# DISORDERS OF THE LARGE BOWEL

Kenneth Alonso, MD, FACP

# 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 3$^{rd}$ 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 ascending colon receives its innervation from T9; transverse colon, T10; the upper two-thirds of the descending colon, T11-T12.
- The lower third of the descending colon receives its innervation from L2, while the sacral roots innervate the rectum and anus.
- Kidneys and adrenal are innervated from T10-L1.

# Anatomy

- The lesser splanchnic nerve (T12) synapses at the renal plexus.
- 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).

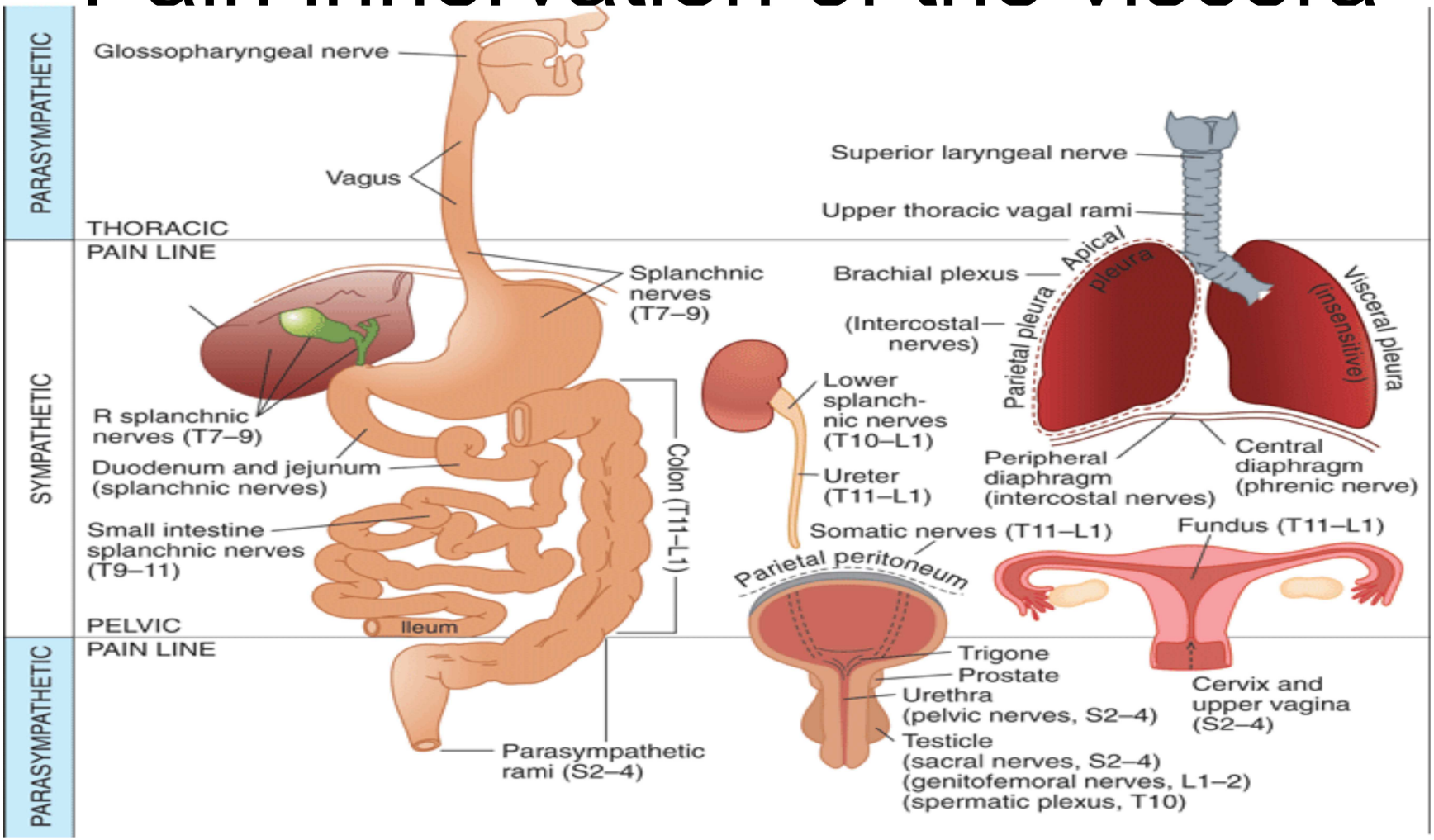
# Anatomy

- The chief artery to the rectum and anal canal is the superior rectal (from the inferior mesenteric artery). Middle and inferior rectal arteries also supply the rectum.
- The pectinate line of the anal canal separates lymphatic drainage (superior, to the inferior mesenteric and internal iliac nodes; inferior, to superficial inguinal nodes).
- Visceral afferents supply the rectum above the pectinate line; somatic innervation, below.
- The pectinate line is also the level of portocaval anastamosis.

# 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



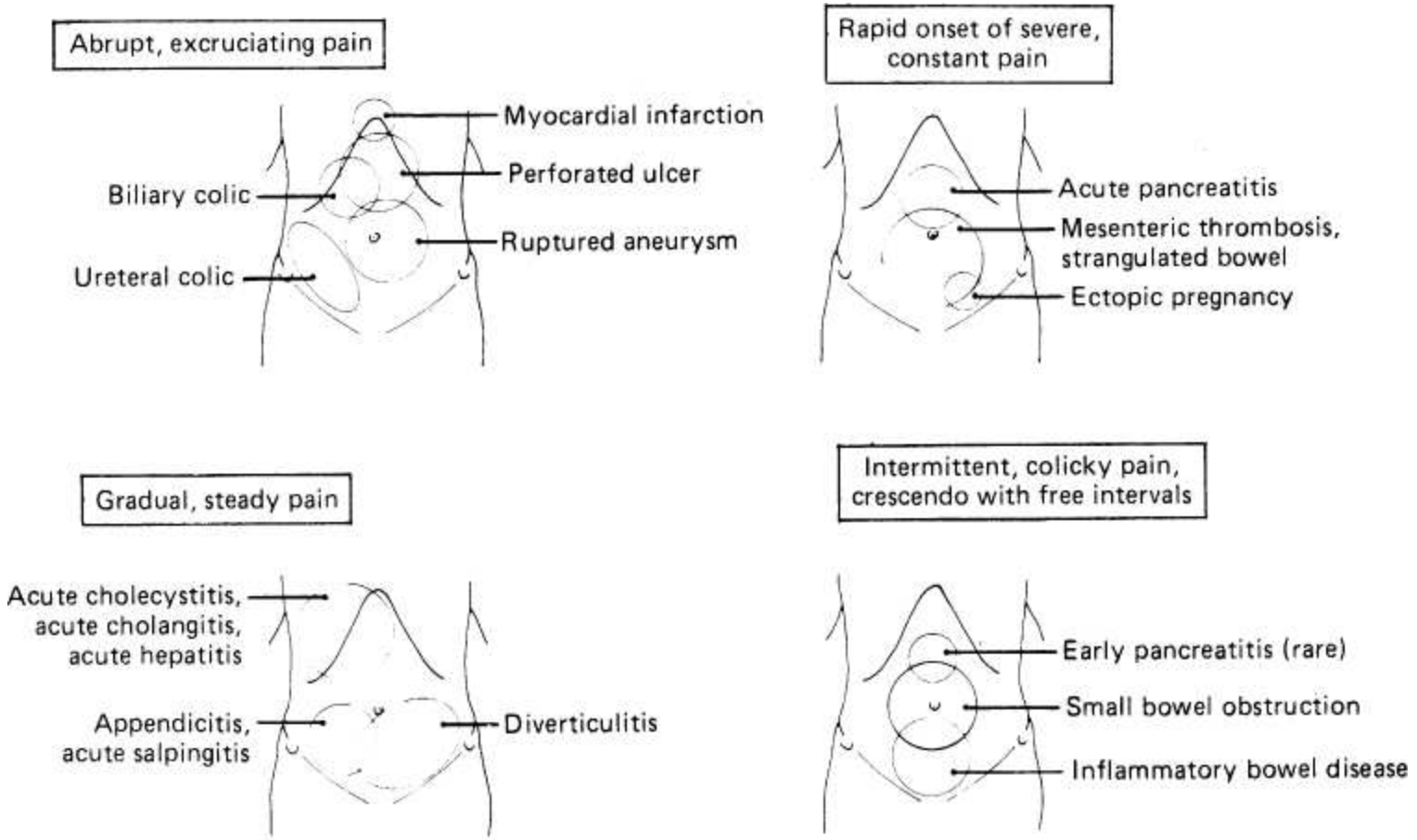

Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(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)
- L2-4 adjacent to transverse process and extending along iliac crest associated with somatic dysfunction of colon
- Posterior inferior sacroiliac joint associated with somatic dysfunction of rectum

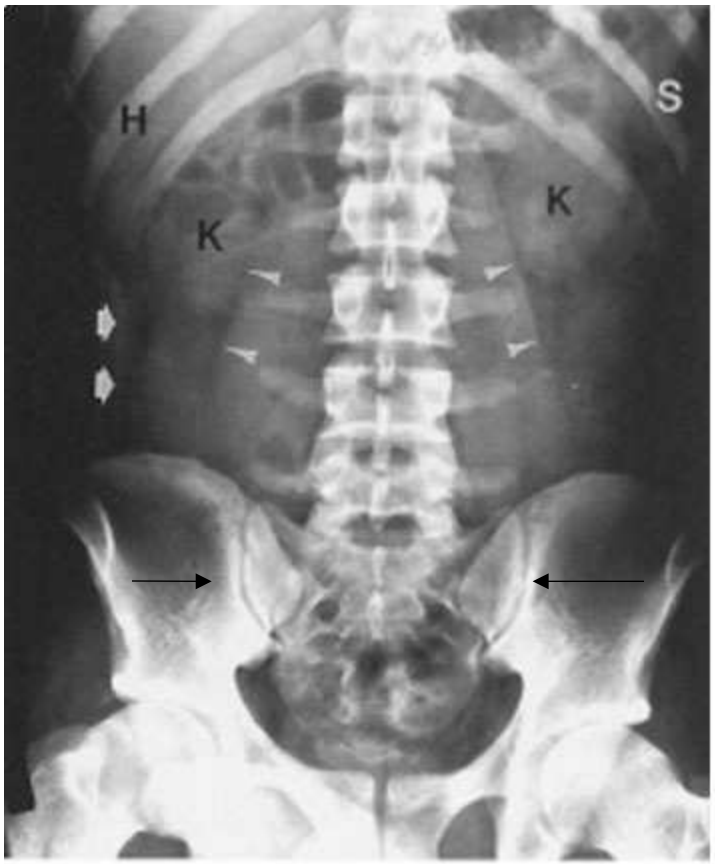
# Abdominal pain






Reproduced, with permission, from Way LW [ed]: *Current Surgical Diagnosis & Treatment*, 9th ed. Lange, 1991.)
Fig. 13-2 Accessed 07/01/2010

# Normal plain film of the abdomen

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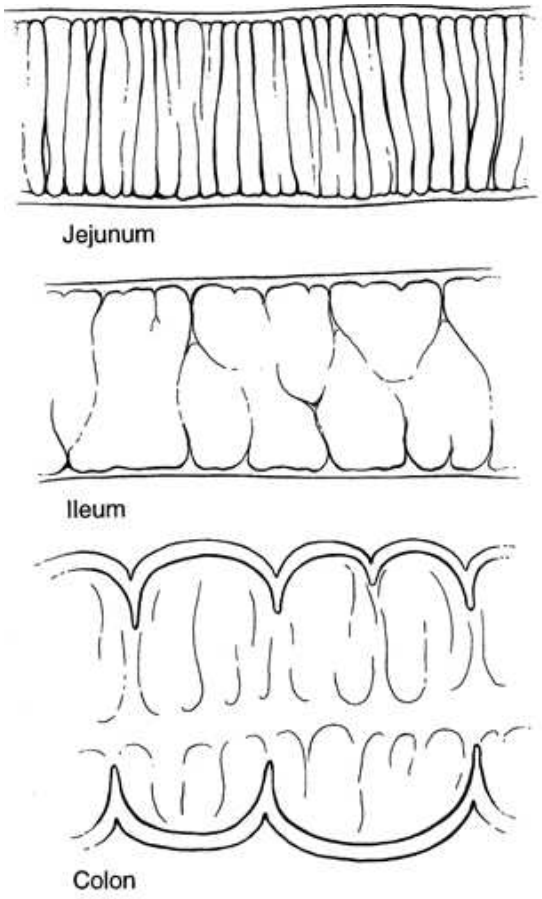
Chen, MYM, Pope Jr., TL, Ott DJ: *Basic Radiology*: http://www.accessmedicine.com



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




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



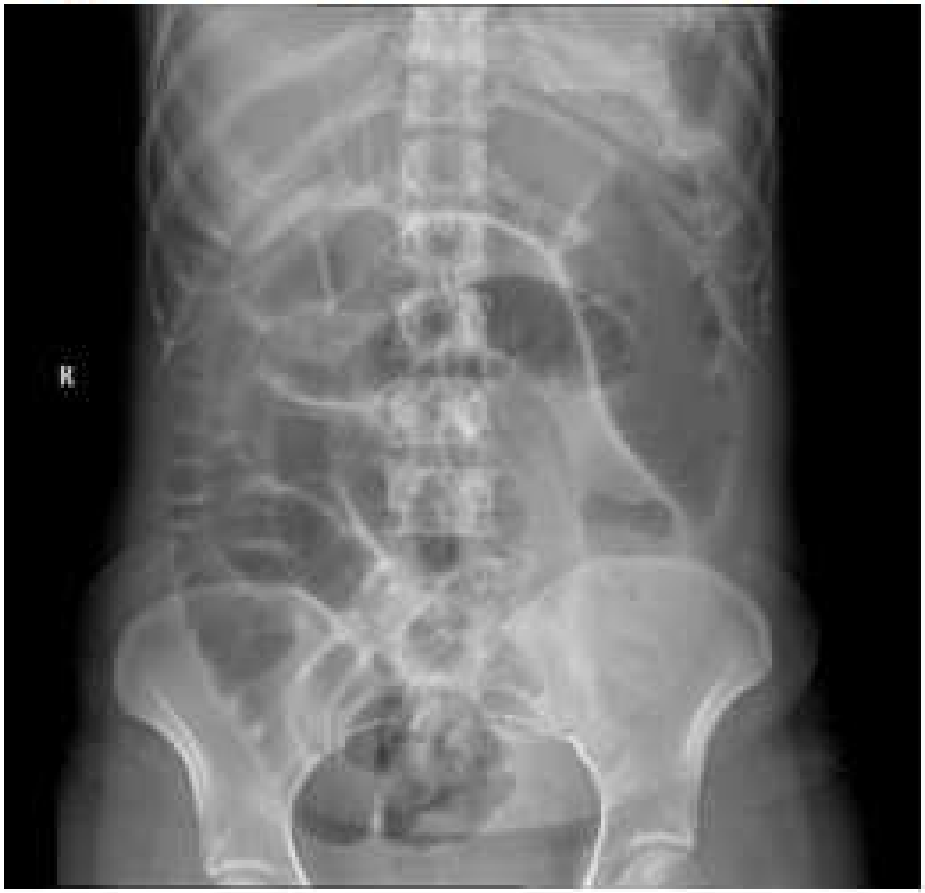
Schematic illustration of portions of bowel. The jejunum shows numerous mucosal folds, whereas the ileum has fewer folds. Both serosa of the jejunum and the ileum are smooth. The colon has serosa indented by haustra, and mucosal folds do not cross the lumen.

Fig. 8-2 Accessed 08/01/2010

# Intestinal atresia

- Imperforate anus as most common form of intestinal atresia
- Hindgut abnormality
- Failure of cloacal diaphragm to involute
- Anal atresia may present with feculent vomitus
- Double bubble sign on x-ray

# Large bowel obstruction




https://radiopaedia.org/articles/large-bowel-obstruction-summary
Accessed 11/09/2019

# Bowel obstruction

- 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

# Large bowel obstruction

- Cancer, volvulus, diverticular disease as major causes (in diminishing order)
- Marked leukocytosis is a late finding and suggests bowel infarction
- Air-fluid levels and bowel distention noted on plain abdominal x-ray;
- Small bowel distention if ileocecal valve is incompetent
- Colonoscopy 98% sensitive and 98% specific; positive likelihood ratio (LR+) 48; LR-, 0.04. Can exclude acute pseudo-obstruction.
- CT scan is also accurate.

# Hirschsprung disease

- Presents as obstruction because unable to pass meconium.
- Coordinated peristalsis is lost
- Distal intestinal segment lacks both the Meissner submucosal and the Auerbach myenteric plexes.
- Defect always begins at the rectum

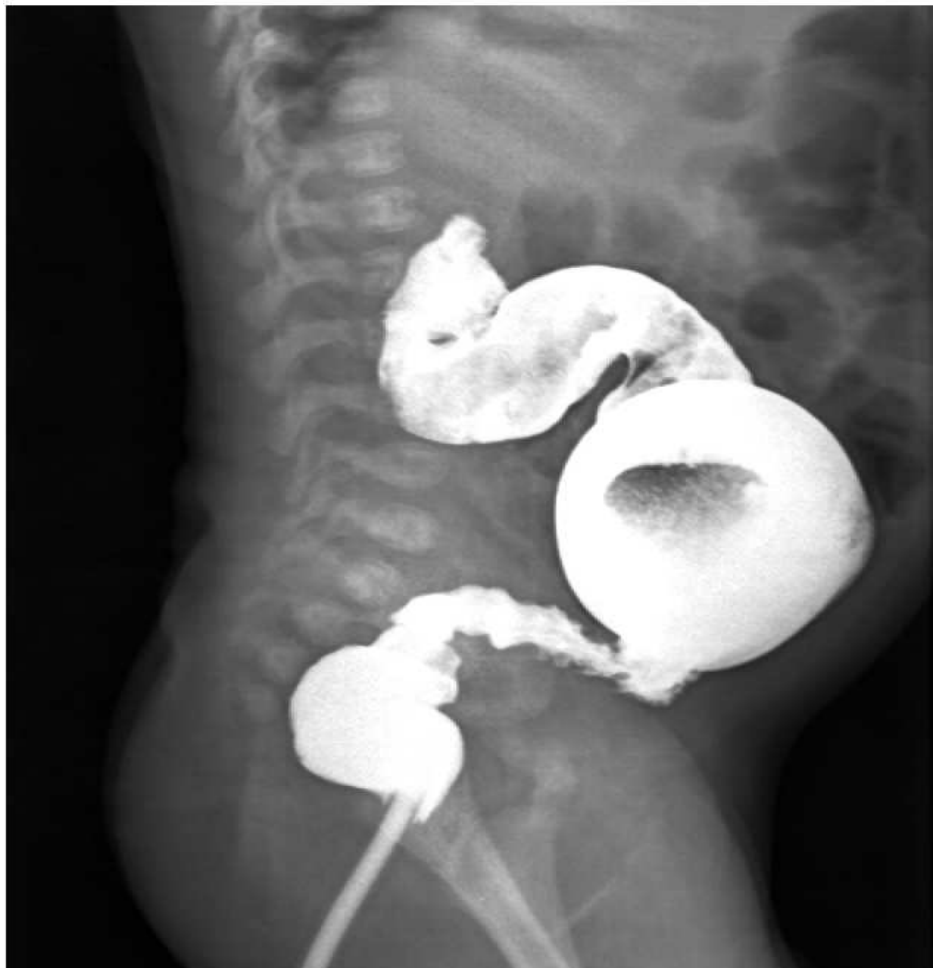
# Hirschsprung disease

- Short segments of bowel involved in male
- Long segments of bowel involved in female.
- Surgical resection of aganglionic segment with end to end anastomosis of the normal proximal colon to the rectum as treatment.
- Normal bowel function and continence develop over time.

# Hirschsprung disease

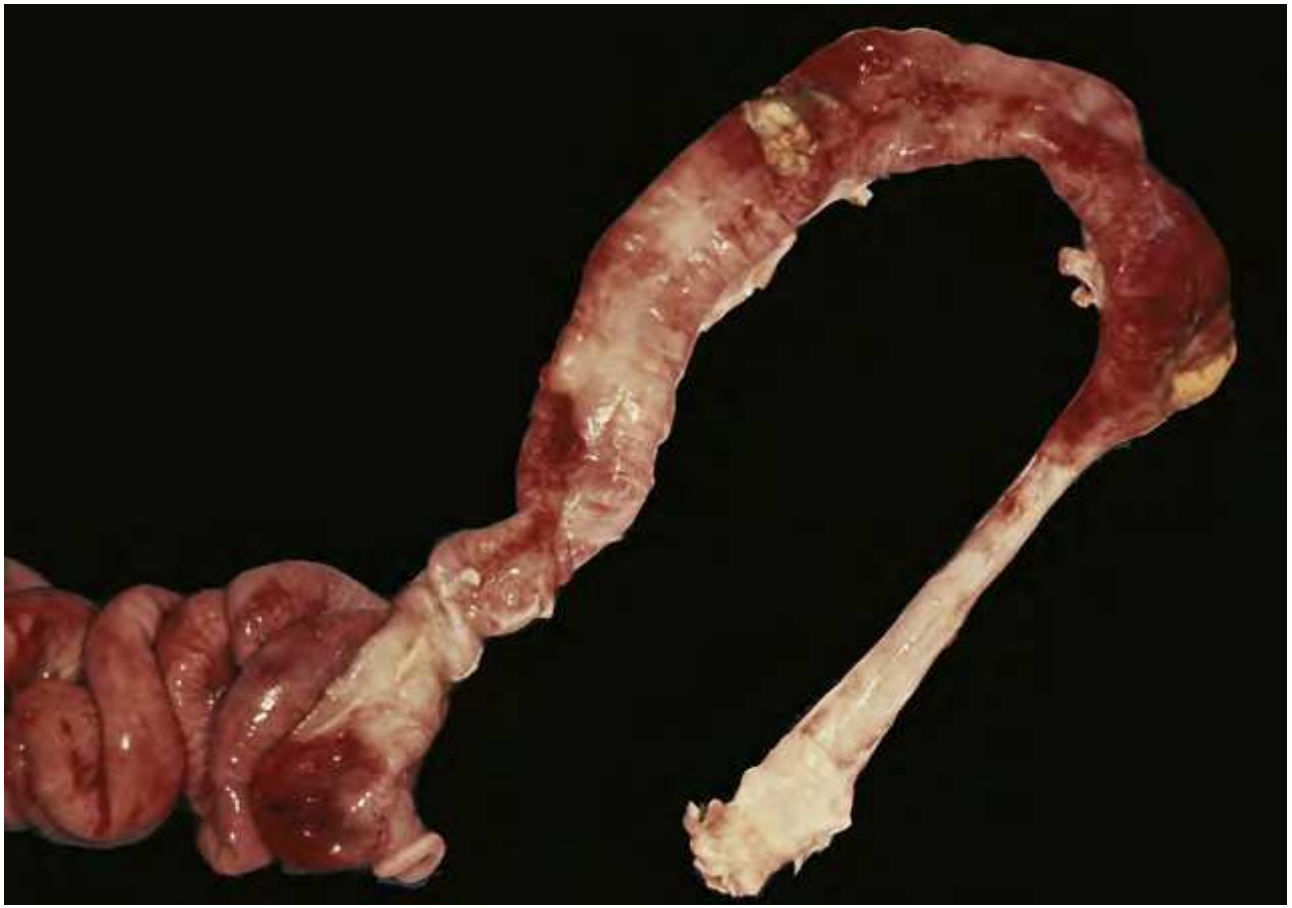
- One in 5000 live births
- 4% of patient siblings affected
- 10% of all cases occur with Down's syndrome
- 5% of all other cases associated with serious neurologic abnormalities
- Loss of function mutation in RET accounts for majority of familial cases and 15% of sporadic cases
- Failure of migration of neural crest cells into the bowel wall during embryogenesis

# Hirschsprung disease



Dilated bowel segment proximal to narrowing.

# Hirschsprung's disease



Klatt, EC, Robbins and Cotran Color Atlas of Pathology. Elsevier. Philadelphia. 2015. Figure 7-64 Accessed 11/07/2019

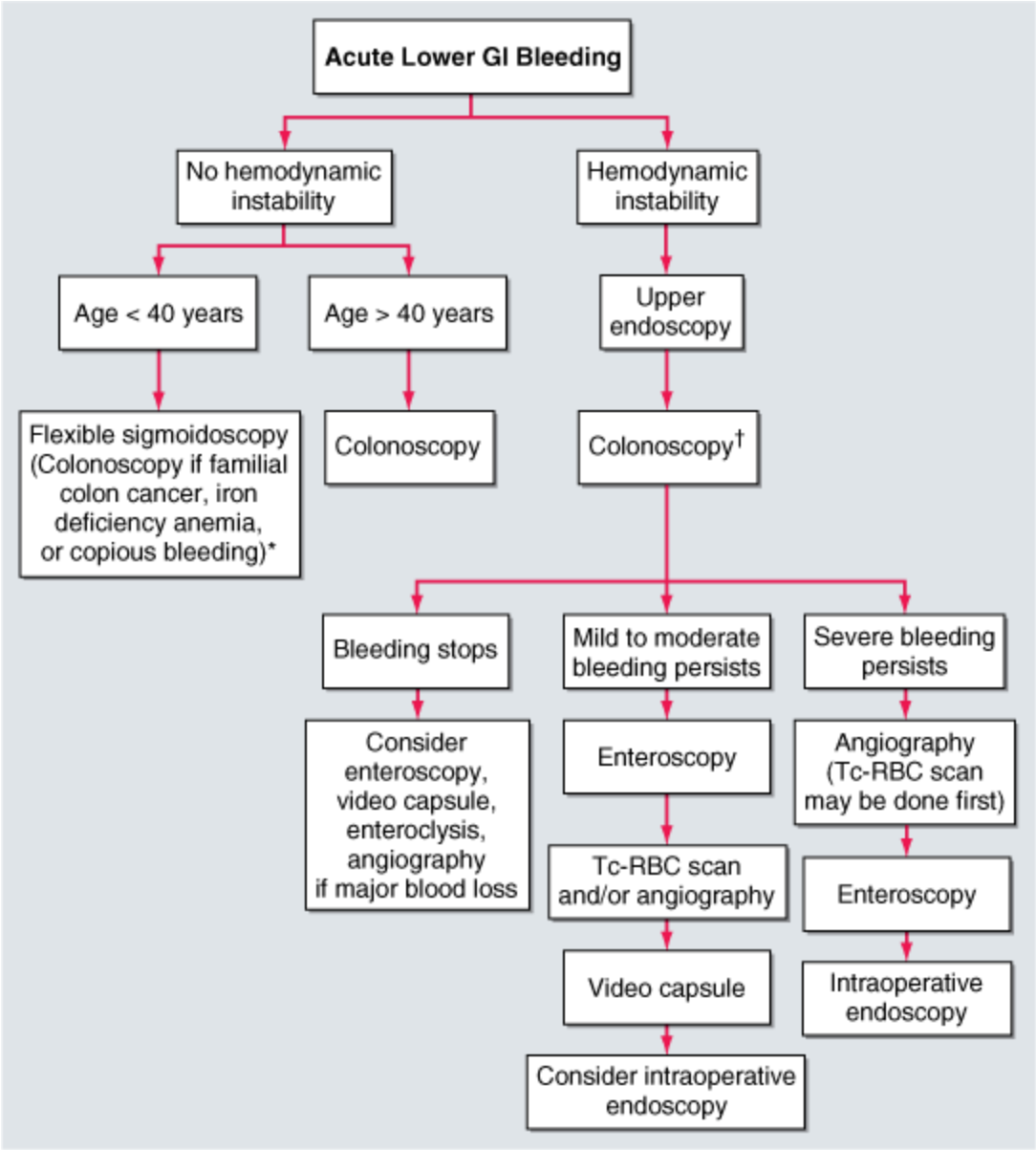



Fig. 42-2
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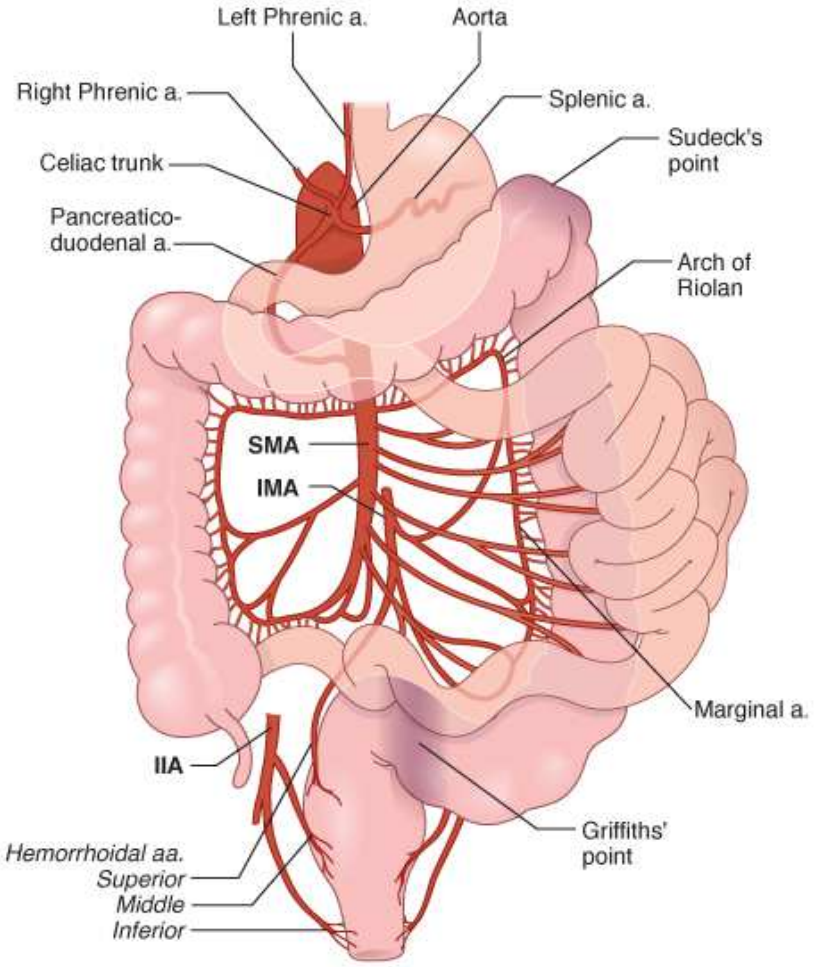
# Blood supply to the intestine






Sudeck's and Griffiths' points, indicated by shaded area, are watershed areas within the colonic blood supply and common locations for ischemia.

Fig. 292-1 Accessed 08/01/2010

# Acute mesenteric ischemia

- Acute colonic ischemia typically presents with sudden onset of cramping, left lower abdominal pain, a desire to defecate, and passage of blood or bloody diarrhea.
- Symptoms are out of proportion to physical findings.
- Often no prior symptoms.
- May have nausea and diarrhea (with blood, late).

# Acute mesenteric ischemia

- 50% of cases due to embolus to superior mesenteric artery or celiac artery from aortic atheromata or cardiac vegetations.
- 25%, arterial thrombosis (often with a history of chronic mesenteric ischemia)
- Causes:
- Atrial fibrillation
- Hypercoagulable states and oral contraceptive use
- Systemic vasculitides
- May occur following cocaine use and endurance exercise.

# Acute mesenteric ischemia

- WBC often markedly abnormal.
- Lactate levels may be elevated (but are not diagnostic).
- Angiography indicated.
- Surgical resection of necrotic bowel and revascularization are principal therapeutic interventions.

# Mesenteric ischemia

- Transmural infarction is typically caused by acute vascular obstruction.
- Mucosal or mural infarctions can follow acute or chronic hypoperfusion
- Intestinal hypoperfusion can be associated with:
- Cardiac failure
- Shock
- Dehydration
- Use of vasoconstrictive drugs

# Ischemic colitis

- 25% of cases
- Usually due to non-occlusive decrease in colonic perfusion.
- Typically involves the watershed areas of the colon, principally on the left side (splenic flexure).
- Post aortic aneurysm repair, involves sigmoid colon as inferior mesenteric and internal iliac artries are compromised
- Abdominal pain usually mild. Tenderness may be present. Rebound tenderness is uncommon.
- Frequently have bloody diarrhea.
- Profuse bleeding unusual.

# Ischemic colitis

- Hemodialysis, diabetes mellitus, hypoalbuminemia, and use of drugs that induce constipation are associated risk factors.
- Thumbprint sign due to edema in bowel wall.
- Double halo on MRI (edematous submucosa with higher attenuation of muscularis mucosae)
- Colonoscopy indicated.
- Resting the bowel is often sufficient therapy.
- Rectum not involved as has dual blood supply from inferior mesenteric artery and internal iliac artery.

# Mesenteric ischemia

- The demarcation between normal and ischemic bowel is sharply defined and the infarcted bowel is initially intensely congested and dusky to purple-red.
- Later, blood-tinged mucus or frank blood accumulates in the lumen and the wall becomes edematous, thickened, and rubbery.
- There is coagulative necrosis of the muscularis propria within 1 to 4 days, and perforation may occur.
- Serositis, with purulent exudates and fibrin deposition, may be prominent.

# Mesenteric ischemia

- Mesenteric venous thrombosis can also lead to ischemic disease
- 5% of cases due to mesenteric venous thrombosis
- Inherited or acquired hypercoagulable states
- Invasive neoplasms
- Cirrhosis
- Trauma
- Abdominal masses that compress the portal drainage

# Mesenteric ischemia

- In mesenteric venous thrombosis, arterial blood continues to flow for a time, resulting in a less abrupt transition from affected to normal bowel.
- However, propagation of the thrombus may lead to secondary involvement of the splanchnic bed.
- The ultimate result is similar to that produced by acute arterial obstruction because impaired venous drainage eventually prevents oxygenated arterial blood from entering the capillaries.

# Mesenteric ischemia

- The initial hypoxic injury occurs at the onset of vascular compromise.
- The epithelial cells lining the intestine are relatively resistant to transient hypoxia.
- The second phase, reperfusion injury, is initiated by restoration of the blood supply and it is at this time that the greatest damage occurs.
- In severe cases this may trigger multi-organ failure.
- Leakage of gut lumen bacterial products, e.g. lipopolysaccharide, into the systemic circulation may trigger cytokine storm.

# Mesenteric ischemia

- Chronic ischemia is accompanied by fibrous scarring of the lamina propria, and, uncommonly, stricture formation.
- Chronic ischemia manifests as intermittent abdominal pain with bloody diarrhea.
- In both acute and chronic ischemia, bacterial superinfection and enterotoxin release may induce pseudomembrane formation that resembles Clostridium difficile–associated pseudomembranous colitis.

# Watershed zones

- The splenic flexure
- Termination of the superior and inferior mesenteric arterial circulations
- The sigmoid colon and rectum
- Termination of inferior mesenteric, pudendal, and iliac arterial circulations.
- Noted with abdominal aortic aneurysm or following its repair
- A pattern of surface epithelial atrophy, or even necrosis and sloughing, with normal or hyperproliferative crypts is a morphologic signature of ischemic intestinal disease.

# Other causes of mesenteric ischemia

- CMV infection due to viral tropism for endothelial cells
- Radiation enterocolitis
- Necrotizing enterocolitis
- Acute disorder of the small and large intestines that can result in transmural necrosis.
- It is the most common acquired GI emergency of neonates, particularly those who are premature or of low birth weight, and frequently presents when oral feeding is initiated

# Chronic mesenteric ischemia

- Recurrent postprandial abdominal pain, often diminishing after several hours.
- Obstructive disease of the superior mesenteric artery or celiac artery or both.
- 91% of patients have both vessels involved.
- Weight loss common and is due to food aversion.
- Duplex ultrasonography is very sensitive (>90%). Normal results make the diagnosis unlikely.
- Angiography indicated if diagnosis likely as stenoses alone do not confirm the diagnosis (18% of those over age 65 have stenoses).

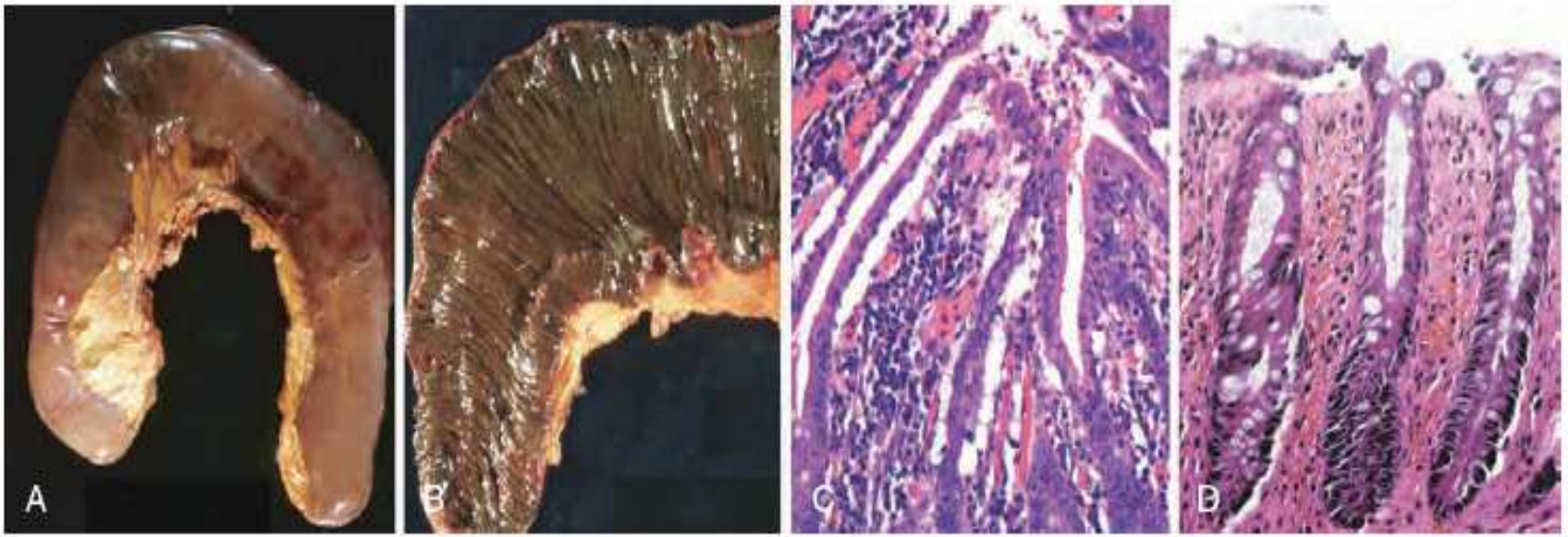



**Figure 17-24** Ischemic bowel disease. **A,** Jejunal resection with dusky serosa of acute ischemia (mesenteric thrombosis). **B,** Mucosa is stained with blood after hemorrhage. **C,** Characteristic attenuated villous epithelium in this case of acute mesenteric thrombosis. **D,** Chronic colonic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

# Angiodysplasia

- Usually occurs in the elderly.
- Occurs most often in the cecum or right colon
- 20% of major episodes of lower intestinal bleeding
- Intestinal hemorrhage may be chronic and intermittent or acute and massive.
- Normal distention and contraction may intermittently occlude the submucosal veins that penetrate through the muscularis propria and can lead to focal dilation and tortuosity of overlying submucosal and mucosal vessels.
- Associated with Von Willebrand disease.
- Diagnosed by angiography or colonoscopy.
- Right hemicolectomy curative.

# Histology of the colon

- Colon is where water balance is maintained.
- Mucosa lined by microvilli [brush border].
- Goblet cells secrete mucus; interspersed in mucosa.
- Paneth cells in crypt base secrete antimicrobial proteins.
- Endocrine cells are also scattered throughout mucosa.
- Parasympathetic control via myenteric plexus.

# Colon

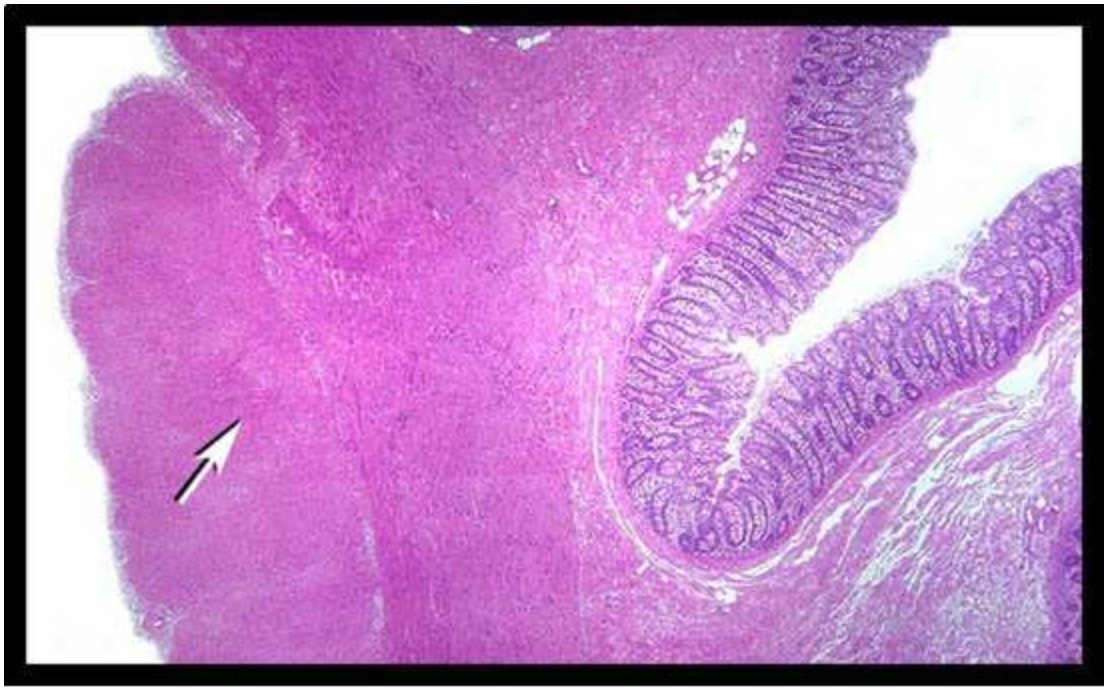




Fig. 14-72 Accessed 03/01/2010

# Inflammatory bowel disease

- The mucosal immune system responds to ingested pathogens but is unresponsive to normal intestinal microflora.
- Inflammatory bowel disease results from unregulated and exaggerated local immune responses to commensal microbes in the gut, in genetically susceptible individuals.
- The cause of generating a strong immune responses against normal flora and the cause of defects in epithelial barrier function are not well established, however.

# Inflammatory bowel disease

- The hallmark of inflammatory bowel disease is chronic mucosal injury.
- Presents in teens and early twenties
- Women slightly more affected than men
- 10% of cases overlap
- Sclerosing cholangitis may develop
- More common in ulcerative colitis
- Systemic amyloidosis is a late consequence
- Increased risk for development of carcinoma

# Inflammatory bowel disease

- A high-fat diet is highly associated with gut dysbiosis-mediated inflammation and intestinal permeability
- Elevated presence of systemic lipopolysaccharides related to high fat diet-induced microbiota disruption leads to enhanced inflammatory activity

# Inflammatory bowel disease

- A maternal low-fiber diet  alters the composition of the maternal milk microbiome and assembling infant gut microbiome.
- These microbial changes reduce the secretion of the dendritic cell (DC) growth factor FLT3L by neonatal intestinal epithelial cells and impaired downstream pDC hematopoiesis and perturbation of regulatory T cell expansion in the lungs.

# Inflammatory bowel disease

- High-fiber diets and short-chain fatty acids can promote the development of Foxp3 $T_{regs}$ and improvement in intestinal barrier function, which subsequently suppress CNS autoimmunity.

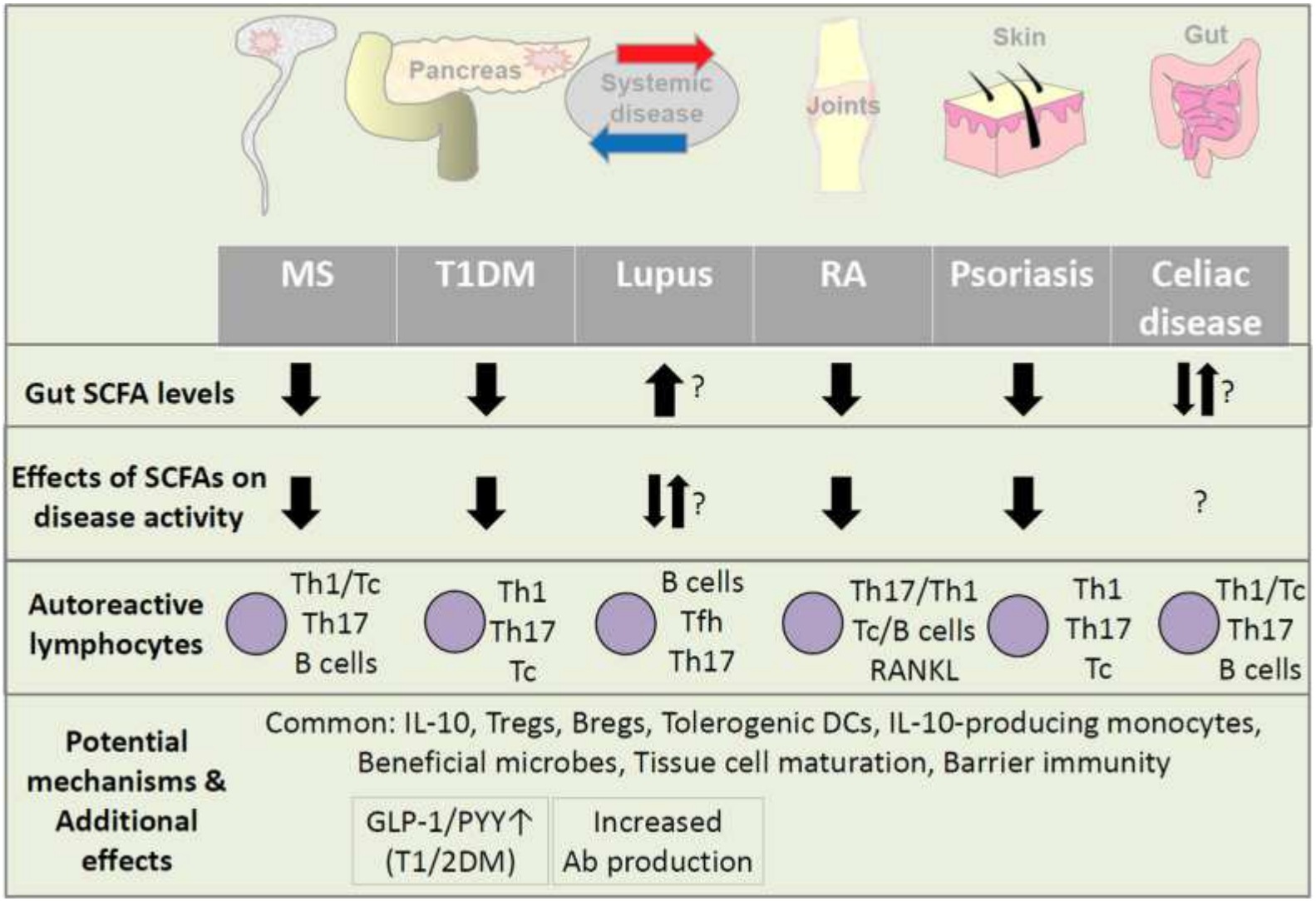
- Therapy with a propionate-producing bacteria isolated from the milk of high-fiber diet-fed mothers, or supplementation with propionate, confers protection against severe lower respiratory infections by restoring gut FLT3L expression and pDC hematopoiesis

# Inflammatory bowel disease

- Rice bran is an effective fiber treatment
- Raises proprionate levels
- Beans do not lead to increase of short chain fatty acids
- Prolong inflammatory changes
- Dysregulate antigen presentation

- A high-fiber diet induces IFN-1 production by intratumoral monocytes
- Leads to more effectice immunotherapy

- Mediterranean diet effective


Pancreas
Systemic disease
Joints
Skin
Gut
MS
T1DM
Lupus
RA
Psoriasis
Celiac disease
Gut SCFA levels
Effects of SCFAs on disease activity
Autoreactive lymphocytes
Th1/Tc Th17 B cells
Th1 Th17 Tc
B cells Tfh Th17
Th17/Th1 Tc/B cells RANKL
Th1 Th17 Tc
Th1/Tc Th17 B cells
Potential mechanisms & Additional effects
Common: IL-10, Tregs, Bregs, Tolerogenic DCs, IL-10-producing monocytes, Beneficial microbes, Tissue cell maturation, Barrier immunity
GLP-1/PYY↑ (T1/2DM)
Increased Ab production

# Familial association

- Fifteen percent of patients have affected first-degree relatives, and the lifetime risk if either a parent or sibling is affected is 9%.
- Dizygotic twins have the concordance rates expected for siblings;
- Monozygotic twins exhibit a 30% to 50% concordance rate for Crohn's disease.
- 15% in Ulcerative colitis
- 10% for dizygotic twins in both diseases
- HLA-DR2 is increased in patients with ulcerative colitis.

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# Mechanisms

- Gene on 5q31, site of many cytokine loci, affected (however, multifactorial cause).
- Crohn's disease is a result of a chronic delayed-type hypersensitivity reaction induced by IFN-γ-producing $T_{H1}$ cells.
- While ulcerative colitis is thought to be caused by excessive activation of $T_{H2}$ cells, IL-4 has not been found in the lesions. Rather, there is no consistent pattern of T cell activation or dominant cytokine production.

# Mechanisms

- MPO-ANCA is positive in 75% of patients with ulcerative colitis; 11%, with Crohn's disease.
- The reverse is true with anti-saccharomyces antibody
- IL-23R mutations may attenuate pro-inflammatory $T_{H17}$ responses.
- Only in ulcerative colitis:
- ECM1 (extracellular matrix protein 1) inhibits matrix metalloproteinase 9 function
- HNFA polymorphisms

# Genetic changes

- 27% Europeans with Crohn's disease have an HLA-DR1/DR1/DQw5 allelic combination.
- NOD2 (nucleotide-binding oligomerization domain) has recently been shown to be associated with Crohn's disease.
- The NOD2 protein is expressed in many types of leukocytes as well as epithelial cells, and is thought to function as an intracellular receptor for microbes.
- Upon binding microbial components, it may trigger the NF-κB pathway.
- Defective organic cation transport (SCLC22A4) and autophagy (ATG16L1 and IRGM ) also noted.

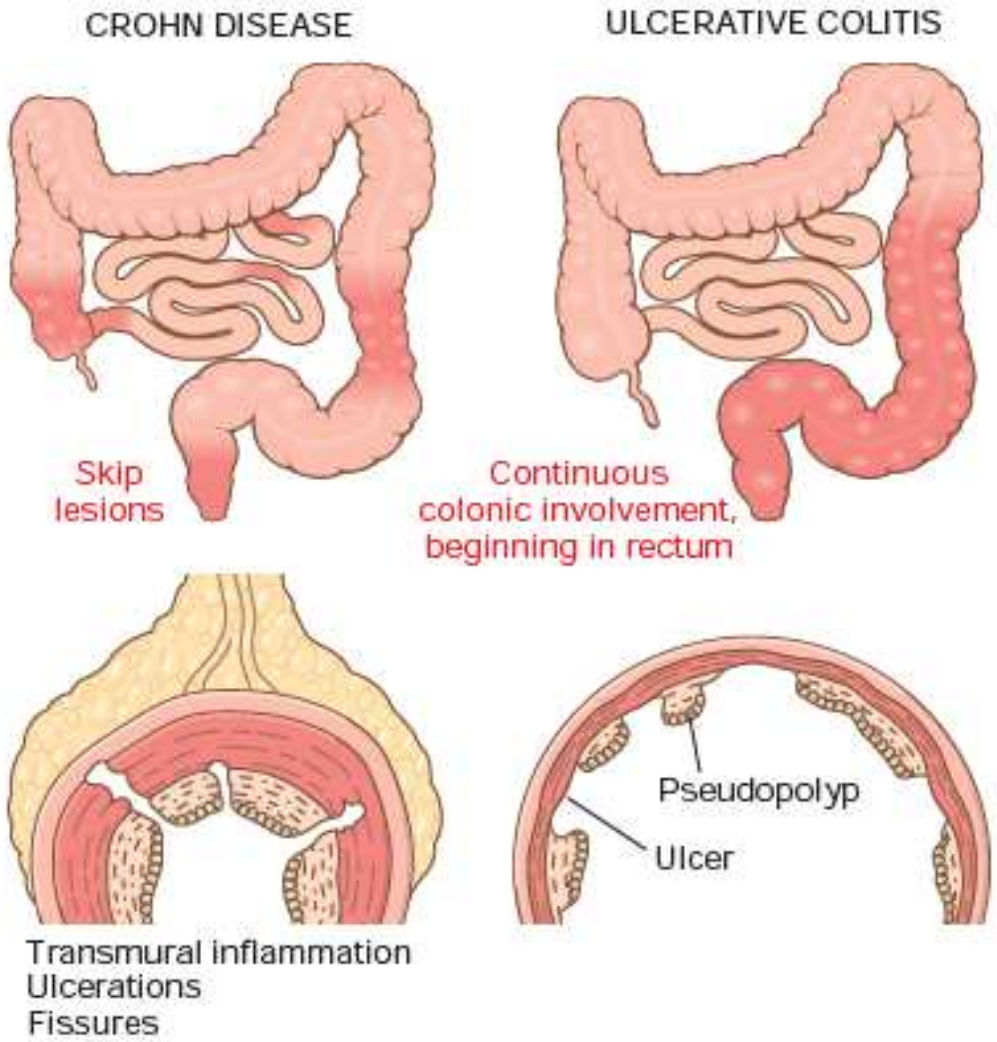



**Figure 17-32** Distribution of lesions in inflammatory bowel disease. The distinction between Crohn disease and ulcerative colitis is primarily based on morphology.

**Table 17-9** Features That Differ between Crohn Disease and Ulcerative Colitis

| Feature | Crohn Disease | Ulcerative Colitis |
|---|---|---|
| **Macroscopic** | | |
| Bowel region | Ileum ± colon | Colon only |
| Distribution | Skip lesions | Diffuse |
| Stricture | Yes | Rare |
| Wall appearance | Thick | Thin |
| **Microscopic** | | |
| Inflammation | Transmural | Limited to mucosa |
| Pseudopolyps | Moderate | Marked |
| Ulcers | Deep, knife-like | Superficial, broad-based |
| Lymphoid reaction | Marked | Moderate |
| Fibrosis | Marked | Mild to none |
| Serositis | Marked | Mild to none |
| Granulomas | Yes (~35%) | No |
| Fistulae/sinuses | Yes | No |
| **Clinical** | | |
| Perianal fistula | Yes (in colonic disease) | No |
| Fat/vitamin malabsorption | Yes | No |
| Malignant potential | With colonic involvement | Yes |
| Recurrence after surgery | Common | No |
| Toxic megacolon | No | Yes |

All features may not be present in a single case.

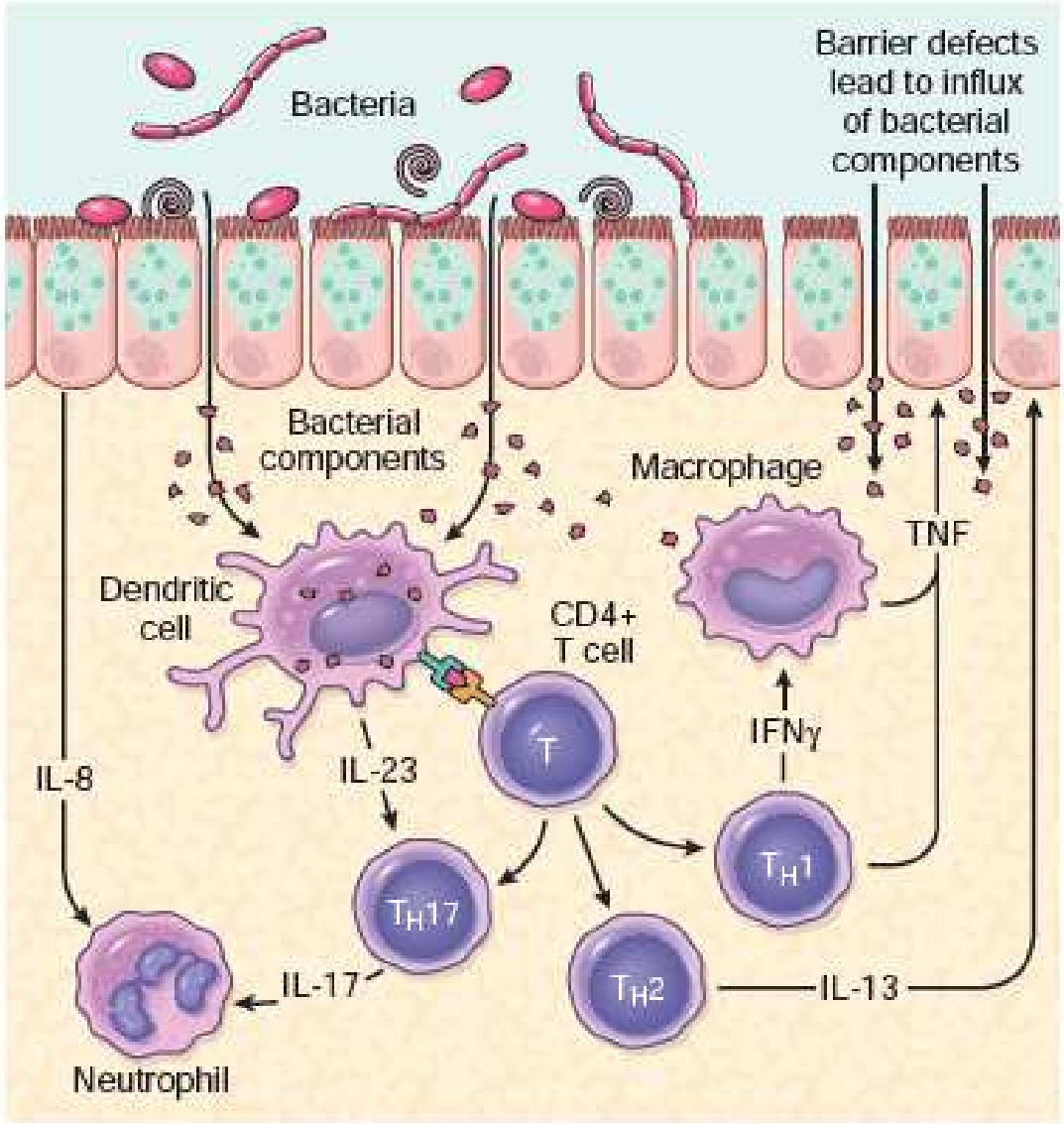



**Figure 17-33** One model of IBD pathogenesis. Aspects of both Crohn disease and ulcerative colitis are shown. See text for details.

# Crohn's disease

- Presents with intermittent bouts of diarrhea, abdominal pain, fever.
- 20% present acutely with right lower quadrant pain
- May be precipitated by emotional stress.
- Anal fissure not located between anal verge and dentate line

# Crohn's disease

- Extraintestinal manifestations may present before intestinal symptoms are manifest:
- Migratory polyarthritis
- Sacroiliitis
- Ankylosing spondylitis
- Erythema nodosum
- Uveitis.

# Crohn's disease

- Most common sites involved at presentation are the terminal ileum, ileocecal valve, and cecum.
- Disease is limited to the small intestine alone in about 40% of cases.
- The small intestine and colon are both involved in 30% of patients
- The remainder have only colonic involvement.
- Uncommonly may involve the duodenum, stomach, esophagus, and mouth.

# Crohn's disease

- The presence of multiple, separate, sharply delineated areas of disease, resulting in skip lesions, is characteristic
- The earliest lesion, the aphthous ulcer, may progress, and multiple lesions often coalesce into elongated, serpentine ulcers oriented along the axis of the bowel.
- Edema and loss of the normal mucosal texture are common.

# Crohn's disease

- The intestinal wall is thickened and rubbery as a consequence of transmural edema, inflammation, submucosal fibrosis, and hypertrophy of the muscularis propria
- In cases with extensive transmural disease, the serosa is granular and gray, and the mesenteric fat frequently extends around the serosal surface (creeping fat)

# Crohn's disease

- Sparing of interspersed mucosa, a result of the patchy distribution of Crohn disease, results in a coarsely textured, cobblestone appearance in which diseased tissue is depressed below the level of normal mucosa
- Narrow fissures develop between the folds of the mucosa, often penetrating deeply through the bowel wall and leading to bowel adhesions and serositis.

# Crohn's disease

- Further extension of fissures leads to fistula or sinus tract formation, either to an adherent viscus, to the outside skin, or into a blind cavity.
- Free perforation or localized abscesses may also develop.
- The mesentery of the involved segment is also thickened, edematous, and sometimes fibrotic.
- As a result, the lumen is almost always narrowed.
- Colon strictures are common.

# Crohn's disease

- The microscopic features of active Crohn disease include abundant neutrophils that infiltrate and damage crypt epithelium.
- Clusters of neutrophils within a crypt are referred to as crypt abscesses and are often associated with crypt destruction.
- Ulceration is common in Crohn disease, and there may be an abrupt transition between ulcerated and adjacent normal mucosa.

# Crohn's disease

- Even in areas where gross examination suggests diffuse disease, microscopic pathology can appear patchy.
- Repeated cycles of crypt destruction and regeneration lead to distortion of mucosal architecture
- The normally straight and parallel crypts take on bizarre branching shapes and unusual orientations to one another

# Crohn's disease

- Epithelial metaplasia takes the form of gastric antral-appearing glands (pseudopyloric metaplasia).
- Paneth cell metaplasia may also occur in the left colon, where Paneth cells are normally absent.
- These architectural and metaplastic changes may persist even when active inflammation has resolved.
- Mucosal atrophy, with loss of crypts, may occur after years of disease.

# Crohn's disease

- Noncaseating granulomas are found in approximately 35% of cases and may occur in areas of active disease or uninvolved regions in any layer of the intestinal wall
- Granulomas may also be present in mesenteric
- lymph nodes.
- Cutaneous granulomas form nodules
- The absence of granulomas does not preclude
- a diagnosis of Crohn disease.

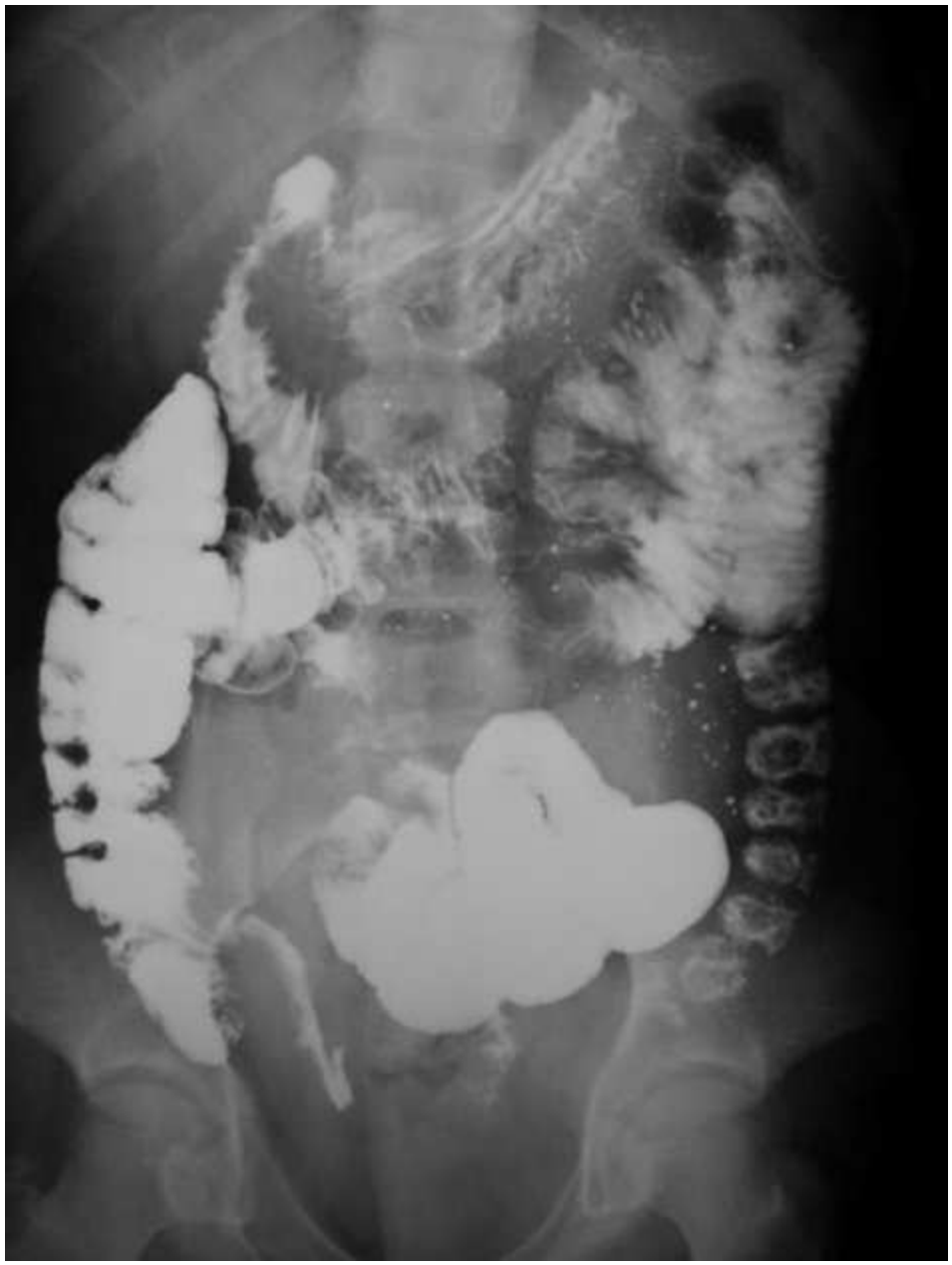
# Crohn's disease

- Fibrosing strictures, particularly of the terminal ileum, are common and require surgical resection.
- Disease often recurs at the site of anastomosis, and as many as 40% of patients require additional resections within 10 years.
- Fistulae develop between loops of bowel and may also involve the urinary bladder, vagina, and abdominal or perianal skin.

# Crohn's disease

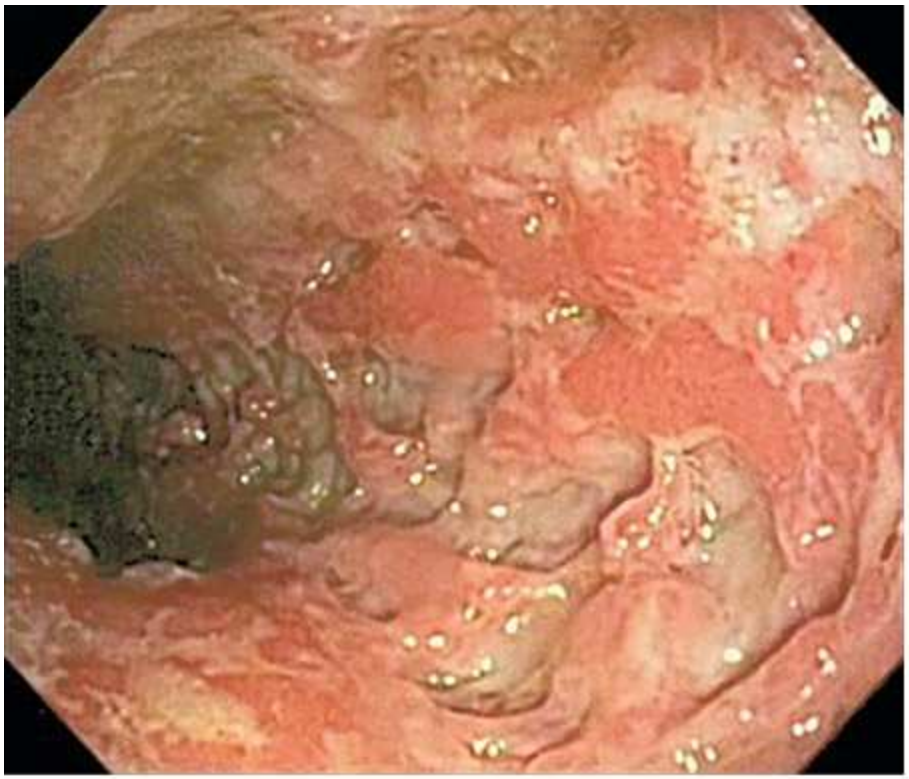
- Capsule endoscopy has the greatest diagnostic yield. 3% of capsules may lodge in strictures, necessitating surgical removal.
- 5-aminosalicylic acid often with metronidazole as primary therapy. 6-mercaptopurine in non-responders.
- TNF inhibitors in severe cases.
- High rates of recurrence following surgery.
- Angiotensin receptor blockers ameliorate disease; ACE inhibitors exacerbate disease (10 year follow-up)

Mucosal ulcers, longitudinal fissures, string sign (bowel narrowing) noted on fluoroscopic image. Duodenal involvement is shown.



Hauoimi, A, Gallard, F, “Crohn Disease,” Radiopaedia.com, Case3 Accessed 10/25/2019

# Crohn's disease



**B**

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
*Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



Deep ulcers.

**Fig. e25-4B**
**Accessed 03/01/2010**

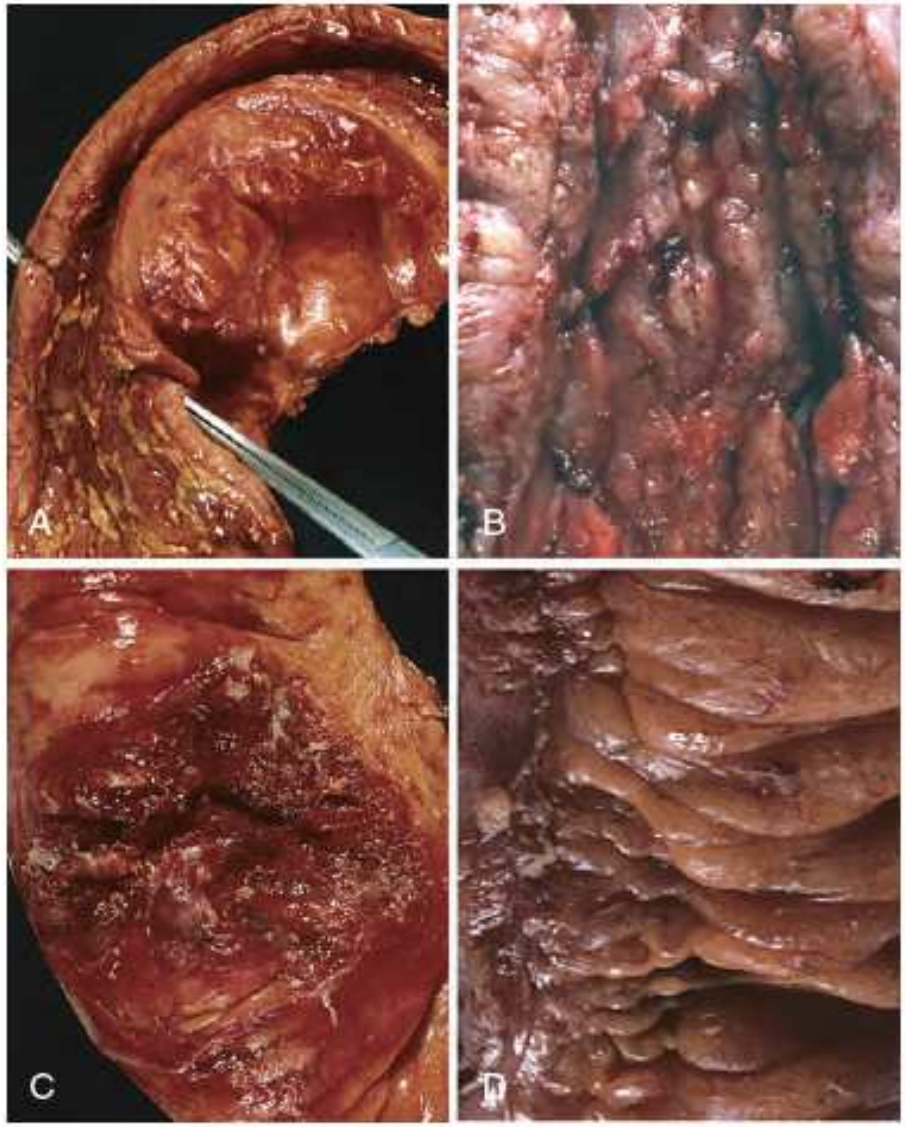



**Figure 17-34** Gross pathology of Crohn disease. **A,** Small-intestinal stricture. **B,** Linear mucosal ulcers, which impart a cobblestone appearance to the mucosa, and thickened intestinal wall. **C,** Perforation and associated serositis. **D,** Creeping fat.

# Crohn’s disease

Focal collections of polyps in a patient with Crohn's colitis. The lumen is narrowed and bowel wall thickening is present. There is serosal extension of mesenteric fat  (creeping fat”).

Fig. 2-52

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.

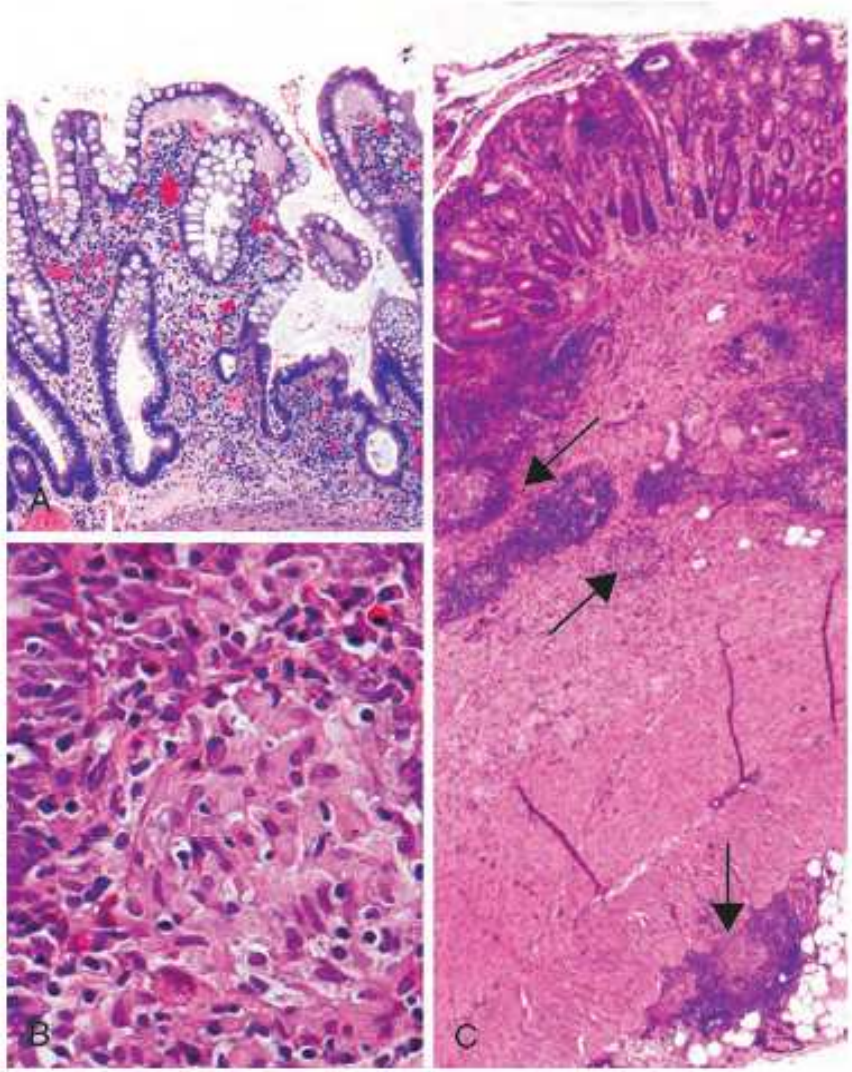
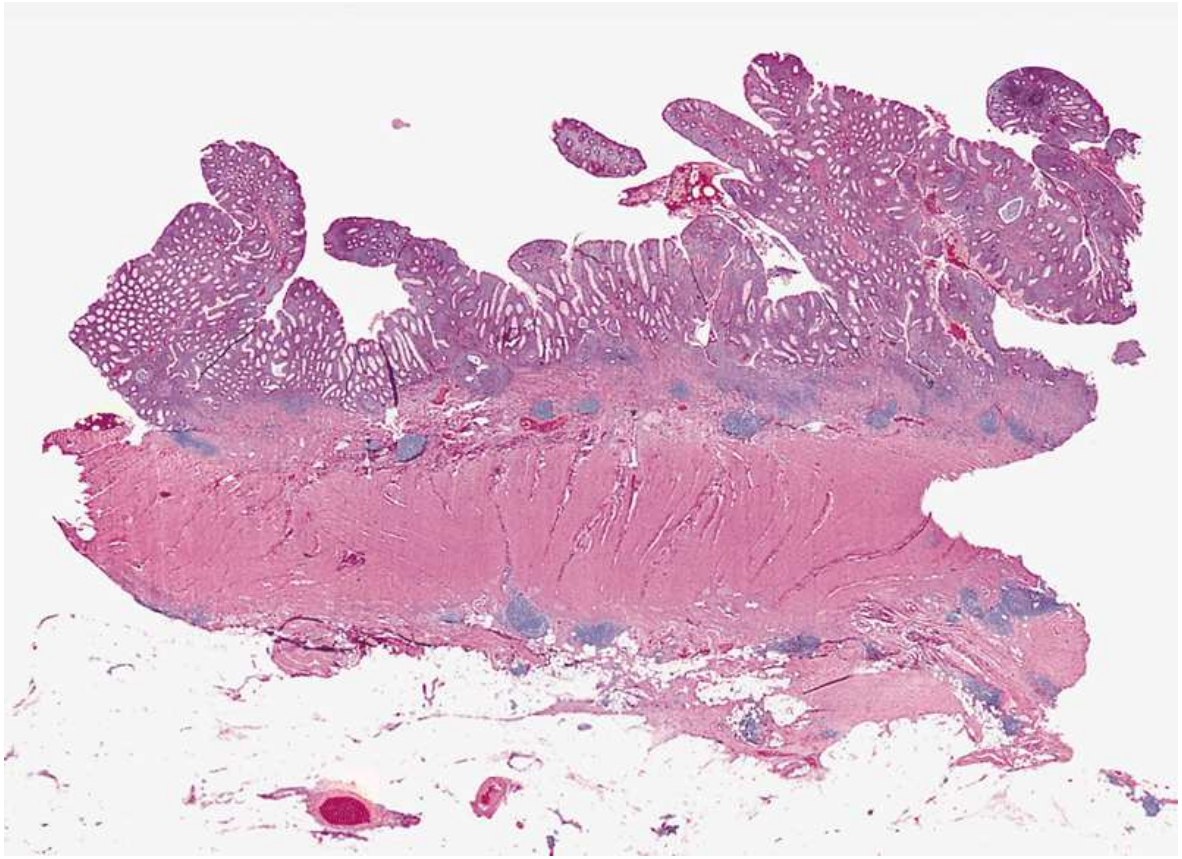



Figure 17-35 Microscopic pathology of Crohn disease. **A,** Haphazard crypt organization results from repeated injury and regeneration. **B,** Noncaseating granuloma. **C,** Transmural Crohn disease with submucosal and serosal granulomas (arrows).

# Crohn’s disease



Distorted inflamed polypoid mucosa in Crohn's disease of the colon. A fissure is not present in this section. Non-caseating granulomata may be found in Crohn’s disease.

Fig. 2-55

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.

# Ulcerative colitis

- Ulcerative colitis typically presents as a relapsing disorder marked by attacks of bloody mucoid diarrhea that may persist for days, weeks, or months and then subside, only to recur after an asymptomatic interval of months to years or even decades.
- In most patients, bloody diarrhea containing stringy mucus, accompanied by lower abdominal pain and cramps usually relieved by defecation, is the first manifestation of the disease.

# Ulcerative colitis

- The explosive initial attack may lead to such serious bleeding and fluid and electrolyte imbalance as to constitute a medical emergency.
- In a small number of patients, constipation may appear paradoxically, due to disruption of normal peristalsis.
- About 60% of patients have clinically mild disease.
- In these individuals, the bleeding and diarrhea are not severe, and systemic signs and symptoms are absent.

# Ulcerative colitis

- Always involves the rectum and extends proximally in a continuous fashion to involve part of the colon.
- Usually left-sided disease extends no farther than the transverse colon
- However, may involve the entire colon (pancolitis)
- In 10% of patients with severe pancolitis, the distal ileum may develop mucosal inflammation ("backwash ileitis"), probably due to iliocecal valve Incompetence.
- The ileitis is often diffuse and limited to within 25 cm from the ileocecal valve.
- The appendix may be involved.

# Ulcerative colitis

- The inflammatory process is diffuse and generally limited to the mucosa and superficial submucosa
- May see extensive and broad-based ulceration of the mucosa in the distal colon or throughout its length.
- The ulcers follow along the axis of the colon, but are not serpentine.
- Isolated islands of regenerating mucosa bulge upward to create pseudopolyps.
- "Skip lesions" are not found.

# Ulcerative colitis

- Often the undermined edges of adjacent ulcers interconnect to create tunnels covered by tenuous mucosal bridges.
- Well-formed granulomas are absent.
- Mural thickening is not present.
- Chronic disease leads to mucosal atrophy.
- Particularly significant in ulcerative colitis is the spectrum of epithelial changes signifying dysplasia and the progression to frank carcinoma.

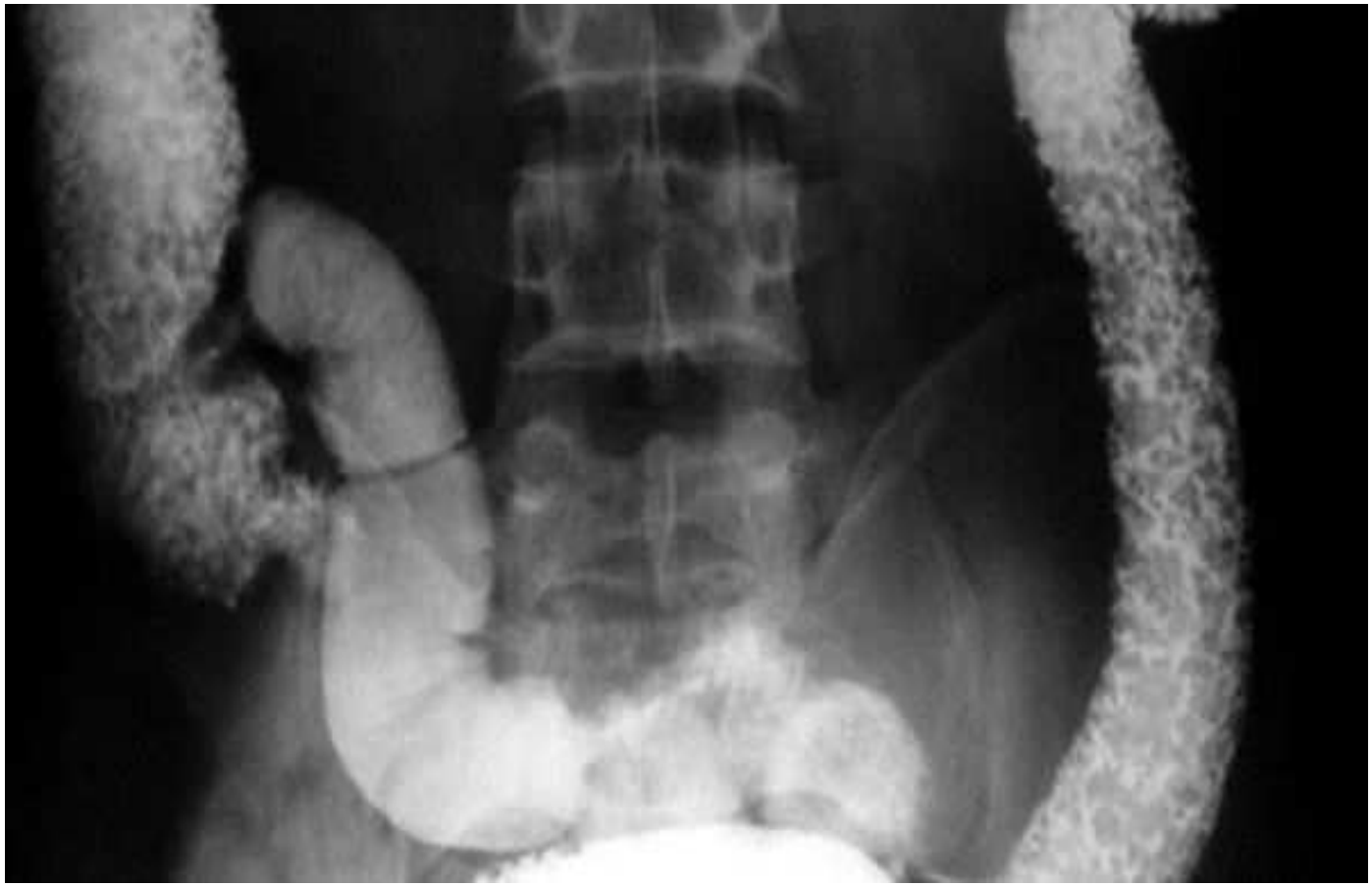
# Ulcerative colitis

- 97% of patients have at least one relapse during a 10-year period
- About 30% of patients require colectomy within the first 3 years of onset due to uncontrollable disease.
- On rare occasion, the disease runs a fulminant course; unless medically or surgically controlled, this toxic form of the disease can lead to death soon after onset.

# Ulcerative colitis

- Toxic megacolon results from damage to the neural plexus.
- 5-aminosalicylic acid oral preparations for proximal disease as well as maintaining remissions; 5-ASA preparations or corticosteroid enemas for distal disease.

# Ulcerative colitis



Granular change and loss of haustrae.
Pinterest.com Accessed 10/25/2019

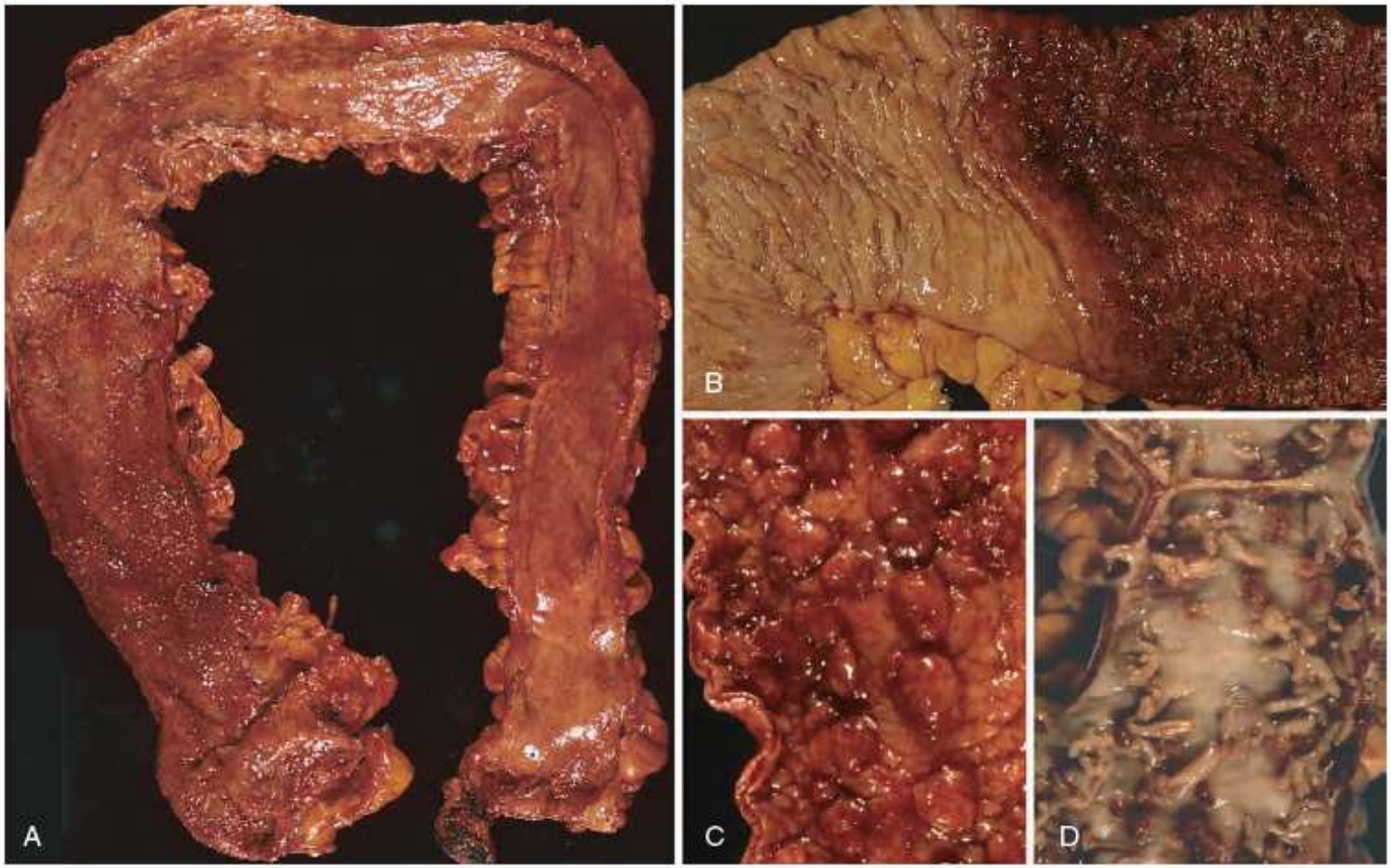
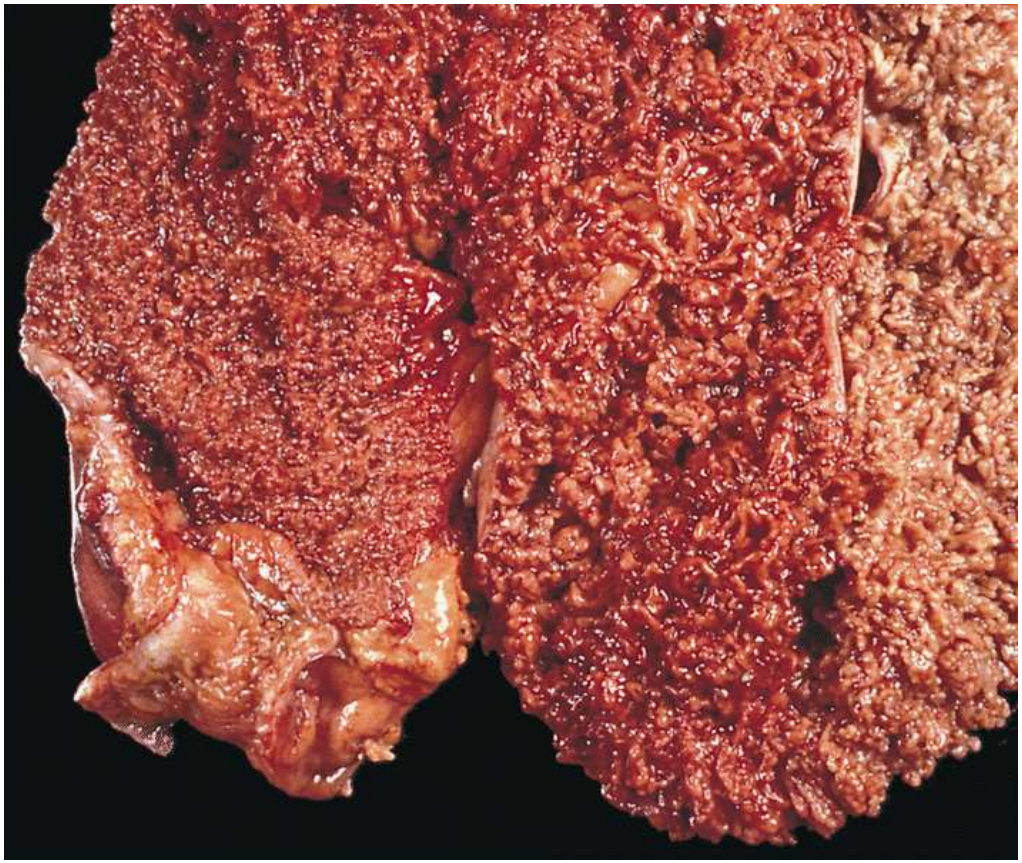



**Figure 17-36** Gross pathology of ulcerative colitis. **A,** Total colectomy with pancolitis showing active disease, with red, granular mucosa in the cecum (left) and smooth, atrophic mucosa distally (right). **B,** Sharp demarcation between active ulcerative colitis (right) and normal mucosa (left). **C,** Inflammatory polyps. **D,** Mucosal bridges.

# Ulcerative colitis

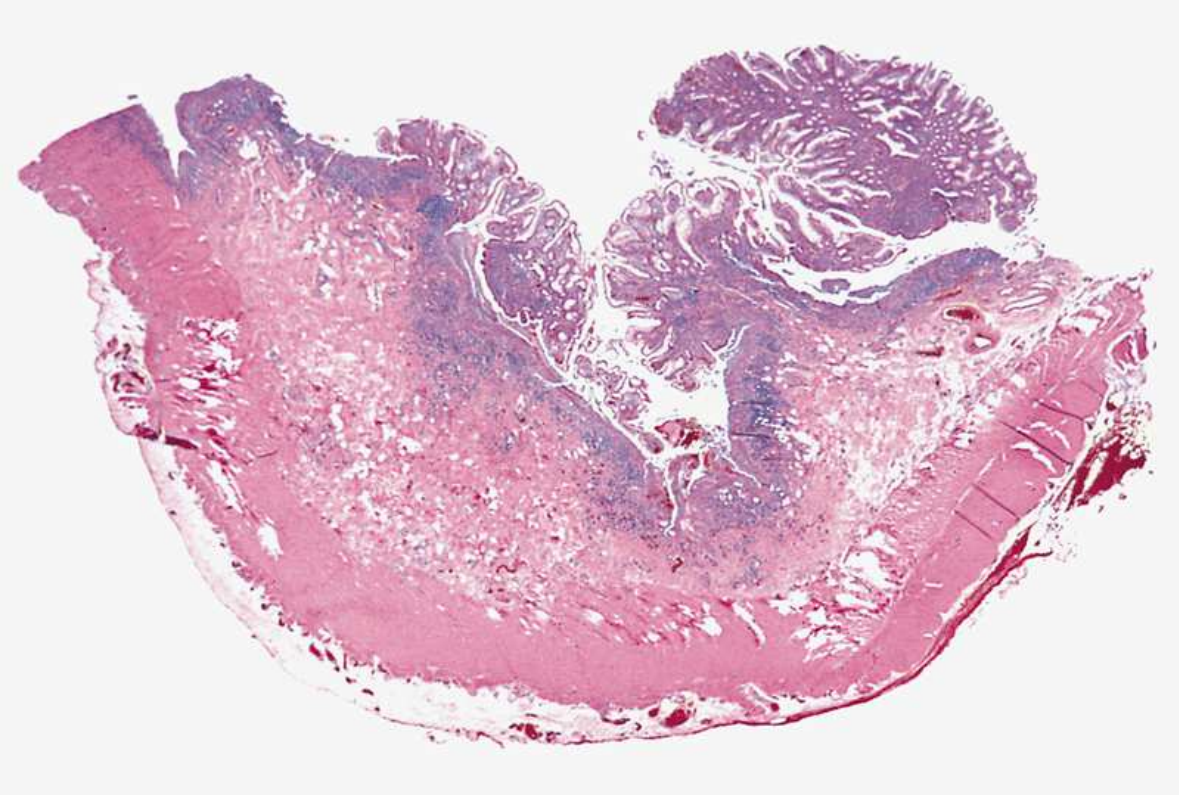


Inflamed mucosa with numerous shaggy inflammatory polyps and pseudopolyps in a patient with ulcerative colitis.

Fig. 2-51

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.

# Ulcerative colitis



Distorted inflamed polypoid mucosa is adjacent to extensive ulcers in a patient with ulcerative colitis.

Fig. 2-54

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.

# Pseudomembranous colitis

- Clostridium dificile
- Antibotic related alteration of microbiota
- 30% of hospitalized patients colonized
- Fever, leukocytosis, abdominal pain, cramps, watery diarrhea
- May have red cells in stool, but no bloody diarrhea
- 40% recur
- Toxins released cause the ribosylation of small GTPases (e.g., Rho)
- Disrupt the epithelial cytoskeleton, the tight junction barrier, promote cytokine release, and apoptosis.

# Pseudomembranous colitis

- The surface epithelium is denuded, and the superficial lamina propria contains a dense infiltrate of neutrophils and occasional fibrin thrombi within capillaries.
- Superficially damaged crypts are distended by a mucopurulent exudate that forms an eruption reminiscent of a volcano (pathognomonic).
- An adherent layer of inflammatory cells and debris at sites of colonic mucosal injury forms.

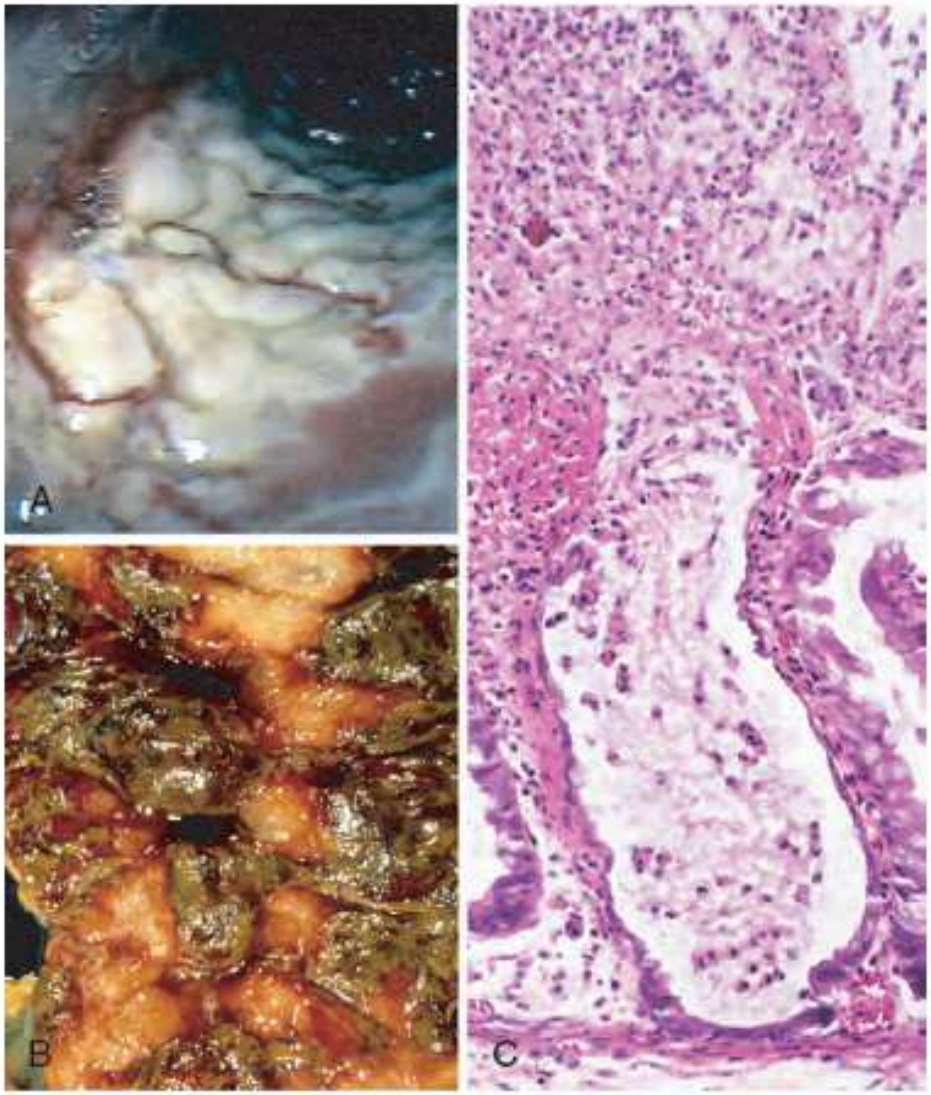



**Figure 17-29** *Clostridium difficile* colitis. **A,** The colon is coated by tan pseudomembranes composed of neutrophils, dead epithelial cells, and inflammatory debris (endoscopic view). **B,** Pseudomembranes are easily appreciated on gross examination. **C,** Typical pattern of neutrophils emanating from a crypt is reminiscent of a volcanic eruption.

# Necrotizing enterocolitis

- Common in very low birth weight infants (<1500 gms).
- Associated with enteral feeding.
- Acute onset of bloody stools, abdominal distention, and circulatory collapse.
- Gas may be demonstrated within the intestinal wall on x-ray (pneumatoides intestinalis).
- Involves the ileum, cecum, and right colon principally.
- May lead to intestinal perforation and necrosis, requiring surgical intervention.

# Necrotizing enterocolitis

- Platelet activating factor implicated in increasing mucosal permeability by promoting enterocyte apoptosis and compromising intercellular tight junctions.

# Microscopic colitis

- Two entities:
- Present with chronic, non-bloody, watery diarrhea without weight loss.
- Collagenous colitis
- Middle aged women
- Characterized by the presence of a dense subepithelial collagen layer, increased numbers of intraepithelial lymphocytes, and a mixed inflammatory infiltrate within the lamina propria

# Microscopic colitis

- Lymphocytic colitis
- The subepithelial collagen layer is of normal thickness and the increase in intraepithelial lymphocytes is striking
- Associated with celiac disease and autoimmune disease

# Other forms of colitis

- Diversion colitis results in the diverted segment of those with temporary of permanent placement of an –ostomy.
- Diversion of fecal stream and alteration of microbiota as possible causes
- Graft versus host disease post-transplant
- Sparse lymphocytic infiltrate of lamina propria. Epithelial apoptosis with destruction of crypt cells.
- Presents with watery diarrhea

# Irritable bowel syndrome

- Characterized by chronic, relapsing abdominal pain, bloating, and changes in bowel habits
- Perturbation of the gut microbiome,
- Increased enteric sensory responses to gastrointestinal stimuli, and abnormal GI motility
- Constipation predominant associated with diminished colonic contractions and transit time
- Diarrhea predominant associated with increased colonic contractions and transit time
- May see excess bile acid synthesis or bile acid malabsorption

# Irritable bowel syndrome

- Women
- 30-50 years of age
- Occurrence of abdominal pain or discomfort at least 3 days per month over 3 months with improvement following defecation and a change in stool frequency or form are diagnostic criteria.
- Abnormalities have been identified with serotonin reuptake transporters, cannabinoid receptors, and TNF-related inflammatory mediators.
- Enhanced activity of ETS2 in inflammatory bowel disease
- No long term sequelae.

# Irritable bowel syndrome

- Greater than 6 month history of intermittent abdominal pain or discomfort at least 3 days per month, and accompanied by diarrhea or constipation or both.
- Relieved by defecation.
- Onset of symptoms associated with a change in frequency and appearance of stool.
- Symptoms often exacerbated by stress.
- No history of weight loss, anemia, fever.
- 10-15% of adults; twice as common in women

# Irritable bowel syndrome

- Those patients with weight loss, fever, or anemia, or who are over 50 years of age should undergo colonoscopy with biopsy to exclude cancer and colitis.
- All patients should be examined for sprue (particularly if diarrhea prominent), thyroid abnormalities, Clostridium dificile infection, and the presence of parasites.
- Food triggers such as fatty foods, dairy products, gas-producing vegetables, and sorbitol products are often implicated.

# Irritable bowel syndrome

- Poorly absorbed antibiotics may be useful in reducing the frequency of symptoms.
- Micro-ulcerations are commonly found in the irritable bowel syndrome.
- Chronic inflammation may alter the sensitivity of the enteric nervous system.
- Cognitive therapy is as effective as anticholinergics or smooth muscle relaxants in those in whom abdominal pain is the most prominent symptom.

# Irritable bowel syndrome

- When diarrhea is the predominant system, loperamide or diphenoxylate may be useful.
- Use of 5HT3 receptor antagonists is restricted for treatment failures as they are associated with precipitation of ischemic colitis as well as bowel obstruction.
- When constipation is the predominant system, the addition of fiber is indicated. The use of an osmotic laxative such as lactulose or polyethylene glycol may be of use.
- All patients should be treated for underlying lactose intolerance.

# Diverticulosis

- Diverticulum is an “out-pouching” or herniation of mucosa through the muscle wall into the mesentery.
- Area of weakness is where vasa recta penetrate the muscular propria.
- Tenia musculature does not reinforce these gaps.
- Diverticulum is juxtaposed to a blood vessel.
- Colonic diverticula have a thin wall composed of a flattened or atrophic mucosa, compressed submucosa, and attenuated or totally absent muscularis propria

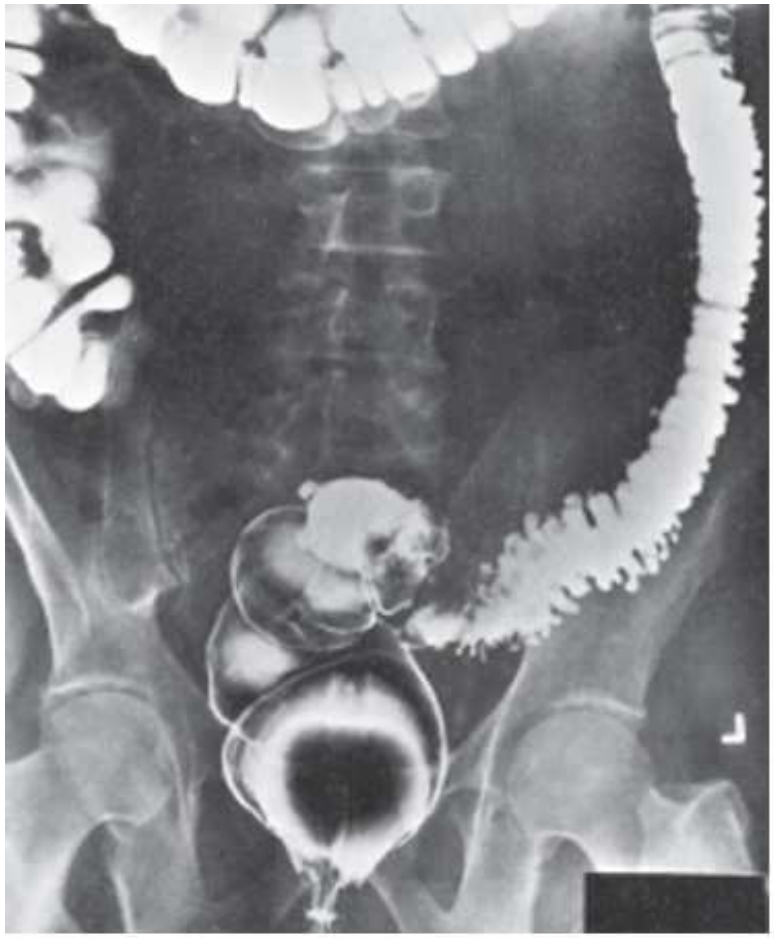
# Diverticulosis

- Hypertrophy of the circular layer of the muscularis propria in the affected bowel segment is common.
- Inflammation and increased pressure within an obstructed diverticulum can lead to perforation.
- Thought to reflect result of exaggerated peristaltic contractions, with spasmodic sequestration of bowel segments
- Low fiber diet may aggravate (loss of stool bulk)

# Diverticulosis

- 50% of those persons >50 years old have diverticulosis
- 80%, if over age 85.
- 95% of diverticula are in the descending and sigmoid colon.
- (Rectum has neither haustrae nor diverticula.)
- Obstruction of diverticula leads to inflammatory changes, producing diverticulitis and peri-diverticulitis.
- Perforation unlikely
- May lead to fibrosis and stricture

# Diverticulosis



Diverticulosis of sigmoid colon on barium enema.

[Reproduced with permission from Nivatvongs S, Becker ER: Colon, rectum and anal canal, in James EC, Corry RJ, Perry JCF Jr. (eds): *Basic Surgical Practice.* Philadelphia: Hanley & Belfus, 1987. Copyright Elsevier.]

Fig. 29-20
Accessed 07/30/2010

# Diverticulitis

- Most common cause of lower gastrointestinal tract bleeding.
- Right sided lesions associated with heavier bleeds.
- Spontaneous bleeding, however, is uncommon in diverticulitis.
- Cease spontaneously; 40% recurrence rate.

# Diverticulitis

- May not see elevated white counts or fever in diverticulitis.
- Colonoscopy diagnostic.
- CT scan is test of choice.
- Ciprofloxacin and metronidazole for 7-10 days for acute attacks.
- Drain abscesses >5cm under CT guidance.

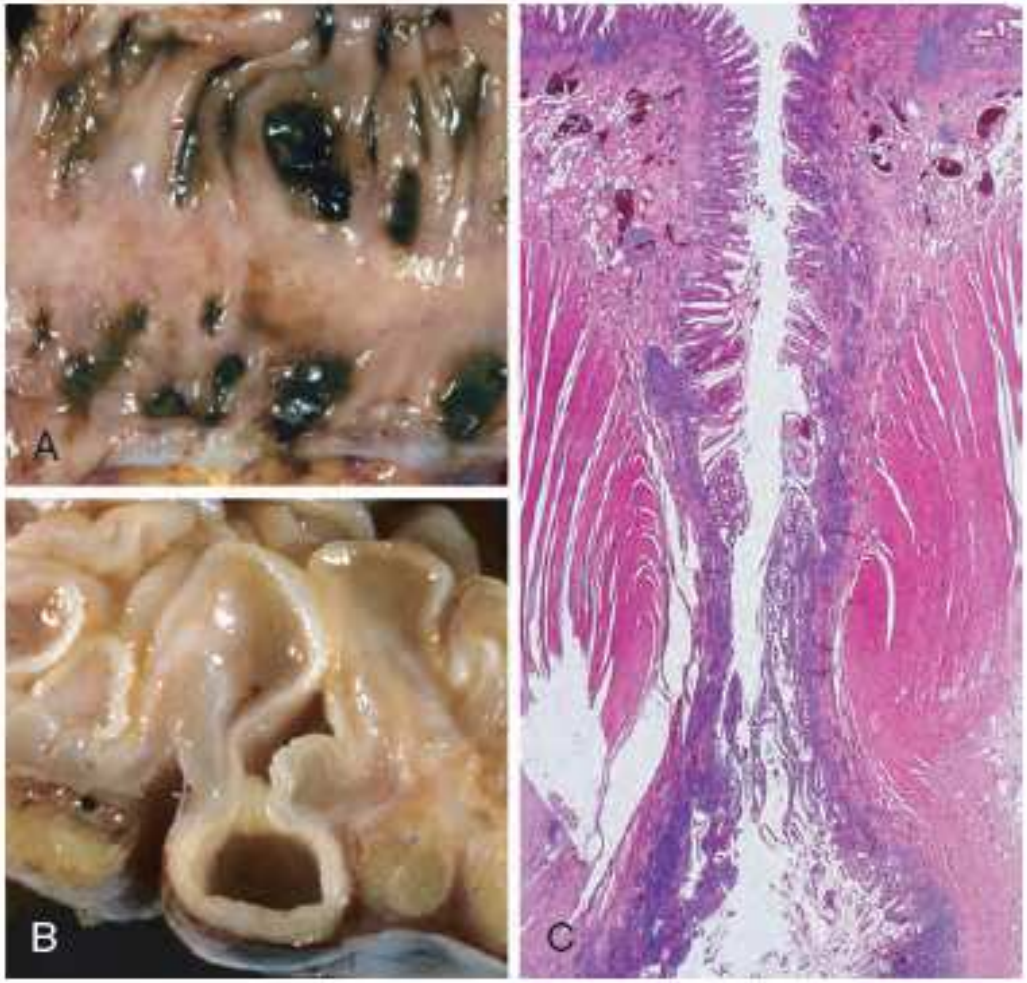
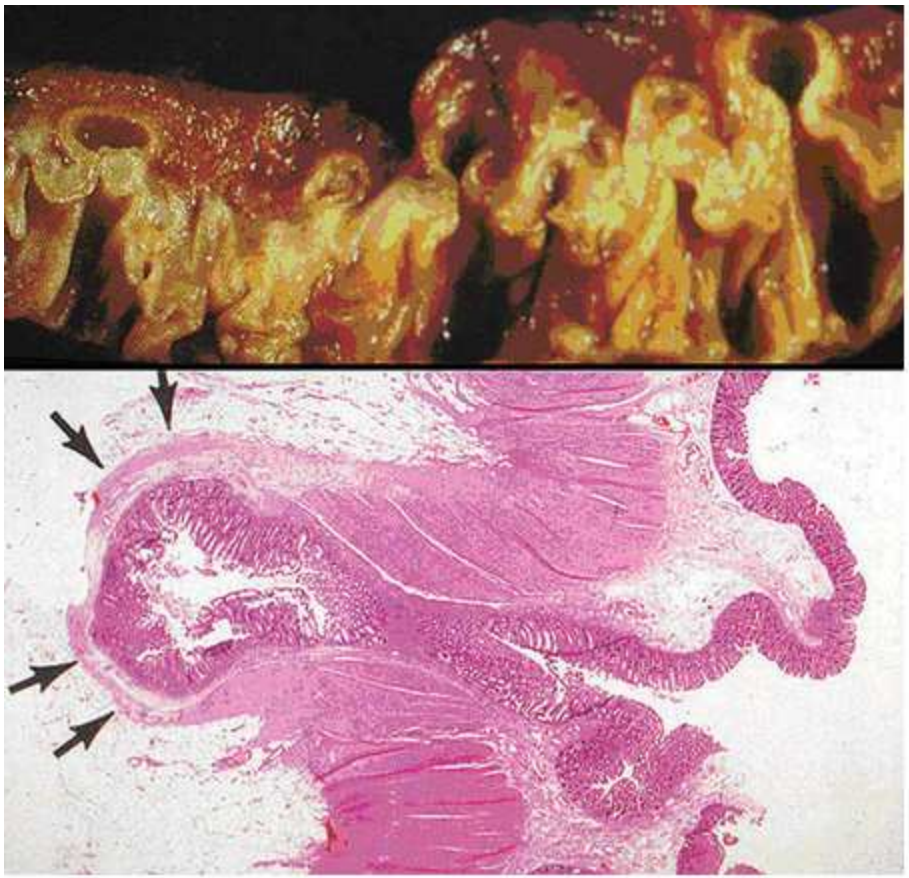



**Figure 17-40** Sigmoid diverticular disease. **A,** Stool-filled diverticula are regularly arranged. **B,** Cross-section showing the outpouching of mucosa beneath the muscularis propria. **C,** Low-power photomicrograph of a sigmoid diverticulum showing protrusion of the mucosa and submucosa through the muscularis propria.

# Diverticulitis



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
*Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



Arrows mark an inflamed diverticulum with the diverticular wall made up only of mucosa.

Fig. 291-1
Accessed 07/30/2010

# Hemorrhoids

- Internal hemorrhoids cause painless bleeding.
- Internal hemorrhoids are dilated superior hemorrhoidal veins in mucosa and submucosa, located above pectinate line.
- Often prolapse
- External hemorrhoids are dilated inferior hemorrhoidal veins located below the pectinate line.
- Often thrombose and are painful.
- Increased abdominal pressure aggravates presentation.
- Ligation effective.
- Hemorrhoidectomy curative.

# NEOPLASIA

# Screening for colon cancer

- Screen all asymptomatic patients >50yo.
- Screen earlier if first degree relative with colon cancer or polyps before age 50.
- Amsterdam criteria:
- Consider gene study if three or more family members have been diagnosed with hereditary non-polyposis colon cancer and one is a first degree relative of the others
- Or, if colon cancers have occurred in two successive generations
- And, there is no history of familial adenomatous polyposis

# Screening for colon cancer

- Although screenign sigmoidoscopy alone is associated with improved outcomes,
- Currently recommended:
- Immunochromatographic fecal occult blood test annually AND Flexible Sigmoidoscopy
- Six common fecal occult blood tests annually may be sufficient if the imunochromatographic method is not available.
- Methylated septin 9 as screen only if colonoscopy or barium enema refused by patient.
- Or, Double Contrast Barium Enema every 5 years
- Or, Virtual Colonoscopy every 5 years

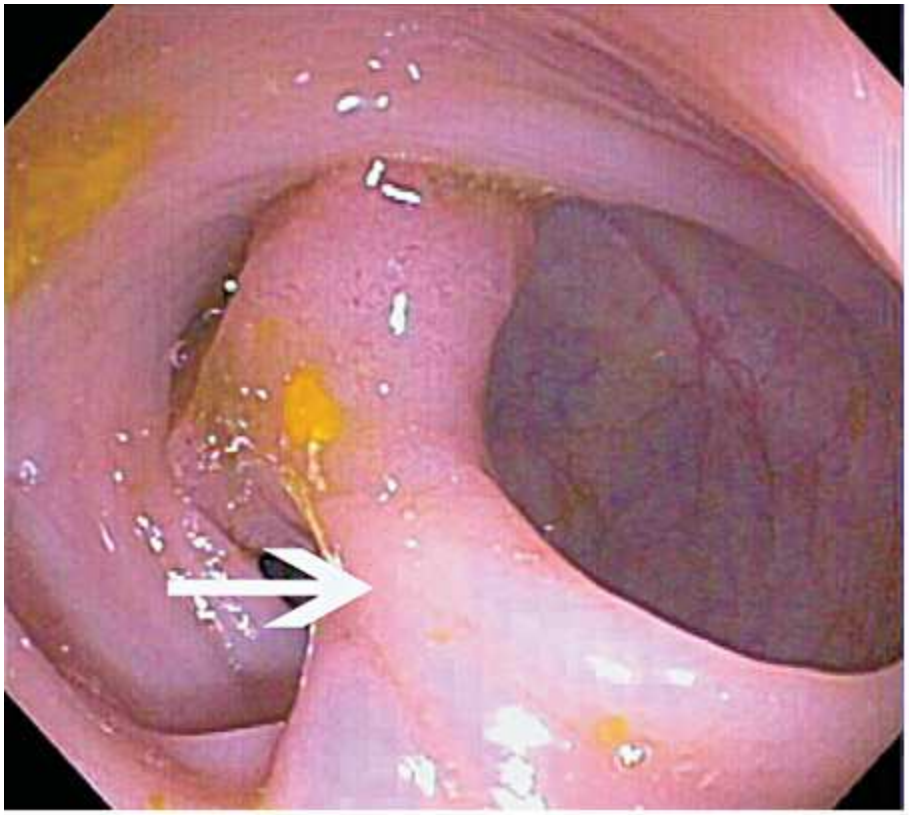
# Screening for colon cancer

- Virtual colonoscopy recommended for the elderly as well as for those with a high risk of perforation if instrumentation employed.
- Colonoscopy only for positive screens
- Repeat every 10 years if negative or if low grade adenomas completely resected.
- If higher grade lesions identified, repeat every 3 years

# Hyperplastic polyps

- Sporadic.
- Increase in frequency with age.
- 90% of all epithelial polyps in the large intestine.
- Often found incidentally in the sixth and seventh decades.
- They are found in more than half of all persons age 60 and older.
- Decreased epithelial cell turnover and accumulation of mature cells on the surface.
- Architecture preserved.

# Hyperplastic polyp



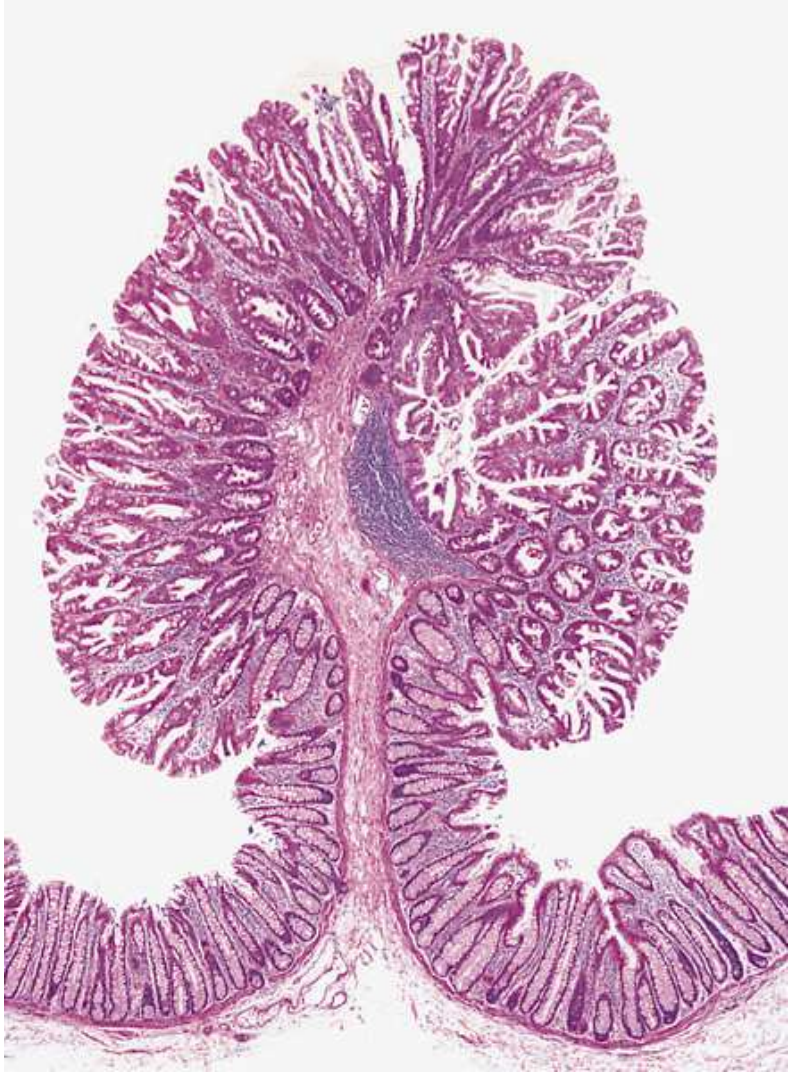
**A**

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



**Fig. e25-5A**
**Accessed 03/01/2010**

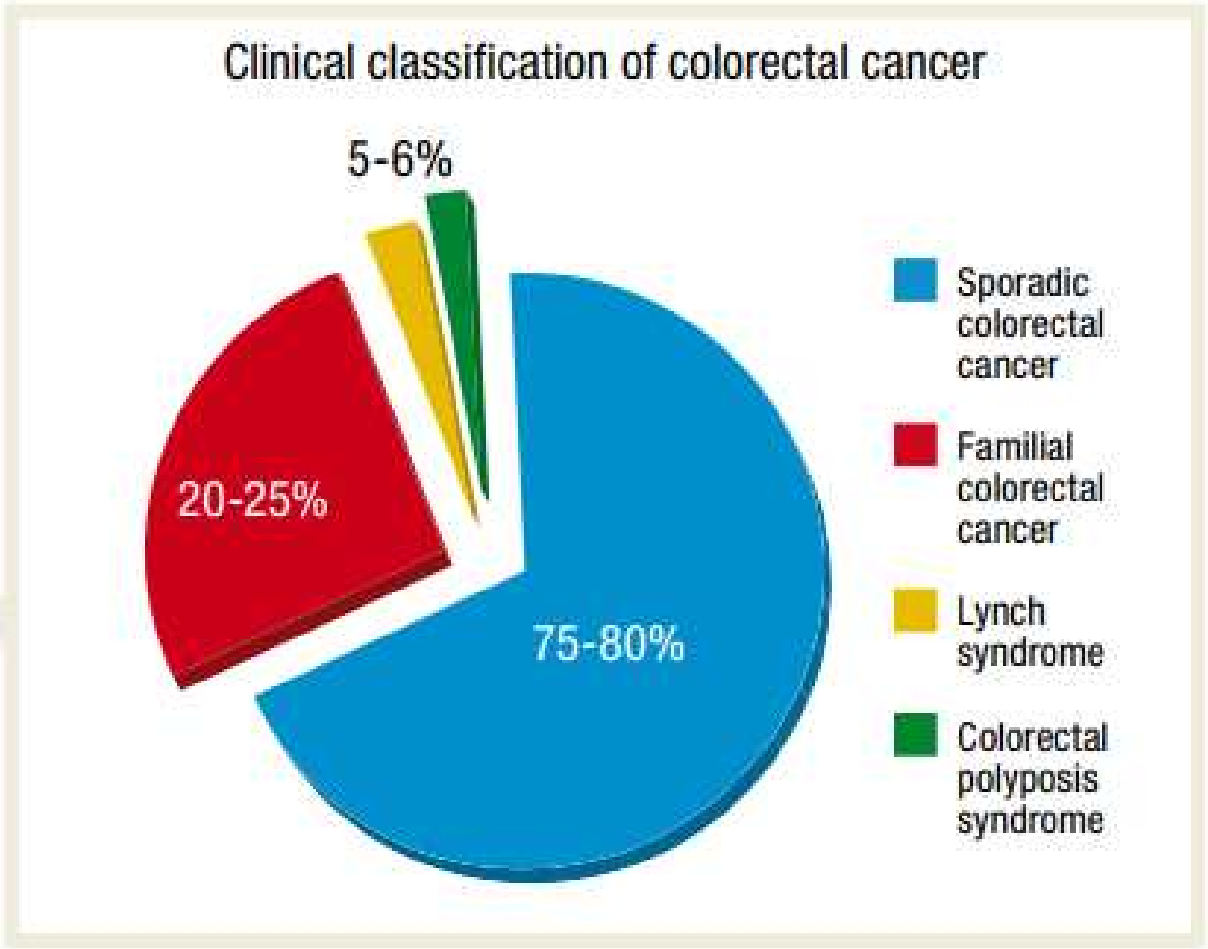
# Hyperplastic polyp

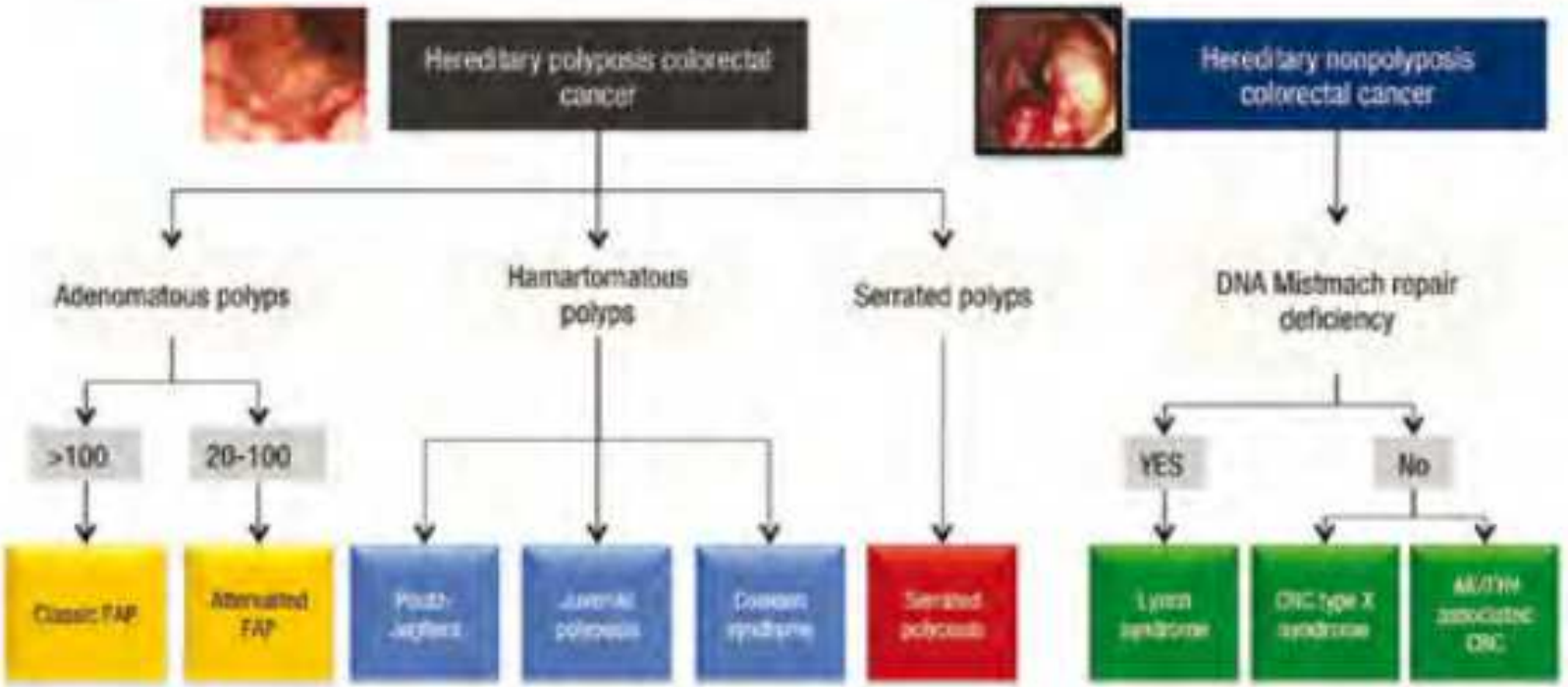


This pedunculated polyp has complex glandular structures focally.

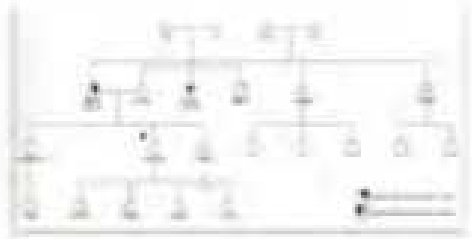
Fig. 2-002

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.


Clinical classification of colorectal cancer
5-6%
20-25%
75-80%
Sporadic colorectal cancer
Familial colorectal cancer
Lynch syndrome
Colorectal polyposis syndrome




CRC, Colorectal cancer; FAP, familial adenomatous polyposis.



| | | |
|---|---|---|
| Lynch syndrome | Autosomal dominant | 80-10% |
| APC-Familial adenomatous polyposis | Autosomal dominant | 100% |
| MUTYH associated polyposis | Autosomal recessive | 80% |
| Peutz-Jeghers syndrome | Autosomal dominant | 50% |
| Juvenile polyposis | Autosomal dominant | 40-60% |
| Cowden syndrome | Autosomal dominant | 10% |
| Serrated polyposis | Unknown | 50% |

# Hamartomatous polyps

- Hamartomatous polyps generally have very low malignant potential.
- Malformations of the glands and the stroma.
- Juvenile polyposis syndrome usually autosomal dominant but may be nonhereditary.
- <5 years of age
- Rectum
- Mutations in the SMAD4/DPC4 gene at 18q21.2 (which encodes signaling intermediate that binds to DNA) or BMPRIA at 10q23.2 (TGF-β superfamily kinase) account for fewer than 50% of juvenile polyposis syndrome.

# Hamartomatous polyps

- Typically pedunculated, smooth-surfaced, reddish lesions with characteristic cystic spaces apparent after sectioning.
- Microscopic examination shows these cysts to be dilated glands filled with mucin and inflammatory debris
- The remainder of the polyp is composed of lamina propria expanded by mixed inflammatory infiltrates. The muscularis mucosae may be normal or attenuated.

# Hamartomatous polyps

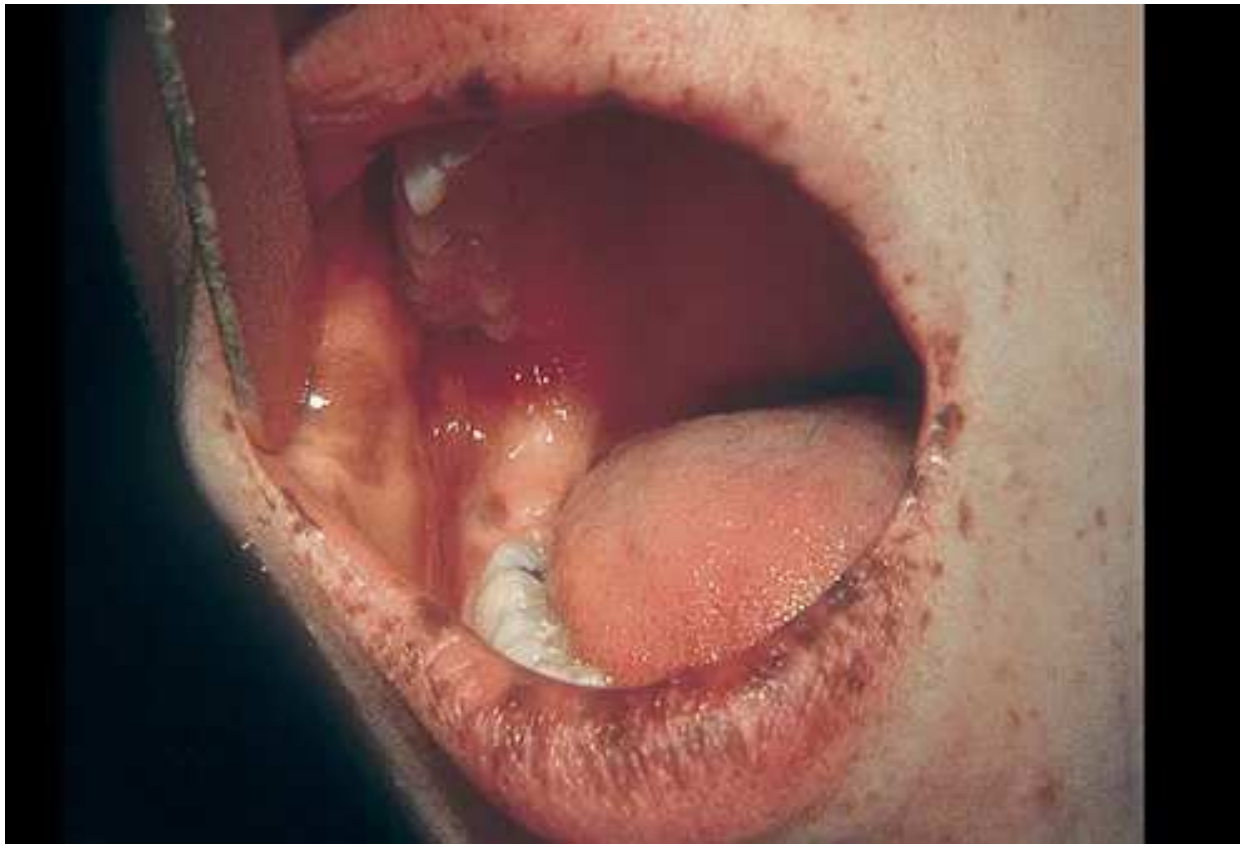
- Cronkhite-Canada syndrome is non-hereditary.
- Presents in those over 50 years of age
- Nail atrophy
- Areas of skin hyperpigmentation and hypopigmentation.

# Peutz-Jeghers syndrome

- Hamartomatous polyps predominate in small bowel but may also be found in colon and stomach.
- Can initiate intussusception
- Mucosal pigmentation of buccal mucosa, lips.
- Germline mutation of the gene STK11 (LKB1) at 19p.13.3
- The gene encodes a protein with serine/threonine kinase activity that regulates cell polarization and growth.
- Autosomal dominant.

# Peutz-Jeghers syndrome

- An arborizing network of connective tissue, smooth muscle, lamina propria, and normal appearing intestinal epithelium characterize the polyp.
- The presence of lamina propria differentiates Peutz-Jeghers syndrome polyps from juvenile polyps.
- 50% increased risk for colorectal, breast, gynecologic cancers



https://www.medicinenet.com/image-collection/peutz-jeghers_syndrome_picture/picture.htm

# Peutz-Jeghers polyp

Delicate arborizing muscular infrastructure forms lobules of colonic mucosa in a 5-year-old boy (Masson trichrome stain).

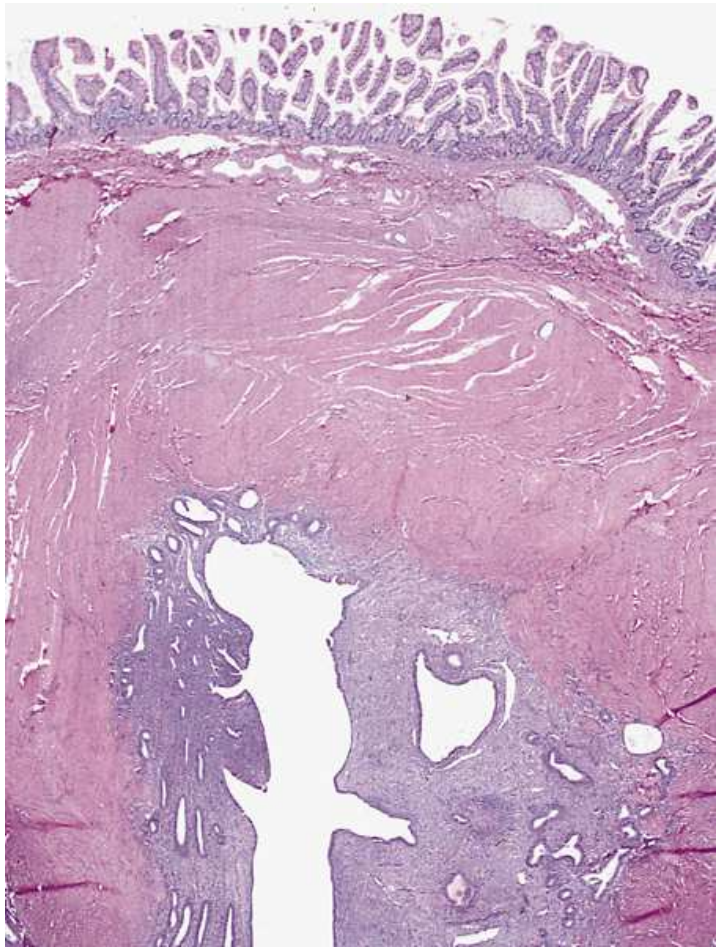
Fig. 2-23L

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.

# Cowden syndrome

- Intestinal hamartomatous polyps
- Hamartomatous polyps in skin and oral as well as nasal mucosa
- Macrocephaly
- Trichilemmoma.
- Males may have pigmented macules on the glans penis.
- Autosomal dominant.
- Increased risk of breast, endometrial, thyroid cancers
- Loss of function mutations in PTEN gene at 10p23.21 (inhibitor of $P1_3K$/AKT signaling pathway)

# Endometriosis



The large endometrial deposit has a prominent muscular component resembling myometrium. Lesions are usually found on the serosal surface.

Fig. 2-92

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.

# Adenomatous polyp

- All adenomatous lesions arise as the result of epithelial proliferative dysplasia
- Histologically, the hallmark of epithelial dysplasia is nuclear hyperchromasia, elongation, and stratification
- These changes are most easily appreciated at the surface of the adenoma and are often accompanied by prominent nucleoli, eosinophilic cytoplasm, and a reduction in the number of goblet cells.
- Notably, epithelial cells fail to mature as they migrate from crypt to surface.

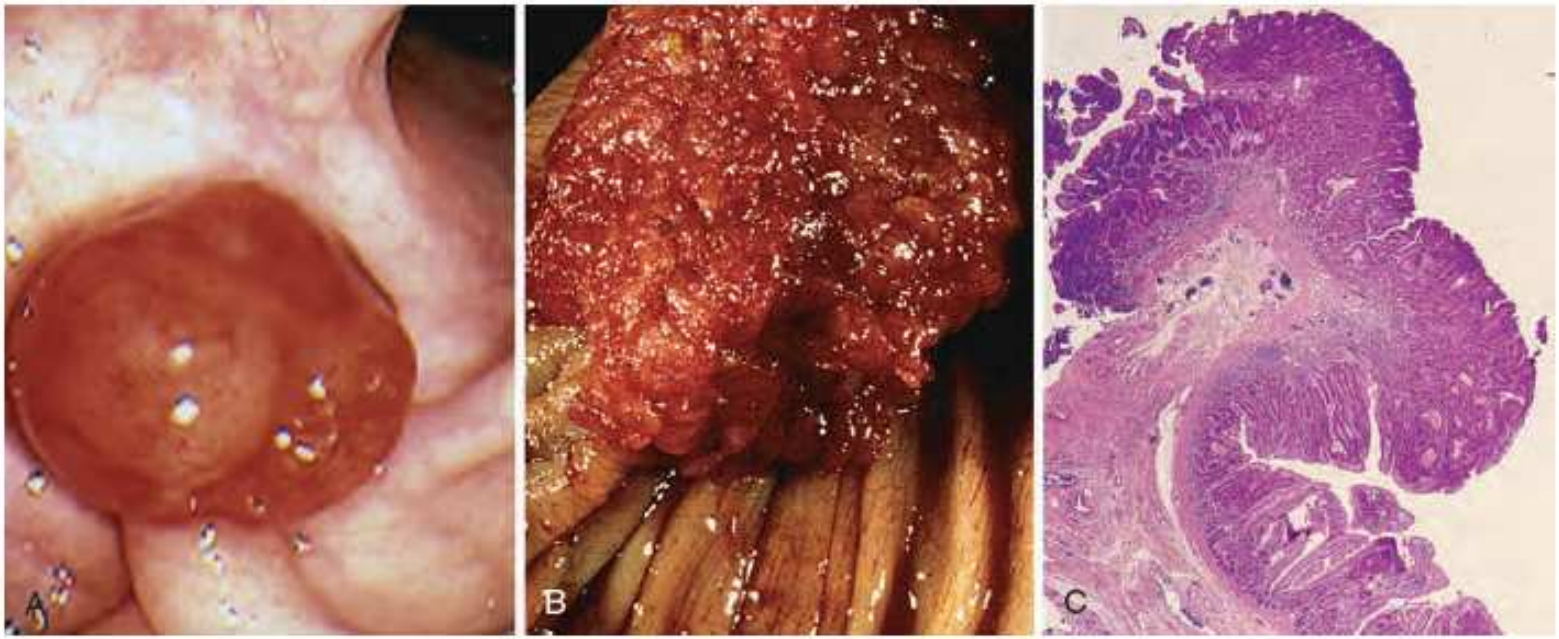



**Figure 17-45** Colonic adenomas. **A,** Pedunculated adenoma (endoscopic view). **B,** Adenoma with a velvety surface. **C,** Low-magnification photomicrograph of a pedunculated tubular adenoma.

# Adenomatous polyps

- Tubular adenoma most common (60% of polyps).
- Most tubular adenomas are small and pedunculated; conversely, most pedunculated polyps are tubular.
- Pedunculated adenomas have slender fibromuscular stalks
- Sigmoid colon most common site.
- Cancer is rare in tubular adenomas smaller than 1 cm in diameter.
- Tubulovillous adenoma are 20-30% of polyps.

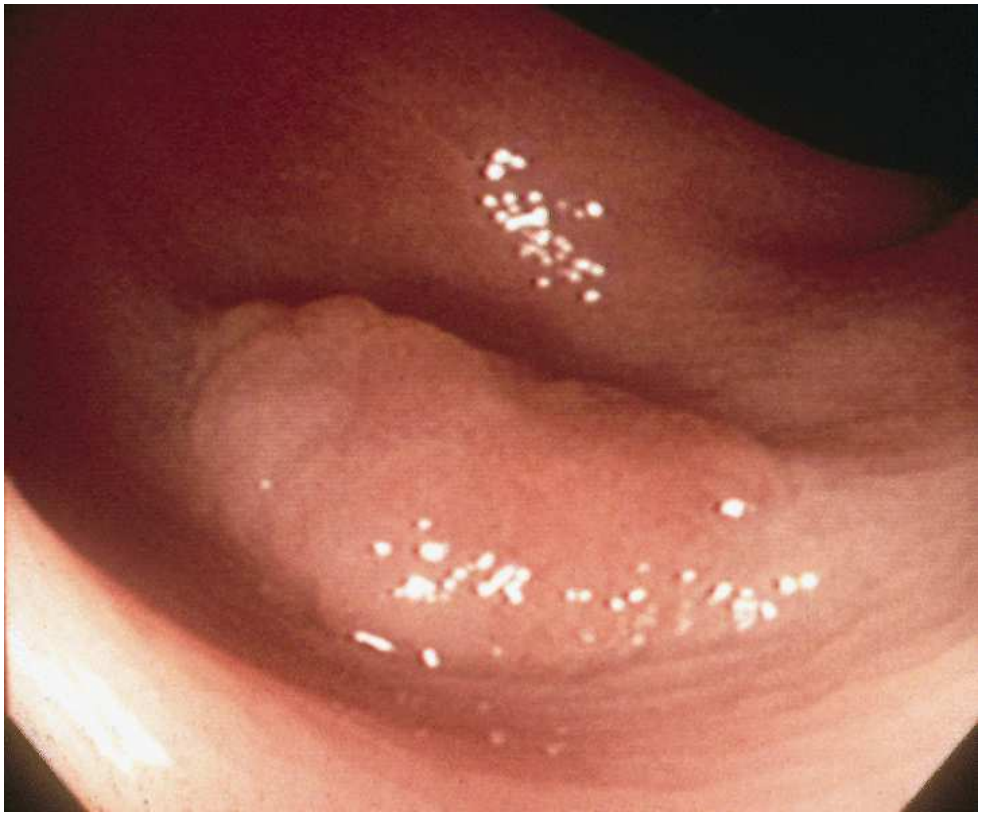
# Adenomatous polyps

- Villous adenomas are 10% of polyps
- Tend to be large and sessile, and sessile polyps usually exhibit villous features.
- Rectosigmoid
- Secrete protein and $K^+$ rich mucus (prostaglandin E).
- May manifest as diarrhea.
- The risk of cancer is high (approaching 40%) in sessile villous adenomas more than 4 cm in diameter.
- Severe dysplasia, when present, is often found in villous areas.

# Sessile serrated polyps

- Histologic criteria for these lesions include serrated architecture throughout the full length of the glands, including the crypt base, crypt dilation, and lateral growth
- Commonly display CpG island methylator promoter (CIMP) and V600E BRAF mutations, which are correlated with CIMP.
- CIMP mutations are associated with microsatellite instability.
- CIMP adenocarcinomas arises from a stem-like cell that is different than the stem-like cell of origin that gives rise to those cancers developing from tubular adenomas.

# Villous adenoma



Endoscopic view. There is no way that an underlying infiltrating component can be excluded until examined in toto microscopically.

Fig. 3-15 R

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.

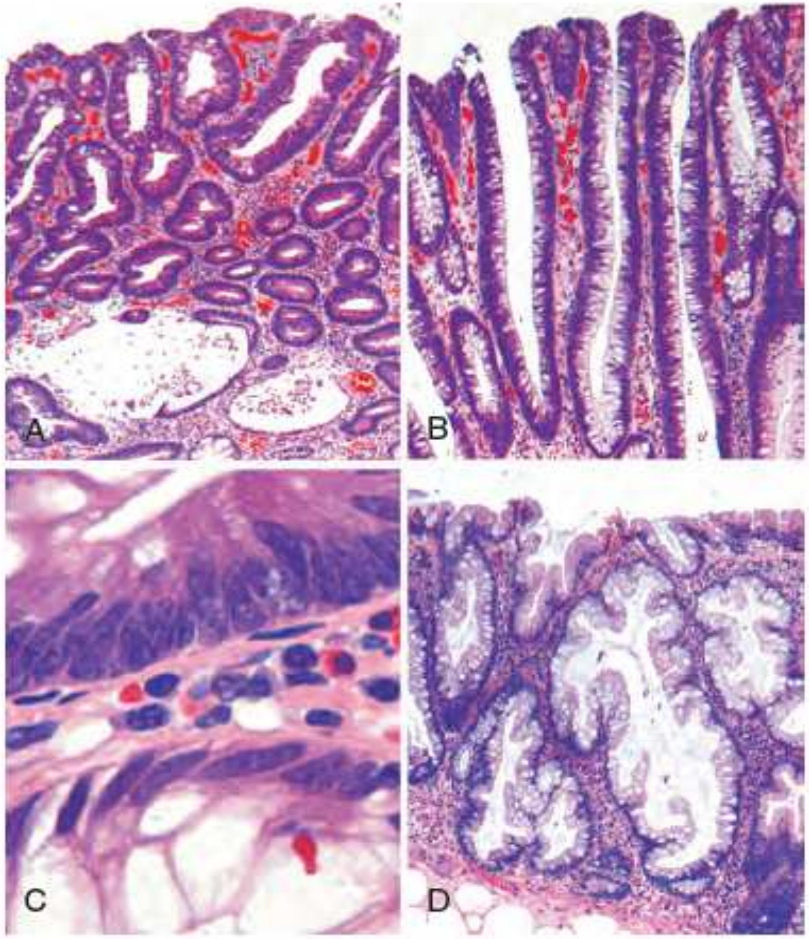
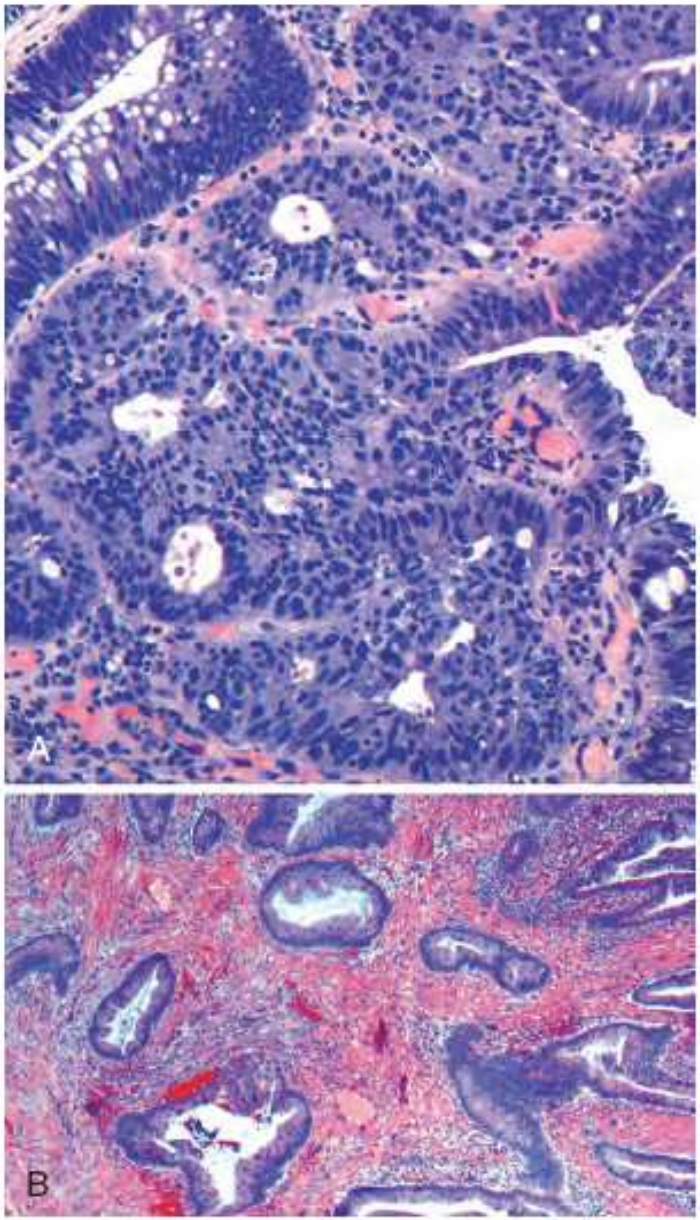



**Figure 17-46** Histologic appearance of colonic adenomas. **A,** Tubular adenoma with a smooth surface and rounded glands. Active inflammation is occasionally present in adenomas, in this case, crypt dilation and rupture can be seen at the bottom of the field. **B,** Villous adenoma with long, slender projections that are reminiscent of small intestinal villi. **C,** Dysplastic epithelial cells (top) with an increased nuclear-to-cytoplasmic ratio, hyperchromatic and elongated nuclei, and nuclear pseudostratification. Compare to the non-dysplastic epithelium below. **D,** Sessile serrated adenoma lined by goblet cells without cytologic features of dysplasia. This lesion is distinguished from a hyperplastic polyp by extension of the neoplastic process to the crypts, resulting in lateral growth. Compare to the hyperplastic polyp in Figure 17-44A.

# Adenomatous polyps

- High-grade dysplasia (carcinoma in situ) has not yet acquired the ability to metastasize and is still a clinically benign lesion.
- Because lymphatic channels are largely absent in the colonic mucosa, intramucosal carcinoma with lamina propria invasion only is regarded also as having little or no metastatic potential.
- If the intramucosal carcinoma penetrates through the muscularis mucosa into the submucosal space, the resultant invasive adenocarcinoma is a malignant tumor with metastatic potential.




ure 17-47 Adenoma with intramucosal carcinoma. **A,** Cribriform glands rface directly with the lamina propria without an intervening basement mbrane. **B,** Invasive adenocarcinoma (left) beneath a villous adenoma ht). Note the desmoplastic response to the invasive components.

# Polyps of the large intestine

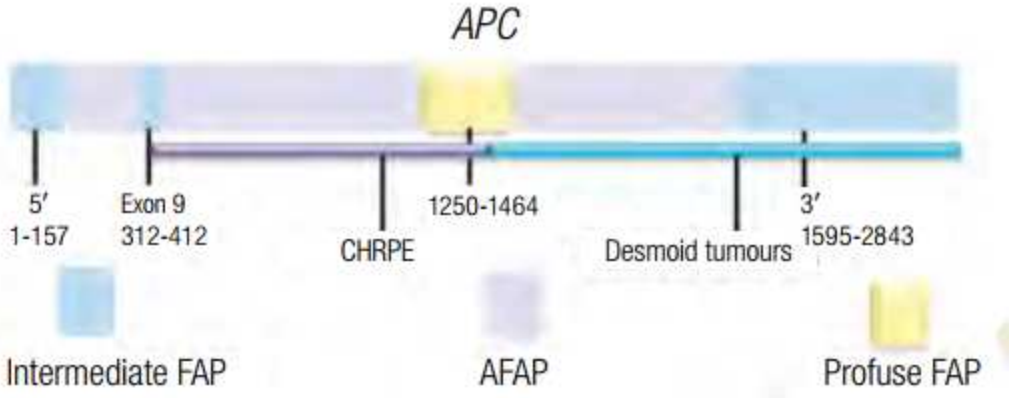
- The only adequate treatment for a pedunculated or sessile adenoma is complete resection.
- If adenomatous epithelium remains behind the patient still has a premalignant lesion or may even be harboring invasive carcinoma in the residual lesion.
- Size correlates with malignant potential
- KRAS/BRAF, 18qLOH mutations in high risk adenoma.

# Familial adenomatous polyposis

- >100 polyps are necessary for diagnosis of FAP.
- 50% have polyps by age 15; 95% by age 35.
- Extracolonic manifestations:
- Gastric and duodenal polyps
- Congenital hypertrophy of the retinal pigmented epithelium (CHRPE)
- Desmoid tumours (10%–15%)
- thyroid cancer (2%–3%)
- Medulloblastoma (<1%)
- Hepatoblastoma (1%)
- Supernumerary teeth, osteomas, epidermoid cysts.

# Familial adenomatous polyposis

- Begin to screen at age 10.
- Autosomal dominant.
- APC germline mutation
- APC is negative regulator of WNT/β-catenin signaling involved in controlling cell proliferation. E-cadherin is lost.
- Morphologically indistinguishable from adenoma.
- There is an attenuated form with <100 adenomas
- Cancer penetrance is incomplete




AFAP; Attenuated FAP; CHRPE, congenital hypertrophy of the retinal pigmented epithelium; FAP, familial adenomatous polyposis.

# Familial adenomatous polyposis

- COX 2 gene is cytokine induced and downstream from EGFR.
- COX 2 inhibitor binds to cis-recognition site of PPAR 8.
- Progression on COX- 2 inhibitor is poor prognostic sign.
- Total colectomy prevents colorectal cancer.
- However, patient remains at risk for carcinoma at the ampulla of Vater or stomach.

# Familial adenomatous polyposis

- Gardner's syndrome is associated with desmoid tumors of abdominal wall as well.
- Autosomal dominant.
- Turcot's syndrome is associated with astrocytoma and medulloblastoma as well.
- Autosomal recessive
- Total colectomy prevents colorectal cancer. However, patient remains at risk for carcinoma at the ampulla of Vater or stomach.

# Familial adenomatous polyposis

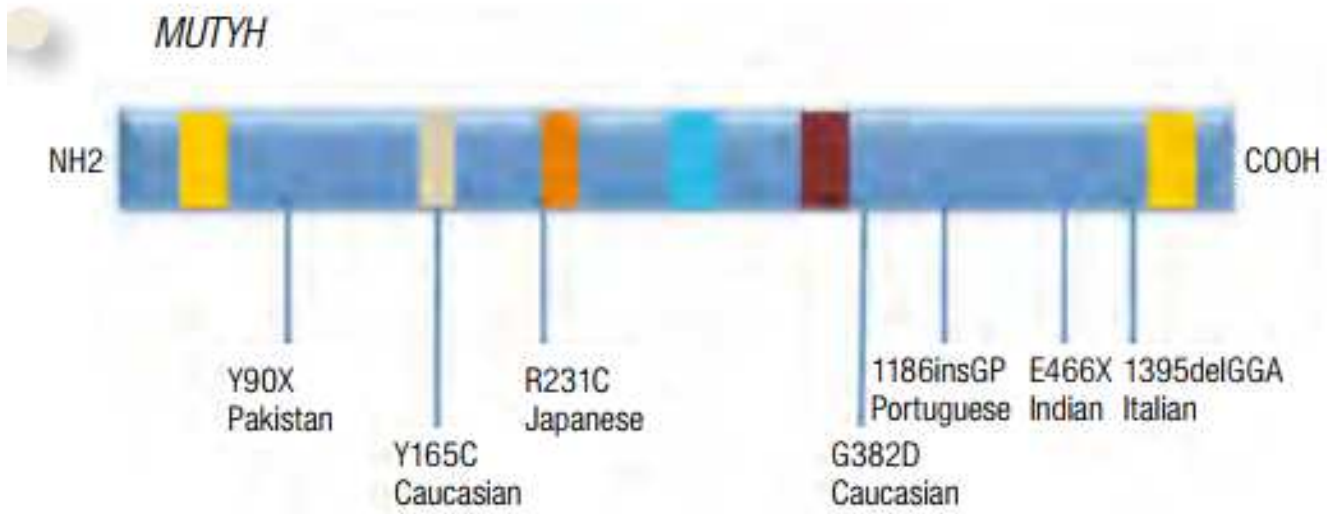

Myriad well-formed polypoid adenomas.

Fig. 3-31A

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.

# MYH-associated polyposis

- Fewer extracolonic mutations
- If no germline APC mutation, there is bi-allelic loss of the base excision repair gene MUTYH (MYH).
- In the Caucasian population, G396D or Y179C missense variants account for >80% of mutations
- Autosomal recessive
- Morphologically indistinguishable from adenoma.
- K-RAS mutated serrated adenoma may be found in these patients
- Polyposis managed with surveillance colonoscopy and polypectomy


MUTYH
NH2
COOH
Y90X
Pakistan
Y165C
Caucasian
R231C
Japanese
G382D
Caucasian
1186insGP
Portuguese
E466X
Indian
1395delGGA
Italian

# Adenocarcinoma

- 90% occur in those over 50 years of age.
- Colon cancer is more common in women; rectal cancer, in men.
- High fiber, low animal-fat diets decrease risk. Smoking is an identifiable risk factor.
- Left sided lesions tend to be annular, produce "napkin-ring" constrictions and luminal narrowing leading to obstruction
- Right sided lesions tend to be polypoid, silent.
- Diarrhea related to COX-2 overexpression ($Ca^{2+}$ transport).

# Adenocarcinoma

- Cancers in the colorectum are found in the:
- Cecum/ascending colon, 22%
- Transverse colon, 11%
- Descending colon, 6%
- Rectosigmoid colon,  55%
- and other sites, 6%.

# Adenocarcinoma

- Most tumors are composed of dysplastic tall columnar cells.
- Tumors may also be composed of signet-ring cells
- Some poorly differentiated tumors form few glands
- May display neuroendocrine differentiation.
- Others may produce abundant mucin that accumulate in the bowel wall.
- Mucin, released into system, has a procoagulant effect

# Adenocarcinoma

- The invasive component of these tumors elicits a strong stromal desmoplastic response, which is responsible for their characteristic firm consistency.
- The two most important prognostic factors are depth of invasion and the presence of lymph node metastases
- Liver is the principal site of metastasis

**Table 17-11** Common Patterns of Sporadic and Familial Colorectal Neoplasia

| Etiology | Molecular Defect | Target Gene(s) | Transmission | Predominant Site(s) | Histology |
|---|---|---|---|---|---|
| Familial adenomatous polyposis | APC/WNT pathway | *APC* | Autosomal dominant | None | Tubular, villous; typical adenocarcinoma |
| *MYH*-associated polyposis | DNA mismatch repair | *MYH* | Autosomal recessive | None | Sessile serrated adenoma; mucinous adenocarcinoma |
| Hereditary nonpolyposis colorectal cancer | DNA mismatch repair | *MSH2, MLH1* | Autosomal dominant | Right side | Sessile serrated adenoma; mucinous adenocarcinoma |
| Sporadic colon cancer (70%-80%) | APC/WNT pathway | *APC* | None | Left side | Tubular, villous; typical adenocarcinoma |
| Sporadic colon cancer (10%-15%) | DNA mismatch repair | *MSH2, MLH1* | None | Right side | Sessile serrated adenoma; mucinous adenocarcinoma |
| Sporadic colon cancer (5%-10%) | Hypermethylation | *MLH1, BRAF* | None | Right side | Sessile serrated adenoma; mucinous adenocarcinoma |

| Environmental and lifestyle factors associated with colorectal cancer risk | | |
|---|---|---|
| FACTORS | INCREASES RISK | DECREASES RISK |
| Tobacco smoking | About 40% increased risk for 40 cigarettes/day | |
| Anthropometry | Body fatness, abdominal fatness, adult attained height | |
| Physical activity | | 11% decrease for 30 min/day of recreational activity; mostly colon |
| Dietary factors | | |
| convincing evidence: | Red meat, processed meat, alcoholic drinks (mainly men) | |
| convincing evidence: | | Foods containing dietary fibre |
| probable evidence: | | Garlic, milk, calcium |
| limited evidence: | Foods containing iron, sugars, abdominal fats, cheese | Non-starchy vegetables, fruits, foods containing vitamin D |
| Other diseases | Inflammatory bowel disease (Crohn's disease, ulcerative colitis) | |
| Medication | | Non-steroidal anti-inflammatory drugs, postmenopausal women, hormone replacement therapy |

# Genetic model of cancer

- The process of colorectal tumorigenesis has been termed the polyp-carcinoma sequence, and it generally takes place over an 8- to 11-year time frame.
- There appears to be acceleration of this process in familial adenomatous polyposis (APC gene) and hereditary nonpolyposis colorectal cancer (MMR, mismatch repair genes).
- Defective DNA repair caused by inactivation of DNA mismatch repair genes is the fundamental and the most likely initiating event in colorectal cancers

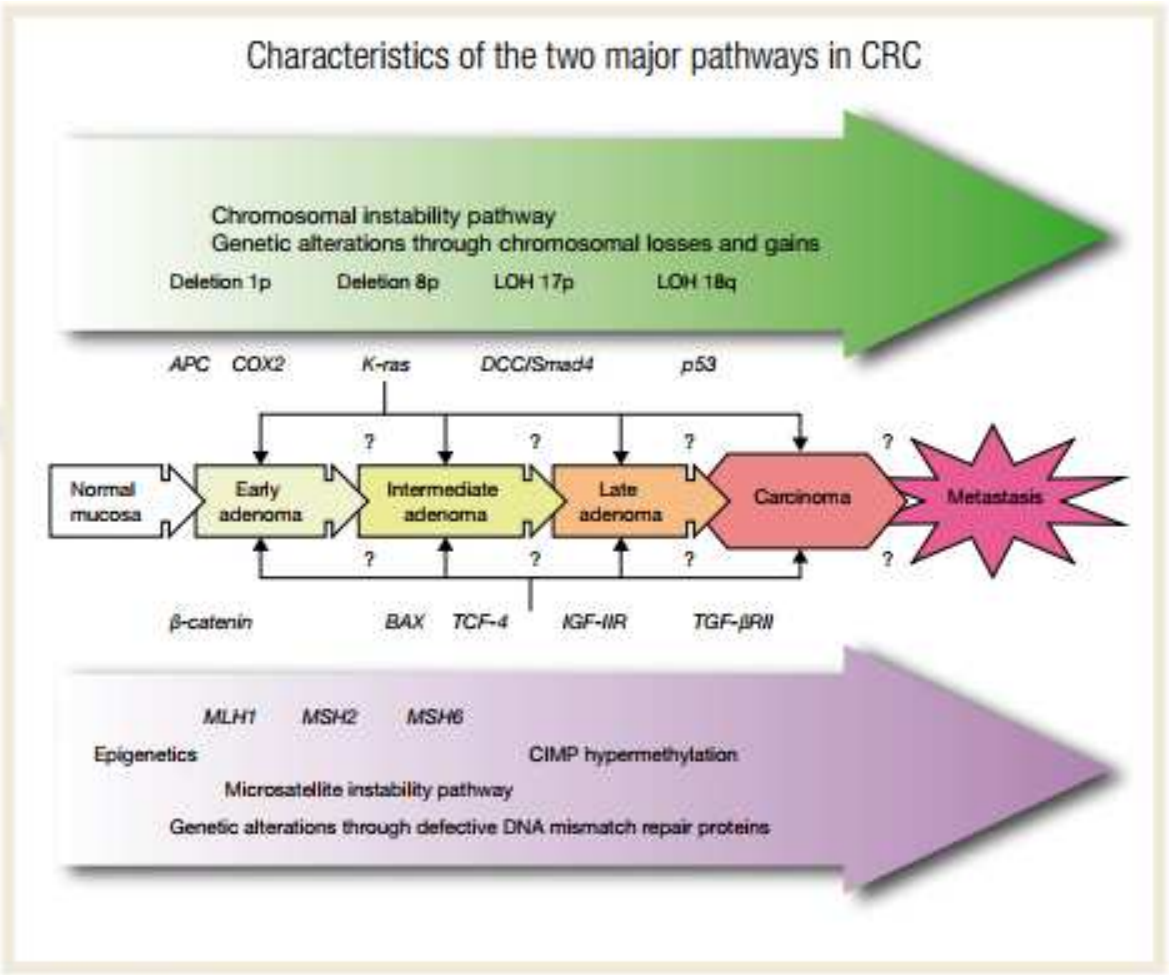
# Genetic model of cancer

- Colon cancer can be divided at the molecular level into at least two distinct molecular categories based on the types of mutations observed.
- The chromosome instability (CIN) group is characterized by the presence of aneuploidy, chromosome translocations, and chromosomal gains and losses
- The microsatellite instability (MSI) group is characterized by the presence of frameshift mutations in repetitive elements of DNA called microsatellite repeats.

# Adenocarcinoma of colon

**Table 1 Features of CRCs based on CIMP status**

| Features | Non-CIMP | CIMP-low | CIMP-high |
|---|---|---|---|
| Tumour location | Distal > proximal | — | Proximal > distal |
| Gender bias | Male=female | Male>female | Male < female |
| *BRAF* mutation status | Wild type | Wild type | Mutant |
| *KRAS* mutation status | Wild type | Mutant | Wild type |
| Genomic instability status | CIN | Similar to non-CIMP | MSI is common |




CRC, Colorectal cancer.

# Adenoma-carcinoma sequence

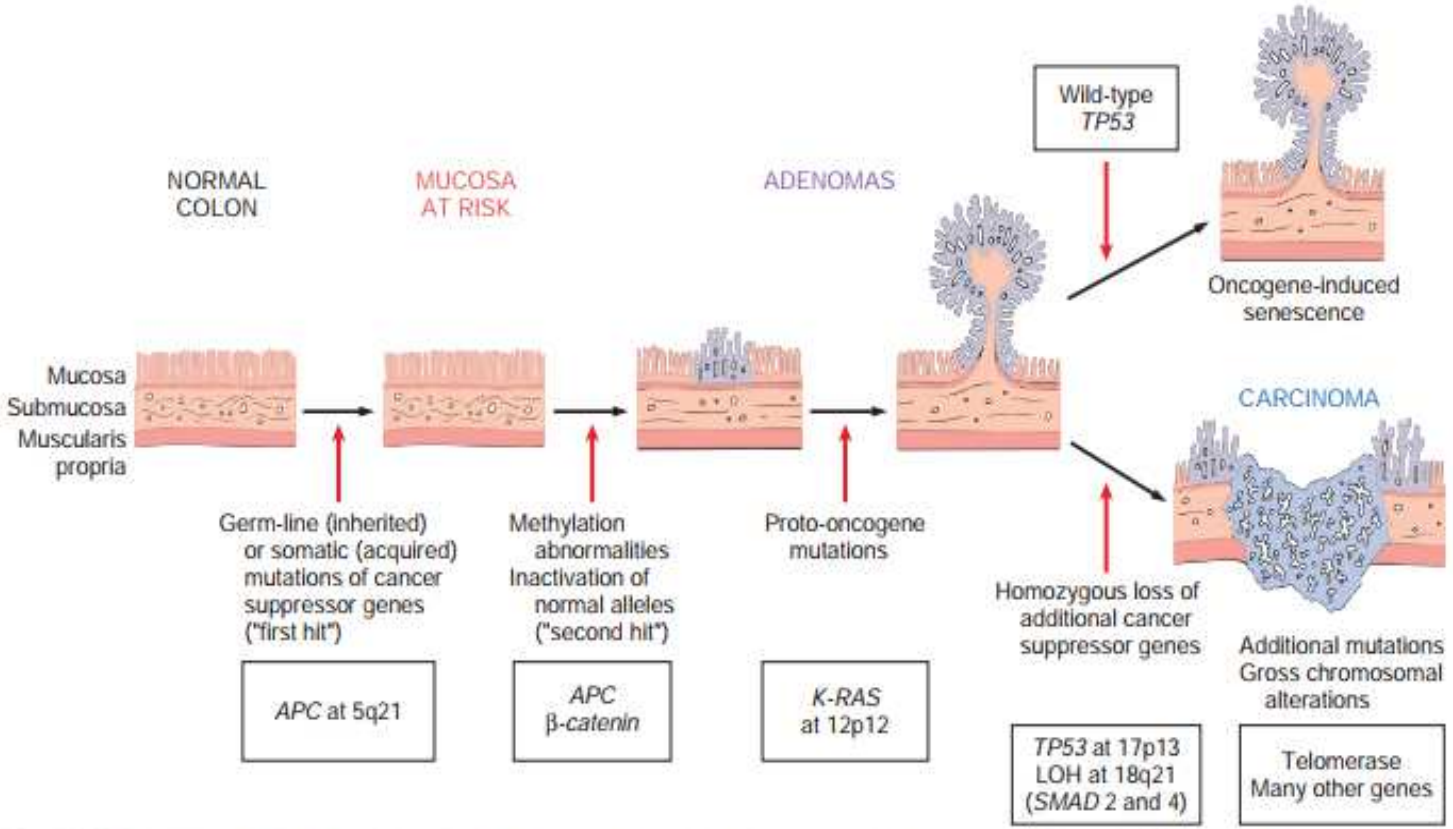



**Figure 7-42** Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. Although *APC* mutation is an early event and loss of *TP53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumors may not have all of the changes listed. *Top right*, cells that gain oncogene signaling without loss of *TP53* eventually enter oncogene-induced senescence. LOH, loss-of-heterozygosity.

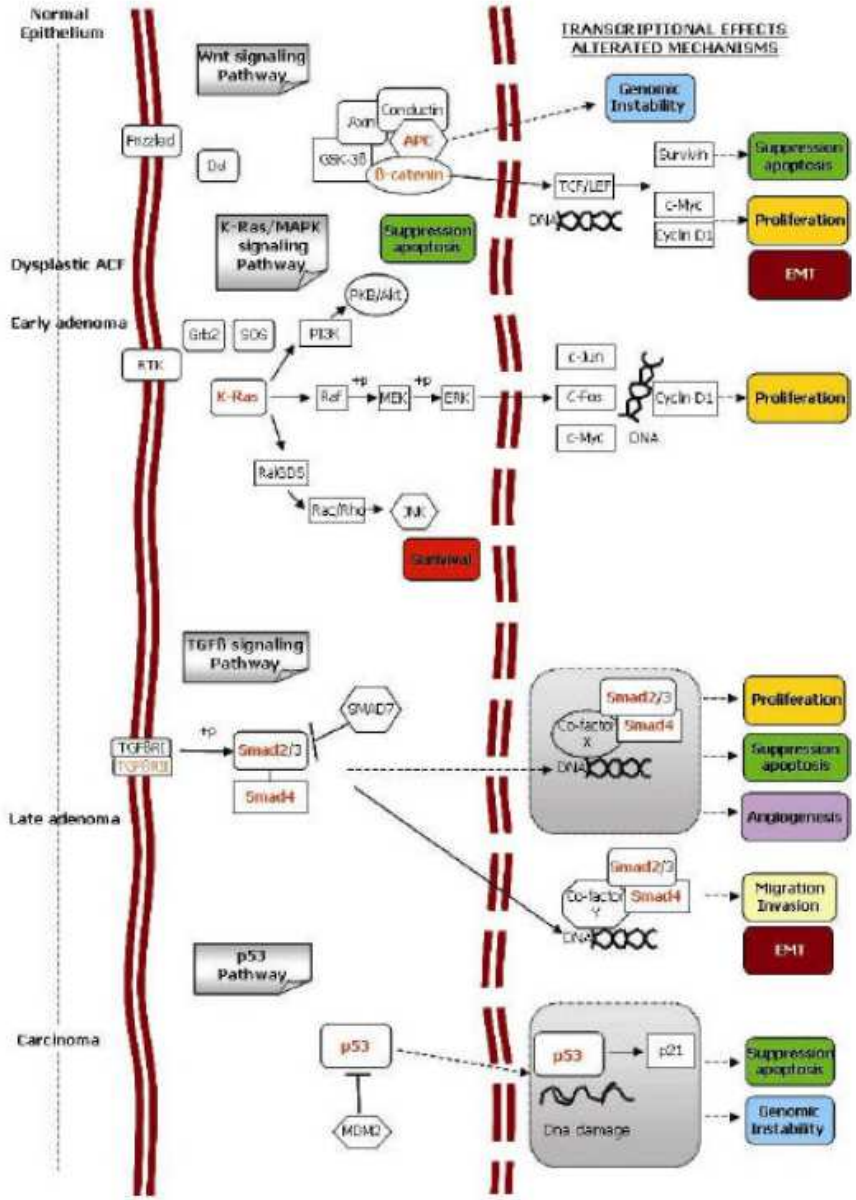



**Figure 2.** Schematic representation of the accumulation of alterations in different pathways along the adenoma-carcinoma sequence. In red are shown the genes frequently mutated in CRC. The different cellular alterations resulting from the accumulations of these signaling defects are listed in the right column.

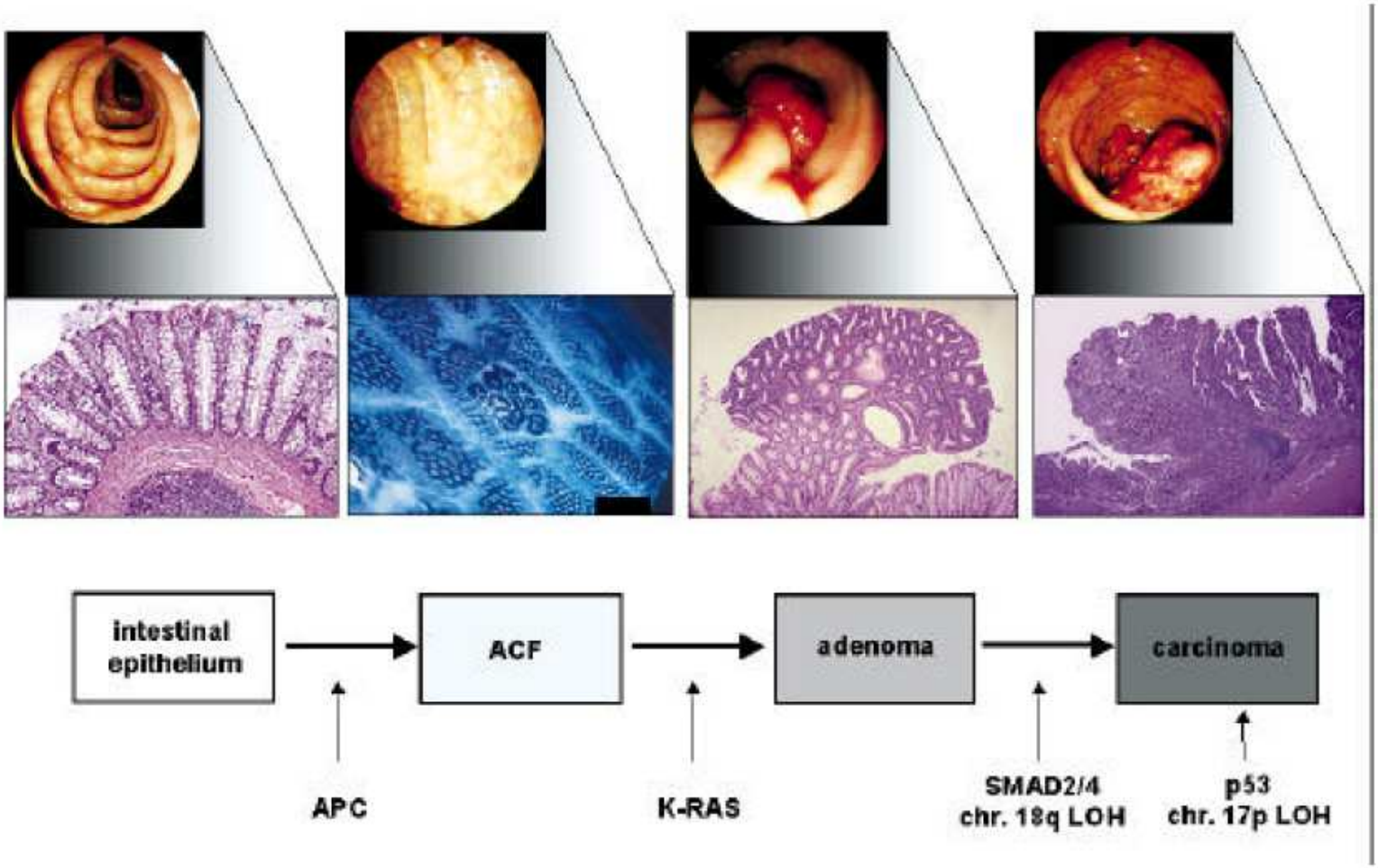



**Figure 1.** The adenoma-carcinoma sequence: a stepwise progression from normal epithelium to carcinoma due to a series of genetic changes. Macro- and microscopical representations of the progression changes are depicted. See text

# Adenocarcinoma

- APC/ β-catenin mutation is first step to dysplastic epithelium.
- More than 80% of colorectal carcinomas have inactivated APC, and 50% of cancers without APC mutations have β-catenin mutations.
- APC is a negative regulator of WNT as it binds to β-catenin
- β-catenin is a member of the cadherin-based cell adhesive complex, consisting of APC, Axin, GSK-3β, and β-catenin, which also acts as a transcription factor if the protein is translocated to the nucleus.

# Adenocarcinoma

- Bind to a family of transcription factors called T-cell factor or lymphoid enhancer factor (TCF or LEF) proteins.
- The TCF contributes a DNA-binding domain and β-catenin contributes a trans-activation domain.
- Genes activated by the β-catenin-TCF complex are thought to include those regulating cell proliferation and apoptosis, such as c-MYC and cyclin D1.
- LOH 18q (SMAD2 and SMAD4) mutations lead to loss of TGF-β signaling and unrestrained cell growth.

# Mis-match carcinogenesis

- 90% of the mutations of “caretaker genes” involve MSH2 and MLH1.
- Mutations in the mismatch repair genes lead to microsatellite instability.
- CpG rich zones or CpG islands (5’ region that frequently includes promoter and transcriptional start sites) may be silenced by methylation (CIMP gene)
- BRAF is a serine-threonine protein kinase that acts as downstream effector of KRAS signaling.
- KRAS in the absence of BRAF

# Adenocarcinoma

- KRAS codes a GTP/GDP binding protein facilitating ligand binding tyrosine kinase growth factor signaling.
- KRAS activates the RAF-MEK-ERK pathway.
- p53 mutation occurs late in adenoma carcinoma transition.

# Mis-match repair carcinogenesis

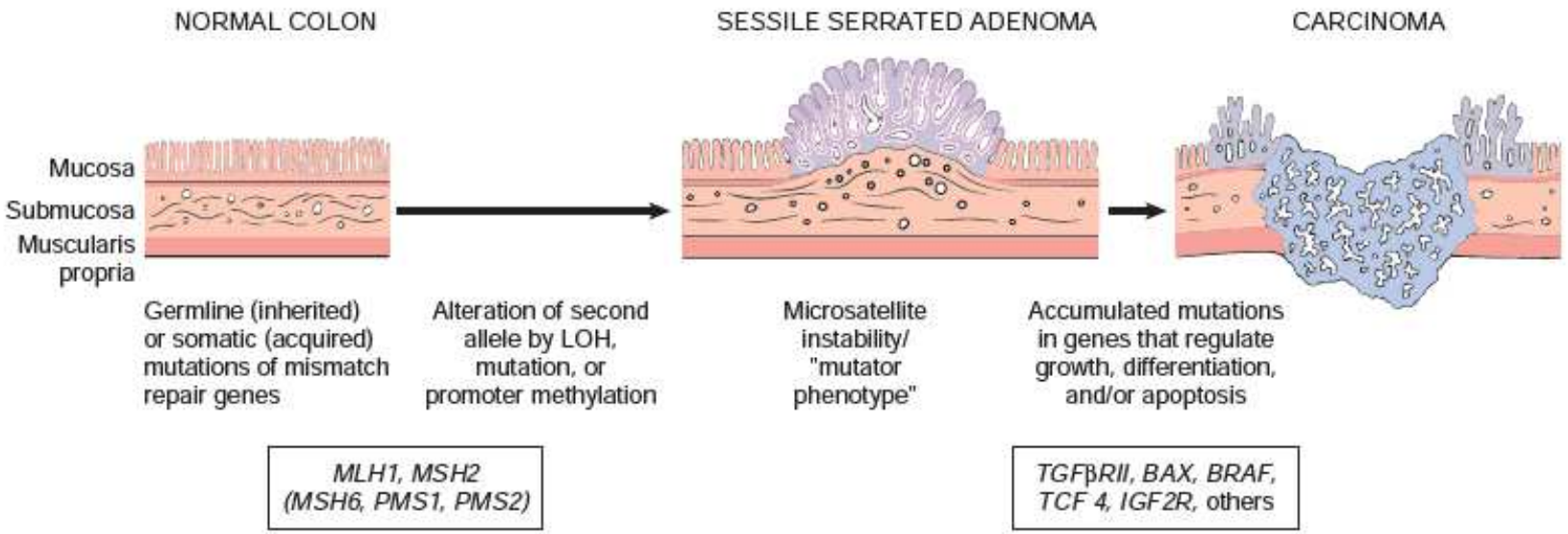



**Figure 17-50** Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop.

# Adenocarcinoma

- RAS mutation associated with poor prognosis
- BRAF V600E mutation associated with poor prognosis.
- Notch 1 over-expression associated with poor prognosis (T3/T4 common) as is Notch 2 under-expression.
- RNF43 mutation associated with poor prognosis.
- Stem cell ligase that negatively regulates WNT signaling
- Deletion associated with adenoma formation

# Adenocarcinoma

- KRAS mutations are found in 42.6% of whites and 56.8% of blacks. The differences are significant.
- DDR mutations are found in 12.9% of Asians and 21.7% of whites.  The differences are significant.
- RNF43 mutation more common in blacks.

# Adenocarcinoma

- p53 and EGFR over-expression more common in left sided lesions (favorable sign).
- Those with left sided lesions with DNA mismatch repair mutations have better prognosis than those with right sided lesions and the same mutations in Stage II or III disease.
- LRBP mutation (10% of colon cancers) generally left sided lesions.
- No benefit to use of cetuximab or bevicuzumab
- Respond to immunomodulators

# Lynch syndrome

- Hereditary non-polyposis colon cancer (HPNCC)
- 2% of all colon cancers
- Most common syndromic form
- Two-thirds of the cancers occur in the proximal colon.
- Often tumors show mucinous change.
- Average age of diagnosis is mid-forties.
- 80% lifetime risk of colon cancer
- AND, for women, endometrial cancer as well
- Endometrial cancer may present first in women.

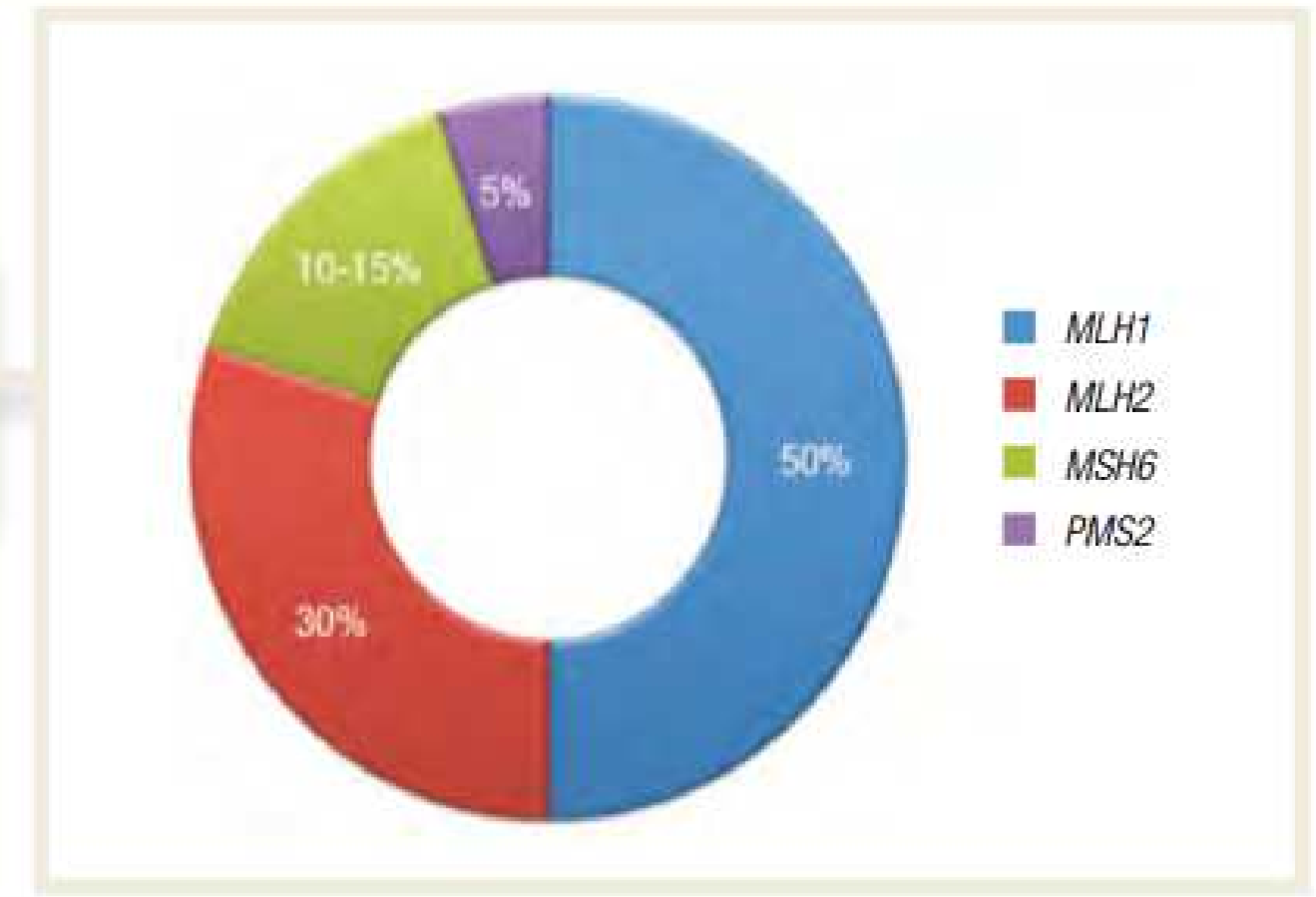
# Lynch syndrome

- Associated with ovarian cancer
- Presents in the thirties
- For those presenting in the fifties
- May also see gastric cancer of intestinal type
- Small bowel adenocarcinoma
- Transitional cell cancers in the genitourinary tract
- Glioblastoma

# Lynch syndrome

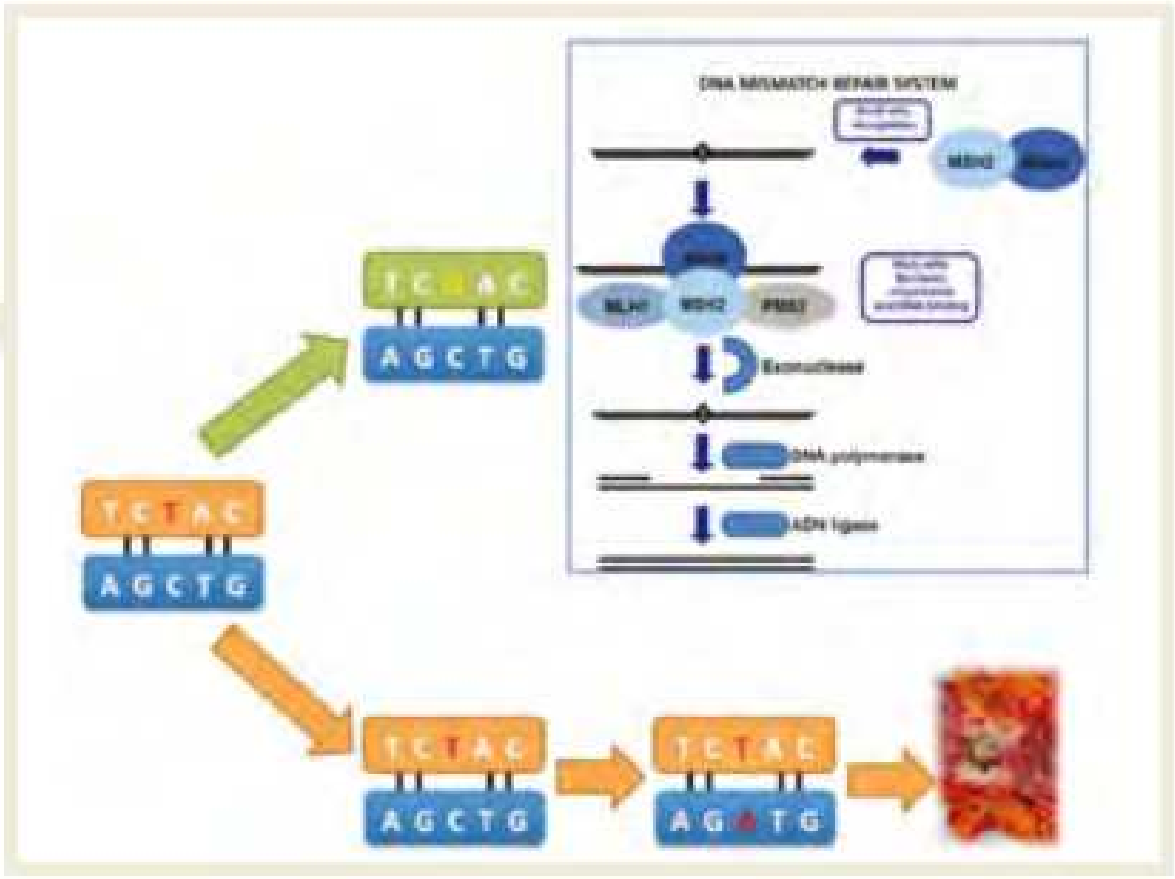
- Inherited mutations (germ-line mutations) in any of five genes that are involved in involved in genetic "proofreading" during DNA replication:
- hMSH2 (2p22), hMLH1 (3p21), MSH6 (2p21), hPMS1 (2q31-33), and hPMS2 (7p22).
- Carcinogenesis is promoted when mismatches occur within the coding region of tumor suppressor genes (TGF-BRII, BAX, IGF2R, PTEN, CASP5).
- Up to 15% of all CRCs show MLH1/PMS2 protein loss due to somatic MLH1 promoter hypermethylation, usually associated with somatic BRAF mutations.

# Mismatch mutation frequency



# Lynch syndrome

- Germline 3'EPCAM deletions also cause Lynch syndrome by epigenetic silencing of MSH2 by hypermethylation of its promoter region.
- TGFβRII mutation leads to unrestrained epithelial cell proliferation.
- BAX mutation permits cell to escape apoptosis.
- Microsatellite instability (MSI) is a marker for the presence of mismatch proteins as is the presence of tumor infiltrating lymphocytes.


DNA MISMATCH REPAIR SYSTEM
MSH2
MLH1
MSH2
PMS2
Exonuclease
DNA polymerase
ADN ligase
TCTAC
AGCTG
TCTAC
AGCTG
TCTAC
AGCTG
TCTAC
AGATG

# Lynch syndrome

- Screen every 1-2 years by colonoscopy beginning at age 25 (30 if MSH6 or PMS2 mutations).
- The risk of metachronous colorectal cancer is 16% at 10 years and 41% at 20 years.
- Screen women with endometrial biopsy beginning at age 30.
- Transvaginal ultrasound and CA125 have not been useful screening tools in ovarian cancer.

# Familial colorectal cancer type X

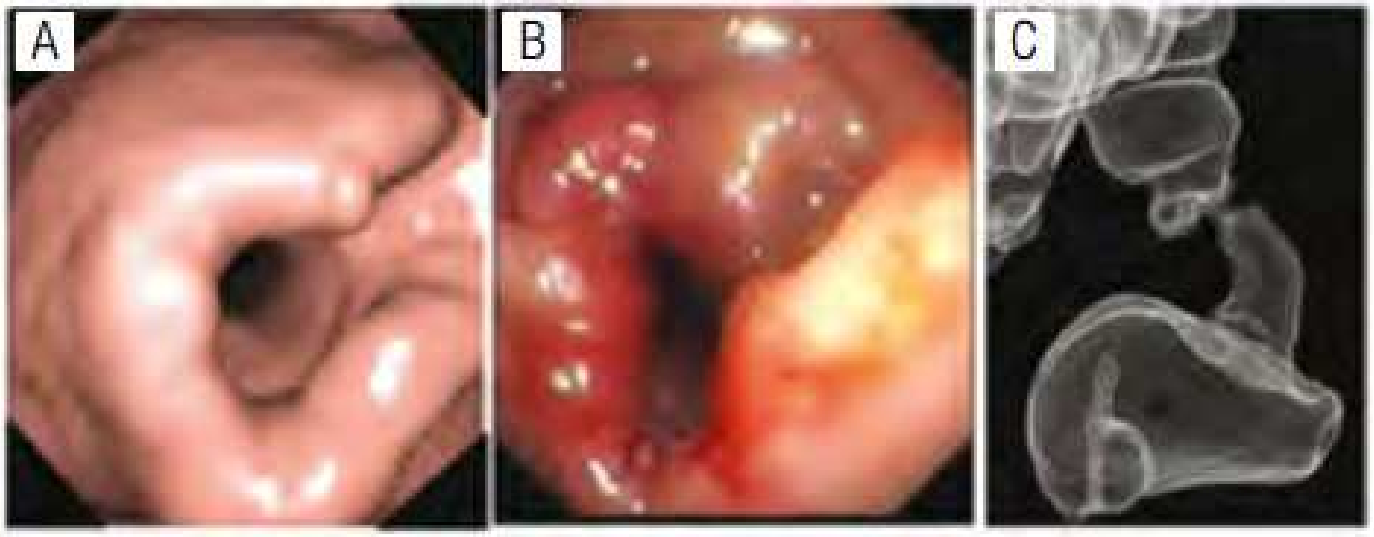
- 40% of those who fulfill the Amsterdam criteria for diagnosis of Lynch syndrome do not have a mismatch repair abnormality.
- Adenocarcinoma without polyposis
- Genetic basis has not been identified. However, in some cases, germline mutations have been identified
- BMPR1A, BMP4, GALNT12
- Cancer risk is lower than in Lynch syndrome

# Familial colorectal cancer MUTYH associated

- Up to 30% of biallelic mutation carriers display adenocarcinoma without polyposis.
- MUTYH encodes a member of the base excision repair system which contributes to protect cells against the mutagenic effects of aerobic metabolism.

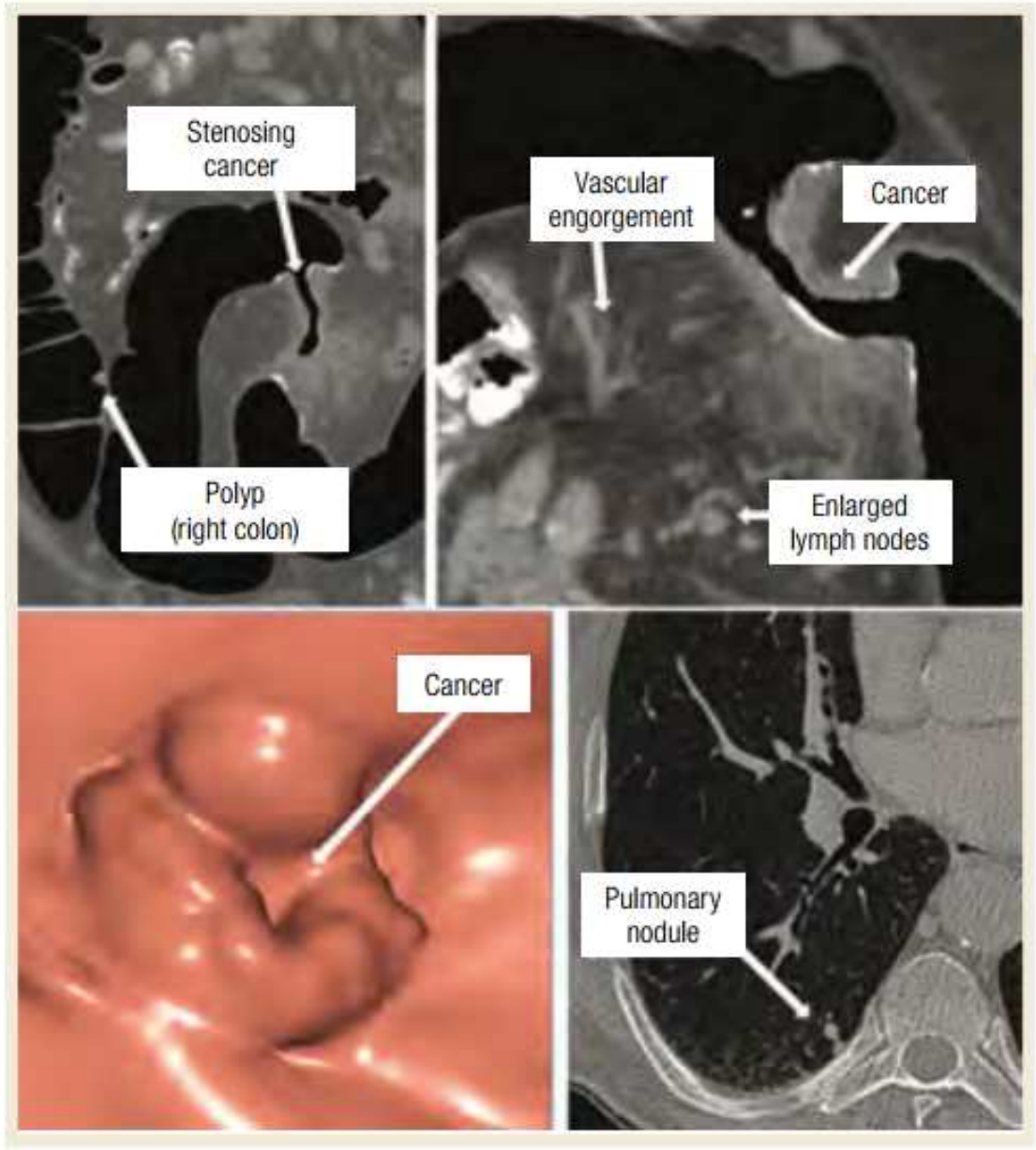
# Adenocarcinoma of the large intestine

- Diagnosis of colon cancer is obtained with colonoscopy and biopsy.
- CT colonography (CTC) as an alternative.
- CT of the chest, abdomen and pelvis is appropriate to detect distant metastasis.
- If initial colonoscopy is incomplete (also due to the presence of a stenosing cancer), the adjunct of CTC to CT can be used to detect synchronous colonic lesions.
- Contrast-enhanced MRI is suggested if CT is contraindicated or if liver lesions require further characterization.

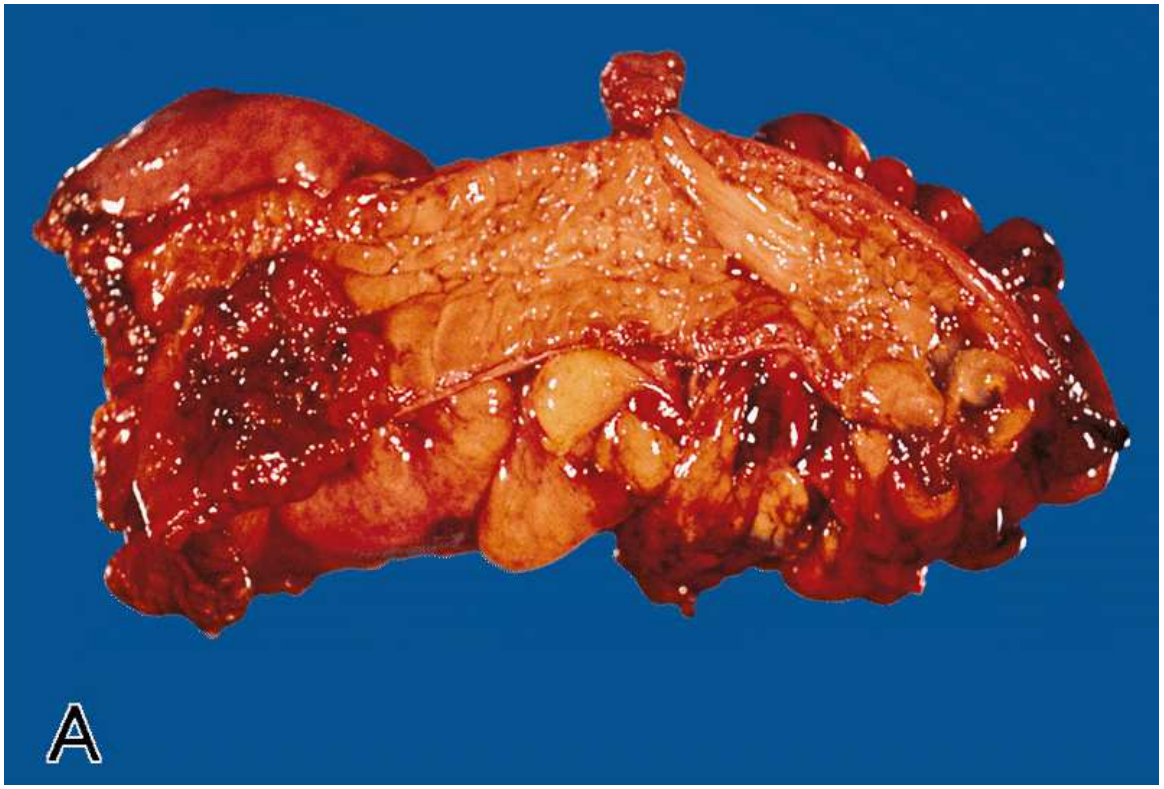



Stenosing Colon Cancer: (A) 3D endoluminal image from CTC, (B) optical colonoscopy and (C) double-contrast barium enema reconstruction from CTC.

CTC, Computed tomography colonography.


Stenosing cancer
Polyp (right colon)
Vascular engorgement
Cancer
Enlarged lymph nodes
Cancer
Pulmonary nodule

# Adenocarcinoma

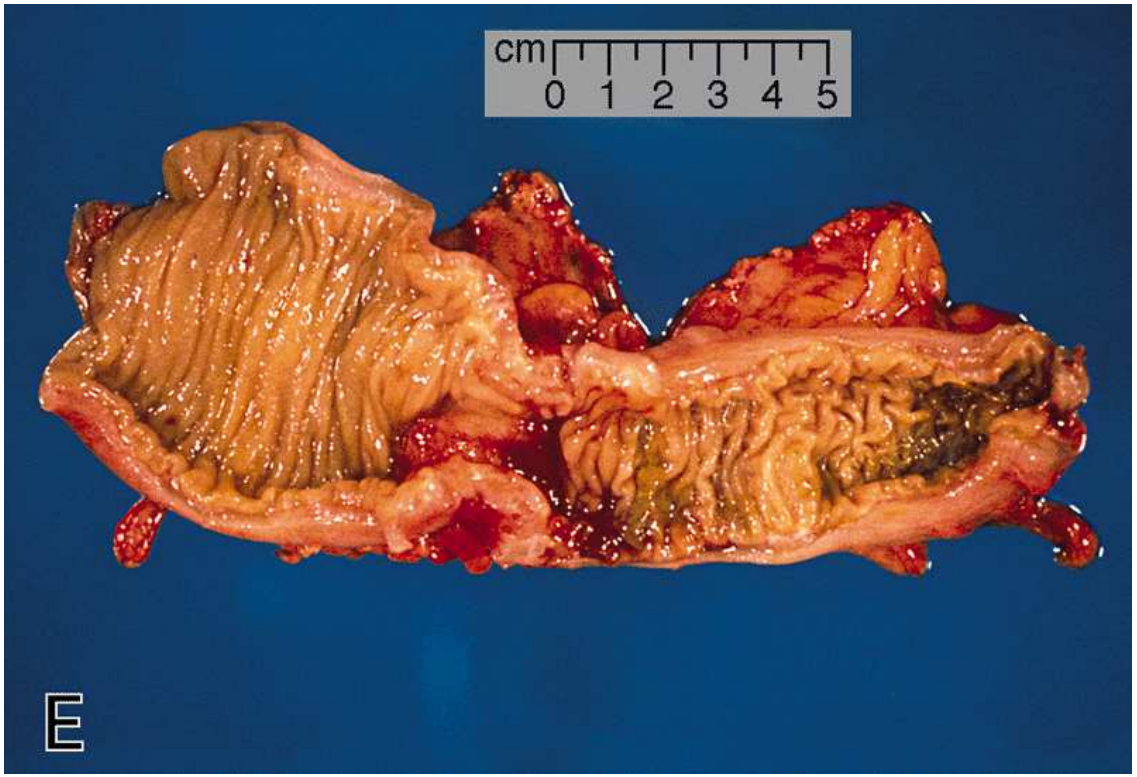



Typical tumor with central depression and raised, rolled, everted edges.

Fig. 3-45A

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.

# Adenocarcinoma




Annular stenosing carcinoma of sigmoid colon associated with diverticular disease.

Fig. 3-45E

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.

# Adenocarcinoma

- When the rare multiple carcinomas are present, they are often at widely disparate sites in the colon.
- 1% to 3% of colorectal carcinomas occur in patients with familial syndromes or inflammatory bowel disease.
- 98% of all cancers in the large intestine are adenocarcinomas.
- Carcinomas arising in the anorectal canal constitute a distinct subgroup of tumors, dominated by squamous cell carcinoma.

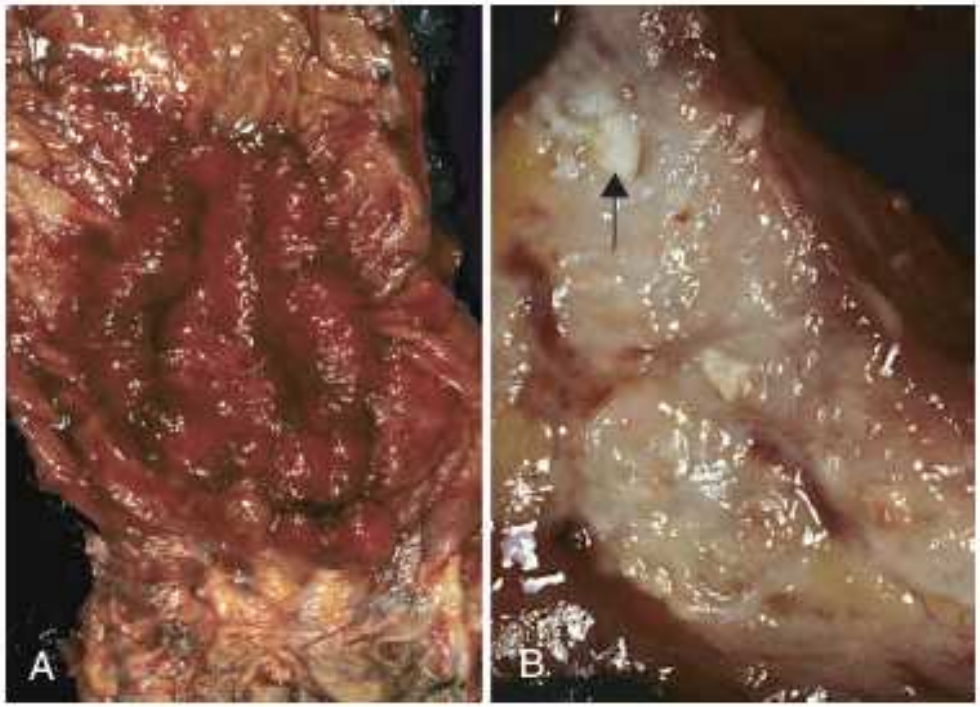



**Figure 17-51** Colorectal carcinoma. **A,** Circumferential, ulcerated rectal cancer. Note the anal mucosa at the bottom of the image. **B,** Cancer of the sigmoid colon that has invaded through the muscularis propria and is present within subserosal adipose tissue (left). Areas of chalky necrosis are present within the colon wall *(arrow)*.

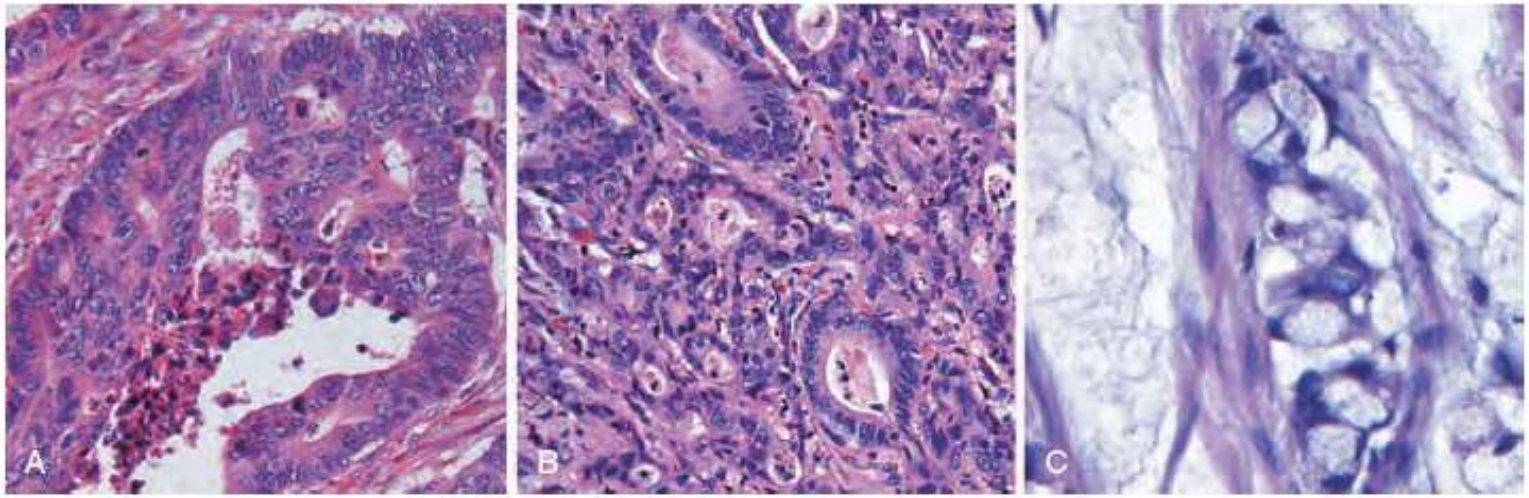
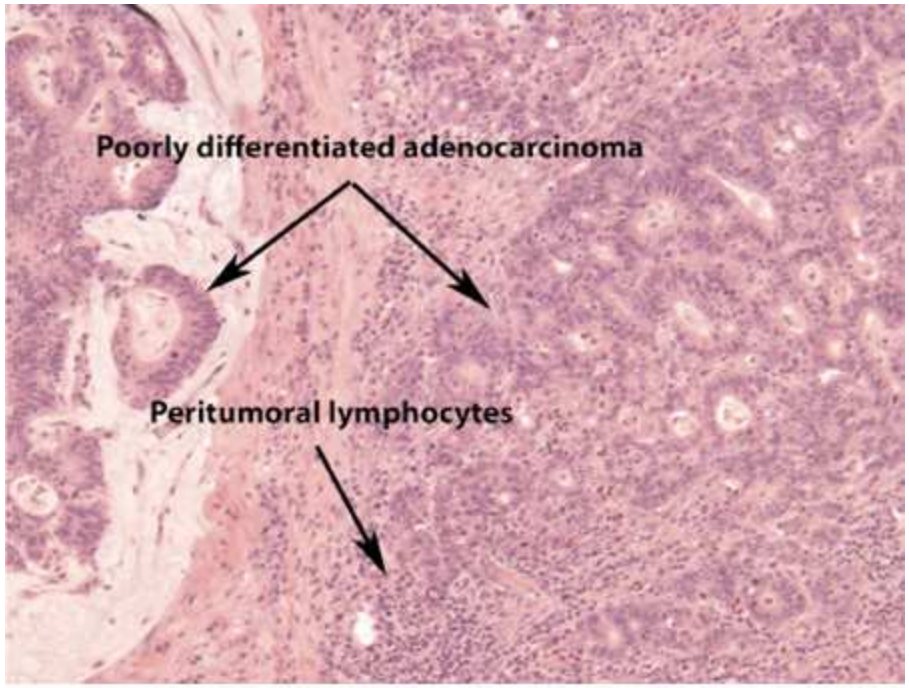



**Figure 17-52** Histologic appearance of colorectal carcinoma. **A,** Well-differentiated adenocarcinoma. Note the elongated, hyperchromatic nuclei. Necrotic debris, present in the gland lumen, is typical. **B,** Poorly differentiated adenocarcinoma forms a few glands but is largely composed of infiltrating nests of tumor cells. **C,** Mucinous adenocarcinoma with signet-ring cells and extracellular mucin pools.

# Adenocarcinoma




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



Photomicrograph of a tumor with microsatellite instability. Upper arrows point to poorly differentiated malignant cells with some glandular differentiation and mucin. Lower arrow shows peritumoral lymphocytes clustering near areas of malignant cells and permeating the local stroma.

Fig. 16-1 Accessed 03/01/2010

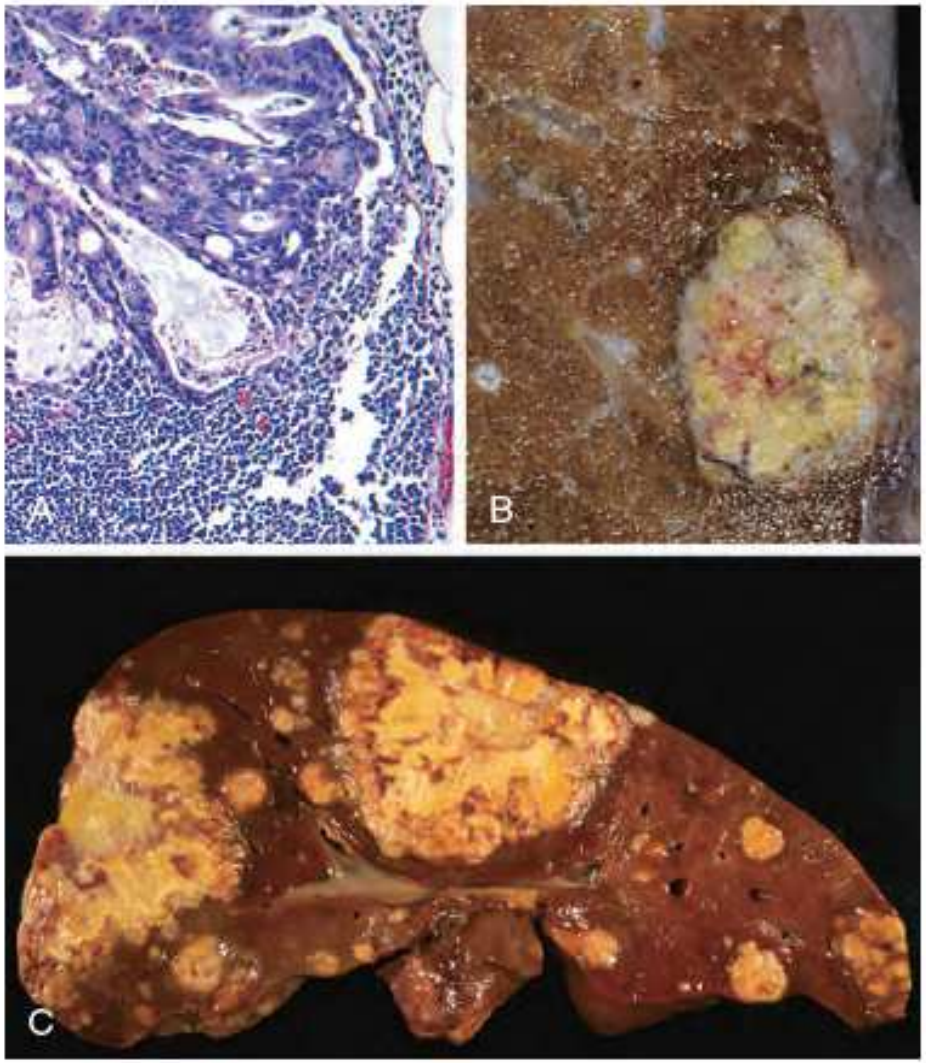
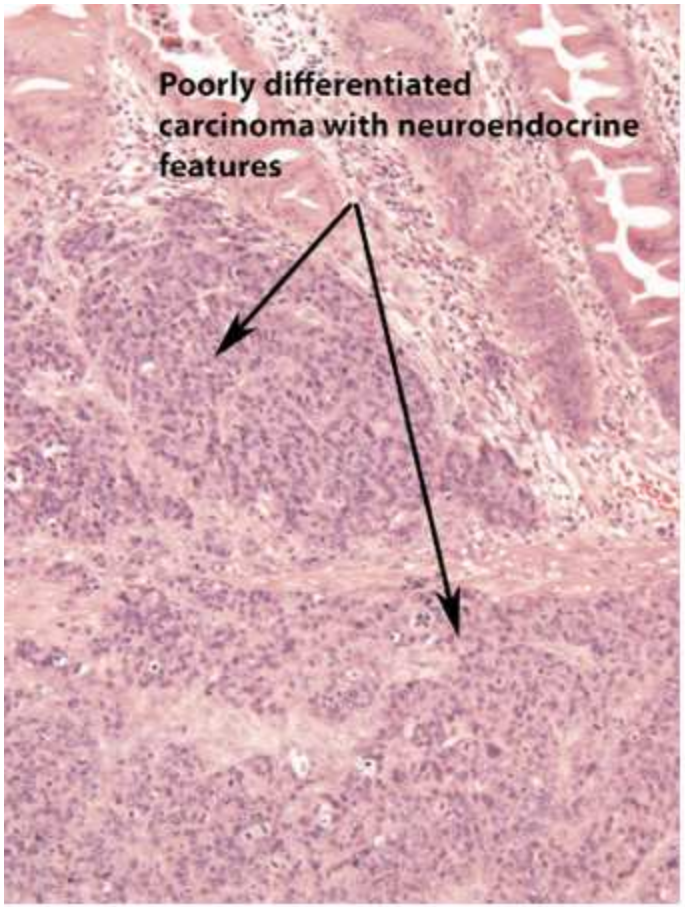



**Figure 17-53** Metastatic colorectal carcinoma. **A,** Lymph node metastasis. Note the glandular structures within the subcapsular sinus. **B,** Solitary subpleural nodule of colorectal carcinoma metastatic to the lung. **C,** Liver containing two large and many smaller metastases. Note the central necrosis within metastases.

# Neuroendocrine change




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

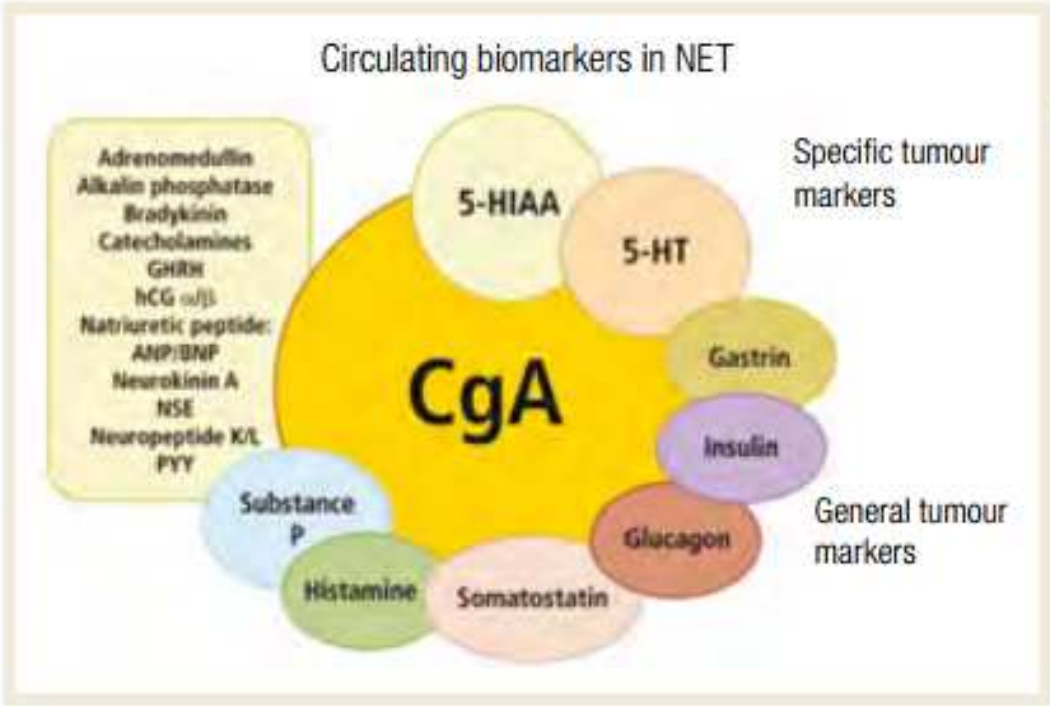


Photomicrograph of a poorly differentiated carcinoma of the colon with neuroendocrine features. Tumor appears in sheets of fairly monotonous cells without glandular or mucinous characteristics.

Fig. 16-2 Accessed 03/01/2010

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

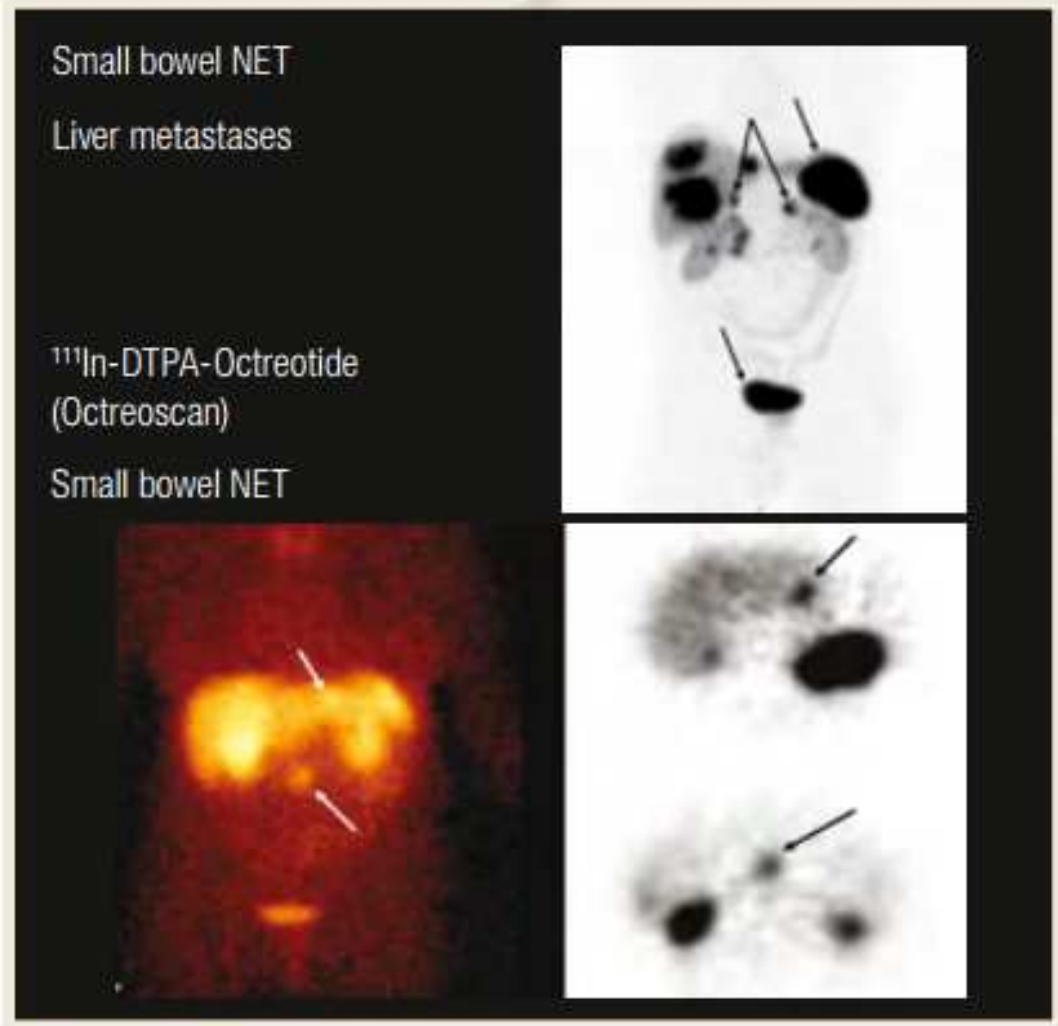
GEP, Gastroenteropancreatic; WHO, World Health Organisation.




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.

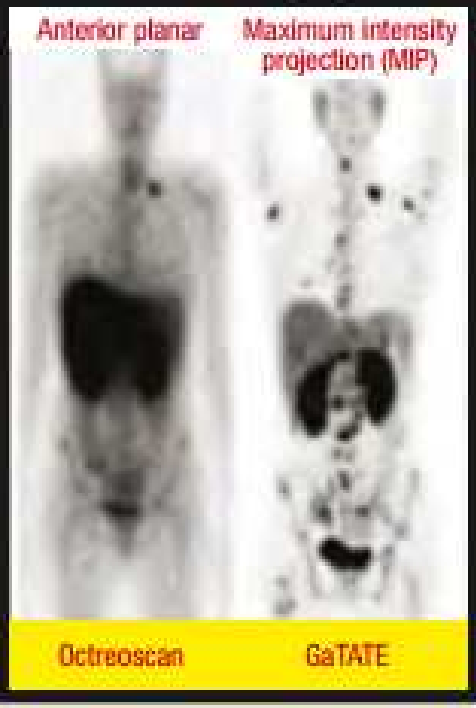
| Imaging of Neuroendocrine Tumours: Techniques | |
|---|---|
| **Morphological** | **Functional** |
| Ultrasound<br>Computed tomography (CT)<br>Magnetic resonance imaging<br>Endoscopic ultrasound | Diffusion-weighted magnetic resonance<br>Somatostatin receptor scintigraphy<br>$^{68}$Ga-DOTA-TATE/TOC/CT<br>$^{11}$C-5-HTP, $^{18}$F-DOPA/CT<br>$^{18}$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.

# Adenocarcinoma

- Foci of endocrine differentiation may be found in about 10% of colorectal carcinomas.
- The small-cell undifferentiated carcinoma appears to arise from endocrine cells per se and elaborates a variety of bioactive secretory products.
- In some cancers the cells take on a signet-ring appearance.
- Some cancers, particularly in the distal colon, have foci of squamous cell differentiation and are therefore referred to as adeno-squamous carcinomas.

**Table 17-12** American Joint Committee on Cancer (AJCC) TNM Classification of Colorectal Carcinoma

| TNM | |
|---|---|
| **Tumor** | |
| Tis | In situ dysplasia or intramucosal carcinoma |
| T1 | Tumor invades submucosa |
| T2 | Tumor invades into, but not through, muscularis propria |
| T3 | Tumor invades through muscularis propria |
| T3a | Invasion < 0.1 cm beyond muscularis propria |
| T3b | Invasion 0.1 to 0.5 cm beyond muscularis propria |
| T3c | Invasion > 0.5 to 1.5 cm beyond muscularis propria |
| T3d | Invasion > 1.5 cm beyond muscularis propria |
| T4 | Tumor penetrates visceral peritoneum or invades adjacent organs |
| T4a | Penetration into visceral peritoneum |
| T4b | Invasion into other organs or structures |
| **Regional Lymph Nodes** | |
| NX | Lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in one to three regional lymph nodes |
| N1a | Metastasis in one regional lymph nodes |
| N1b | Metastasis in two or three regional lymph nodes |
| N1c | Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis |
| N2 | Metastasis in four or more regional lymph nodes |
| N2a | Metastasis in four to six regional lymph nodes |
| N2b | Metastasis in seven or more regional lymph nodes |
| **Distant Metastasis** | |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Metastasis confined to one organ or site |
| M1b | Metastases in more than one organ/site or the peritoneum |

**Table 17-13** Colorectal Cancer Staging Systems

| American Joint Committee on Cancer (AJCC) Stage | | | | Astler-Coller Modification of Dukes Classification |
|---|---|---|---|---|
| | T | N | M | |
| I | T1 | N0 | M0 | A |
| | T2 | N0 | M0 | B1 |
| IIA | T3 | N0 | M0 | B2 |
| IIB | T4a | N0 | M0 | B2 |
| IIC | T4b | N0 | M0 | B3 |
| IIIA | T1-T2 | N1/N1c | M0 | C1 |
| | T1 | N2a | M0 | C1 |
| IIIB | T3, T4a | N1 (any) | M0 | C2 |
| | T2, T3 | N2a | M0 | C1/C2 |
| | T1, T2 | N2b | M0 | C1 |
| IIIC | T4a | N2a | M0 | C2 |
| | T3, T4a | N2b | M0 | C2 |
| | T4b | N1, N2 | M0 | C3 |
| IVA | Any T | Any N | M1a | D* |
| IVB | Any T | Any N | M1b | D* |

*Stages not included in original Dukes classification; added later for comparison with AJCC staging.

# Adenocarcinoma of the large intestine

- Increased levels of NK and CD8+ cells in right sided lesions.
- Increase in Homeobox transcription factor 1 in right sided lesions
- Increased number of mutations in right sided lesions
- Increase in Homeobox transcription factor 2  in left sided lesions

# Adenocarcinoma of the large intestine

- p53 and EFGR over-expression more common in left sided lesions (favorable sign).
- Those with left sided lesions with DNA mismatch repair mutations have better prognosis than those with right sided lesions and the same mutations in Stage II or III disease.
- RAS and BRAF mutations are associated with adverse outcome.

# Treatment strategy

- En block extirpation of the involved bowel segment along with mesentery as well as pericolic and intermediate lymphadenectomy is primary modality.
- No colostomy required.
- 5FU by infusion, oxaliplatin, and leucovorin (FOLFOX) is recommended adjuvant regimen following resection of stage III disease (colon).
- CAPOX (capecitabine with oxaliplatin) as alternative
- Survival advantage for those <70 years of age

# Treatment strategy

- FOLFOX preferred if RAS mutation and no multisatellite mutations.
- PD1 inhibitor preferred over chemotherapy if mismatch gene mutations
- 5FU plus panitumumab in ROS mutated, wild type BRAF disease
- Capecitabine maintenance therapy associated with better progression free survival
- Left primary with PI3K mutation, no PTEN loss, no EFGR inhibitor did best

# Treatment strategy

- Patients with loss of MMR (mismatch repair genes) do not benefit from 5FU.
- Benefit from check point inhibitors
- KRAS wild type lesion may respond to cetuximab (anti- EGFR).
- KRAS codon mutations 12 (40%), 13 (20%), or both (20%) associated with poor response to cetuximab.
- BRAF mutation testing if KRAS wt.
- Right sided EGFR+, KRAS- lesions respond to bevacizumab but not cetuximab
- Left sided EGFR+, KRAS- lesions respond to cetuximab as well as bevacizumab

# Treatment strategy

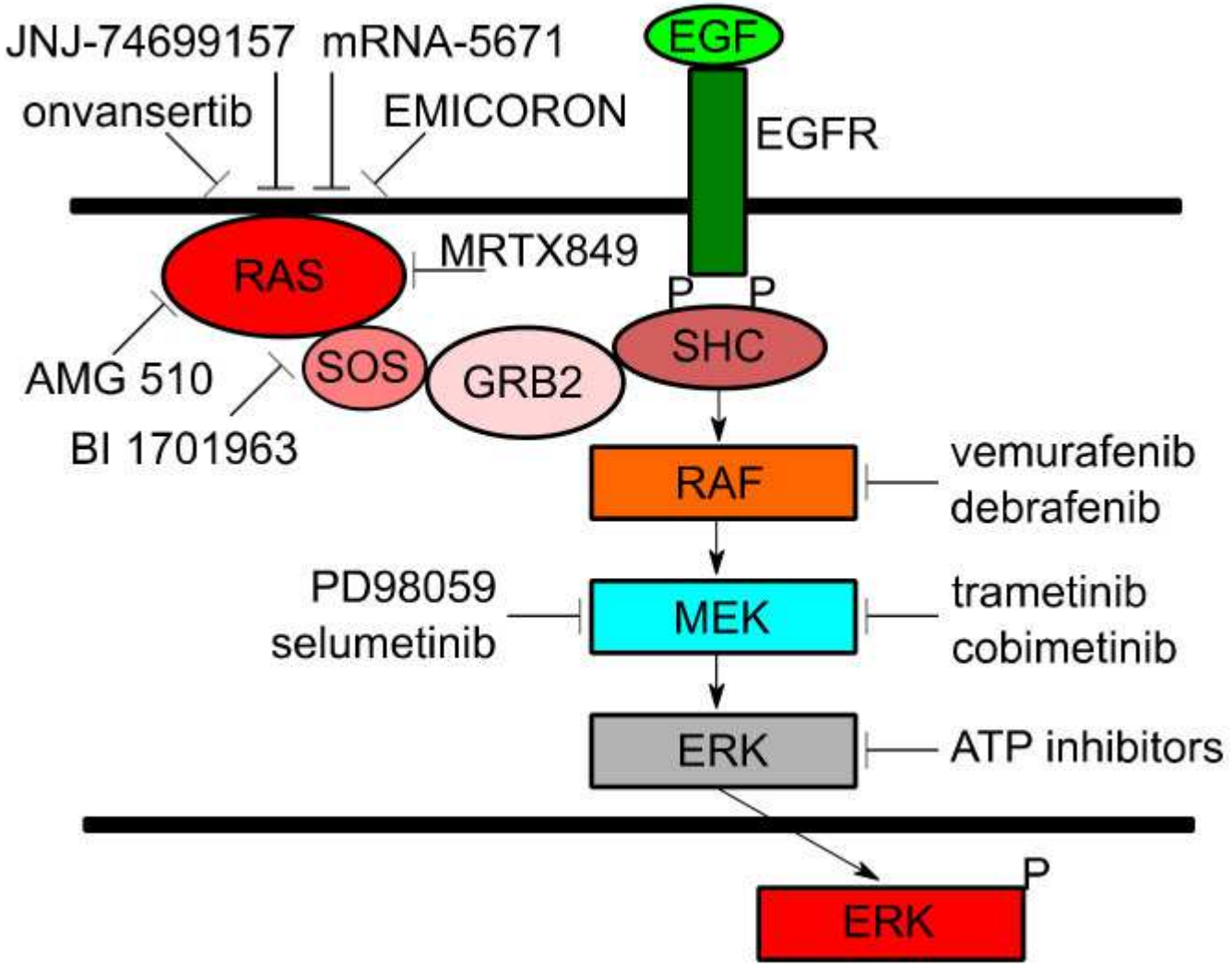
- RAS wild type lesion may respond to cetuximab (anti-EGFR).
- If HER2+, trastuzumab with tucatinib is an option
- KRAS codon mutations 12 (40%), 13 (20%), or both (20%) associated with poor response to cetuximab.
- KRAS G12C mutation associated with poor response to fluropyrimidines
- Common in tobacco use
- Sotorasib (AMG 510) binds to cysteine residue, holding protein in inactive form
- If fail first line therapy

# Treatment strategy

- Encrafenib  and cetuximab if BRAF and Notch mutations is another alternative
- Hypomagnesemia surrogate marker for cetuximab success.

# Treatment strategy

- Asymptomatic primary lesions with (synchronous) metastases may not require resection but solely treatment with chemotherapy (FOLFOX) and bevacizumab, an anti-VEGF agent
- Bleeding common.
- Better response if hypertension ensues.
- Median survival is 2 years.
- Not for use if surgery anticipated as is associated with increased risk of thrombosis.

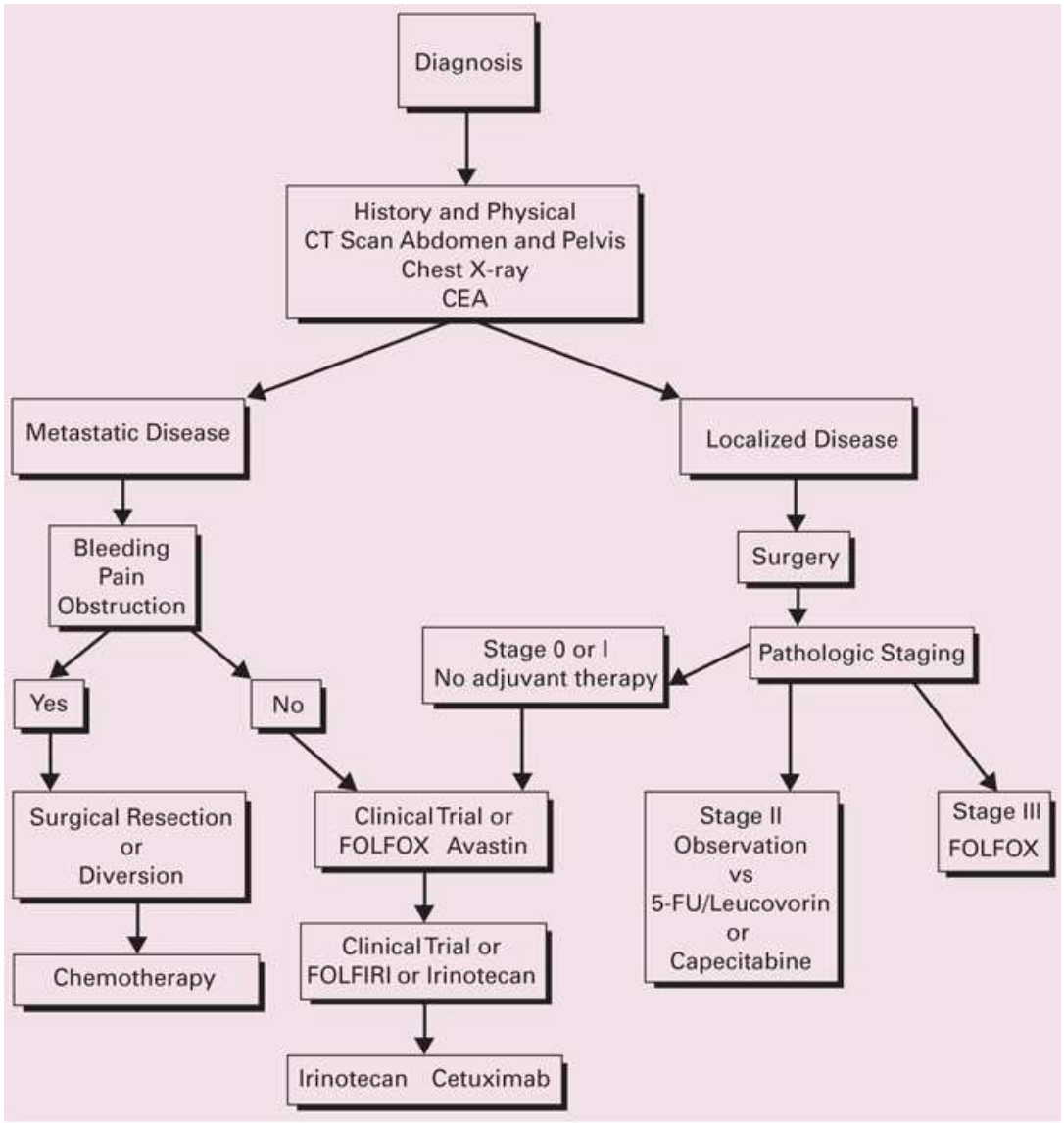



Mustachio LM, Chelariu-Raicu A, Szekvolgyi L, Roszik J. Targeting KRAS in Cancer: Promising Therapeutic Strategies. Cancers (Basel). 2021;13(6):1204. Fig. 1 Published 2021 Mar 10. doi:10.3390/cancers13061204

# Treatment strategy

- >20% of patients have metastases confined to the liver
- Resection, ablation, and embolization of feeding blood vessels as effective means of local control if metachronous metastases (develop sequentially)
- Isolated pulmonary or peritoneal metastases may be resected
- >40% of patients will survive 5 years

# Colon cancer

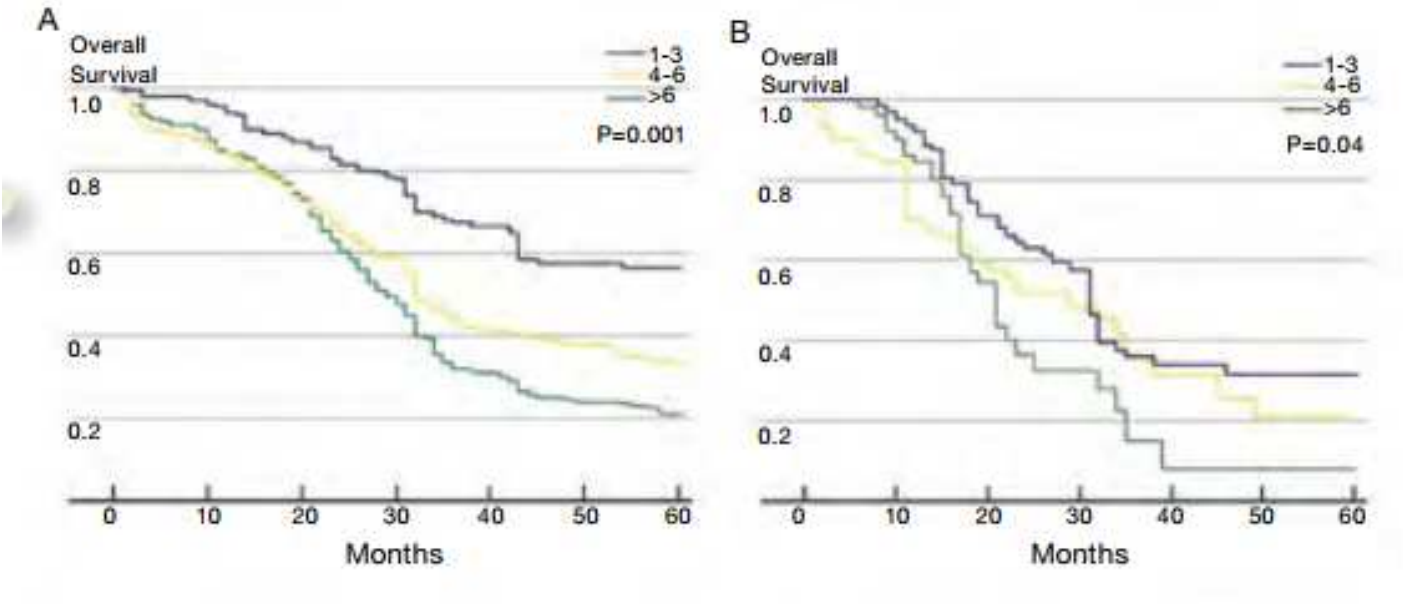



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



Fig. 16-4 Accessed 04/01/2010

A: Overall survival among patients with isolated colorectal liver metastases (CLM) stratified by the number of resected metastases. B: Overall survival among patients with CLM + extrahepatic disease stratified by the number of resected metastases



# 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

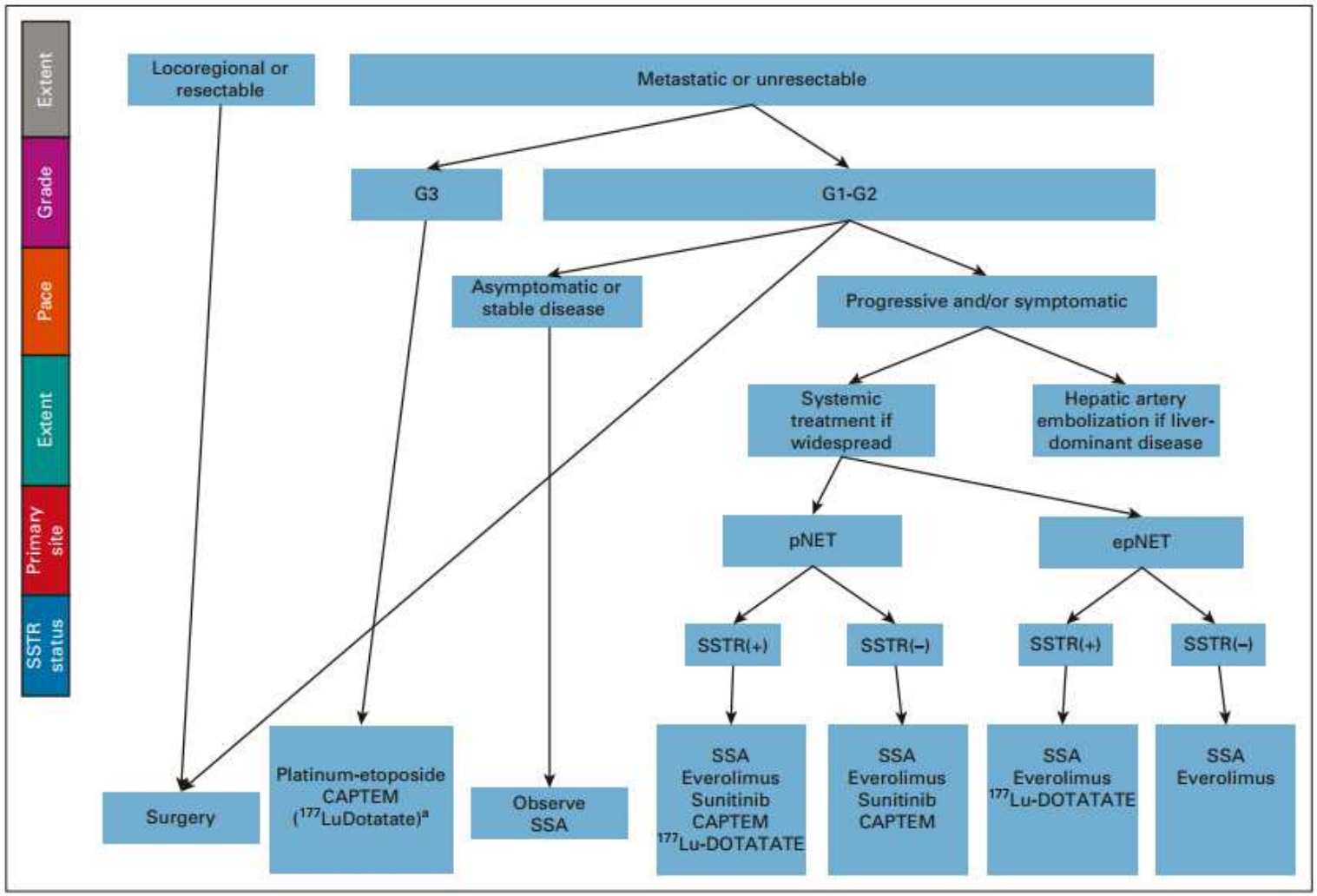



**FIG 1.** [a]For select cases. Schema for management of well-differentiated neuroendocrine tumors according to patient and tumor characteristics. CAPTEM, temozolomide plus capecitabine; epNET, extrapancreatic neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; SSA, somatostatin analog; SSTR,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

# Evaluating anti-EGFR therapy

- IHC staining for HER2 (3+)
- >5 positive cells adjacent to each other in biopsy
- >10% positive cells in resected specimen
- In breast, circumferential staining
- In gastric cancer, basolateral or parallel staining
- >50% cells 3+ staining
- FISH (if IHC 2+ staining)
- HER2/CEP >2.2
- If in 50% of metastatic colorectal cancer

# Evaluating anti-EGFR therapy

- If 2+ staining:
- First line therapy if not candidate for standard therapy in those with left sided colon lesion with KRAS exon 2 and ROS/RAF wild type
- If 3+ staining:
- Resistant to cetuximab in colorectal cancer
- Resistant to trastuzuman in gastroesophageal cancer
- Resistance to TKIs

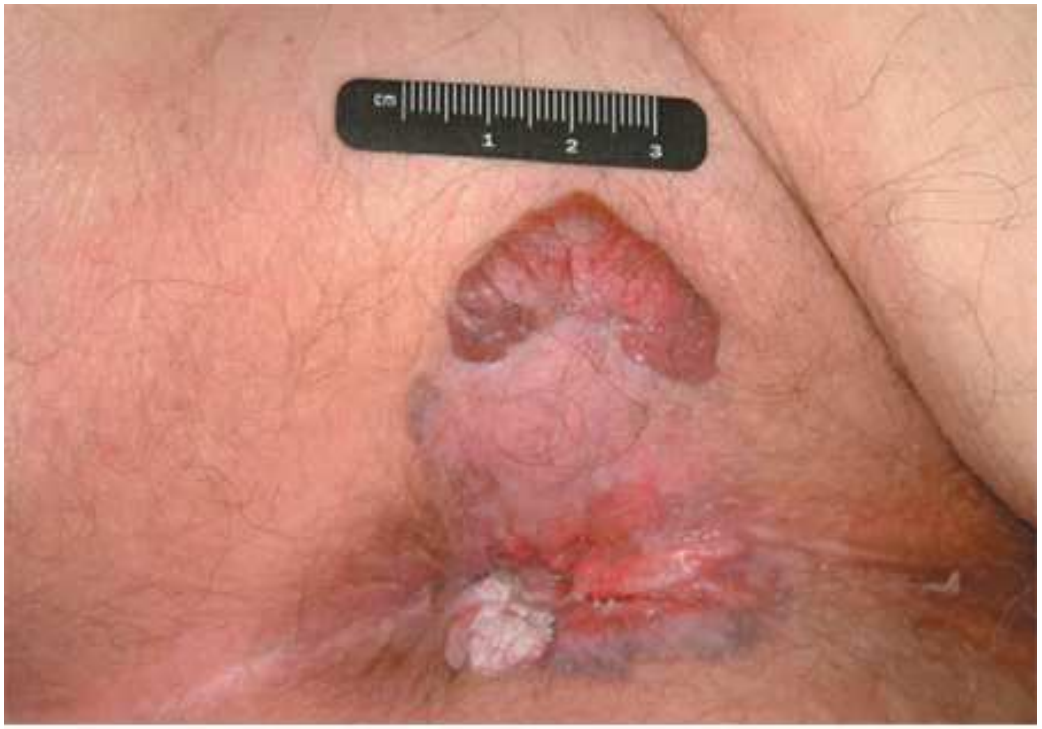
# Treatment strategy

- Asymptomatic primary lesions with metastases may not require resection but solely treatment with chemotherapy (FOLFOX) and bevacizumab, an anti-VEGF agent
- Bleeding common
- Better response if hypertension ensues
- Median survival is 2 years.
- Hypomagnesemia surrogate marker for cetuximab success.

# Ano-rectal carcinoma

- Diagnosis of rectal cancer is based on digital rectal examination and proctoscopy with biopsy.
- Tumors with distal extension ≤15 cm from the anal margin are classified as rectal.
- EUS is able to differentiate T1 and T2 tumors, selecting patients for local excision.
- MRI is the recommended technique for staging invasive cancer (≥T3).
- Local staging with CT can be an alternative to MRI in advanced tumors located in the mid-high rectum.

# Perianal mass

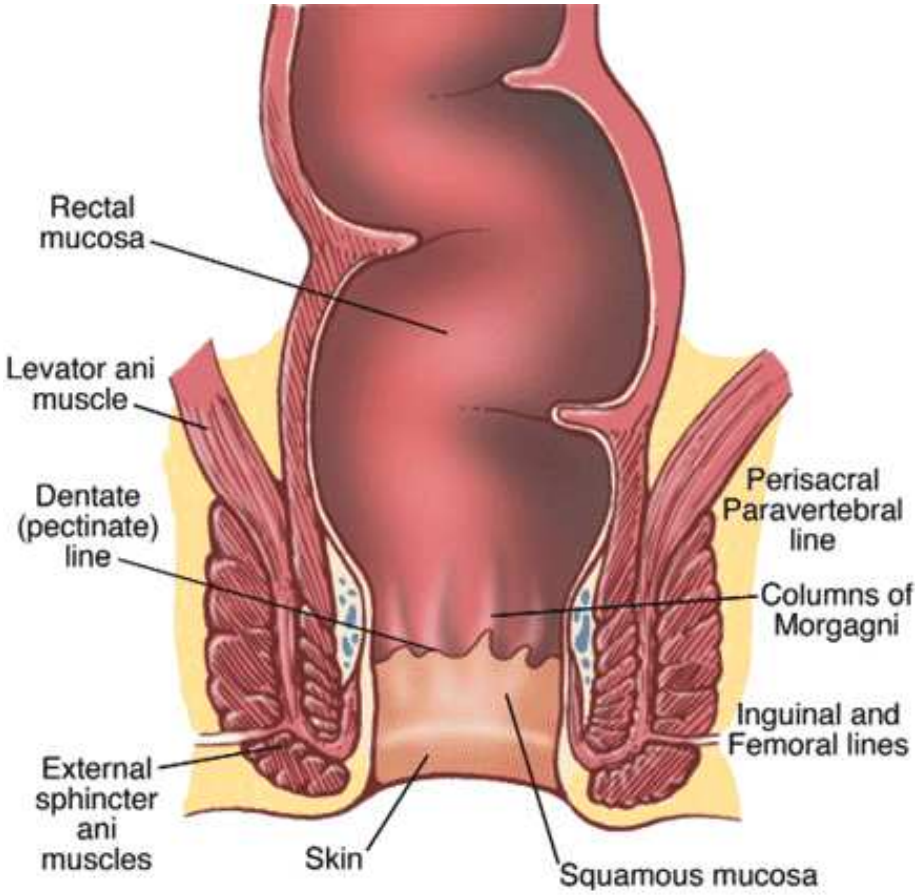



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



Fig.17-6 Accessed 04/01/2010

# Ano-rectal junction



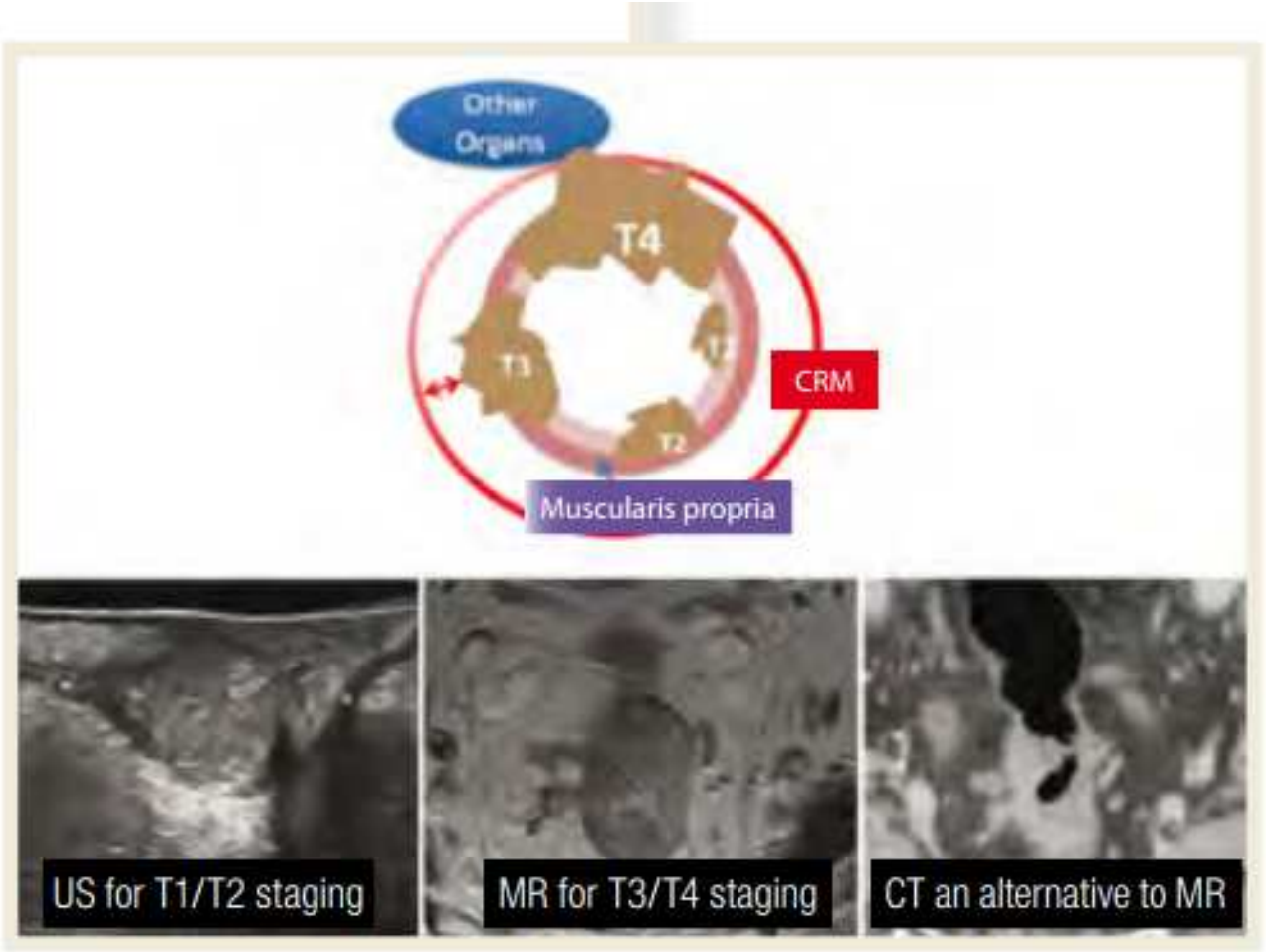

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



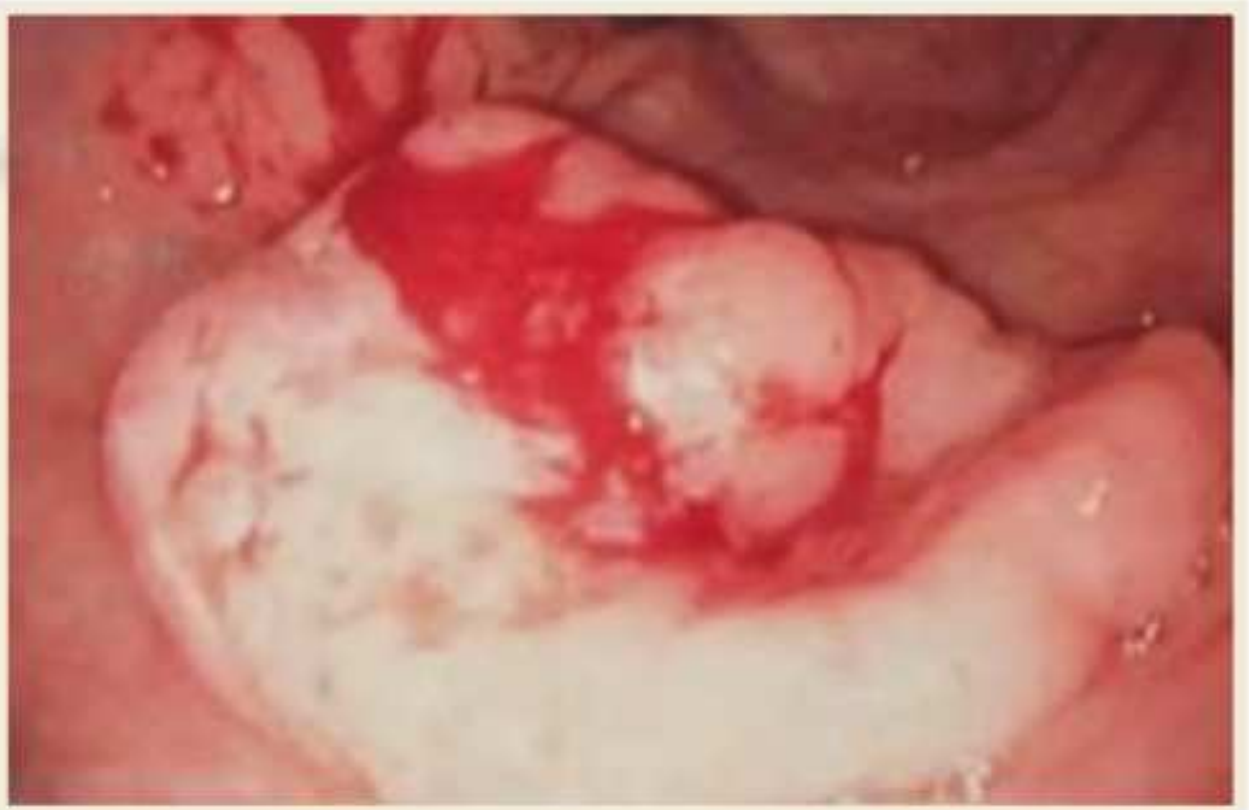
Fig. 17-1 Accessed 04/01/2010

# Ano-rectal carcinoma

- 4% of lower intestinal tract cancers.
- HPV infection often precedes.
- Bleeding and pain are most common symptoms.
- May be obstructing mass.
- Pruritis more commonly noted with perianal lesions
- Squamous carcinoma and basaloid (cloacogenic) carcinomas comprise more than 85% of tumors.
- Melanoma accounts for 4%.



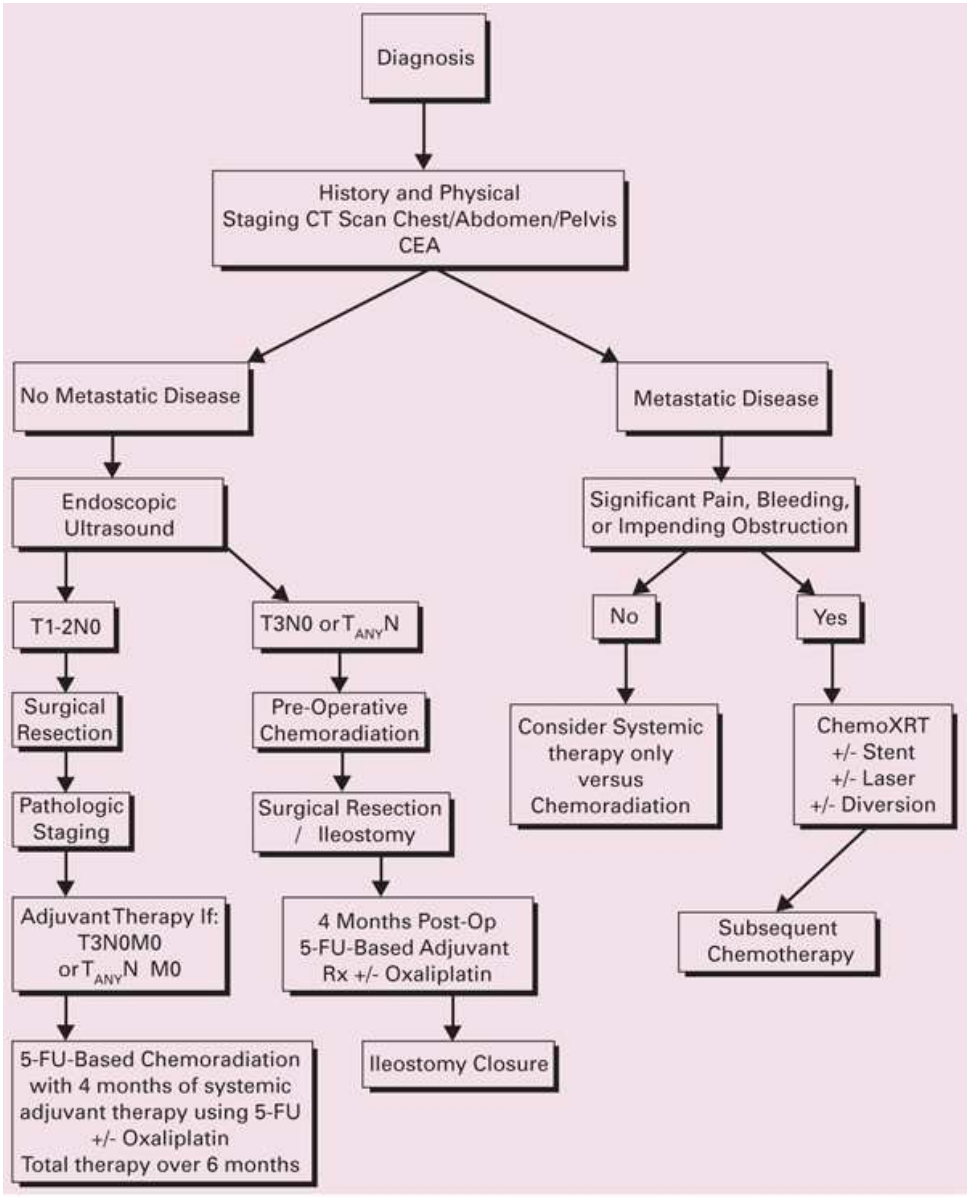

CRM, Circumferential resection margins; CT, computed tomography; MR, magnetic resonance; US, ultrasound.



# Treatment strategy

- 10-18% failure rate after curative resection (TME) for rectal cancer.
- MRI crucial in determining depth of invasion (>5mm has poor prognosis).
- Adjuvant chemotherapy with radiation therapy recommended for stage II and III disease.
- Avoid chemotherapy free intervals in metastatic disease.
- Daily low-dose aspirin (but not a COX-2 inhibitor) associated with improved survival in those with PIK3CA mutations and tumor expression of HLA I antigens.

# Rectal cancer




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



Fig. 16-5 Accessed 04/01/2010

# Anal canal carcinoma

- Carcinomas of the anal canal may have typical glandular or squamous patterns of differentiation, recapitulating the normal epithelium of the upper and lower thirds, respectively.
- An additional differentiation pattern, termed basaloid, is present in tumors populated by Immature cells
- All are considered variants of anal canal carcinoma
- Pure squamous cell carcinoma is associated with HPV

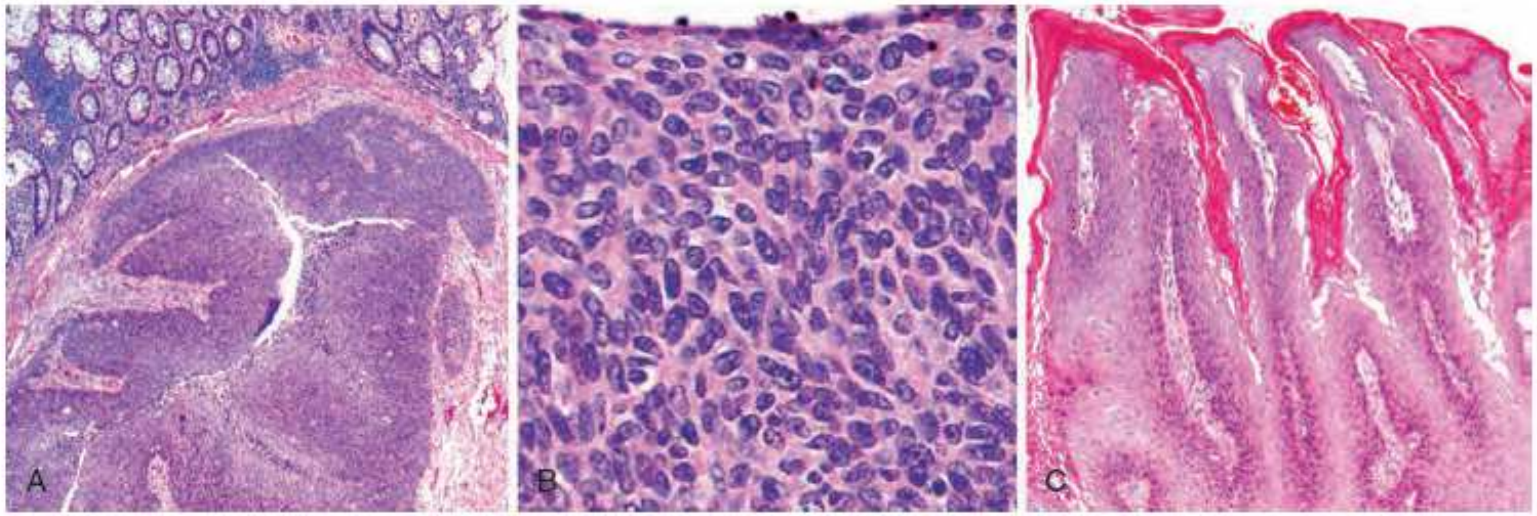



**Figure 17-54** Anal tumors. **A,** This anal transition zone carcinoma demonstrates a multilayered organization reminiscent of benign squamous mucosa. The adjacent rectal mucosa is intact. **B,** This basaloid anal transition zone tumor is composed of hyperchromatic cells that resemble the basal layer of normal squamous mucosa. **C,** Condyloma acuminatum with verrucous architecture.

# Non-keratinizing squamous carcinoma

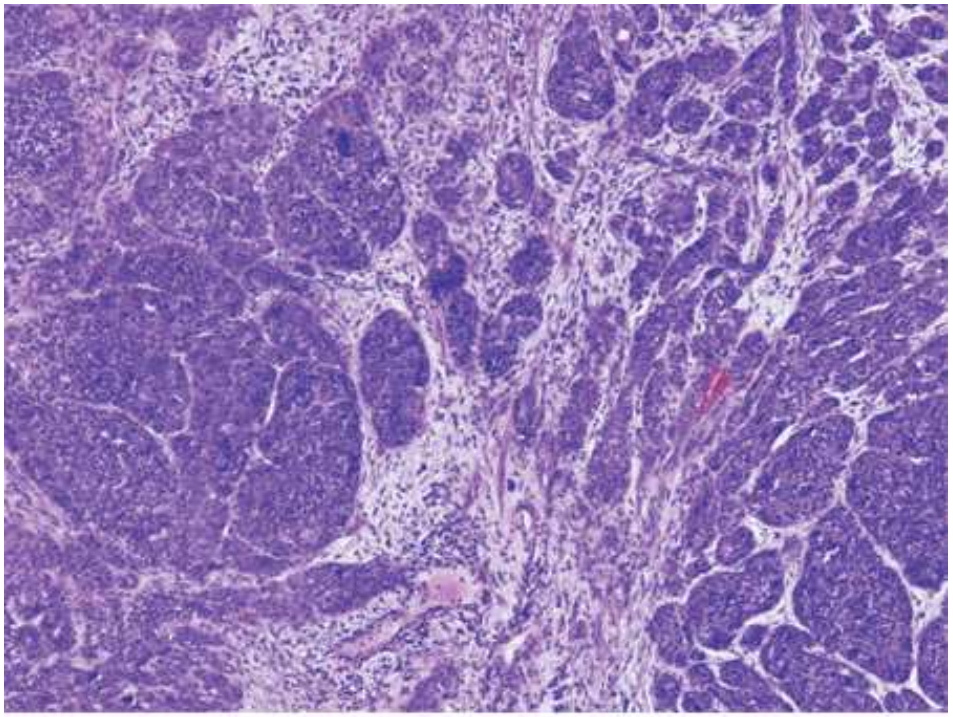




Fig. 17-2 Accessed 04/01/2010

# Keratinizing squamous carcinoma

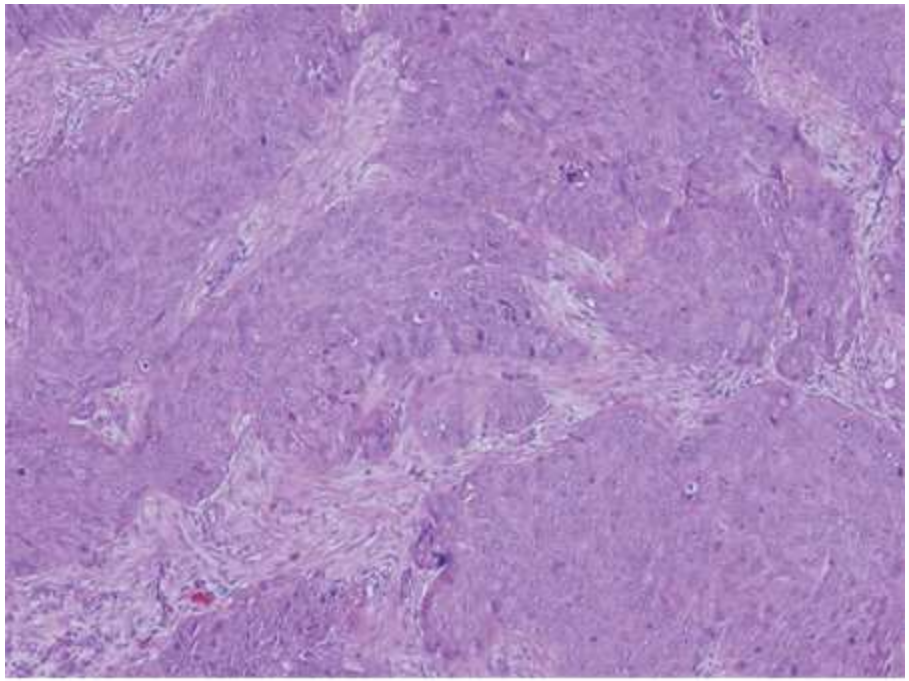
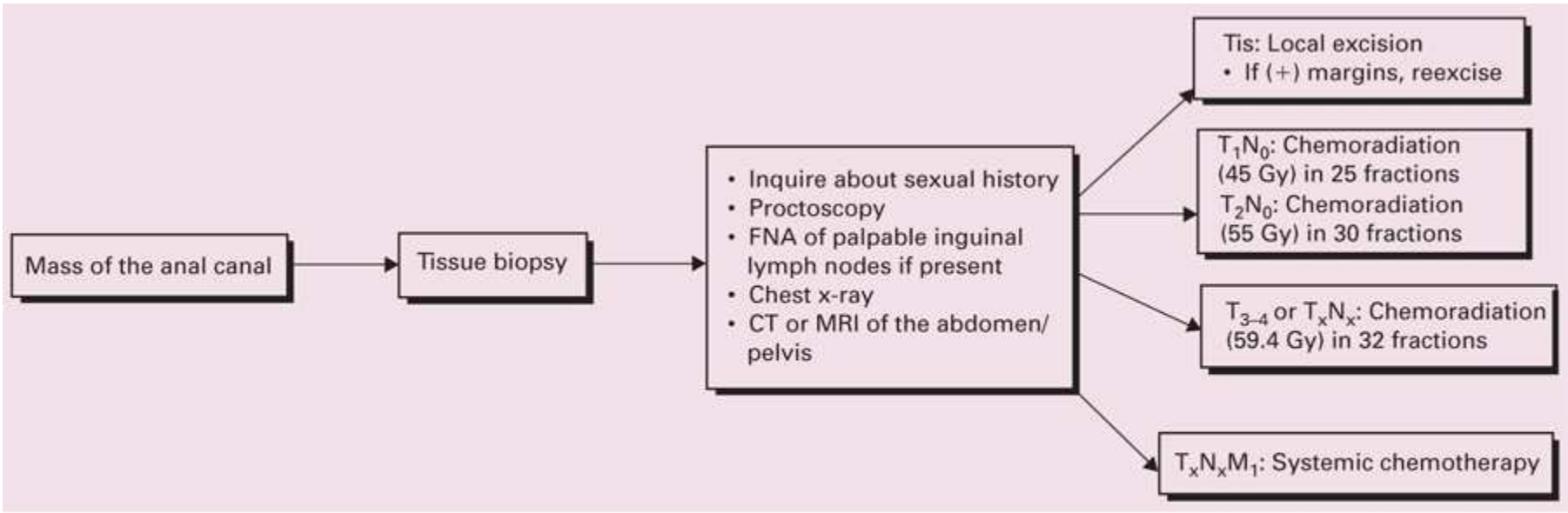




Fig. 17-4 Accessed 04/01/2010

# Anal cancer




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



Fig. 17-8 Accessed 04/01/2010

# Treatment of anal carcinoma

- Incisional biopsy preferred for diagnosis.
- Cancers of the anal margin (area distal to the anal canal) can be treated with wide local excision without need for colostomy.
- Cancers of the anal canal are first treated with radiation therapy combined with 5FU and mitomycin C or cisplatin chemotherapy.
- If clinical examination post treatment demonstrates residual tumor, total mesorectal excision is performed as a salvage procedure.
- Anal function is preserved.
- No colostomy.

# Treatment of anal carcinoma

- Inguinal lymph node metastases are poor prognostic sign.
- May require radiation boost.