal medulla.
- The lesser splanchnic nerve (T12) synapses at the renal plexus.

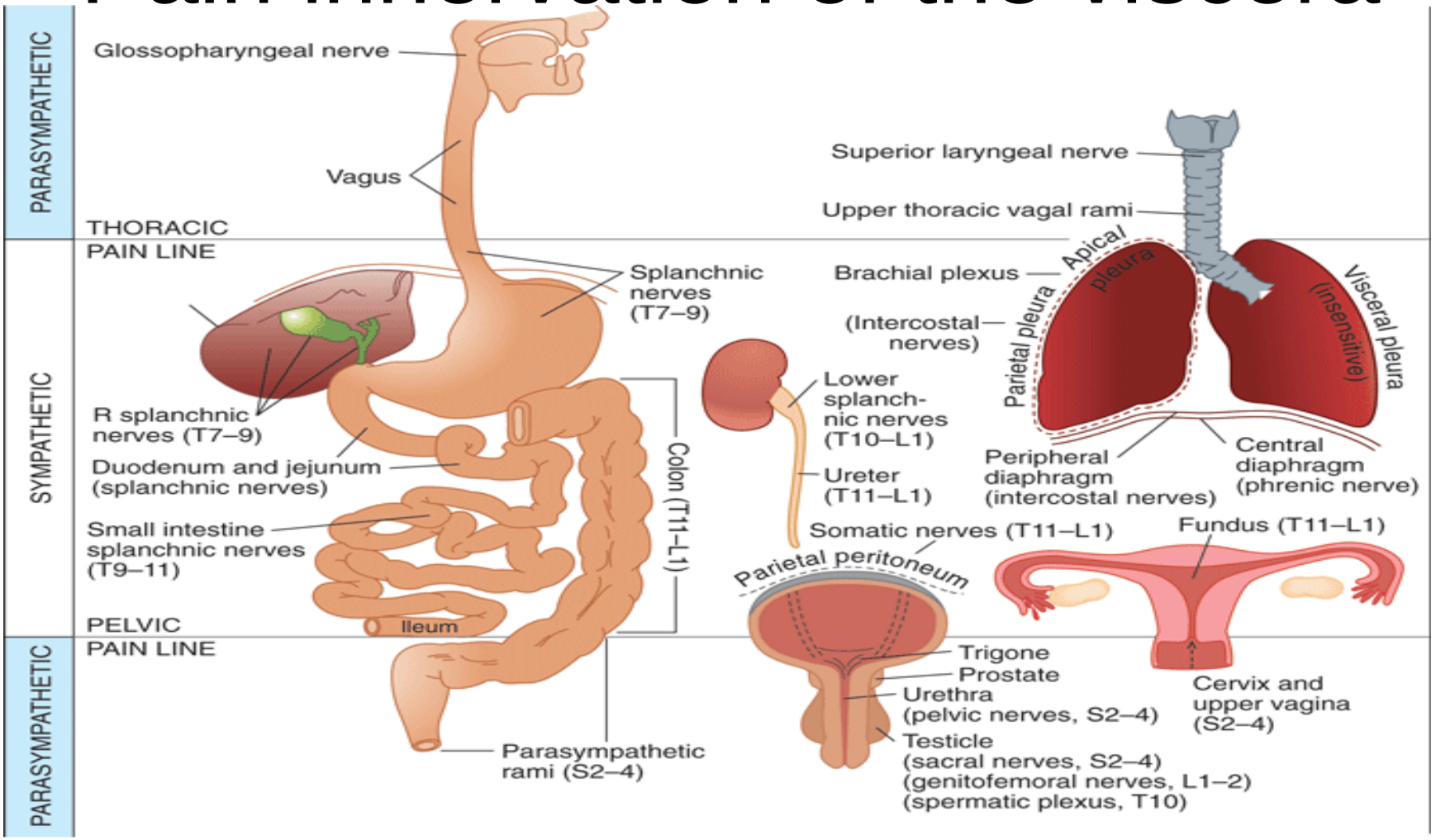
Anatomy

- Sensations of organ distension travel via parasympathetics.
- Pain afferents (general visceral afferent) travel with sympathetics to the level of preganglionic origin. Referred pain is perceived at the level of preganglionics.
- Peritoneal irritation, however, is localized (general somatic afferent).

Anatomy

- Paracolic gutters lie lateral to the ascending colon and descending colon. The phrenicolic ligament on the left limits fluid passage through the left gutter.
- Infracolic gutters lie medial to the large intestine. The root of the mesentery limits fluid passage to the pelvis from the right infracolic gutter.

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)
- T7-9 at base and left of spinous process is associated with somatic dysfunction of the small intestine
- At tip of 12^{th} rib, associated with somatic dysfunction of the appendix

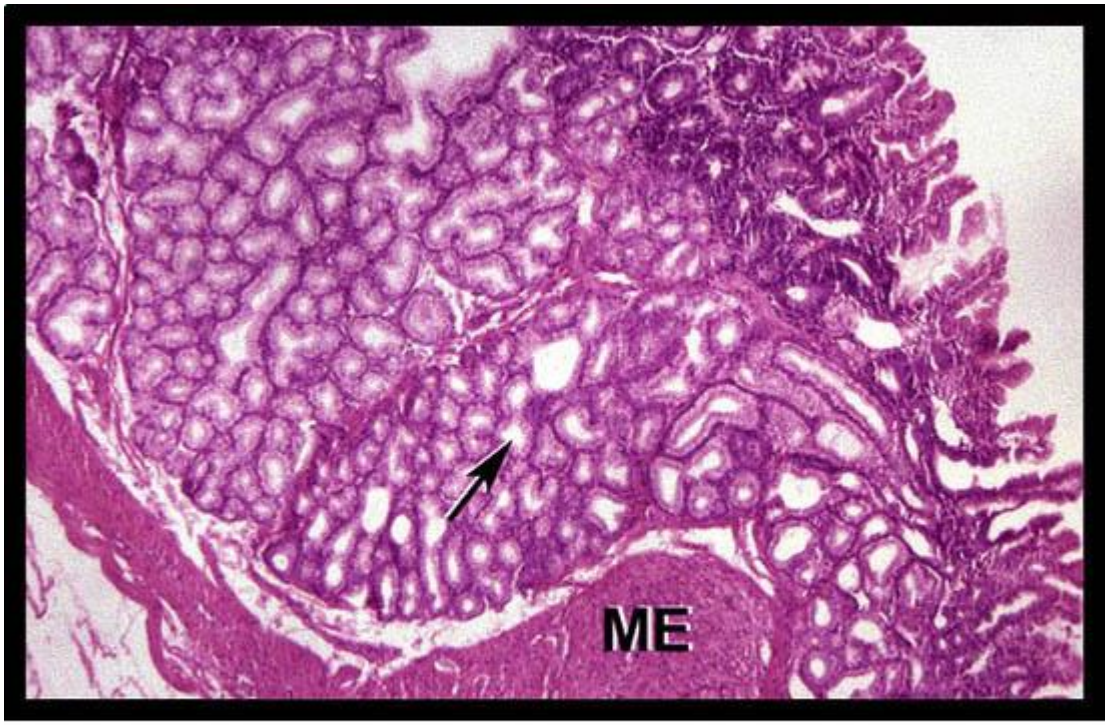
Histology of small bowel

- Small bowel is site of terminal digestion of foodstuffs.
- Small bowel mucosal lining studded with innumerable villi covered with epithelial cells.
- Central core of fibrovascular tissue.
- Crypts of Lieberkühn extend to muscularis mucosae. Source of stem cells.
- Villous:crypt ratio 5:1.

Small intestine

- Within the duodenum are abundant submucosal mucous glands, termed Brunner glands.
- These glands secrete bicarbonate ions, glycoproteins, and pepsinogen II and are virtually indistinguishable from the pyloric mucous glands.
- Small intestine mucosal lining is studded with innumerable villi that extend into the lumen as finger-like projections covered by epithelial lining cells.

Normal duodenum



Arrow points to Brunner's glands.

Fig. 14-34 Accessed 03/01/2010

Small intestine

- The central core of lamina propria contains blood vessels, lymphatics, a minimal population of lymphocytes, eosinophils and mast cells, and scattered fibroblasts and vertically oriented smooth muscle cells.
- Between the bases of the villi are the pit-like crypts of Lieberkühn, which contain stem cells that replenish and regenerate the epithelium. The crypts extend down to the muscularis mucosa.
- The muscularis mucosa is a smooth, continuous sheet, serving to anchor the configuration of villi and crypts alike.
- In normal individuals, the villus-to-crypt height ratio is about 4 to 5:1.

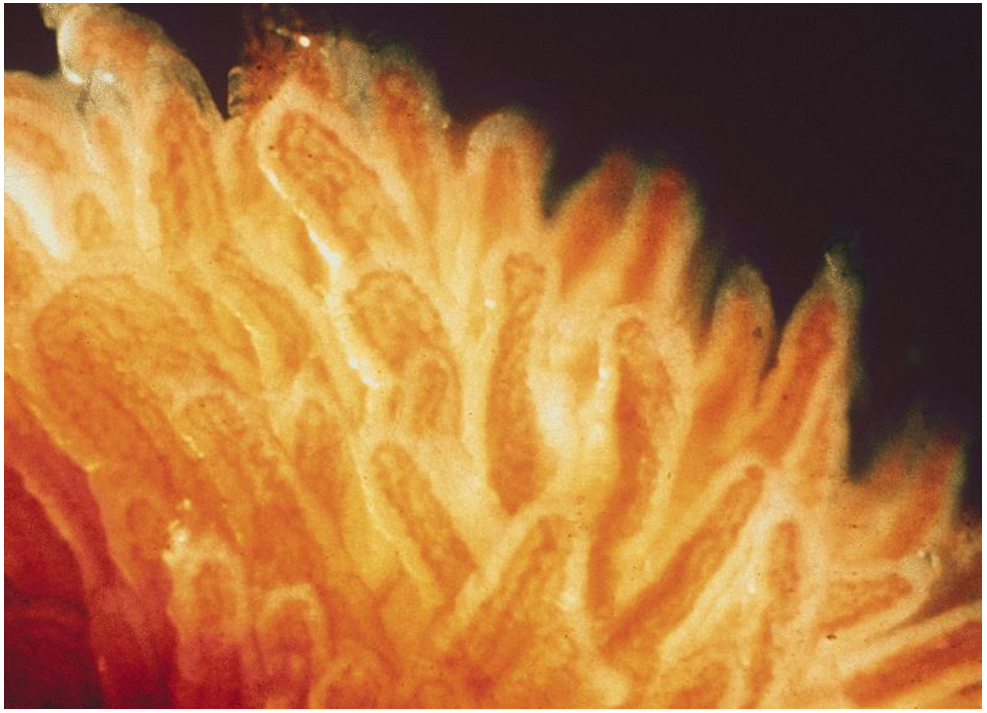
Small intestine

- Columnar absorptive cells are recognized by the dense array of microvilli on their luminal surface (the brush border) and the underlying mat of microfilaments (the terminal web).
- Interspersed regularly between the absorptive cells are mucin-secreting goblet cells and a few endocrine cells.
- Within the crypts reside stem cells, goblet cells, endocrine cells, and scattered Paneth cells.
- Paneth cells have apically oriented bright eosinophilic granules and contain a variety of antimicrobial proteins (e.g, defensins), which are part of the innate defense to bacterial infection.

Small intestine

- Site for terminal digestion and absorption of foodstuffs through the action of the columnar absorptive cells.
- The crypts secrete ions and water, deliver immunoglobulin A (IgA) and antimicrobial peptides to the lumen, and serve as the site for cell division and renewal.
- The mucous cells of both crypts and villi generate an adherent mucous coat, which both protects the surface epithelium and provides an ideal local milieu for uptake of nutrients.
- Specific receptors are also present on surface epithelial cells (e.g. vitamin B12 in the ileum).

Normal jejunum

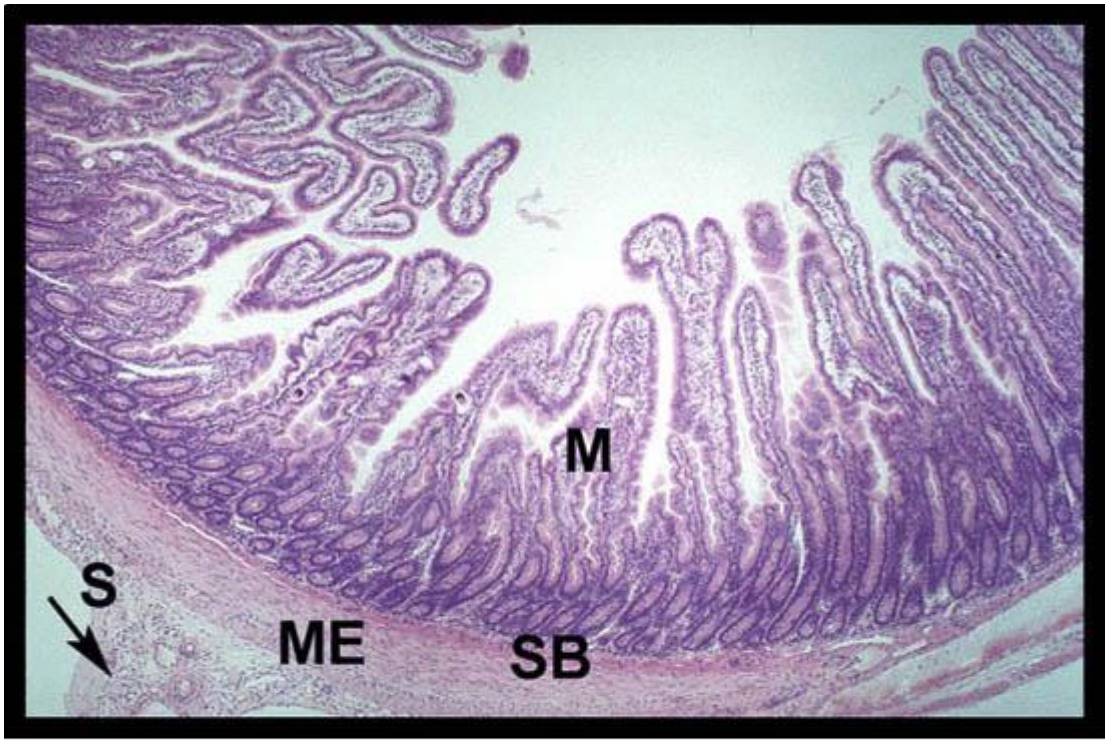


Dissecting microscopic appearance of normal finger-like villi on the surface of a jejunal biopsy.

Fig. 1-2

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.

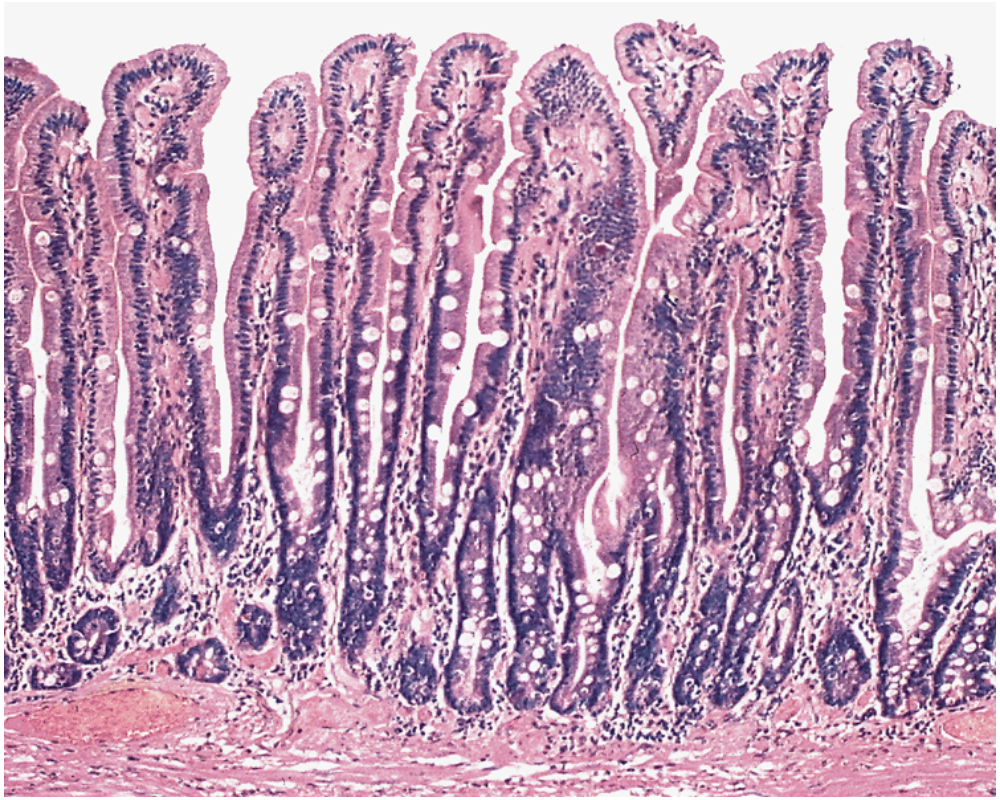
Normal jejunum



Source: Wilson FJ, Kestenbaum MG, Gibney JA, Matta S: *Histology Image Review*: http://www.accessmedicine.com

Fig. 14-55
Accessed
03/01/2010

Normal jejunum

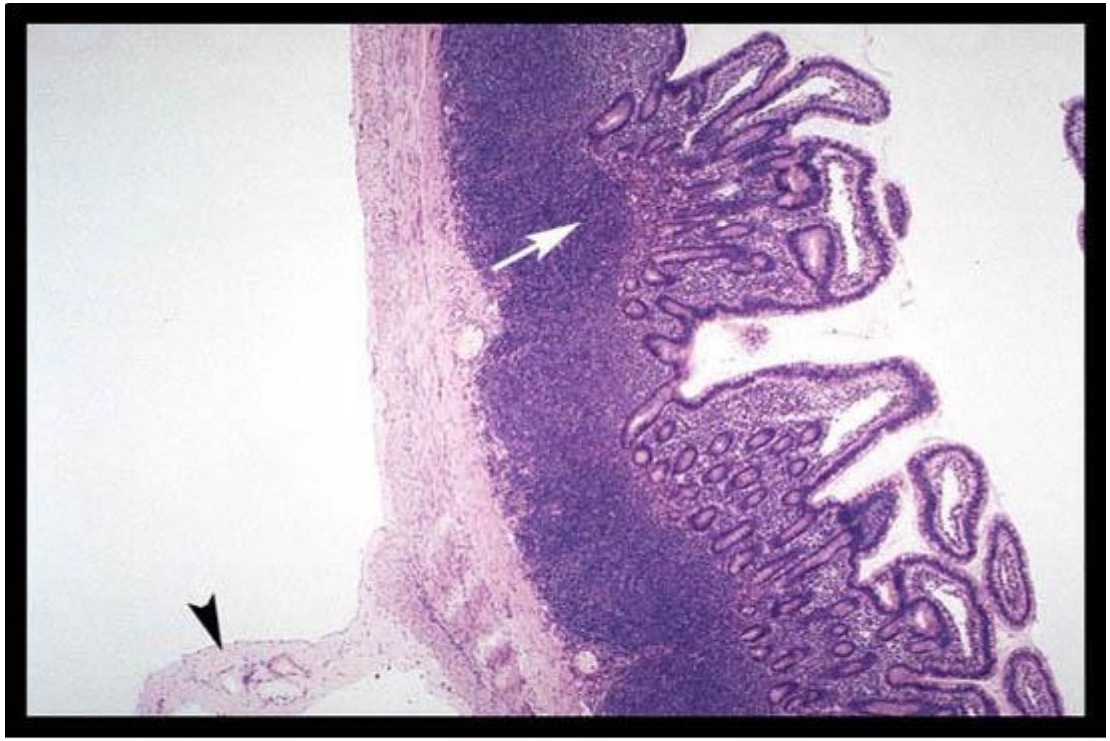


Normal jejunal mucosa has tall, finger-like villi that are covered mainly by absorptive cells, with relatively few interspersed goblet cells.

Fig. 1-3

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.

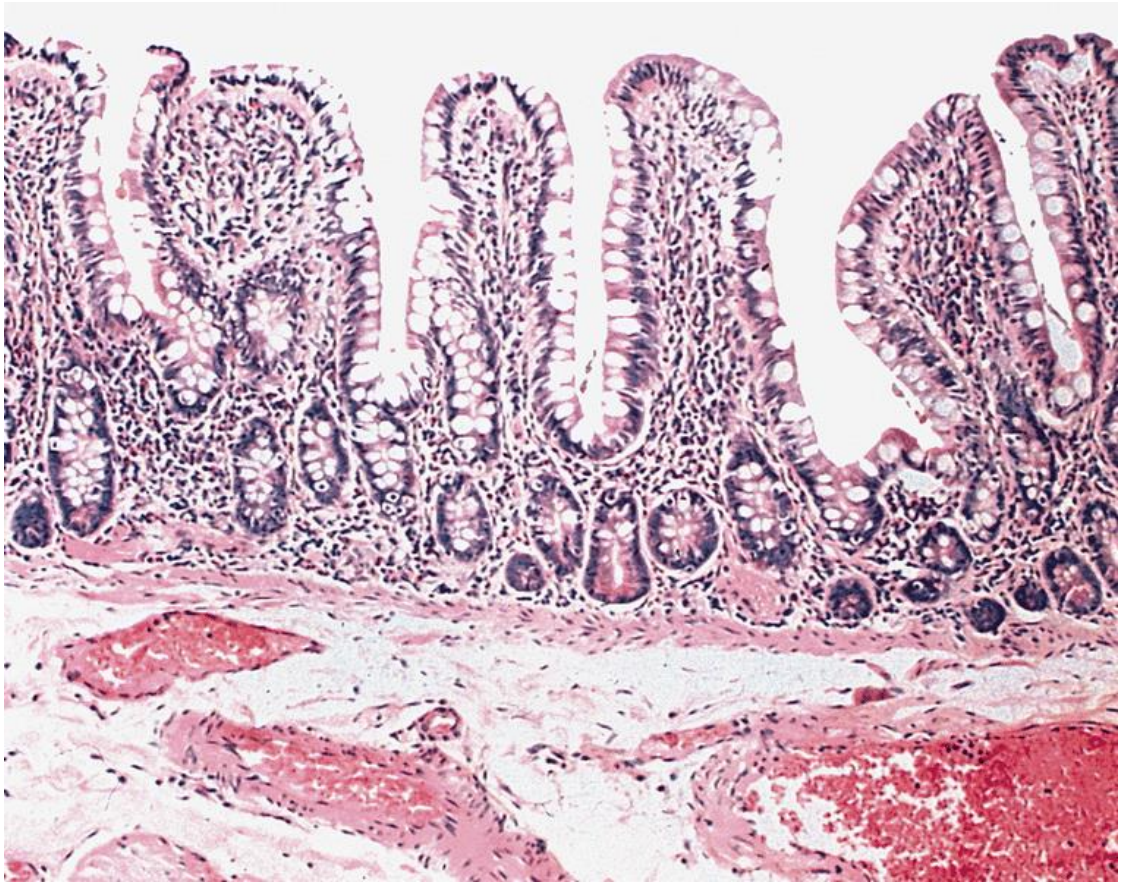
Normal ileum



The white arrow points to Peyer's patches. The black arrowhead points to the mesentery

Fig. 14-65 Accessed 03/01/2010

Normal ileum

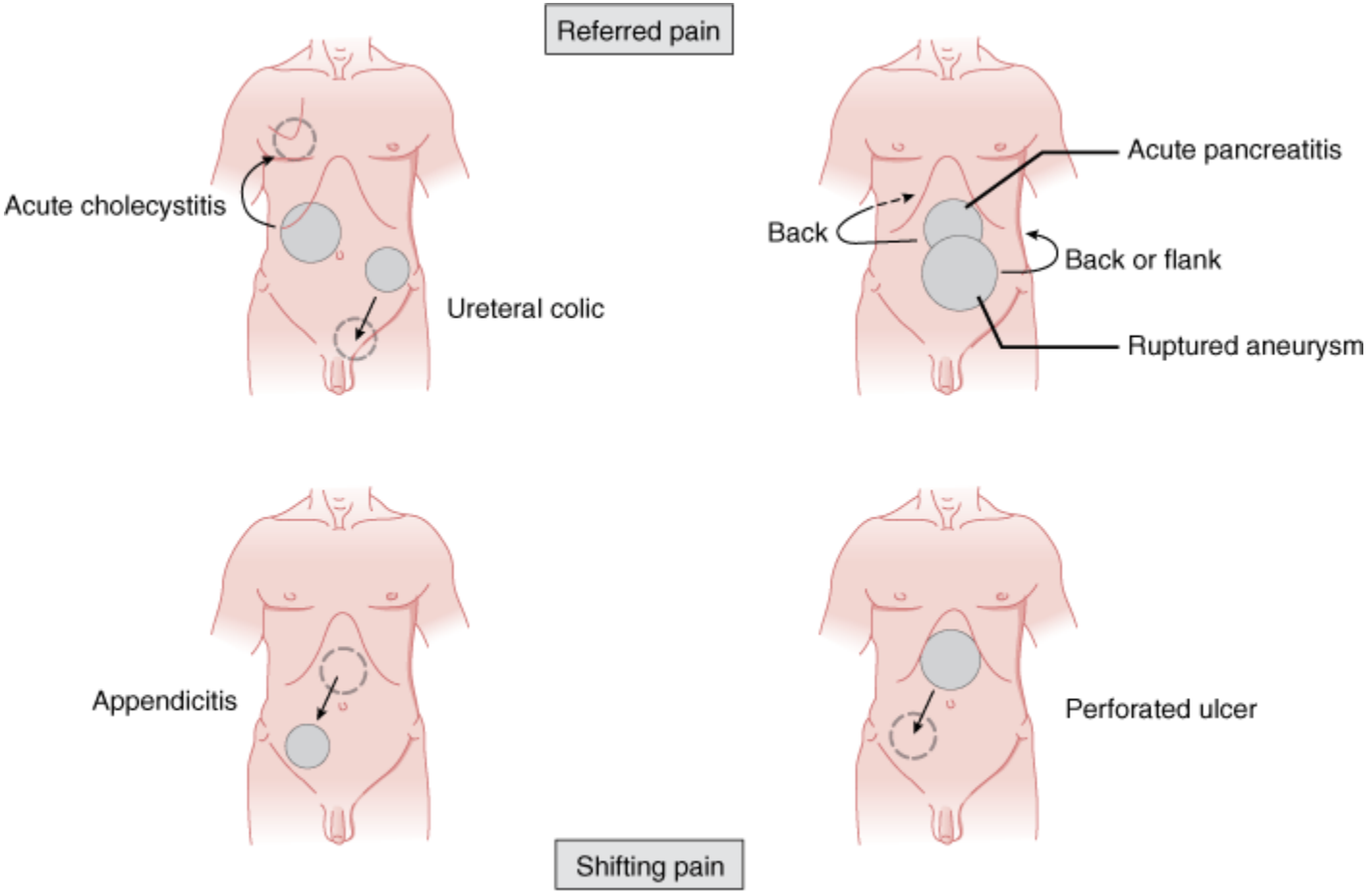


Normal terminal ileal mucosa has shorter villi than the jejunum. Goblet cells predominate in the surface epithelium. Bright red Paneth cell granules are conspicuous within one crypt towards the middle of the field.

Fig. 1-4

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.

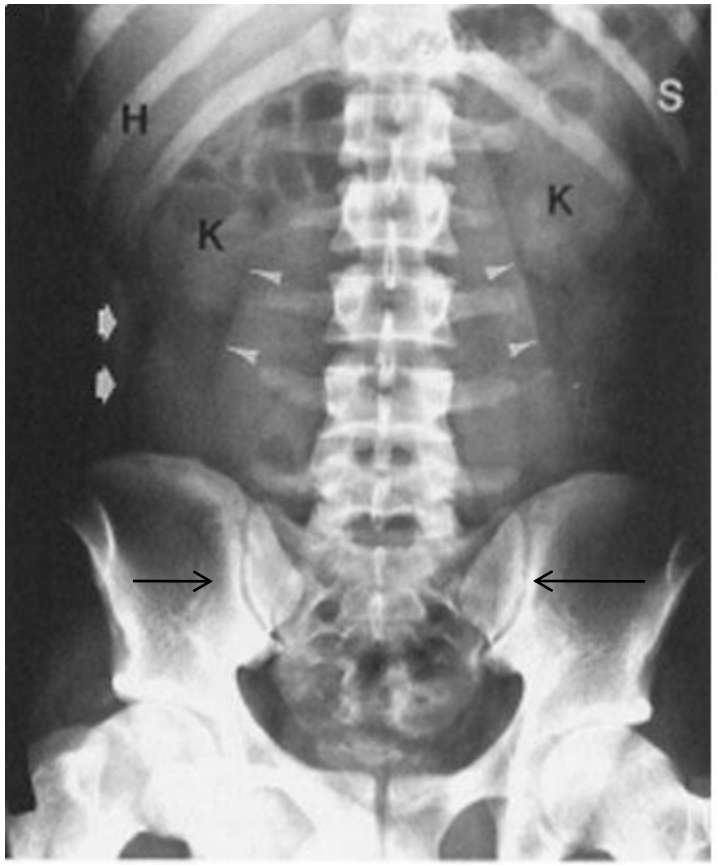
Referred abdominal pain



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

Fig. 21-2
Accessed 07/30/2010

Normal plain film of the abdomen

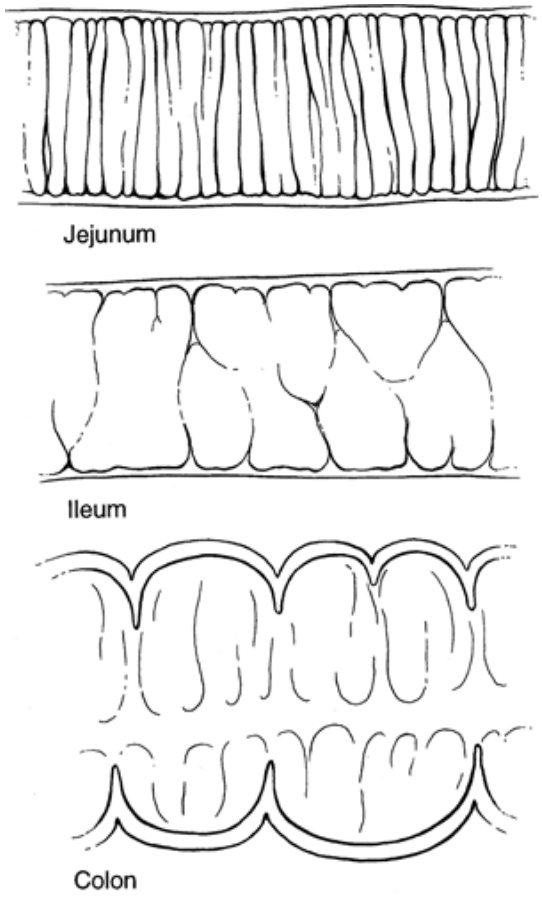


A

The lower margins of the posterior portion of the liver, the hepatic angle (H), and the lower part of the spleen (S) are delineated by a fat shadow. Both kidneys (K) and the psoas muscle shadows (arrowheads) are outlined by a fat shadow. The preperitoneal fat stripe is also shown bilaterally (arrows). The sacro-iliac joints are also shown bilaterally (dark arrows).

Fig. 8-1A Accessed 08/01/2010

Recognizing intestinal structures by their folds

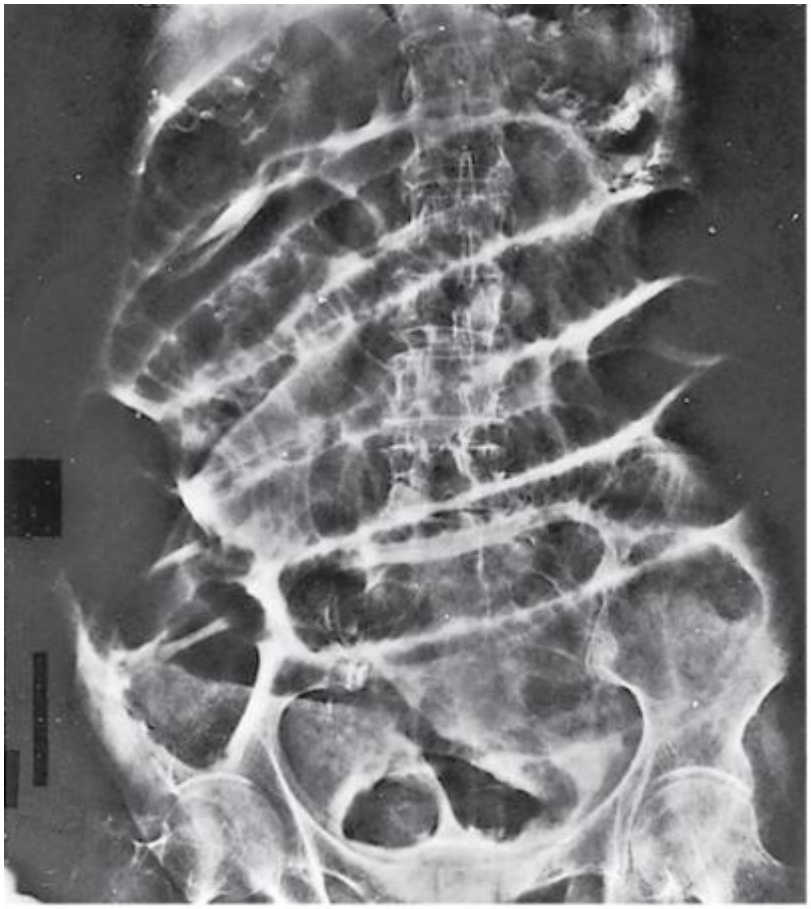


Schematic illustration of portions of bowel. The jejunum shows numerous mucosal folds, whereas the ileum has fewer folds. Both serosa of the jejunum and the ileum are smooth.
The colon has serosa indented by haustra, and mucosal folds do not cross the lumen.

Chen, MYM, Pope Jr, TL, Ott DJ: *Basic Radiology*: http://www.accessmedicine.com

Fig. 8-2 Accessed 08/01/2010

Small bowel obstruction



Upright abdominal X-ray showing dilated loops of small bowel in stair step pattern, with air–fluid levels and no gas in the colon. Patient had small-bowel obstruction.

(Reproduced, with permission, from Way LW [ed]: *Current Surgical Diagnosis & Treatment*, 9th ed. Lange, 1991.)
Fig. 13-4 Accessed 07/01/2010

Small bowel obstruction

- 80% of all bowel obstructions
- Peri-umbilical pain with episodes of cramping, progressing to constant pain
- Associated nausea and vomiting
- Loud intestinal sounds associated with exacerbations of pain
- Initially, may have bowel movements as bowel distal to obstruction is emptied. Constipation, absence of flatus, abdominal distention are late developments.
- Tinkling bowel sounds proximal to obstruction

Small bowel obstruction

- Adhesions or metastatic cancer common causes
- 20-40% of complete obstructions progress to strangulation and infarction. Clinical signs do not allow for identification of strangulation prior to infarction.
- Air-water soluble contrast study of small bowel is test of choice. CT scan sensitive at determining high-grade obstruction and should be performed before naso-gastric suction (proximal bowel decompression).
- If contrast reaches large bowel, obstruction will likely resolve spontaneously

Intestinal obstruction

- Obstruction of the GI tract may occur at any level, but the small intestine is most often involved because of its relatively narrow lumen.
- Hernias, intestinal adhesions, intussusception, and volvulus account for 80% of mechanical obstructions
- Tumors, infarction, and other causes of strictures, for example, Crohn disease, account for an additional 10% to 15%.
- The clinical manifestations of intestinal obstruction include abdominal pain and distention, vomiting, and constipation.

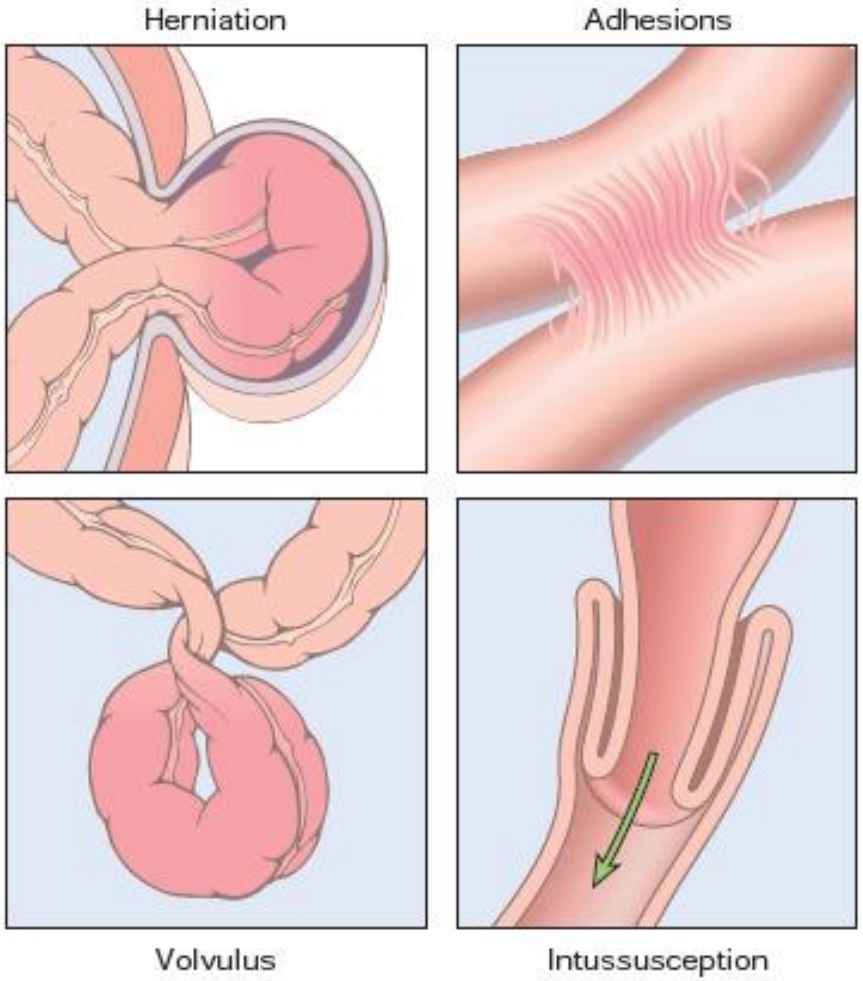


Figure 17-22 Intestinal obstruction. The four major causes of intestinal obstruction are (1) herniation of a segment in the umbilical or inguinal regions, (2) adhesion between loops of intestine, (3) volvulus, and (4) intussusception.

Hernias

- Obstruction usually occurs because of visceral protrusion (external herniation)
- Most frequently-associated with inguinal hernias, which tend to have narrow orifices and large serosal lined sacs.
- Small bowel loops are typically involved in obstruction, but omentum or large bowel may also protrude, and any of these may become entrapped.
- Pressure at the neck of the pouch may impair venous drainage of the entrapped viscus.

Hernias

- The resultant stasis and edema increase the bulk of the herniated loop.
- Complications:
- Permanent entrapment (incarceration)
- Arterial and venous compromise (strangulation)
- Infarction.

Adhesions

- The most common cause of obstruction in the US.
- Inflammation, endometriosis, surgical procedures lead to formation of fibrin bands that bind segments of bowel to each other or to the abdominal wall.
- Fibrous bands create closed loops through which other viscera may slide and become entrapped, resulting in internal herniation.

Volvulus

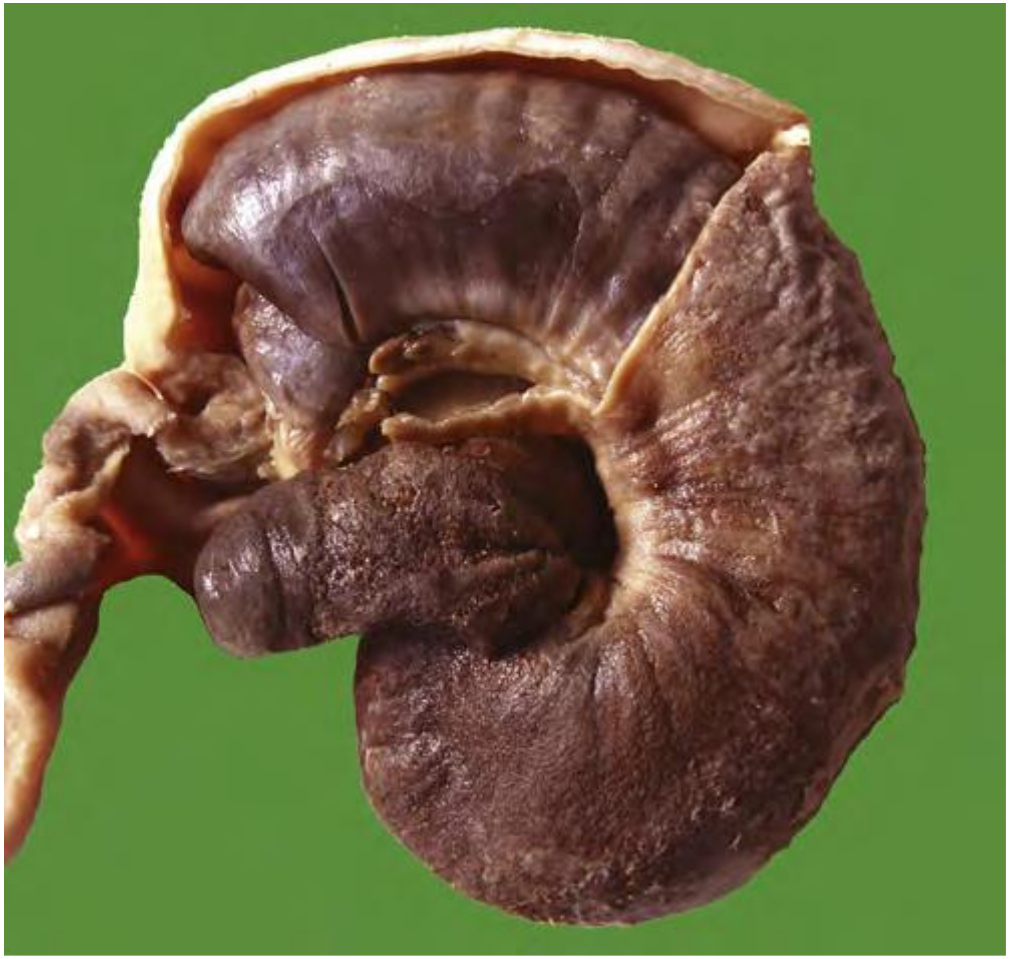
- A twisting of a loop of bowel about its mesenteric point of attachment
- Results in both luminal and vascular compromise (obstruction and infarction).
- May reduce spontaneously, particularly in children.
- It occurs most often in large redundant loops of sigmoid colon, followed in frequency by the cecum, small bowel, stomach, or, rarely, transverse colon.

Intussusception

- Occurs when a segment of the intestine, constricted by a wave of peristalsis, telescopes into the immediately distal segment.
- Once trapped, the invaginated segment is propelled by peristalsis and pulls the mesentery along.
- May progress to intestinal obstruction, compression of mesenteric vessels, and infarction.
- Intussusception is the most common cause of intestinal obstruction in children younger than 2 years of age
- May follow vaccination or viral infection
- Hyperplasia of Peyer's patches

Intussusception

Portion of bowel carried by peristalsis into distal segment. Compromises blood supply. Often led by polyp in lumen of compromised bowel. Presents as intestinal obstruction.



Klatt, EC, Robbins and Cotran Color Atlas of Pathology. Elsevier. Philadelphia. 2015. Figure 7-69 Accessed 11/07/2019

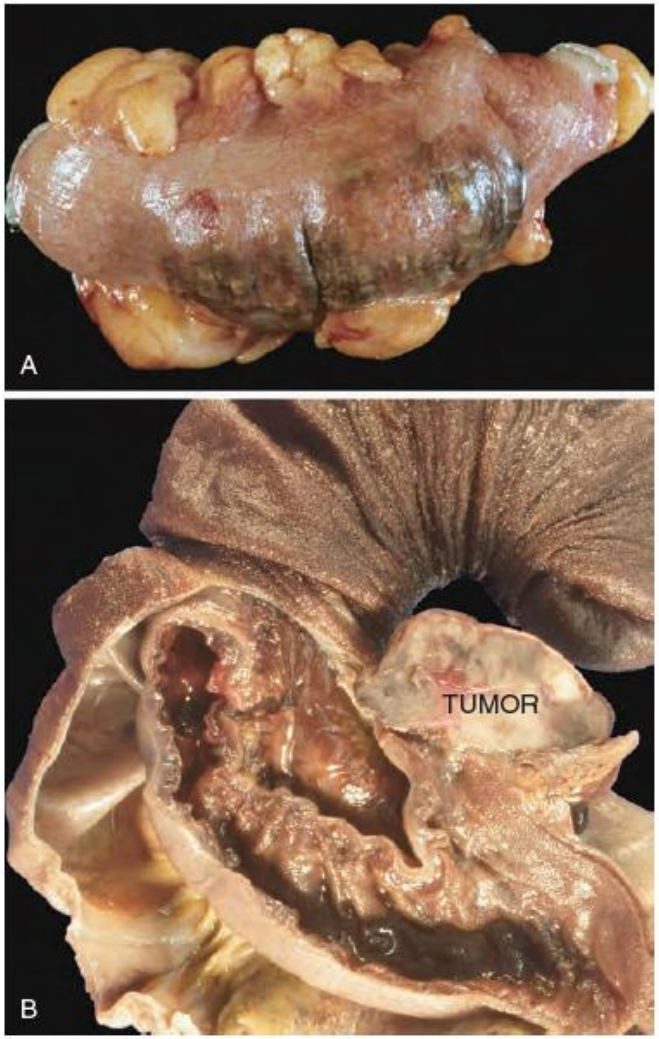


Figure 17-23 Intestinal obstruction. **A,** Portion of bowel incarcerated within an inguinal hernia. Note dusky serosa and hemorrhage that indicate ischemic damage. **B,** Intussusception caused by a tumor. The outermost layer of intestine with external serosa has been removed, leaving the mucosa of the second layer exposed. The serosa of the second layer is apposed to the serosa of the intussuscepted intestine. A tumor mass (right, labeled tumor) is present at the leading edge of the intussusception. Compare to Figure 17-22. **(B,** Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)

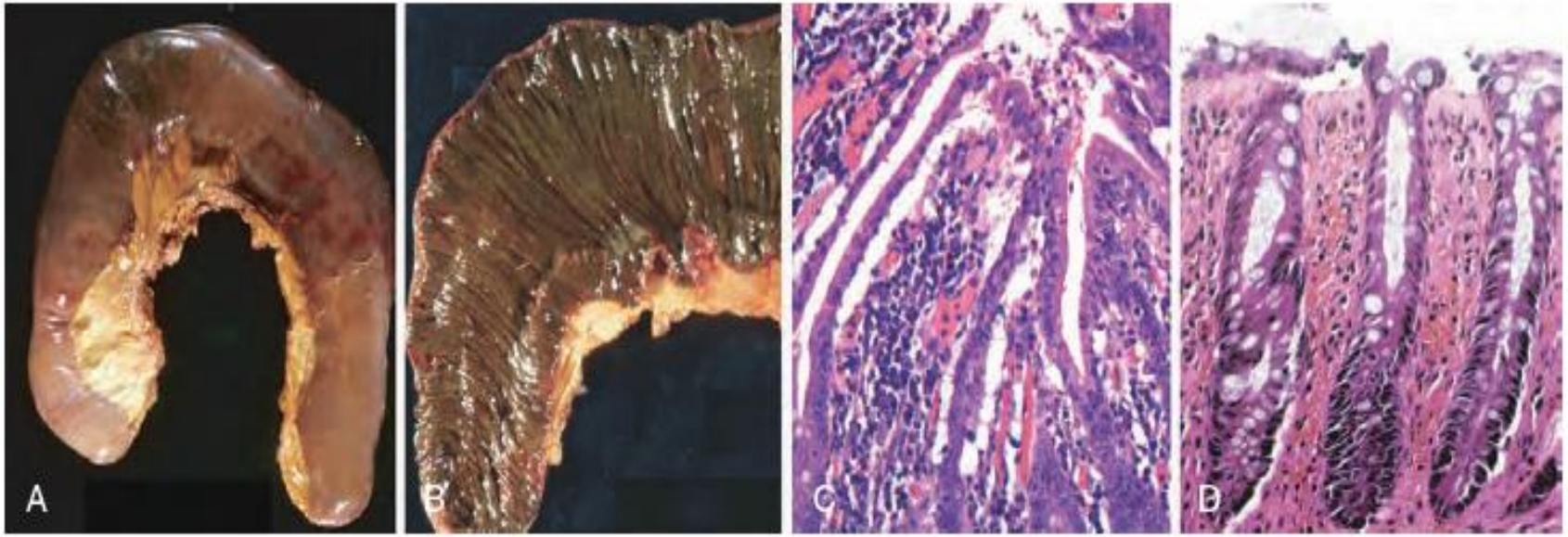
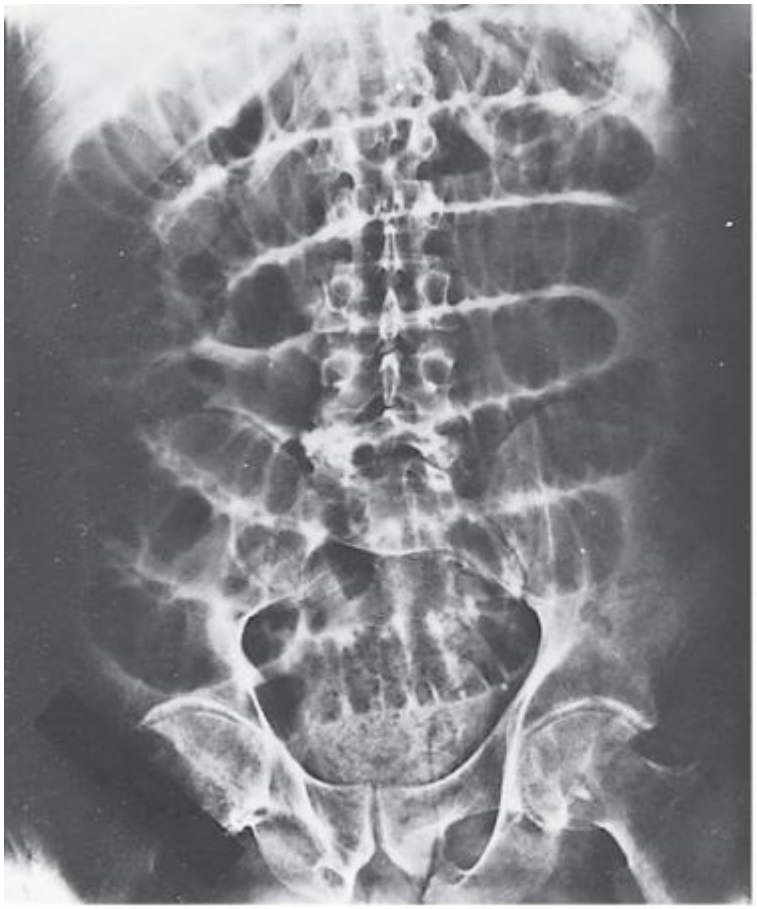


Figure 17-24 Ischemic bowel disease. **A,** Jejunal resection with dusky serosa of acute ischemia (mesenteric thrombosis). **B,** Mucosa is stained with blood after hemorrhage. **C,** Characteristic attenuated villous epithelium in this case of acute mesenteric thrombosis. **D,** Chronic colonic ischemia with atrophic surface epithelium and fibrotic lamina propria.

Diffuse peritonitis



Abdominal X-ray showing dilated loops of small and large bowel without air–fluid levels, typical of diffuse peritonitis.

(Reproduced, with permission, from Way LW [ed]: *Current Surgical Diagnosis & Treatment*, 6th ed. Lange, 1983.)

Fig. 13-3 Accessed 07/01/2010

Peritonitis

- Leakage of bile or pancreatic enzymes, which produces sterile peritonitis
- Perforation or rupture of the biliary system
- Acute hemorrhagic pancreatitis
- Talc or sutures
- Endometriosis
- Ruptured ovarian dermoid cyst (leaks keratin)
- Perforation of abdominal viscus
- Spontaneous bacterial peritonitis (cirrhosis, nephrotic syndrome)
- IgG4 sclerosing retroperitonitis

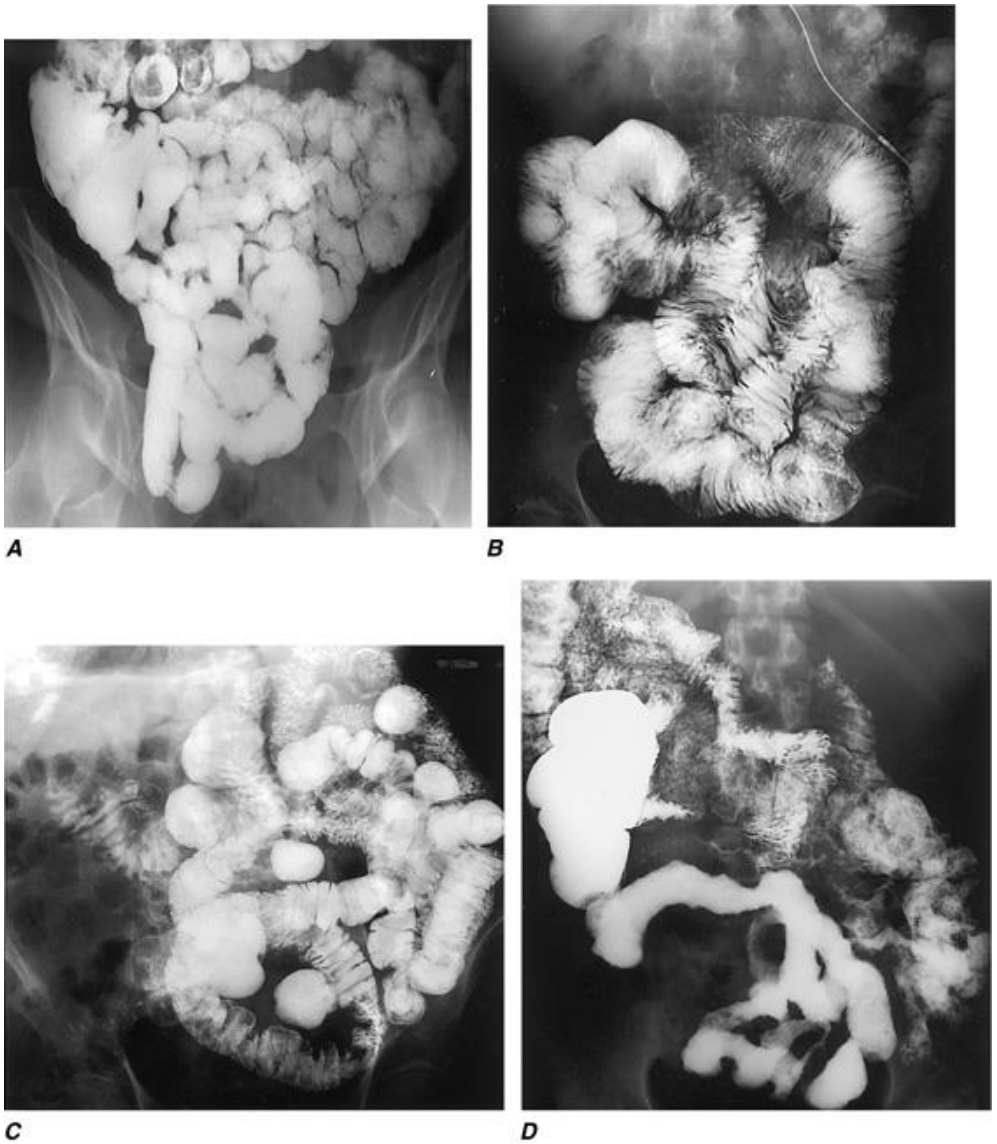
Mucosal injury

- Villous atrophy (small bowel).
- Diminished disaccharide enzymatic activity.
- Diminished Na^+ linked glucose and protein transport.
- Diminished NaCl absorption.
- Increased Cl^- secretion.
- Malabsorption may occur for many nutrients or for specific carbohydrates, fats, or micronutrients.

X-ray appearance

- X-rays may be nonspecific.
- Upper GI series with small bowel follow- through may show coarse fragmentation of the barium column, and
- Dilated bowel loops with thinned mucosal folds
- Suggesting celiac disease
- Thickened mucosal folds
- Suggesting Whipple’s Disease

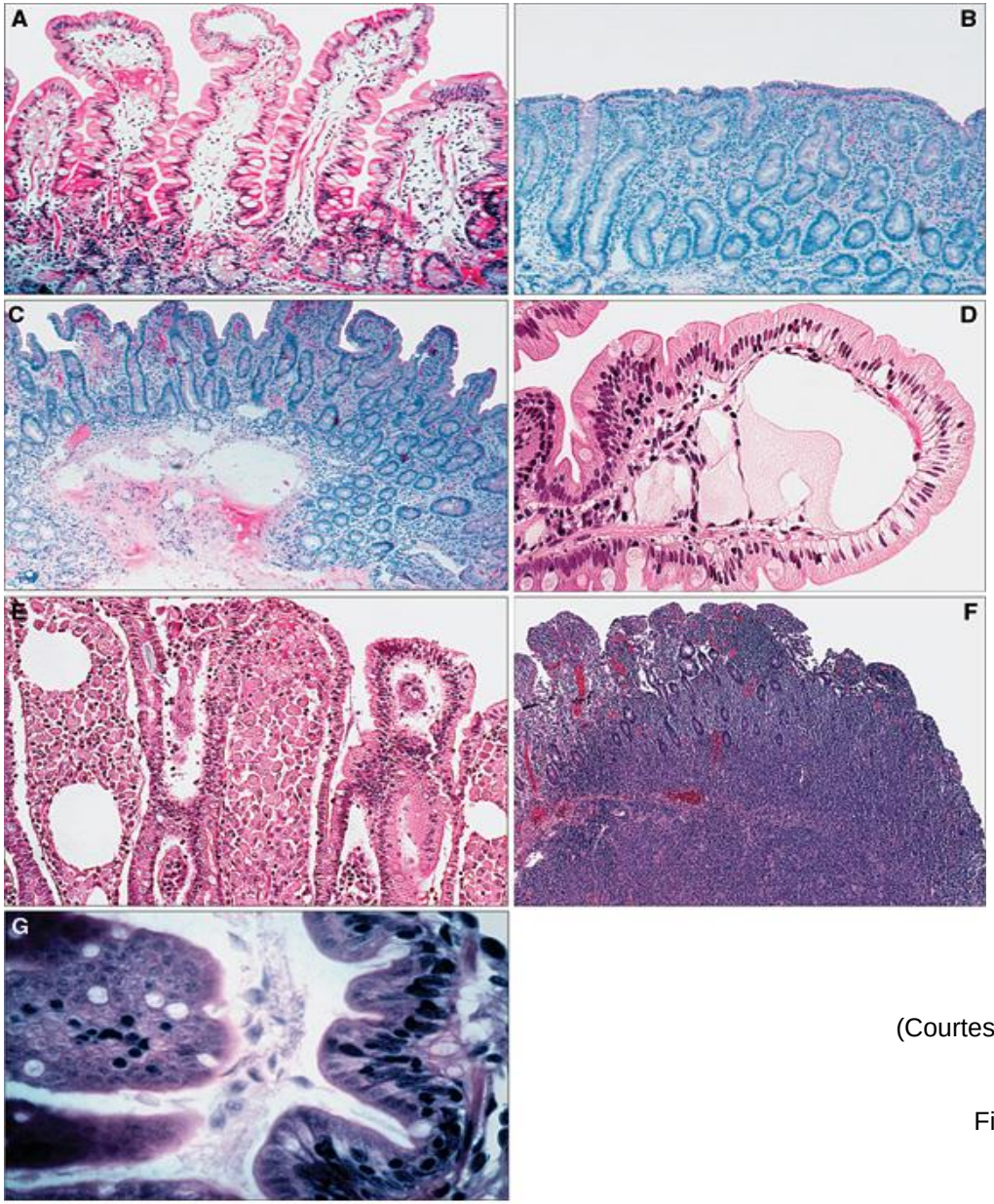
X-ray appearance



Barium contrast small-intestinal radiologic examinations.
A. Normal individual.
B. Celiac sprue.
C. Jejunal diverticulosis.
D. Crohn's disease.

(Courtesy of Morton Burrell, MD, Yale University; with permission.)

Fig. 288-3 Accessed 02/01/2010



Small bowel biopsy

A. Normal individual.
B. Untreated celiac sprue.
C. Treated celiac sprue.
D. Intestinal lymphangiectasia.
E. Whipple's disease.
F. Lymphoma.
G. Giardiasis.

(Courtesy of Marie Robert, MD, Yale University; with permission.)

Fig. 288-4 Accessed 02/01/2010

Jejunal appearance in celiac disease

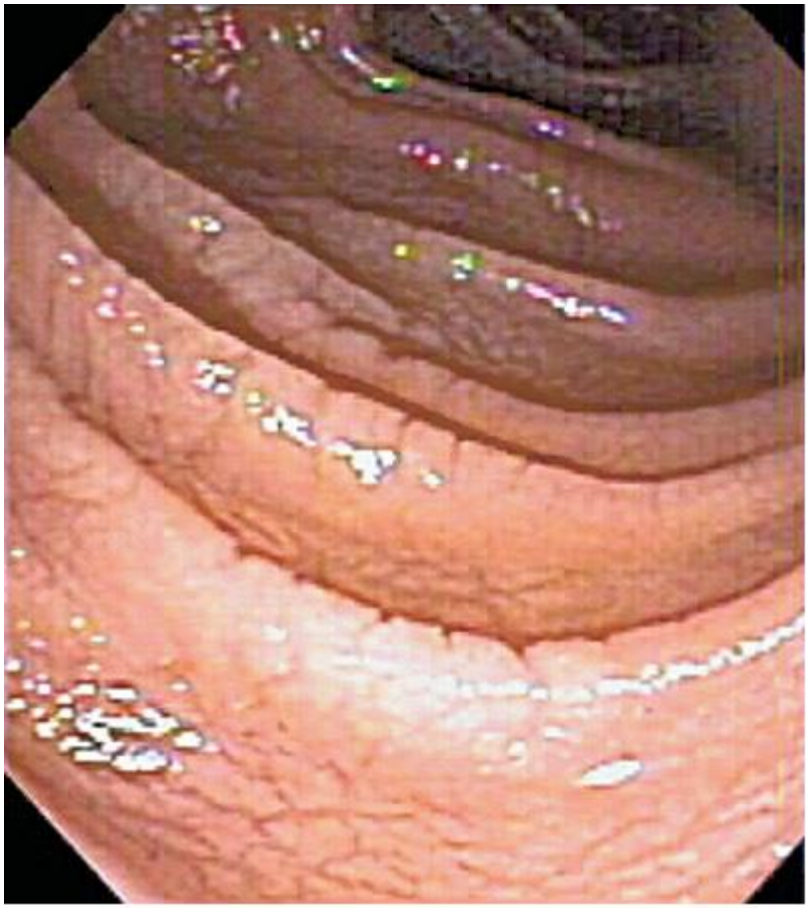


Fig. e25-27 Accessed 02/01/2010

Celiac disease

- Prevalence of 1% in North America.
- 60% of cases are in women.
- Highest incidence in infancy with introduction to gluten containing products.
- May see delayed puberty
- Frequent association with pregnancy in the third decade.
- Bloating
- Fatigue
- Anemia
- Chronic diarrhea (or constipation)

Celiac disease

- May see dermatitis herpetiformis
- Circulating immune complexes may lead to arthritic symptoms.
- Reaction to gliadin (alcohol soluble form of gluten).
- The most common celiac disease-associated cancer is enteropathy-associated T-cell lymphoma, an aggressive lymphoma of intraepithelial T lymphocytes.
- Small intestinal adenocarcinoma is also more frequent in individuals with celiac disease.

Dermatitis herpetiformis

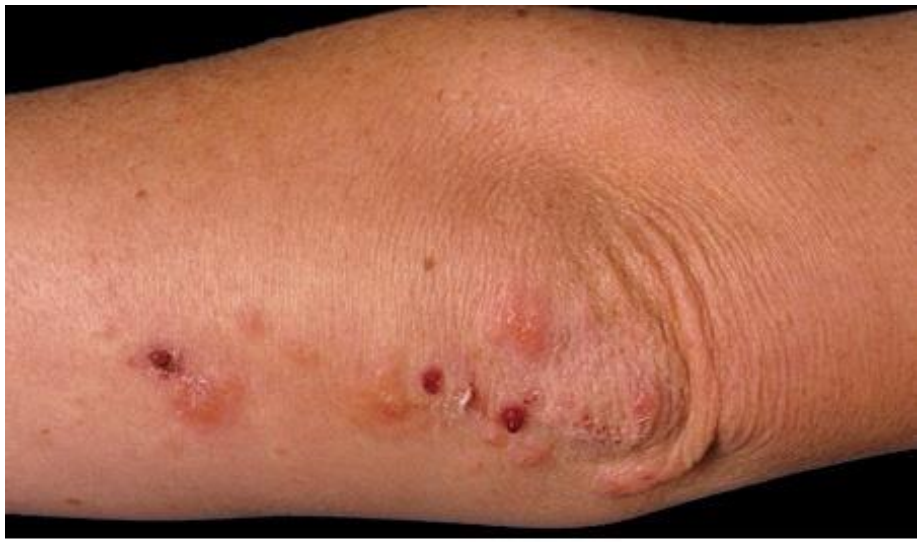


Fig. 6-16 Accessed 07/16/2010

Classic early lesions:

Papules, urticarial plaques, small grouped vesicles, and crusts on the elbow.

Intensely pruritic.

May present in butterfly pattern over face.

Correlates with severity of celiac disease.

Celiac disease

- Gliadin passes through interstices, induces expression of IL-15 by epithelial cells.
- CD4+ recognize gliadin as antigenic.
- Intraepithelial CD8+ lymphocyte activation and natural killer cell transformation (NKG2D+) is triggered.
- NKG2D is the receptor for the MHC class-I like protein MIC-A expressed by stressed enterocytes.
- Leads to cell death.

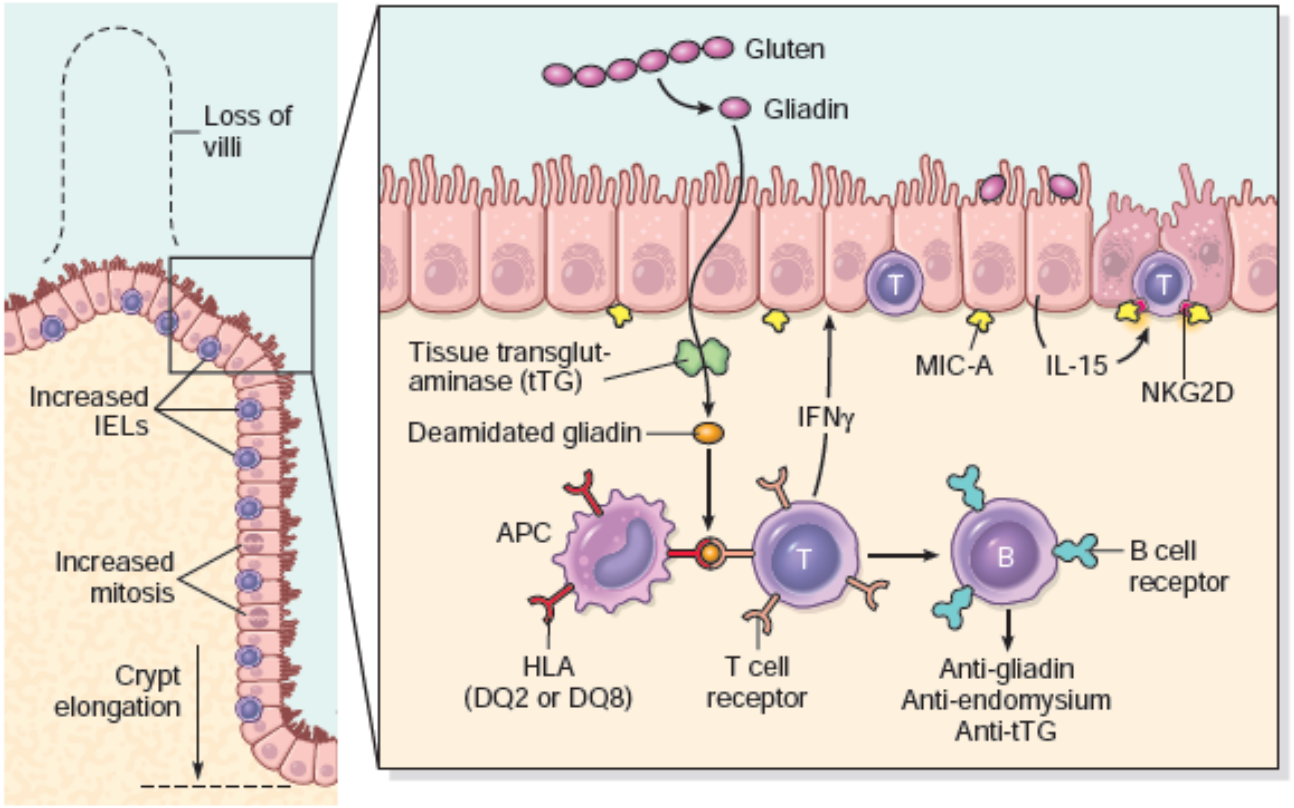


Figure 17-25 The left panel illustrates the morphologic alterations that may be present celiac disease, including villous atrophy, increased numbers of intraepithelial lymphocytes (IELs), and epithelial proliferation with crypt elongation (compare to Fig. 17-26). The right panel depicts a model for the pathogenesis of celiac disease. Note that both innate (CD8+ intraepithelial T cells, activated by IL 15) and adaptive (CD4+ T cells, and B cells sensitization to gliadin) immune mechanisms are involved in the tissue responses to gliadin.

Celiac disease

- Tissue transglutamase found in lamina propria has pivotal role.
- Deaminates gluten and enhances immunostimulatory effect of gliadin peptides.
- Gliadin peptides interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and, in turn, can stimulate CD4+ T cells to produce cytokines that contribute to tissue damage.
- Only 50% of patients manifest the HLA type

Celiac disease

- Anti-endomysial antibodies (IgA) found in 90% of patients with celiac disease. Positive likelihood ratio, LR+, 100; LR-, 0.1.
- Tissue transglutaminase antibody (IgA tGT) has an LR+ of 10; LR-, 0.1.
- Levels may be low in IgA deficiency.
- Must then look at IgG tGT antibody.
- 95% have HLA-DQ2 allele; 5%, HLA-DQ8.
- Diagnosis is made on small bowel biopsy.

Celiac disease

- Histology:
- Loss of brush border.
- Vacuolar degeneration of cells.
- Increased number of crypt mitoses.
- Inflammation and fibrosis.
- Heavy intraepithelial lymphocyte (NKG2D+ CD8+) infiltrate.
- Other features of fully developed celiac disease include increased numbers of plasma cells, mast cells, and eosinophils, especially within the upper part of the lamina propria.

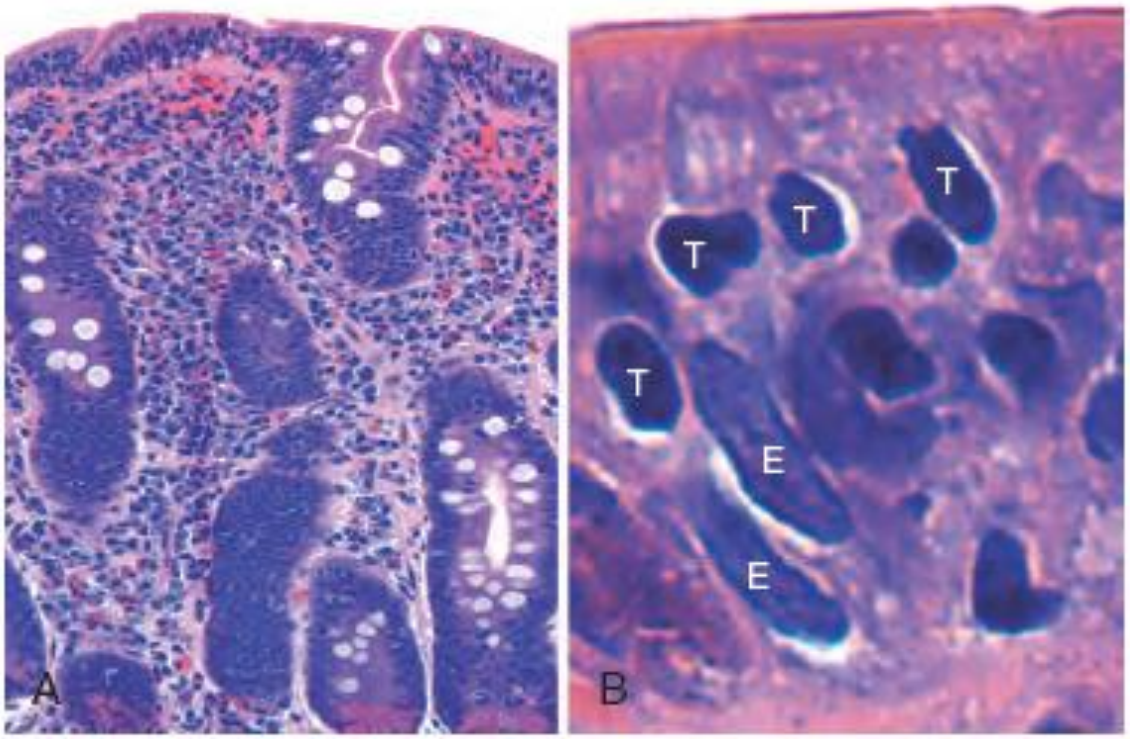


Figure 17-26 Celiac disease. **A,** Advanced cases of celiac disease show complete loss of villi, or total villous atrophy. Note the dense plasma cell infiltrates in the lamina propria. **B,** Infiltration of the surface epithelium by T lymphocytes, which can be recognized by their densely stained nuclei (labelled **T**). Compare to elongated, pale-staining epithelial nuclei (labeled **E**).

Celiac disease treatment

- All grains contain gliadin.
- There are those who believe oats or quinoa or corn or brown rice or amaranth or may be consumed without aggravating celiac disease.
- However, these contain prolamines and saponins which are immunostimulatory and promote a leaky gut.
- Paleo diet.
- May take up to 1 year to resolve. Some 10-15% may also require steroids.
- Treat osteoporosis.
- If gliadin exposure is restricted, the incidence of T-cell lymphoma of the gut falls.

Autoimmune enteropathy

- Characterized by severe persistent diarrhea and autoimmune disease that occurs most often in young children.
- X-linked
- Germline mutation in the FOXP3 gene
- FOXP3 is a transcription factor expressed in CD4+ regulatory T cells
- Immune dysregulation, poly-endocrinopathy, and enteropathy (IPEX)
- Autoantibodies to enterocytes and goblet cells are common, and some patients may have antibodies to parietal or islet cells.

Environmental enteropathy

- Tropical sprue
- Prevalent in areas and populations with poor sanitation and hygiene, such as those in developing countries, including many parts of sub-Saharan Africa, such as Gambia; aboriginal populations within northern Australia; and some groups within South America and Asia

Environmental enteropathy

- Defective intestinal barrier function, chronic exposure to fecal pathogens and other microbial contaminants, and repeated bouts of diarrhea within the first 2 or 3 years of life are likely involved
- Defective intestinal mucosal immune function
- Injury present in all levels of small bowel.
- May see megaloblastboid changes.

Whipple's disease

- Middle-aged white men.
- Multisystem disease with prominence of migratory arthropathy, fever, and steatorrhea.
- May present with dementia
- Dense accumulation of distended, foamy macrophages in the small intestinal lamina propria
- Macrophages contain PAS positive diastase resistant granules on biopsy that are lysozomes containing bacteria (Tropheryma whippelli)
- Distinguish from celiac disease
- Negative acid-fast stains distinguish from intestinal tuberculosis

Whipple's disease

- The villous expansion caused by the dense macrophage infiltrate imparts a shaggy gross appearance to the mucosal surface.
- Lymphatic dilatation and mucosal lipid deposition account for the common endoscopic detection of white to yellow mucosal plaques.
- Impaired lymphatic transport
- Bacteria-laden macrophages can accumulate within mesenteric lymph nodes, synovial membranes of affected joints, cardiac valves, the brain, and other sites.

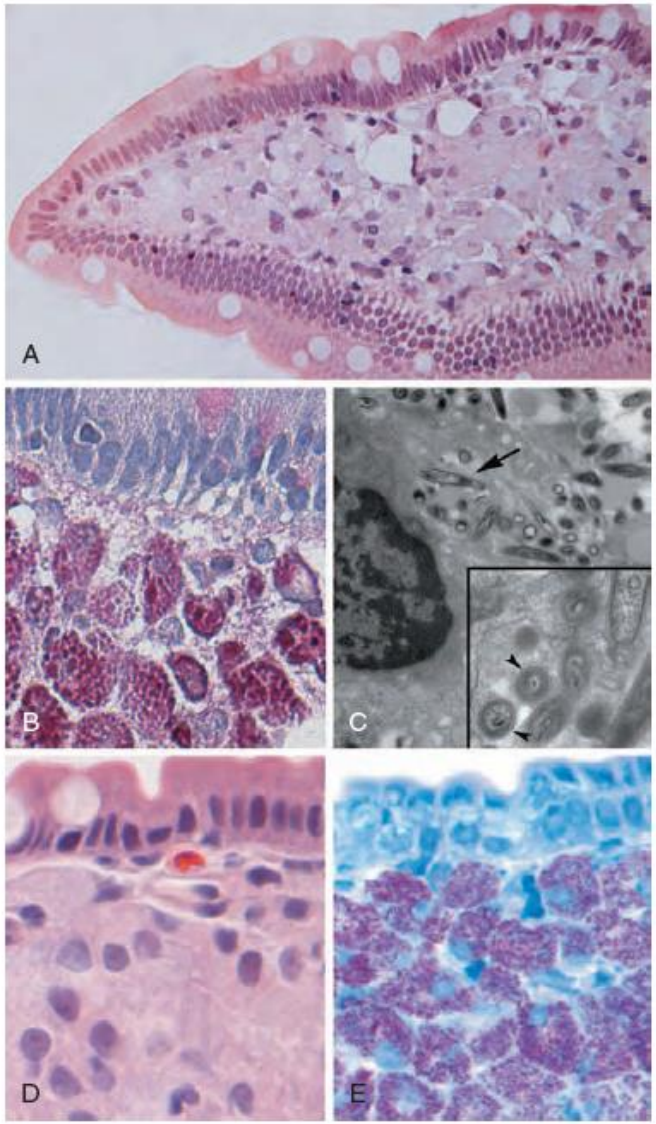


Figure 17-30 Whipple disease and mycobacterial infection. **A,** hematoxylin and eosin staining shows effacement of normal lamina propria by a sheet of swollen macrophages. **B,** PAS stain highlights macrophage lysosomes full of bacilli. Note the positive staining of mucous vacuoles in the overlying goblet cells. **C,** An electron micrograph of part of a macrophage shows bacilli within the cell (top arrow); also seen at higher magnification (inset). **D,** The morphology of mycobacterial infection can be similar to Whipple disease, particularly in the immunocompromised host. Compare with **A**. **E,** Mycobacteria are positive with stains for for acid-fast bacteria. (**C,** Courtesy George Kasnic and Dr. William Clapp, University of Florida, Gainesville, Fla.)

Other associated diseases

- Abetalipoproteinemia
- Retinitis pigmentosa
- Neuropathy
- Procoagulant deficiency
- Hepatic steatosis
- Anemia with acanthocytes (Burr cells)
- Autosomal recessive (MTTP gene)
- Enterocytes unable to absorb or transport lipoproteins
- Triglycerides accumulate (Oil Red O stain positive)
- Diagnose with lipoprotein electrophoresis

Lactase deficiency

- Congenital form is autosomal recessive
- Acquired form is caused by down-regulation of lactase gene expression
- Native American, African, and Chinese populations
- Also follow enteric infections
- Diarrhea and flatulence common
- This is not malabsorption

Cystic fibrosis

- In US, screened for in neonates
- Some patients may not have symptoms until adolescence
- Signs and symptoms:
- Parents may taste salt when kissing the child
- Slow growth rate.
- Often listless and irritable, tire easily.
- Difficult to clear airways.
- Repeated bouts of bronchitis.
- Lung infections due to thick mucous secretions.
- Generally, Pseudomonas.

Cystic fibrosis

- Drying and thickening of pancreatic secretions leads to
- Clogged pancreatic ducts
- Decreased digestion of dietary proteins and lipids.
- Foul-smelling, glistening, bulky stools.
- Meconium ileus
- Rectal prolapse in a child
- Infertility
- Low concentrations of serum proteins
- Indicating protein malnutrition

Cystic fibrosis

- Thickened, viscous secretions
- Abnormal transport of Cl^- and Na^+ across the epithelium of the:
- Pancreatic ducts
- Biliary ducts
- Airways
- Mutation that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein on chromosome 7.
- The CFTR protein belongs to the ABC (ATP-Binding Cassette) family of proteins.

Cystic fibrosis

- CFTR malfunction leads to
- Defective cAMP-dependent Cl^- secretion
- In addition, Na^+ absorption is increased,
- Possibly due to a failure of CFTR-mediated regulation of Na^+-channel activity.
- Bacterial killing by neutrophils and β-defensins requires a normal chloride concentration.
- The chloride content of epithelial secretions is high in cystic fibrosis.
- Disease largely found in those of Northern European ancestry.

Cystic fibrosis

- Associated abnormalities in cystic fibrosis:
- Transforming growth factor-beta is a potent suppressor of T cell activation.
- Deficiency in mannose-binding lectin
- Important component of complement system
- Poor phagocytosis
- Increases the risk for pyogenic infections.
- Pancreatic insufficiency
- 85% of patients with cystic fibrosis..

Cholera

- Abrupt onset of watery diarrhea 1-5 days post exposure
- Voluminous loss of fluid
- Stools resemble rice water
- Fishy odor.
- Vibrio organisms are noninvasive and remain within the intestinal lumen.
- Comma shaped organisms
- Oral rehydration often sufficient therapy

Cholera

- Cholera toxin, encoded by a virulence phage and released by the Vibrio organism, causes disease.
- Flagellar proteins, involved in motility and attachment, are necessary for efficient bacterial colonization.
- Hemagglutinin, a metalloproteinase, is important for bacterial detachment and shedding in the stool.
- Shellfish and plankton may serve as reservoirs for the bacterium.

Cholera

- Cholera toxin stimulates adenylate cyclase
- Increases intracellular cAMP
- Opens CFTR
- Releases chloride ions into the lumen.
- Chloride and sodium absorption are also inhibited by cAMP.
- Chloride, bicarbonate, and sodium assumulate within the lumen
- Massive osmotic diarrhea results
- Mucosal biopsies show only minimal histologic change.

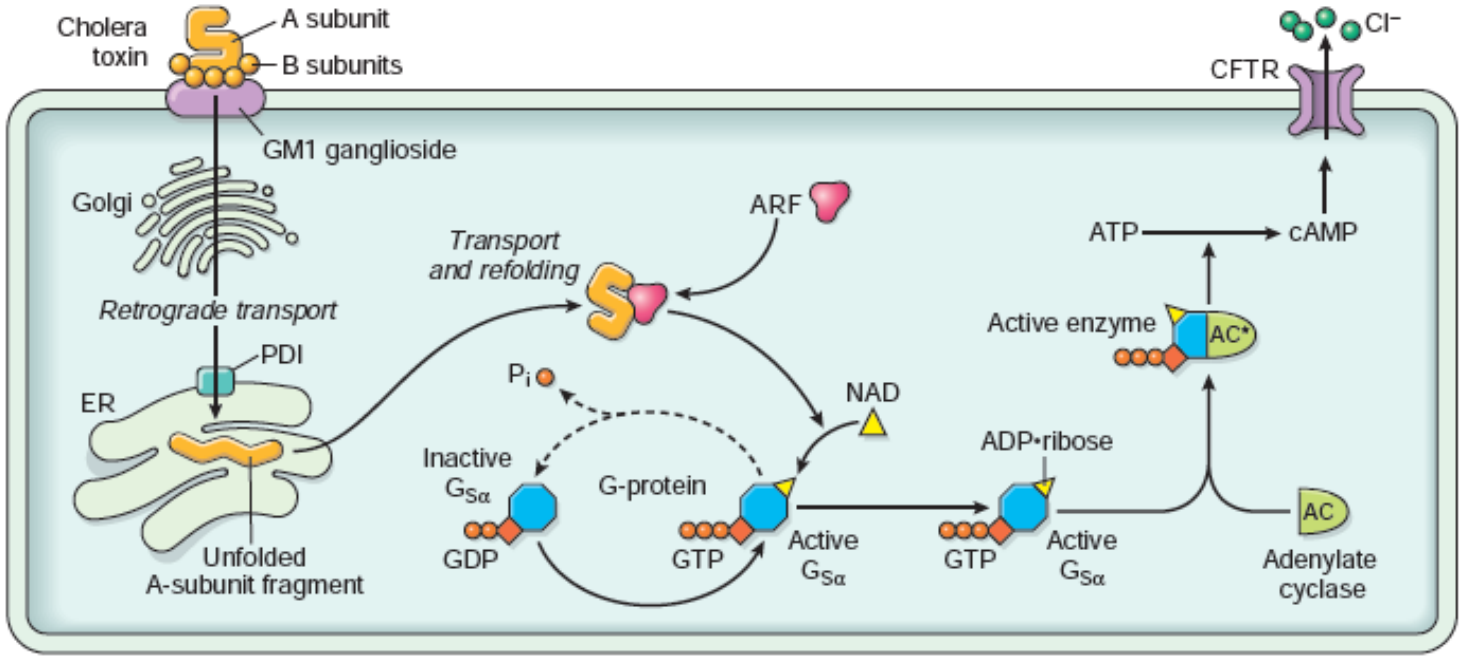


Figure 17-27 Cholera toxin transport and signaling. After retrograde toxin transport to the endoplasmic reticulum (ER), the A subunit is released by the action of protein disulfide isomerase (PDI) and is then able to access the epithelial cell cytoplasm. In concert with an ADP-ribosylation factor (ARF), the A subunit then ADP-ribosylates $G_s\alpha$, which locks it in the active, GTP-bound state. This leads to adenylate cyclase (AC) activation, and the cAMP produced opens CFTR to drive chloride secretion and diarrhea.

Appendicitis

- The prevalence of appendicitis in patients presenting to emergency departments is 25% if <60 years of age; 5% if >60 years of age.
- Develops secondary to obstruction of appendiceal orifice.
- Migration of periumbilical pain, anorexia, and vomiting precede right lower quadrant pain in appendicitis.
- Rebound tenderness associated with the constellation of symptoms above is strongly suggestive of appendicitis.
- Fever and left shift (particularly if leukocytosis) are suggestive.

Appendicitis

- Fever, severe tenderness, guarding, and rebound tenderness in the right lower quadrant may be absent in patients with appendicitis.
- Alvarado score >7 (where two points each are given for right lower quadrant pain and for leukocytosis while one point each is given for other symptoms and signs noted above) has a sensitivity 81% for appendicitis. The positive likelihood ratio (LR+) is 3.1; LR-, 0.26.
- Positive likelihood ratio (LR+) of abnormal CT scan is 15.6; LR- 0.06

Appendicitis

- Diagnosis of acute appendicitis requires neutrophilic infiltration of the muscularis propria.
- In more severe cases a prominent neutrophilic exudate generates a serosal fibrino-purulent reaction.

Meckel diverticulum

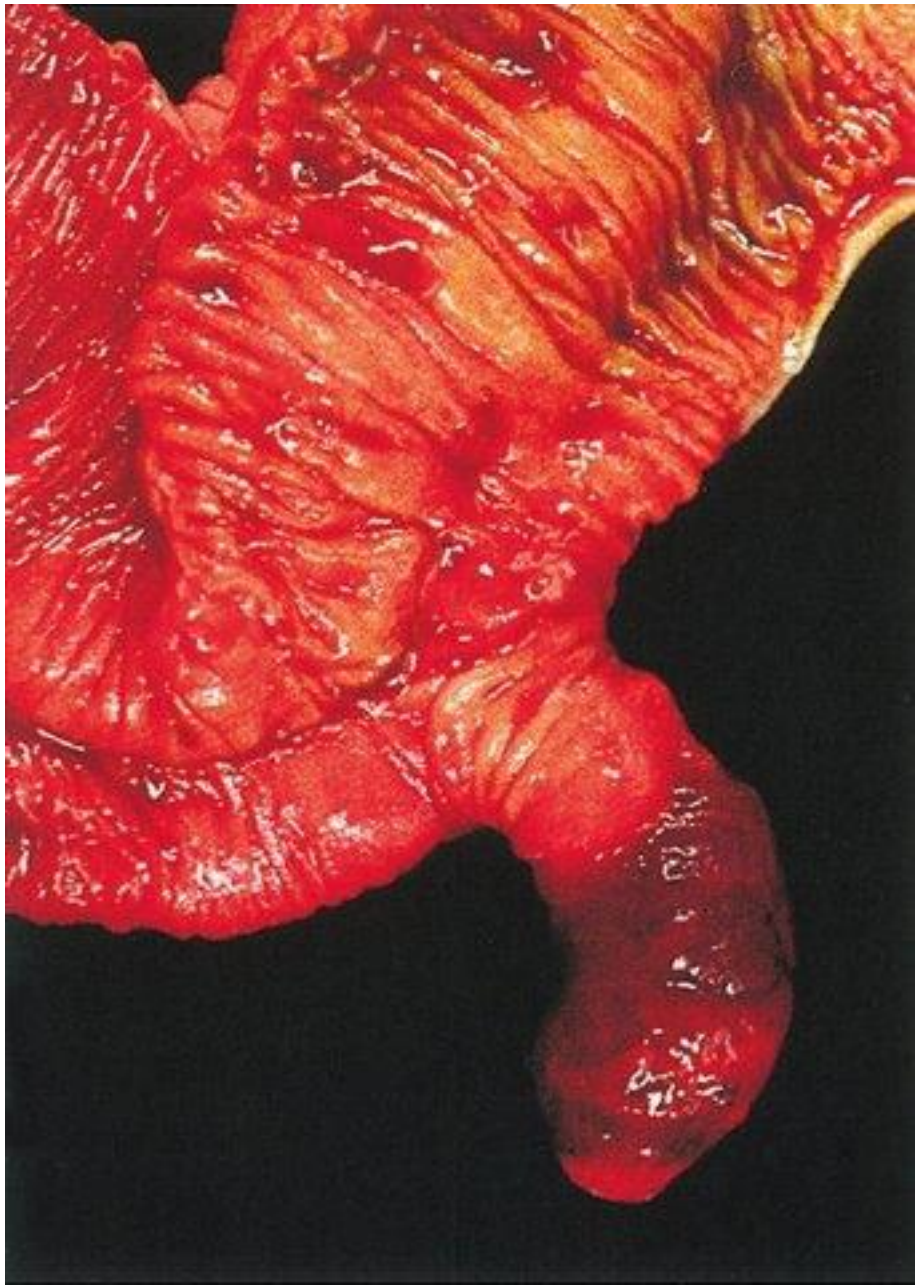
- This is the most common congenital abnormality of the gastrointestinal tract.
- Failed involution of vitelline duct which connects the lumen of the developing gut to the yolk sac
- Mucosal lining may resemble that of normal intestine (true diverticulum in which all three layers of bowel are present) but ectopic gastric or pancreatic tissue may be present

Meckel diverticulum

- Found in the Ileum
- Bleeding most common presentation in young child
- Newborn may have fecal material in umbilical area due to persistence of vitelline duct

Meckel diverticulum

- 2 inches long
- 2 feet from ileocecal valve
- 2% population
- 2 times more common in males
- 2% symptomatic
- May be symptomatic by age 2
- Older children and adults may present with obstruction or diverticulitis (mimics appendicitis)

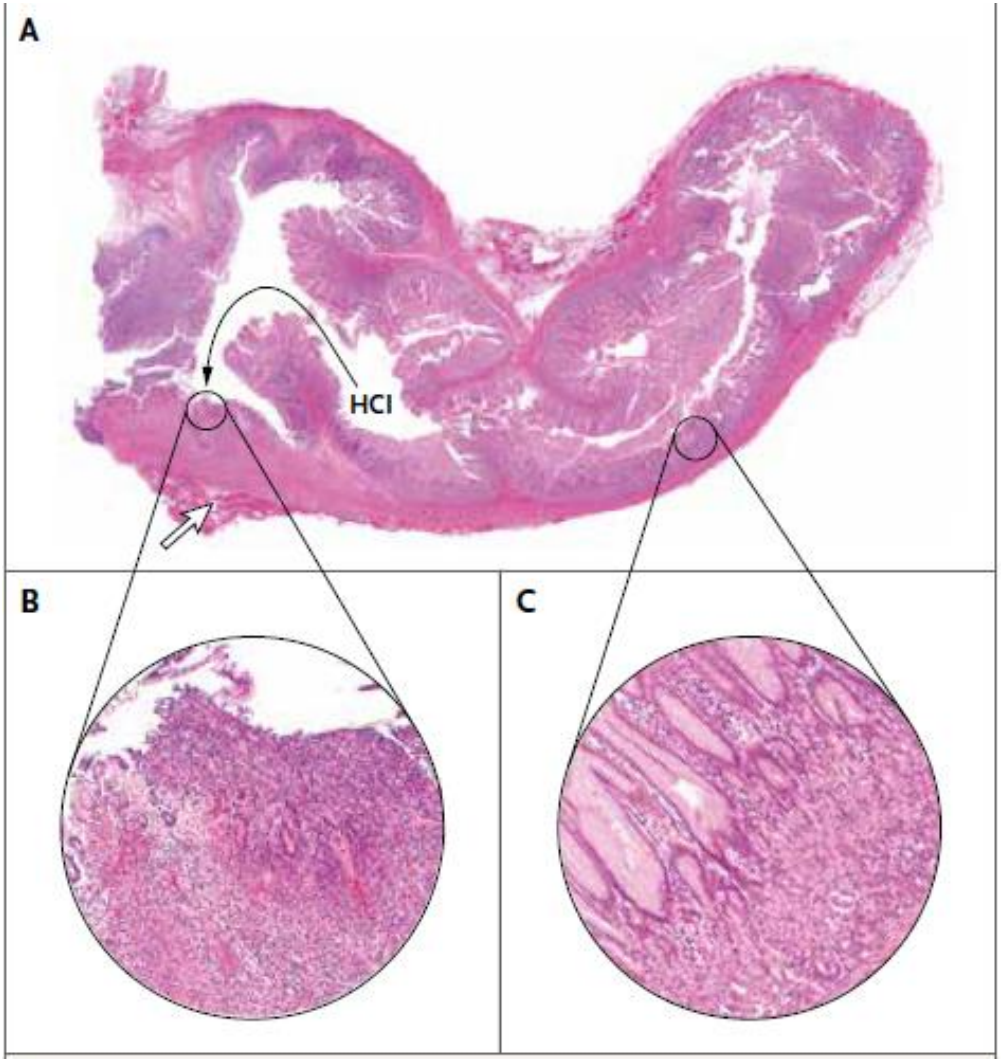


Meckel's diverticulum

Armed Forces Institute of Pathology, Public Domain, https://commons.wikimedia.org/w/index.php?curid=10645588

Accessed 12/10/2019

Meckel's diverticulum



Present are all three layers of bowel wall (Panel A); serosal fibrinous exudate is present (white arrow); peptic ulceration is present in the adjacent intestinal mucosa (black arrow).

The intestinal mucosa at the opening of the diverticulum shows mucosal erosion, acute inflammation, and underlying granulation tissue, findings consistent with an ulceration (Panel B).

Heterotopic gastric mucosa lines the entire diverticulum and is composed of surface foveolar cells, mucous neck cells, parietal cells, and basal chief cells (Panel C).

NEJM.org Cases in Primary Care (2017)

Benign tumors of the small intestine

- Adenomas are 25% of benign small intestinal tumors.
- Benign mesenchymal tumors (especially leiomyomas), lipomas, and neuromatous lesions follow adenomas in frequency.
- Most adenomas occur in the region of the ampulla of Vater
- The usual presentation is that of a 30- to 60-year-old patient with occult blood loss
- Rarely present with obstruction or intussusception
- Some are discovered incidentally during radiographic investigation.

Benign tumors of the small intestine

- Patients with familial polyposis coli are particularly prone to developing periampullary adenomas.
- Macroscopically, the ampulla of Vater is enlarged and exhibits a velvety surface.

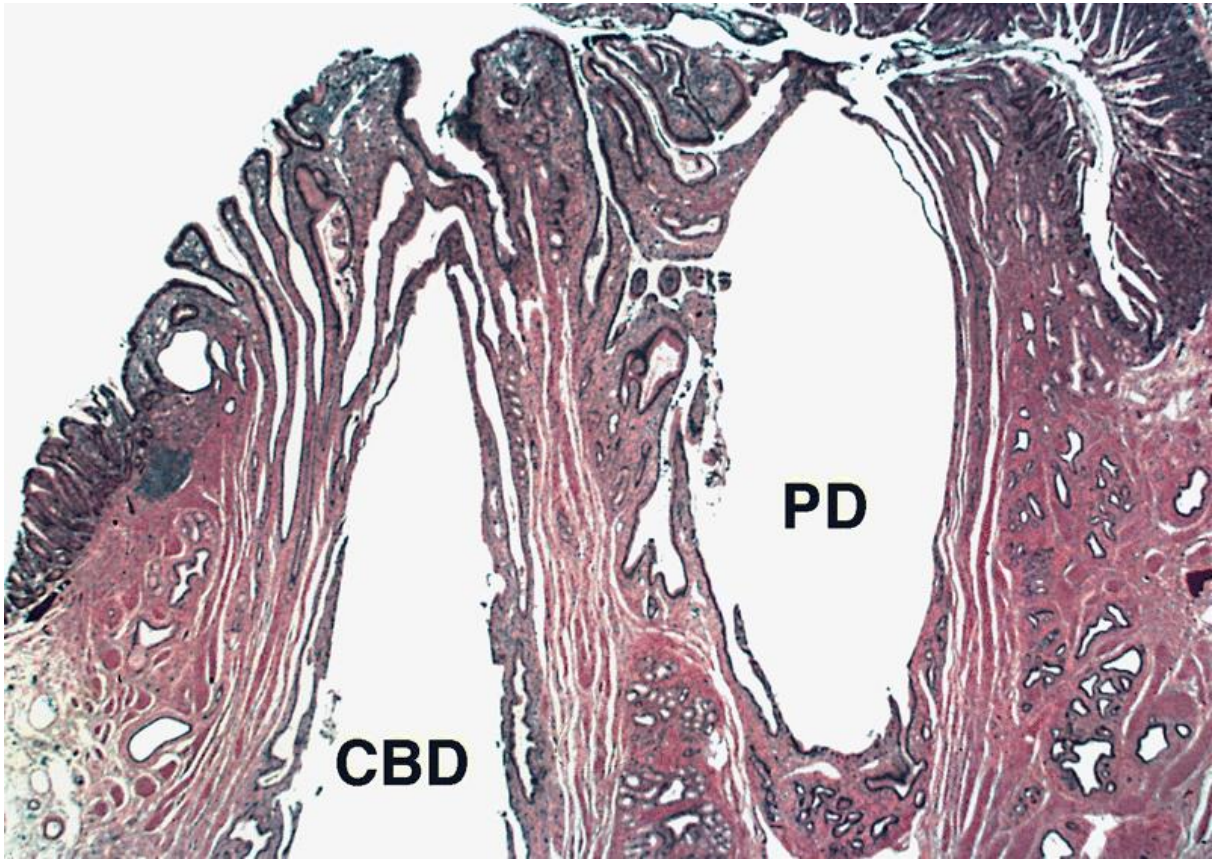
Adenocarcinoma of the small intestine

- 40% are adenocarcinomas.
- 40% of tumors are carcinoids.
- 15% are gastrointestinal stromal tumors.
- Increased risk conferred by Crohn's disease, familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer.
- Surgical resection necessary.
- In limited series, chemoradiation (with infusional 5FU) of adenocarcinomas has shown improved survival.

Adenocarcinoma of the small intestine

- The large majority occur in the duodenum, usually in 40- to 70-year-old patients.
- These tumors grow in a napkin-ring encircling pattern or as polypoid exophytic masses.
- Fatigue from occult blood loss may be the only sign.
- Tumors in the duodenum, particularly those involving the ampulla of Vater, may cause obstructive jaundice early in their course.
- More typically, intestinal obstruction is the presenting event. Rarely, the tumorous mass is a lead point for intussusception.

Normal ampulla of Vater

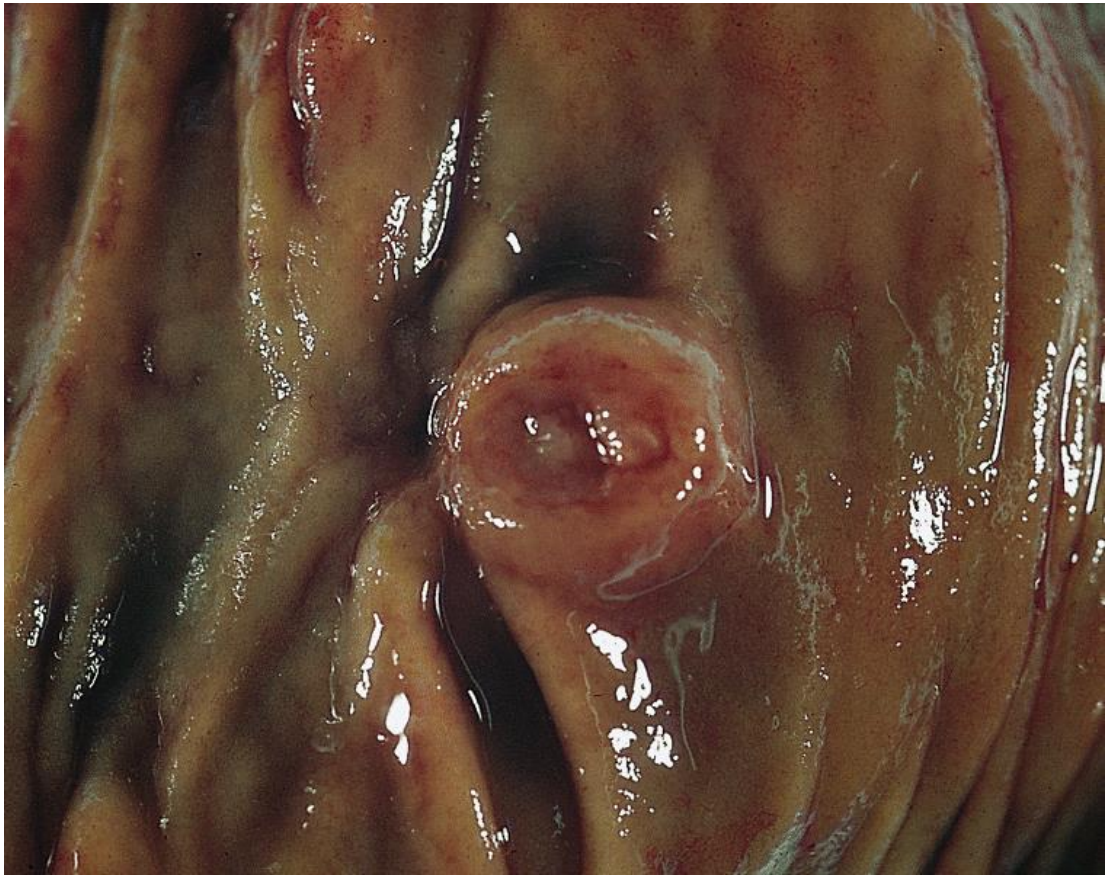


In this low-power view, the larger terminal common bile duct (CBD) and the smaller pancreatic duct (PD) drain separately into the duodenum.

Fig. 1-15

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Ampullary adenocarcinoma

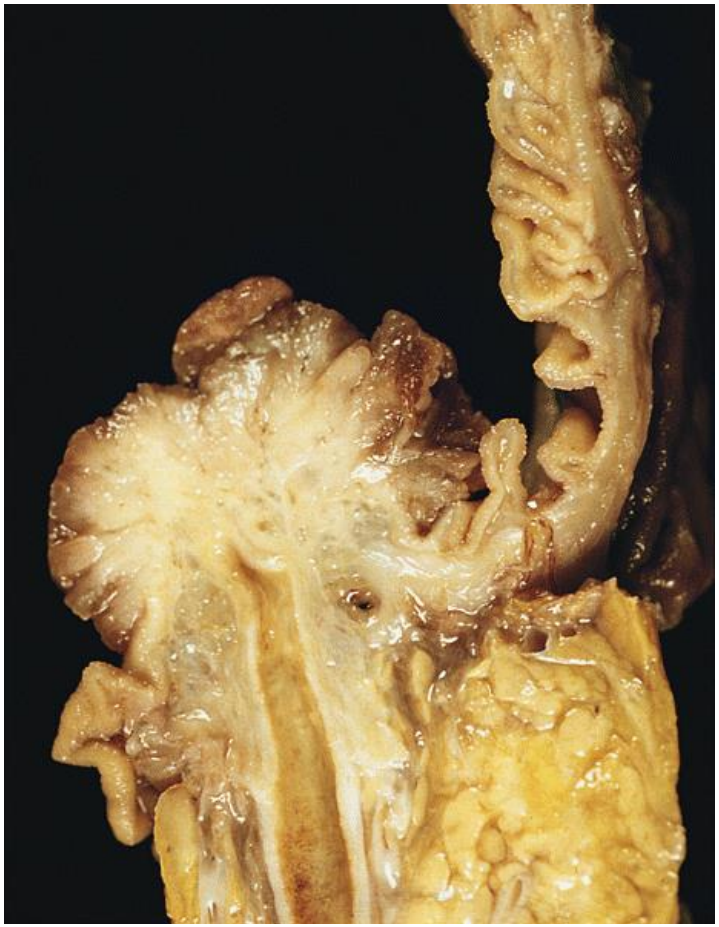


This intra- ampullary carcinoma is small, producing only slight prominence to the ampulla from the luminal aspect. Minimal
tumor is visible through the ampullary orifice.

Fig. 20-4L

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Ampullary adenocarcinoma



This exophytic mucinous carcinoma involves the ampulla and duodenal mucosa but also extends into the common bile duct.

Fig. 20-7

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Tumors of the appendix

- There are five main histopathologic subtypes of appendiceal neoplasms:
- Neuroendocrine neoplasms (NENs)
- Epithelial neoplasms
- Mucinous neoplasms
- Goblet cell adenocarcinomas (GCAs)
- Colonic-type (non-mucinous) adenocarcinomas
- Signet ring cell adenocarcinomas

Carcinoid

- 40% of gut carcinoid tumors occur in the appendix
- Small intestine (primarily terminal ileum, 20%), rectum, stomach, and colon are other sites
- Those that arise in the stomach and ileum are frequently multicentric, but the remainder tend to be solitary lesions.
- In the appendix they appear as bulbous swellings of the tip, which frequently obliterate the lumen.
- Elsewhere in the gut, they appear as intramural or submucosal masses that create small, polypoid or plateau-like elevations.

Carcinoid syndrome

- Fewer than 10% manifest carcinoid syndrome.
- Tricuspid insufficiency, vasomotor signs, diarrhea, and wheezing are the syndrome.
- Niacin deficiency may be seen as it is required for tryptophan conversion to serotonin (5-HT).
- 5-HT produced by gastrointesinal carcinoid tumors is degraded to functionally inactive 5-HIAA in the liver.
- Carcinoids also may secrete histamine, bradykinin, kallikrein, and prostaglandins.

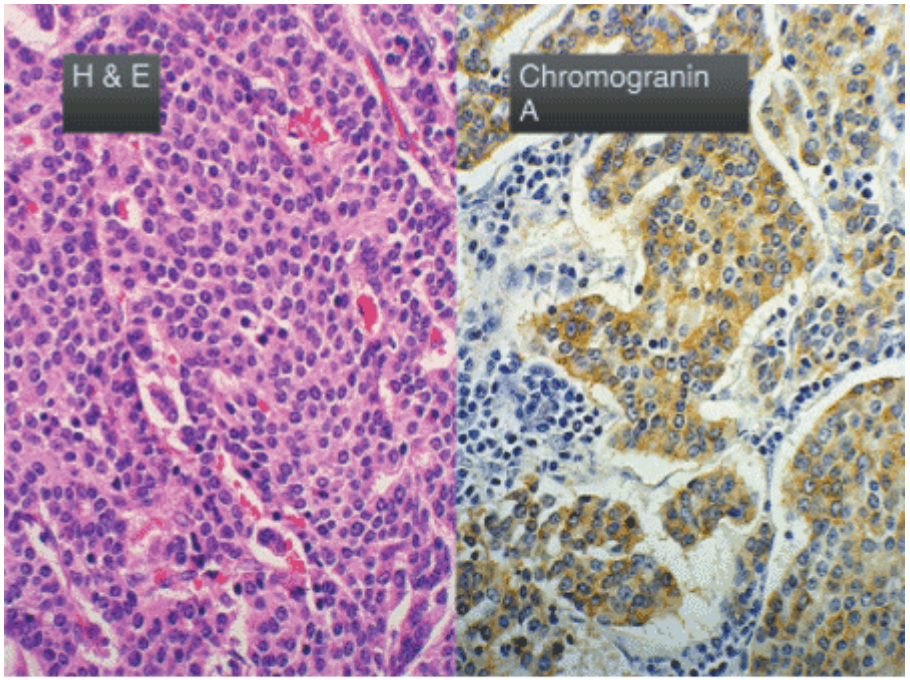
Carcinoid syndrome

- Hepatic metastases are usually present for the development of the syndrome from gastrointestinal carcinoids.
- Rectal tumors may represent up to half of tumors that come to clinical attention, presenting with carcinoid syndrome.
- Hepatic metastases are usually not required for the production of a carcinoid syndrome by extraintestinal or rectal carcinoids
- Venous drainage from the ovary as well as the rectum is directly into the vena cava and bypass the portal circulation to the liver.

Carcinoid

- Foregut tumors rarely metastasize and are generally cured by resection.
- Midgut carcinoid tumors are often multiple and aggressive.
- Hindgut carcinoid tumors arising in the appendix are generally benign.
- Those arising in the rectum rarely metastasize.
- Those arising in the proximal colon may grow to large size and metastasize.

Carcinoid



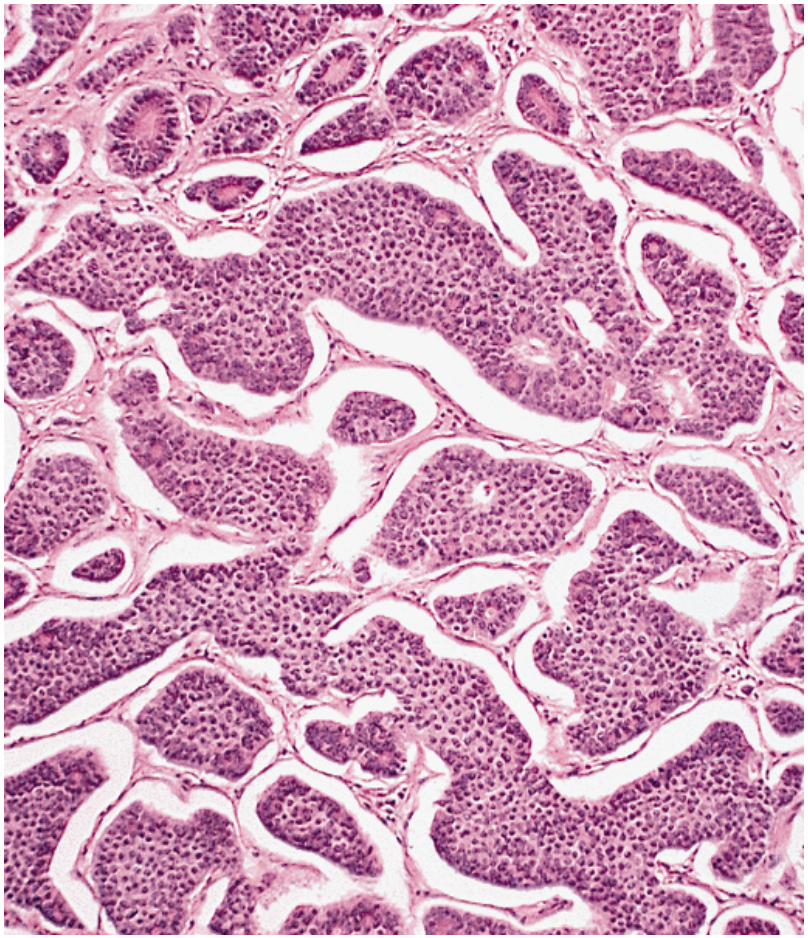
Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 18-4 Accessed 04/01/2010

Carcinoid

- Histologically:
- The neoplastic cells may form discrete islands, trabeculae, stands, glands, or undifferentiated sheets.
- The tumor cells are monotonously similar, having a scant, pink granular cytoplasm and a round to oval stippled nucleus. In most tumors there is minimal variation in cell and nuclear size and mitoses are infrequent or absent.

Enterochromaffin cell tumor of ileum



The classic insular growth pattern shows irregular but well-demarcated islands of uniform tumor cells with a suggestion of peripheral palisading. Marked tumor retraction from the surrounding fibrotic stroma may give a false impression of lymphovascular invasion.

Fig. 6-17

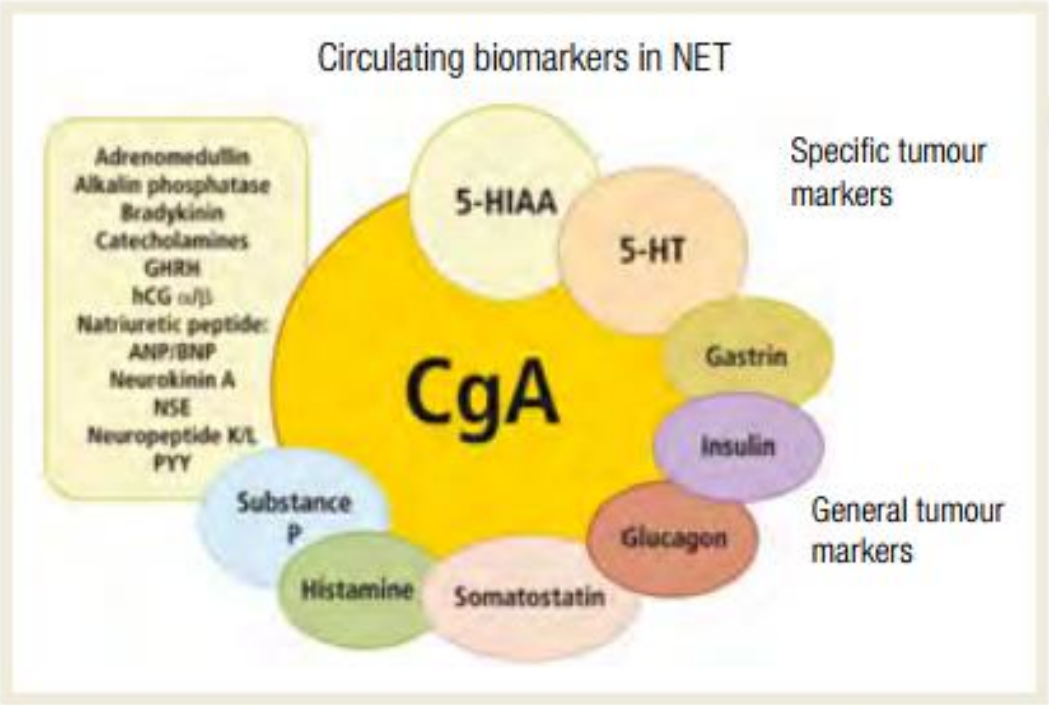
Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Prognosis

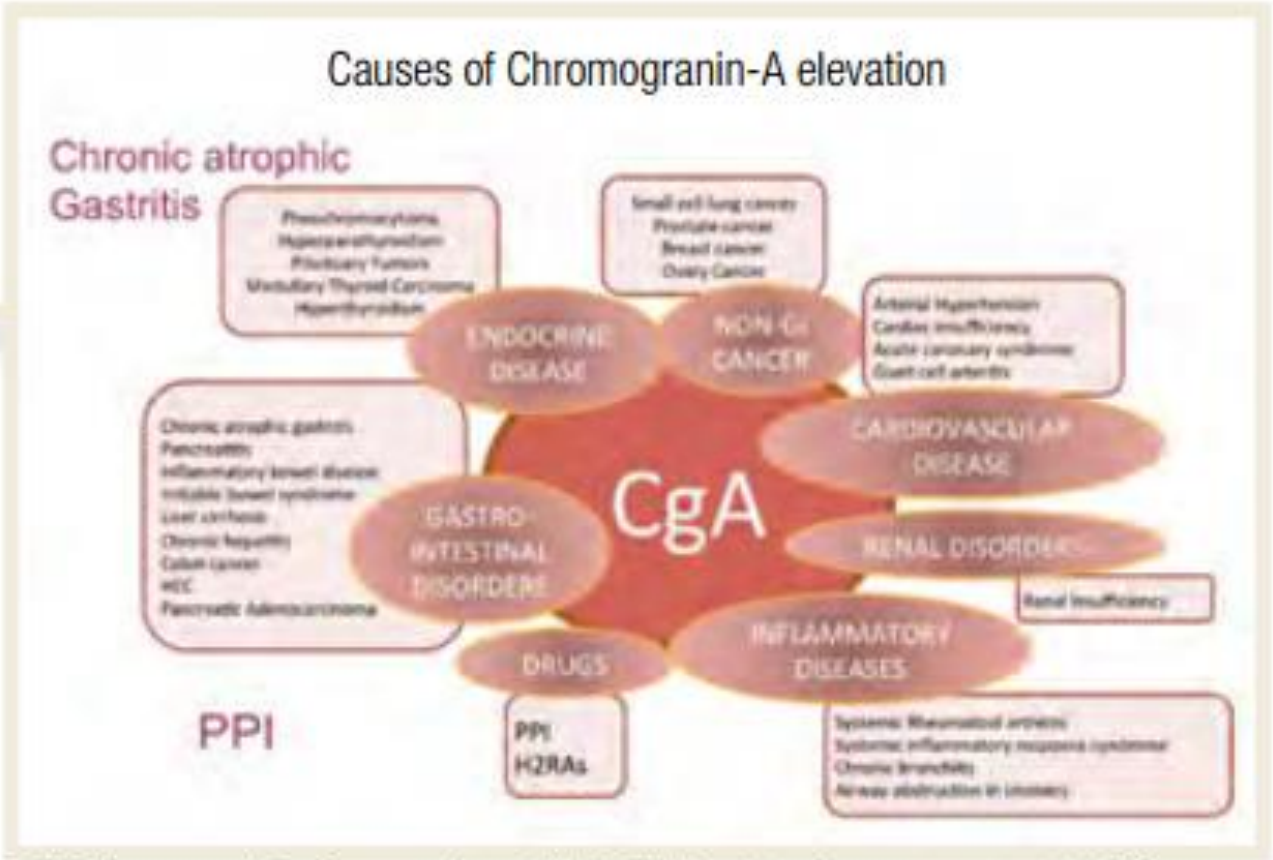
- Lymph node involvement in 15% of appendiceal NENs 1 cm or smaller
- 47% of NENs between 1 and 2 cm
- 86% of NENs larger than 2 cm.
- The corresponding 10-year survival rates for patients with nonmetastatic node-positive disease in these groups were 100%, 92%, and 91%, respectively.

WHO Classifications of Neuroendocrine Neoplasms of the GEP System	
WHO 2000	**WHO 2010**
Well-differentiated endocrine tumour (WDET) Well-differentiated endocrine carcinoma (WDEC)	Neuroendocrine tumours Grade 1 Grade 2
Poorly-differentiated endocrine carcinoma/small-cell carcinoma (PDEC)	Neuroendocrine carcinoma Grade 3
Mixed exocrine–endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

GEP, Gastroenteropancreatic; WHO, World Health Organisation.



5-HIAA, 5-Hydroxy-3-indoleacetic acid; 5-HT, serotonin; ANP/BNP, atrial natriuretic peptide and brain/ventricular natriuretic peptide; GHRH, gonadotropin hormone releasing hormone; hCG, human chorionic gonadotropin; NSE, neurone-specific enolase; PYY, peptide YY.

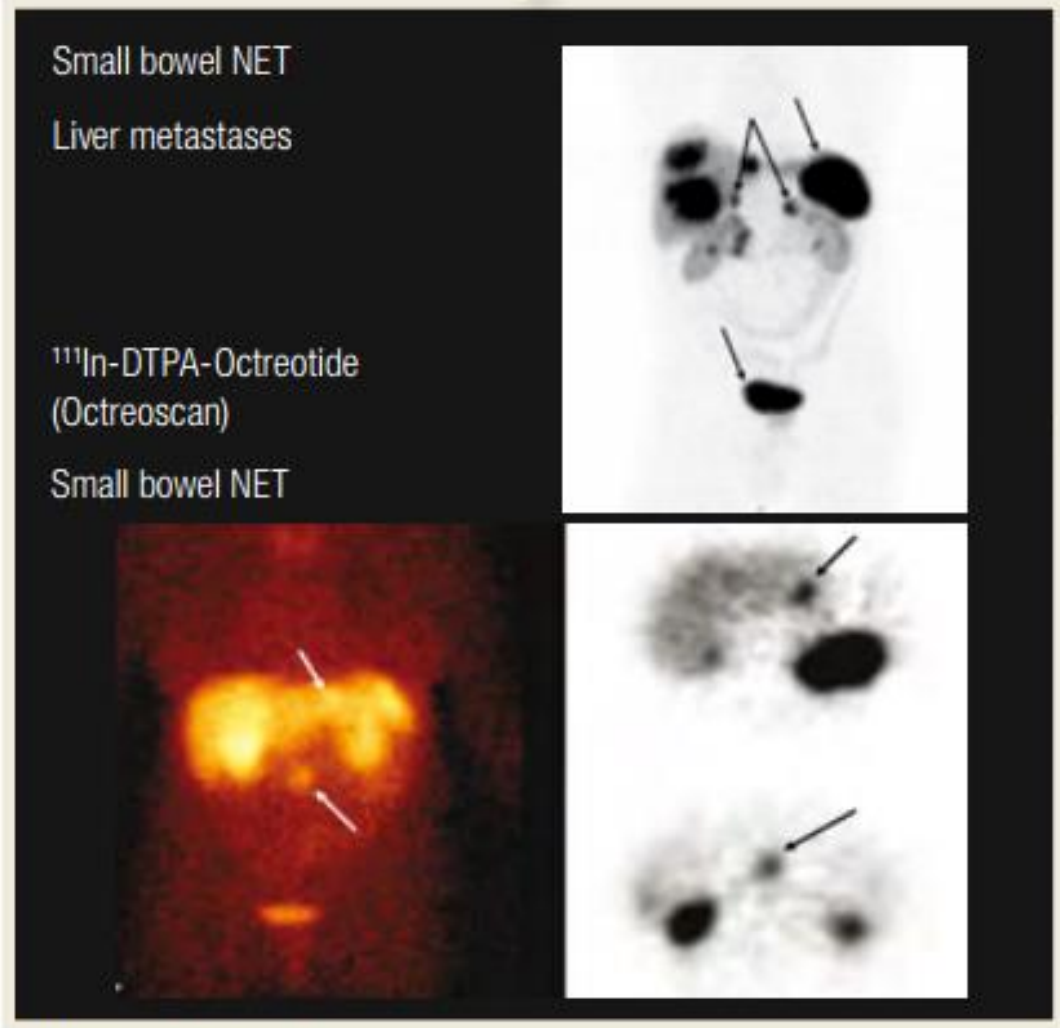


CgA, Chromogranin-A; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; HCC, hepatocellular carcinoma; PPI, proton pump inhibitor.

Chromogranin A is not a useful marker with which to follow patients

Imaging of Neuroendocrine Tumours: Techniques	
Morphological	**Functional**
Ultrasound Computed tomography (CT) Magnetic resonance imaging Endoscopic ultrasound	Diffusion-weighted magnetic resonance Somatostatin receptor scintigraphy ^{68}Ga-DOTA-TATE/TOC/CT ^{11}C-5-HTP, ^{18}F-DOPA/CT ^{18}F-FDG/CT
At diagnosis, CT abdomen and thorax, including a dynamic contrast enhancement of pancreas and liver + somatostatin receptor imaging	

DOPA, Dihydroxyphenylalanine; FDG, fluorodeoxyglucose; HTP, hydroxytryptophan.



NET, Neuroendocrine tumour.

Imaging of Neuroendocrine Tumours

^{68}Ga-DOTATATE PET scan vs SRS

- Increased sensitivity and specificity
- Tomographic
- Exact CT co-registration
- Faster imaging 60–90 min vs 24–72 h
- Quantitative
- Lower radiation
- Onsite production

CT, Computed tomography; SRS, somatostatin receptor scintigraphy; PET, positron emission tomography.

Treatment

- In patients with intestinal neuroendocrine tumors, chemotherapy has no significant benefit (10%–15% objective responses and less than 2 years' median survival).
- Somatostatin analogues are considered to be first-line treatment for low-proliferating tumors with a Ki-67 proliferation index of up to 10%.
- ^{177}Lu-DOTATATE for patients with advanced/metastatic gastrointestinal NETs that are somatostatin receptor–positive on imaging

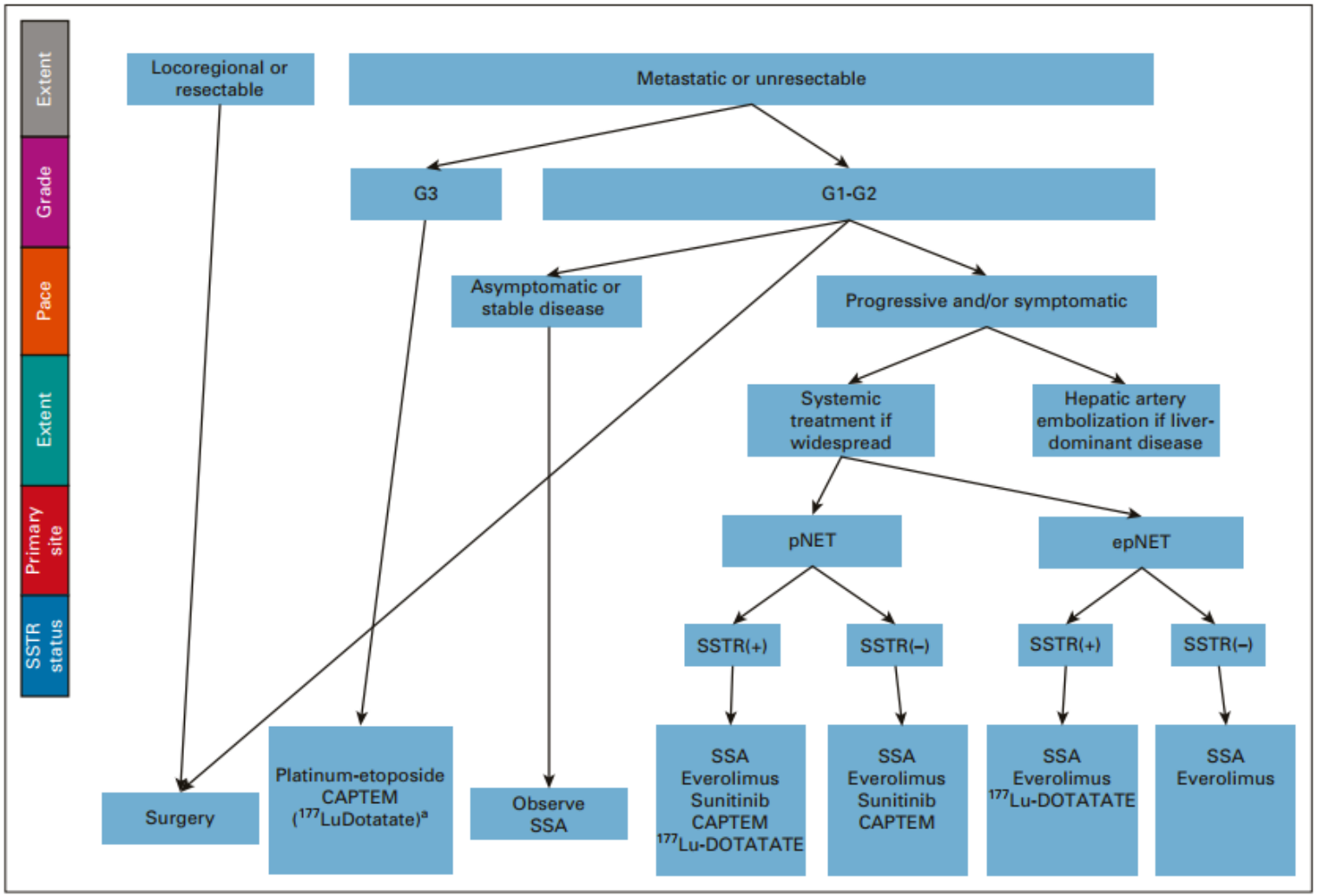
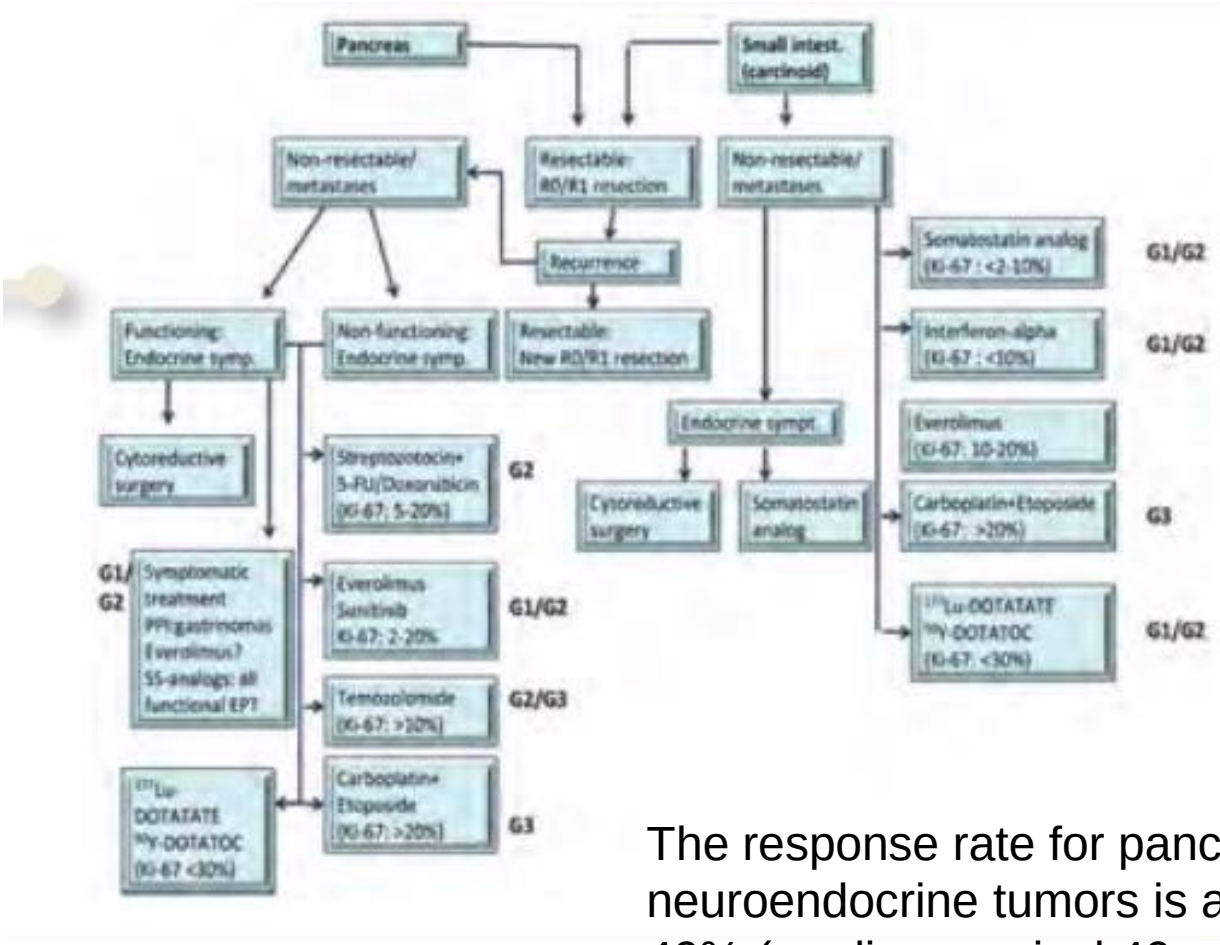


FIG 1. [a]For select cases. Schema for management of well-differentiated neuroendocrine tumors according to patient and tumor characteristics. CAPTEM, temozolomide plus capecitabine; epNET, extrapancreatic neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; SSA, somatostatin analog; SSTR, somatostatin receptor.



The response rate for pancreatic neuroendocrine tumors is about 40% (median survival 40 months).

Epithelial neoplasms

- Low-grade mucinous adenocarcinomas neoplasms (MANs) are characterized by low-grade cytology without evidence of infiltrative (destructive) invasion
- Lymph node involvement is quite rare.
- High-grade (MANs) have high-grade cytologic features but without evidence of infiltrative (destructive) invasion.
- Lymph node involvement noted in 17% of grade 2; 72%, grade 3 lesions

Epithelial neoplasms

- Tumors that demonstrate infiltrative invasion of the appendiceal wall are considered mucinous appendiceal adenocarcinomas (AAs) and carry an increased risk for lymph node metastasis.
- 56% KRAS mutations
- 25% GNAS mutations
- 23% TP53 mutations
- 2% APC mutations
- 2% PIK3CA mutations
- 2-3% high TMB (high MSI status)
- AAs are not genetically identical to colon cancer.

Benign mucinous cystadenoma of the appendix

- Replaces the appendiceal mucosa.
- The cyst is lined by a single cell layer of benign mucin producing columnar epithelium.
- Luminal dilation is associated with appendiceal perforation in 20% of instances, producing localized collections of mucus attached to the serosa of the appendix or lying free within the peritoneal cavity.

Malignant mucinous cystadenocarcinoma of the appendix

- 20% as common as cystadenomas.
- Macroscopically they produce mucin-filled cystic dilatation of the appendix indistinguishable from that seen with benign cystadenomas.
- Penetration of the appendiceal wall by invasive cells and spread beyond the appendix in the form of localized or disseminated peritoneal implants, however, is frequently present.

Malignant mucinous cystadenocarcinoma of the appendix

- Continued cellular proliferation and mucin secretion fills the abdomen with tenacious, semisolid mucin (pseudomyxoma peritoneii**)**.
- Anaplastic adenocarcinomatous cells can be found, distinguishing this process from mucinous spillage.
- Instances in which pseudomyxoma peritoneii is accompanied by both appendiceal and ovarian mucinous adenocarcinomas are usually ascribed to spread of an appendiceal primary lesion.

Epithelial neoplasms

- Goblet cell adenocarcinomas are characterized by the degree of high-grade histologic features observed (infiltrating tumor cells, complex tubules, cribriform masses, loss of tubular or clustered growth, high-grade cytology, and necrosis):
- Grade 1 <25% high-grade pattern
- Grade 2 25% - 50% high-grade pattern
- Grade 3 >50% high-grade pattern
- Signet ring cell carcinomas have the worst outcome
- Epithelial neoplasms are treated with right hemicolectomy; 5FU if stage III-IV

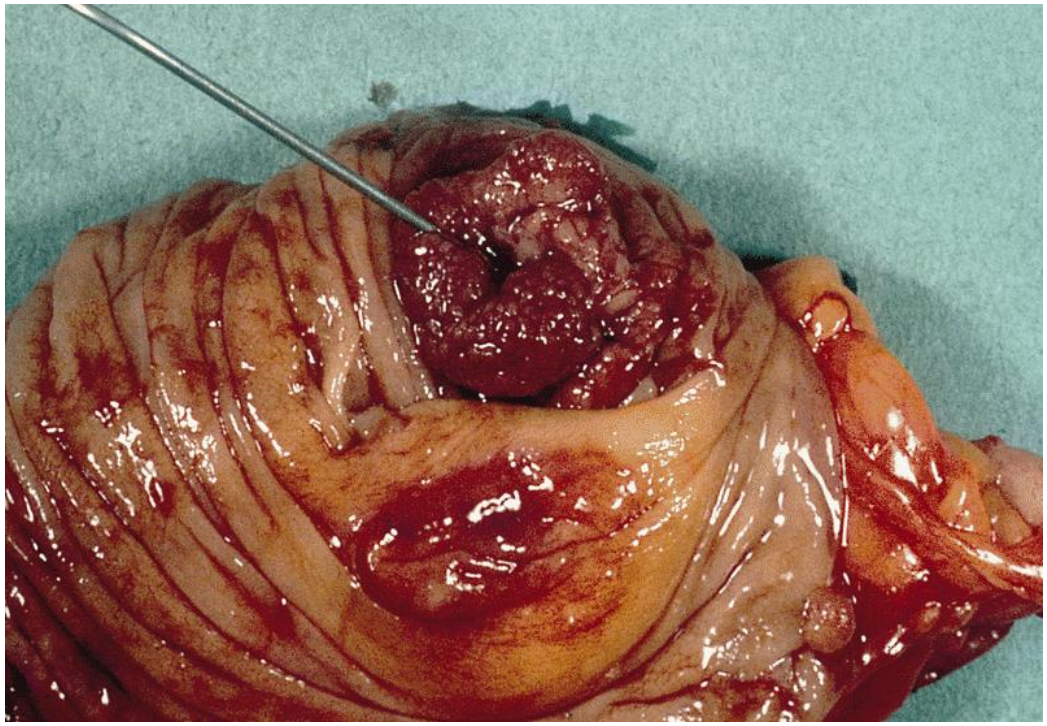
Treatment

- Epithelial neoplasms are treated with right hemicolectomy
- 5FU if stage III-IV
- If extension to serosa and peritoneum, hyperthermic intraperitoneal chemotherapy following cytoreductive surgery

Molecular alterations

- 80-100% of MANs have KRAS hotspot mutations.
- GNAS hotspot mutations are also more commonly enriched in low-grade MANs and are frequently seen in mucinous neoplasms across various organs.
- TP53 mutations are infrequent in low-grade MANs
- 10% of GCAs have KRAS and 6% have GNAS hotspot mutations

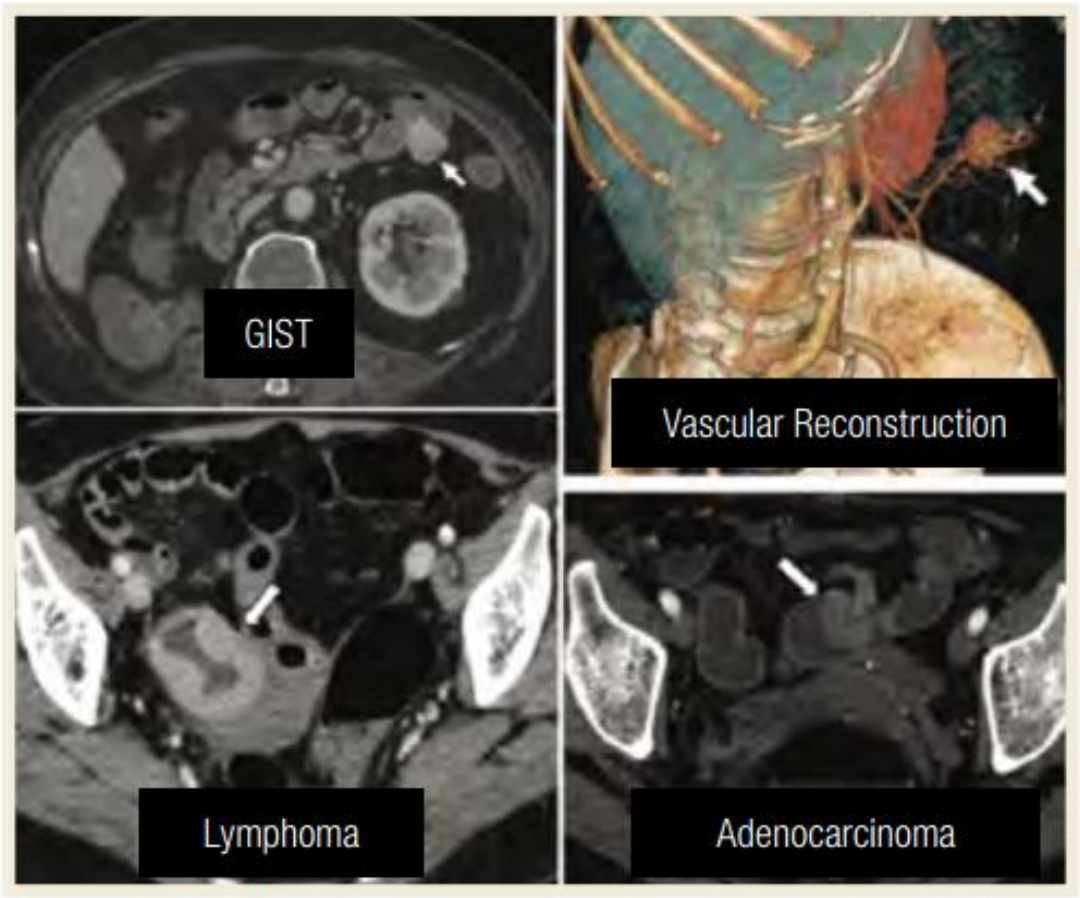
Adenocarcinoma of the appendix



A solid, noncystic lesion is less common than a cystic adenocarcinoma in the appendix.

Fig. 4-8

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.

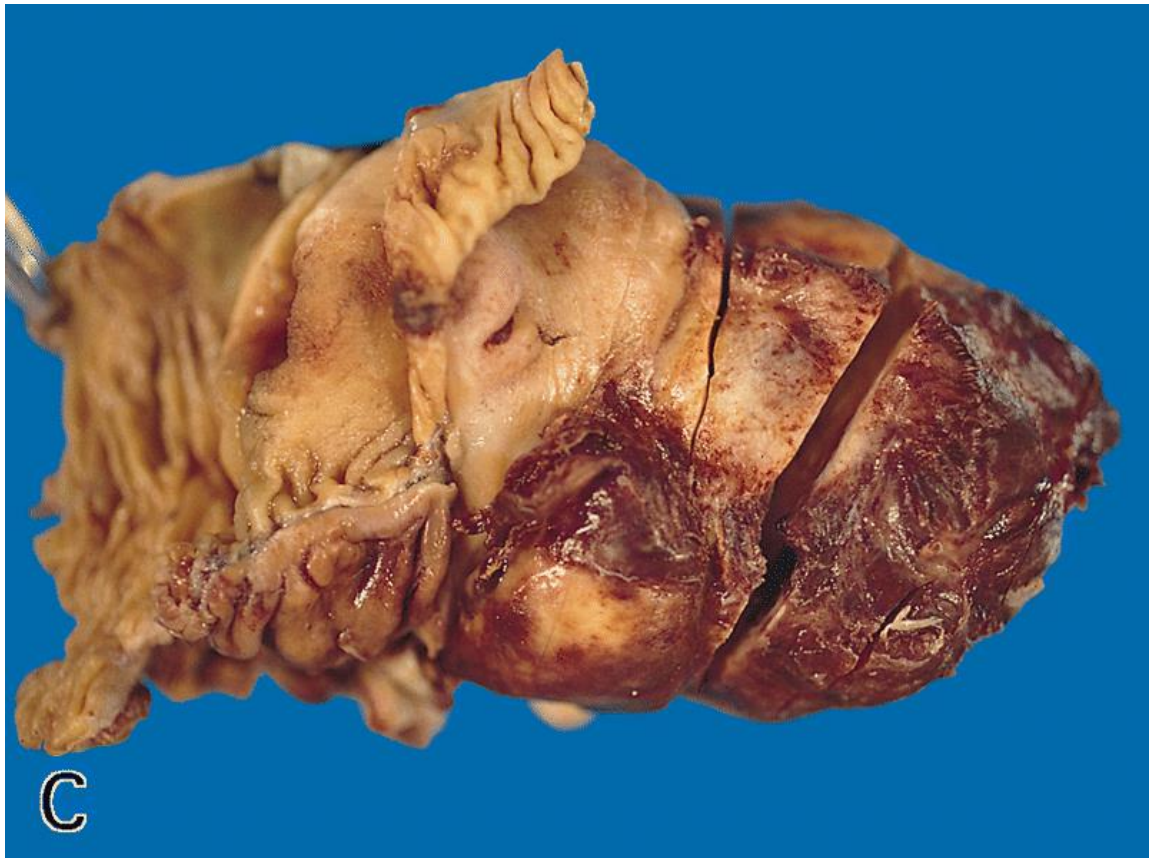


GIST, Gastrointestinal stromal tumour.

Burkitt's lymphoma

- Found principally in children (40-50% of lymphomas).
- Endemic form involves mandible, then kidneys, ovaries, adrenal glands.
- Sporadic form involves mass at the ileocecum and in the peritoneum.
- Mature B-cells of germinal center origin. Endemic form demonstrates EBV transcripts.
- Progression free survival 92% at 2 years following therapy with cyclophosphamide, vincristine, doxorubicin, high dose methotrexate/ifosfamide, etoposide, and high dose cytosine arabinoside.

Burkitt's lymphoma

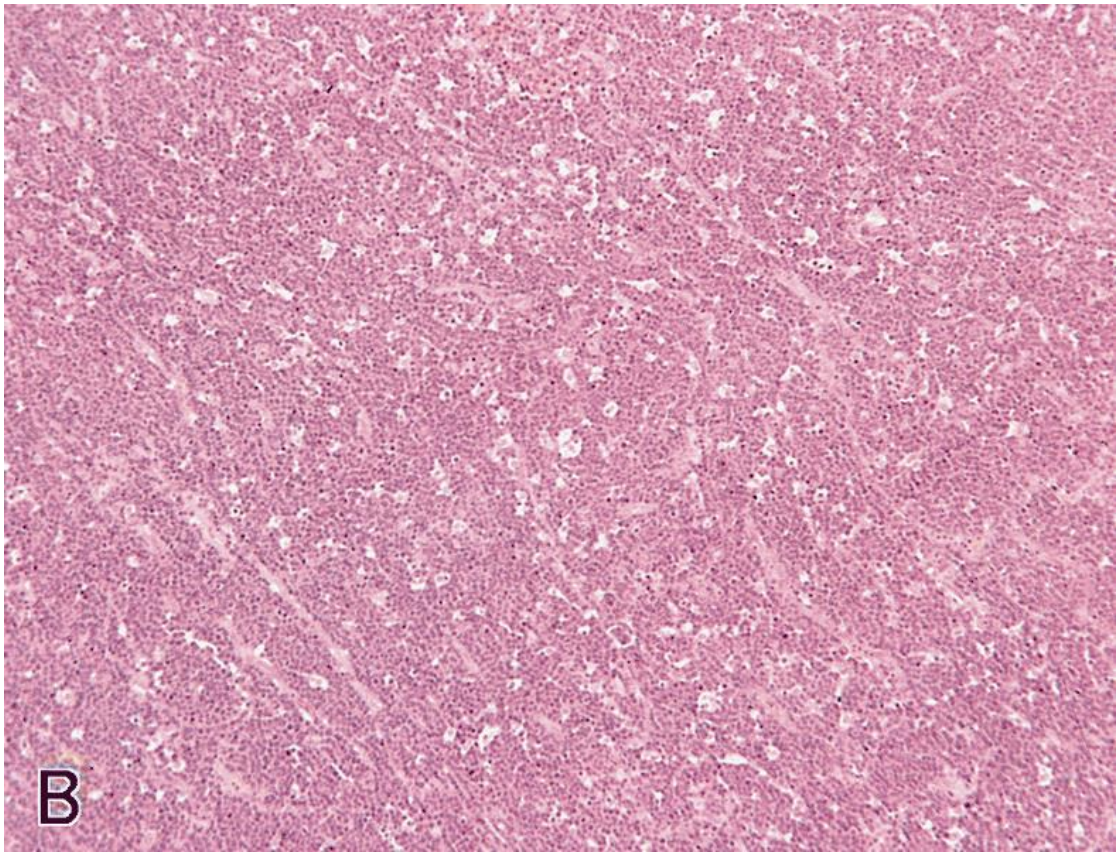


Extensive tumor is pushing into the lumen of the bowel, causing obstructive symptoms, but with a large amount of extramural tumor.

Fig. 8-8C

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.

Burkitt's lymphoma

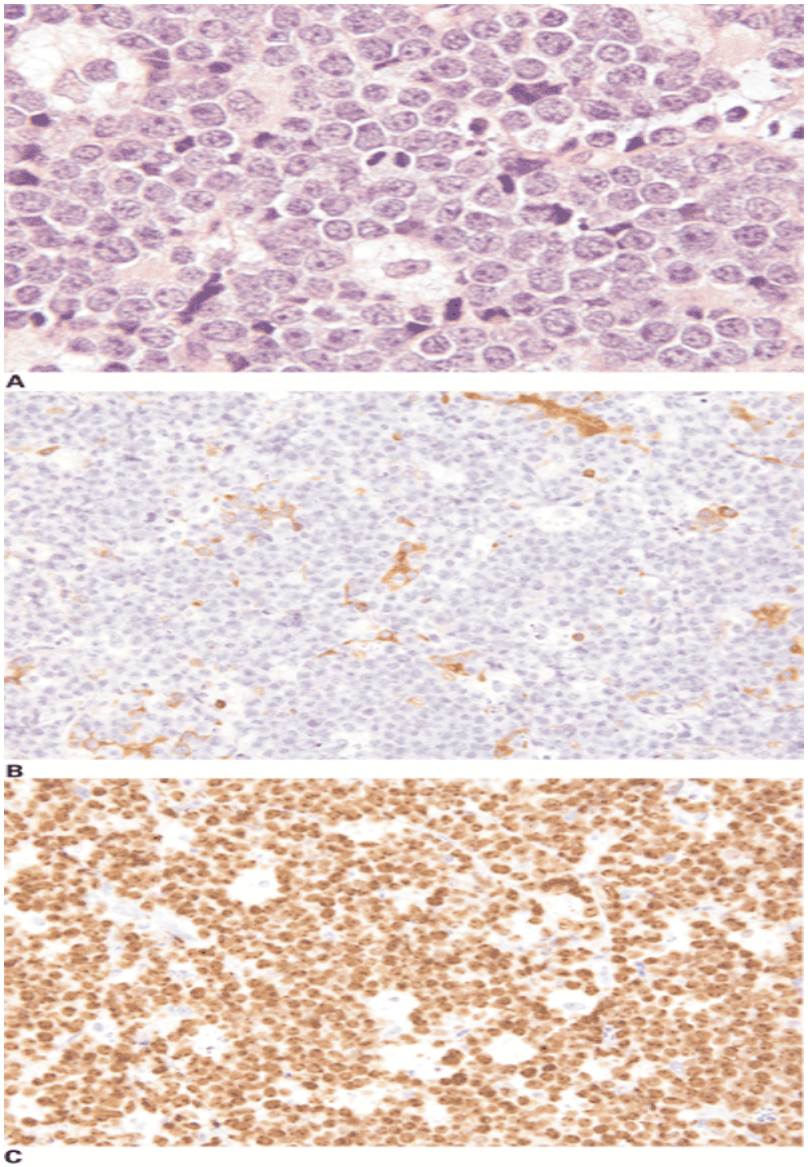


A "starry sky" pattern is evident.

Fig. 8-9B

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.

Burkitt's lymphoma



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

The neoplastic cells are intermediate in size, similar to that of benign histiocyte nuclei, with multiple small nucleoli. A starry-sky pattern is also seen in this field. B,C. The neoplastic cells are negative for BCL-2 (B), and are >99% positive for Ki-67 (C). (A, hematoxylin-eosin, 1000x; B,C, immunohistochemistry, 400x.)

Fig. 6-22 Accessed 04/27/2010

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 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 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 CD 117%
- 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

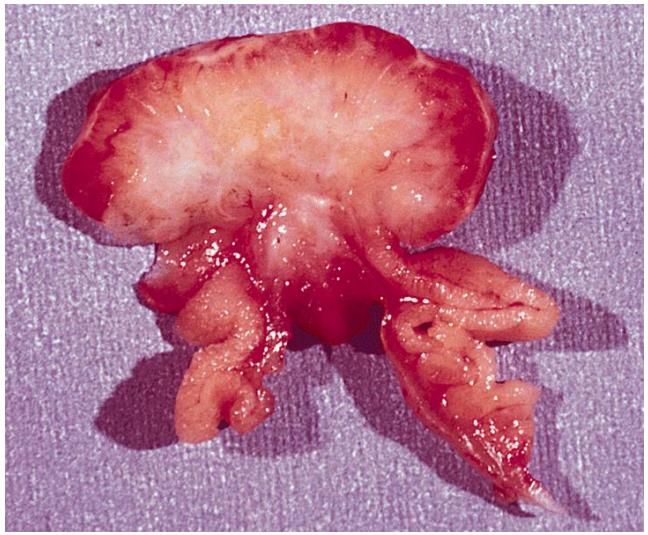
Gastrointestinal stromal cell tumor

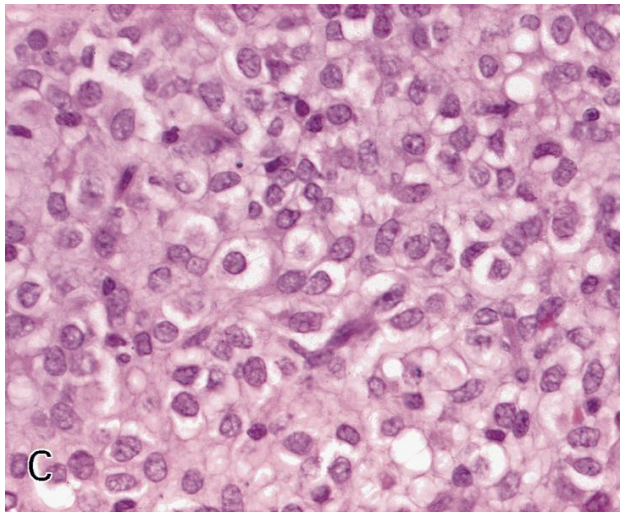
- Spindle:
- Bland spindle cells with faintly eosinophilic cytoplasm in a syncytial pattern; elongated nuclei with inconspicuous nucleoli;
- Subtypes: sclerosing, palisaded, vacuolated, diffuse hypercellular, sarcomatoid features with significant nuclear atypia and mitotic activity

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.

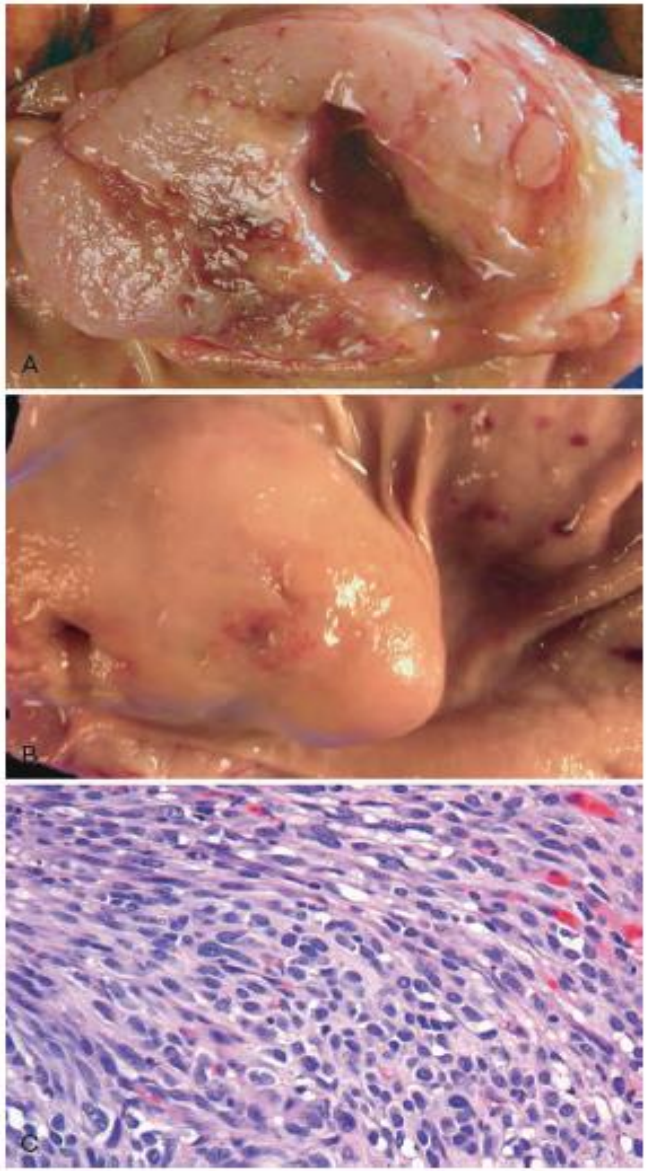
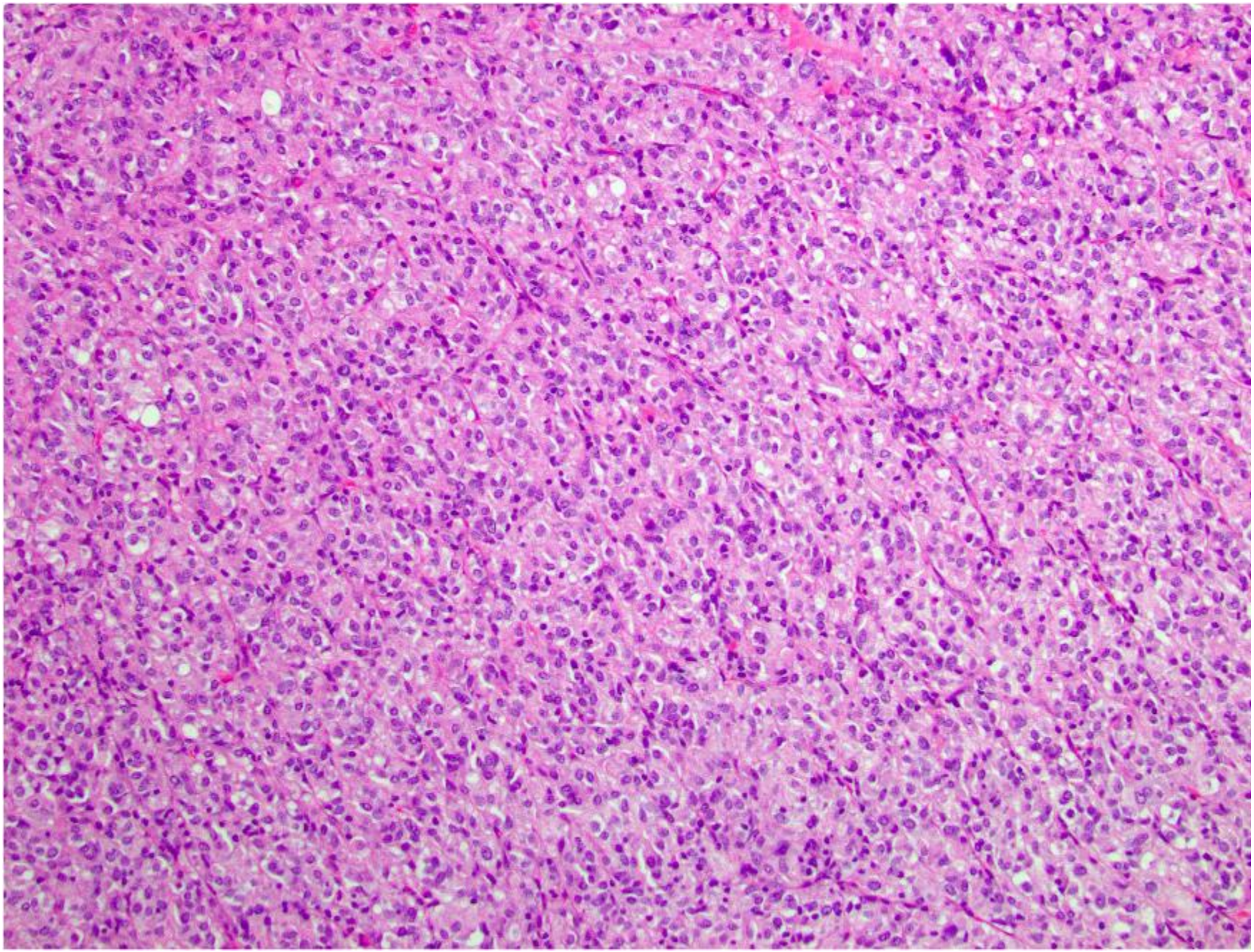
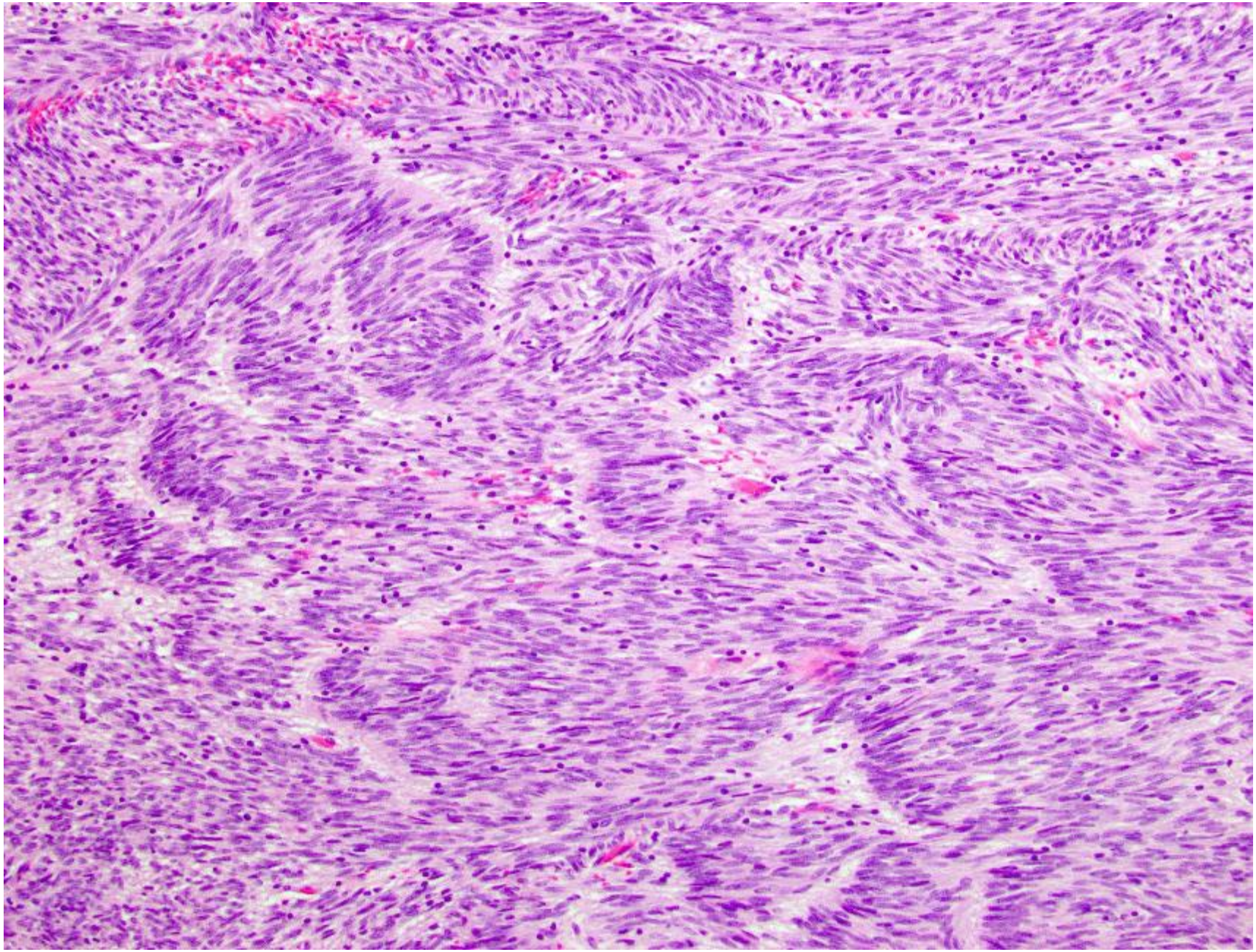
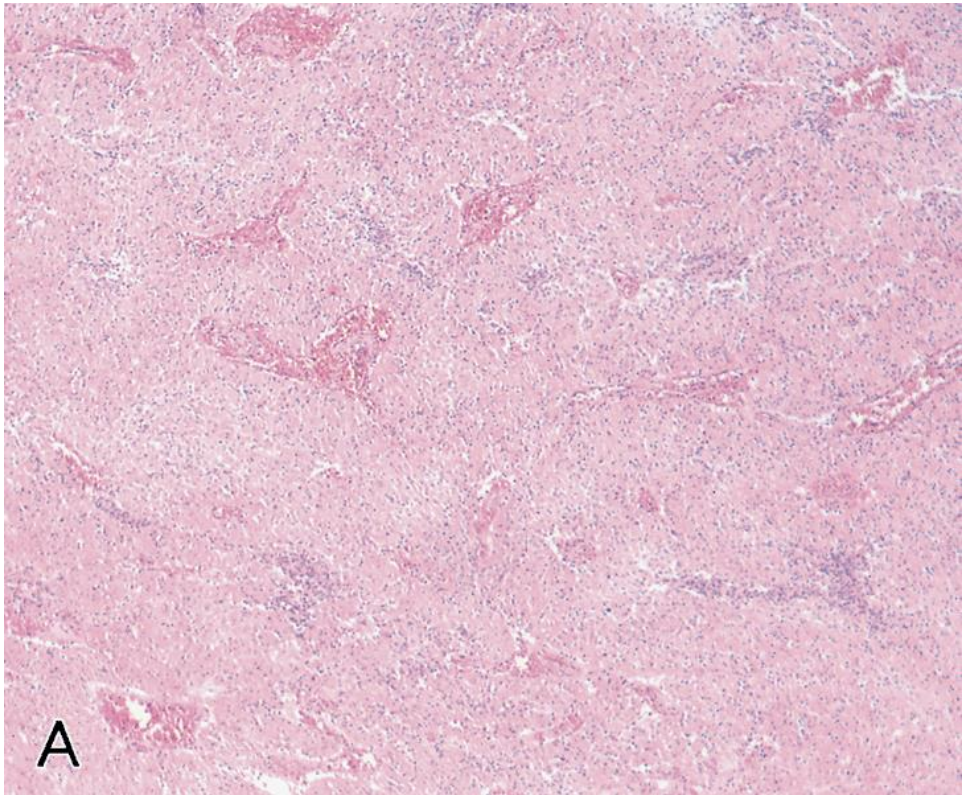


Figure 17-21 GI stromal tumor. **A,** On cross-section a whorled texture is evident within the white, fleshy tumor. **B,** The mass is covered by intact mucosa. **C,** Histologically the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber,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





Gastrointestinal stromal tumor



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

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.

Treatment of stromal tumor

- Imatinib not indicated for low-risk (completely resected) patients. All others receive imatinib.
- PDGFR D842V mutation not responsive to imatinib (tyrosine kinase inhibitor) .
- imatinib blocks c-KIT, leading to tumor regression. Dysuria, edema, nausea common.
- 3 years imatinib improves survival for high risk patients. High-risk includes incomplete resection as well as tumor rupture.
- May add mTOR inhibitor.
- Regorafenib is a multiple tyrosine kinase inhibitor used as third line therapy.

Peritoneal tumors

- Peritoneal mesotheliomas are almost always associated with significant asbestos exposure.
- Desmoplastic small round cell tumor
- Children and young adults
- t(11;22) (p13;q12) that results in the formation of a fusion gene involving EWS and WT1 genes.
- Secondary tumors may involve the peritoneum
- Mucinous carcinomas, particularly those of the appendix may cause pseudomyxoma peritonei.