

LARGE INTESTINE

Important site of infectious and neoplastic disease.

Main signs and symptoms are: diarrhea, blood (gross and occult), low abdominal pain.

Accessible to endoscopy, barium radiography, occult blood testing.

I. MALFORMATIONS

- A. Imperforate anus - relatively common; 1 per 5000 births.
- B. Hirschsprung disease (Megacolon): Congenital absence of ganglion cells in lower rectum leading to enormous dilatation of the proximal, normally innervated, colon. The affected area is of normal or narrowed diameter and generally from 3 to 40 cm long. Marked increase in size and number of nerves but no ganglion cells. Diagnosis by biopsy of the narrow segment. 1 per 20,000 births; males more than females; Severe constipation and episodic obstruction. It is unlike esophageal achalasia where the loss of neurons is in the proximal dilated segment.

II. INFECTIOUS DISEASES: Infection more frequent than in upper GI tract.

- A. Shigellosis: common cause of dysentery (bloody diarrhea); acute inflammation of mucosa with polys, edema and serpiginous ulcers; few lymphoid cells; glands with crypt abscesses are not abnormally arranged (as in chronic ulcerative colitis). These changes are seen in shigella, salmonella, Campylobacter and other bacillary dysenteries.
- B. Salmonellosis: a colitis; not systemic like typhoid fever.
- C. Gonorrhea: purulent mucosal exudate.
- D. Syphilis: chancre in anal canal; plasma cells and vascular thickening.
- E. Lymphogranuloma venereum: viral; acute inflammation followed by rectal scarring and stricture.
- F. Amebiasis: Entameba histolytica; cytolytic enzyme lets protozoa enter colon wall; degenerating polys release lysosomal enzymes. Produces ulcers which undermine mucosa; ameba found in biopsy or stool. Rarely perforates; can form a chronic fibrotic mass, ameboma in cecum or rectum; can spread to liver, amebic abscess.
Usually in tropics, sporadically elsewhere.
Can simulate chronic non-infectious colitis.
- G. Schistosomiasis: adult worms in mesenteric veins; eggs in colonic wall cause granulomatous reaction; can spread to liver and lung.
- H. Pseudomembranous colitis: focal mucosal necrosis with fibrinopurulent membrane

associated with previous antibiotic treatment; due to overgrowth of Clostridium difficile; ischemia may play a role due to vascular thrombi. Cytotoxin produced by intraluminal bacteria damages actin in junctions.

III. ULCERATIVE COLITIS: a chronic inflammatory non-infectious disorder of the mucosa of rectum and colon which is mainly exudative; not scarring. Rectum and left colon most affected; can affect whole colon; always in continuity. Peak onset 3rd decade.

A. Lesions, Grossly:

Shortened bowel due to muscle contraction
 Mucosa: hyperemic, friable, ulcers, no skip areas.
 Distal colon more damaged than proximal.
 Inflammatory polyps: focal enlargement of mucosa due to inflammatory cell infiltrate.
 Pseudopolyps: remnants of mucosa surrounded by ulcers giving a polypoid appearance.

B. Microscopically: congestion and edema of mucosa and submucosa
 Crypt abscesses conspicuous; burst, spread longitudinally beneath mucosa, cause ulcers.
 Goblet cells lose mucus. Inflammation may spill into submucosa but not deeper.
 Chronic inflammatory cells are numerous.

C. Fulminating colitis (toxic megacolon): greatly dilated, friable, thin bowel with transmural edema and inflammation.

D. Healed/quiescent colitis: Atrophic mucosa, irregularly distributed, distorted glands, occasional inflammatory polyps, no scars.

E. Ulcerative colitis Crohn colitis

Gross:	Continuous lesion	Skip areas
	Rectum always diseased	— Rectum normal in half the cases (at least microscopically)
	No deep fissures; no fistulas	— Deep fissures; fistulas
	Serosa normal	— Serosa inflamed
	Muscle shortened; no strictures	— Fibrosis; strictures
	No scars	— Scars
	Anal lesions uncommon	— Anal lesions in 75%
	Intensely vascular	Edematous
Micro:	Mucosa and submucosa inflamed	Transmural inflammation
	Normal or thin submucosa	Wide submucosa, edema, fibrosis

No granulomas	Non-necrotic granulomas in 60%
Dysplasia may occur	Dysplasia is rare
Mucus depletion in cells	_____ Mucus preservation

F. Cancer in ulcerative colitis

Patients with total or extensive colonic disease of over 10 years duration have increased risk of colon carcinoma. Surveillance by biopsy to detect dysplasia. Colectomy done if dysplasia is severe or associated with a mass. Crohn disease also has a cancer risk, but surveillance is not as easily performed, especially on small bowel lesions.

G. Crohn disease and ulcerative colitis: are both referred to as inflammatory bowel disease. Distinction is important because of management: surgery is good for UC, a last resort for Crohn.

IV. RADIATION INDUCED BOWEL LESIONS:

Acute injury: mucosal necrosis
 Chronic injury: scars, fistulas, adhesions, due to chronic ischemia from vascular damage.

V. DIVERTICULAR DISEASE

Common disease; 1/3 adults > 40 have diverticula; rare earlier.
 Diverticulum: outpouching of mucosa through circular muscularis propria.
 Usually in rows especially in sigmoid (never in rectum). Follows vascular tracts.
 Circular muscle between diverticula is thick with a corrugated appearance, causing mucosal folds. Longitudinal muscle, taenia coli, also thick; can cover diverticula.
 Diverticulosis: presence of diverticula

- A. Diverticulitis: inflammation of diverticula.
 Inspissated feces abrade mucosa, cause chronic inflammation; inflammation spreads into pericolic fat or peritoneum; pericolic abscess or peritonitis.
 Bleeding from eroded vessels.
 Fistula to bladder and other structures.
 Left colonic diverticular disease is associated with low roughage diet.
 Muscle deformity important; high intraluminal pressure causes outpouching.
- B. Diverticulosis of right colon is different from left side; possibly congenital.
 Diverticulosis of small intestine is congenital.
 Diverticulosis of appendix is due to inflammation with muscle destruction.

DIVERTICULAR DISEASE
Usual causes

Esophagus:	congenital, inflammatory
Stomach:	congenital; very rare
Small intestine:	_____ congenital
Appendix:	inflammatory
Colon:	_____ dietary
Rectum:	"never"

VI. VASCULAR DISEASE - ischemia and angiodysplasia (see small bowel).

VII. OTHERS

Colitis cystica profunda: cystic displaced mucosa in submucosa following ulceration especially in rectum.

Pneumatosis intestinalis: gas in intestinal lymphatics (more in small bowel)

Melanosis coli: melanin-like lipofuscin pigment in macrophages of the colonic mucosa; related to chronic use of anthracene laxatives (senna, cascara).

VIII. POLYPS OF THE LARGE INTESTINE

- A. A polyp is a localized lesion which projects from the mucosa into the lumen.
- B. Gross:
Pedunculated: on a stalk; pulled out by peristalsis; easily resected endoscopically
Sessile: broad-based; no stalk; difficult to resect
- C. Microscopic: Polyps are classified by their histologic features. They are divided into neoplasms and non-neoplastic lesions, then subdivided.
- D. Adenoma: Benign but precancerous neoplasm of glandular epithelium. Cellular atypia and disorderly glandular architecture = dysplasia (intraepithelial neoplasia); dysplasia is graded as low grade (mild, moderate) and high grade (severe, carcinoma in situ). Metastasis does not occur (in tumors of the large intestine) unless the submucosa is invaded.
- E. Subtypes of adenoma:
1. Tubular adenoma (adenomatous polyp): branching tubules are embedded in lamina propria;
 2. Villous adenoma: finger-like processes of lamina propria are covered by epithelium; and
 3. Tubulovillous adenoma: growth pattern intermediate between tubular and villous or with both tubular and villous patterns present. Adenomas with only minor admixtures are classified by the predominant pattern.

Villous have the highest and tubular the lowest risk of developing malignancy.

Other factors considered to be related to the precancerous nature of adenomas are size, number and degree of dysplasia.

Multiple gene alterations appear to parallel development of carcinoma from adenoma and correlate with histologic type, size and degree of dysplasia.

4. Adenoma-carcinoma sequence: carcinoma usually arises from an adenoma; supported by the association of adenomas and carcinomas in the same populations, patients, sites and lesions. Applies to large and small bowel.
5. Colorectal adenomas often multiple. Therefore, patients with adenoma or carcinoma should be followed to detect metachronous lesions. Patients with an adenoma (or carcinoma) in the distal bowel should have colonoscopy to detect synchronous lesions in the right colon. Colorectal

adenomas are relatively common: at least 25 % of those over age 50 (in the US) have these lesions.

6. Adenomatosis coli (familial adenomatous polyposis): numerous, i.e. over 100, adenomas in large intestine; 100% risk of cancer; familial.
- F. Tumor-like lesions: Non-neoplastic polyps are distinguished from adenomas by absence of dysplasia. They are not precancerous and therefore patients do not need the follow-up required for those with adenomas.
1. Hyperplastic polyp: a non-neoplastic lesion with lengthening of the epithelial tubules, generally less than 1 cm.
 2. Peutz-Jeghers polyp: a hamartoma, an abnormal mixture of normal tissues forming a tumor-like lesion; P-J polyp has branching bands of smooth muscle covered by abnormally arranged glands; more frequent in small bowel; either solitary polyp or a polyposis.
 3. Juvenile polyp: a hamartoma with glands and cysts embedded in excessive lamina propria.
 4. Benign lymphoid polyp: polyp due to reactive hyperplasia of lymphoid tissue; most frequent in rectum.
 5. Inflammatory polyp: nodular enlargement of the stroma due to inflammatory infiltrates; typical of inflammatory bowel disease.
- G. Among other rare forms of polyps are hamartomas containing malformed tissues such as ganglion cells (ganglioneuromas) or vessels.
- H. Components of a complete diagnosis: the topographic site of the lesion; its size; number; the gross type, viz. pedunculated or sessile; the histological type; and for adenomas, the degree of dysplasia.

IX. INTESTINAL POLYPOSIS SYNDROMES

- A. Familial adenomatous polyposis (FAP) [adenomatosis coli, familial polyposis coli]: over 100 adenomas. Duodenal adenomas and carcinomas also occur.
 - Gardner syndrome: adenomatosis plus mesenchymal lesions, eg mesenteric fibromatosis, jaw tumors.
 - Turcot syndrome: adenomatosis plus CNS tumors
- B. Peutz - Jeghers syndrome: autosomal-dominant hamartomatous polyposis due to germ line mutation. Children and young adults usually affected. P-J polyps (usually in small intestine) and mucocutaneous freckles; intussusception not uncommon. Elevated cancer risk: breast, pancreas, GI.
- C. Juvenile polyposis: rare autosomal-dominant hamartomatous polyposis; usually in children; elevated risk for digestive system cancers.

X. ADENOCARCINOMA OF LARGE INTESTINE

One of the most frequent forms of cancer; curable early.
Common in developed countries.
Associated with high fat, high protein, low fiber diets.
Migrant's risk increases in one generation.

Gut flora may play role.

Familial tendency for adenomas and carcinomas.

Most sporadic and inherited colon carcinomas appear to arise through one of two molecular genetic pathways:

1. Tumor suppressor pathway: chromosomal instability, mutations or deletions of tumor suppressor genes, especially the APC gene at chromosome 5q21. Occurs in most colorectal adenomas and carcinomas. Responsible for FAP as well as for most sporadic colorectal polyps and carcinomas.
2. Microsatellite mutator pathway: damage to DNA mismatch repair gene system, resulting in microsatellite instability. Responsible for hereditary non-polyposis colorectal carcinoma (HNPCC) and a minority (10%) of sporadic adenomas.

HNPCC is a relatively common autosomal-dominant inherited syndrome that predisposes to colorectal carcinoma. The tumors occur at an earlier age (40's) with right-sided predominance and have a better prognosis than those associated with the suppressor pathway. There is an elevated risk for cancers at other sites, e.g., endometrium, ovary, stomach, pancreas, brain. Germ line mutation testing used to identify those at risk.

A.	Risk of carcinoma	Incidence
Familial Adenomatous Polyposis	- 100%	1:10,000
Ulcerative colitis	- 5% (after 20yrs.)	
Familial colon cancer-	- 5-10	1:200
History of colon adenocarcinoma	- 5%	
Hereditary nonpolyposis colorectal cancer-HNPCC	- 80%	1:2000
Juvenile polyposis	- 50	1:100,000
Peutz-Jeghers syndrome	- 40	1:200,000

B.	Adenomas
50% in rectum	30%
25% in sigmoid	30%
25% proximal	40%

Shift to more right sided lesions is occurring now.

- C. **Macroscopic:**
 Most have raised periphery with central ulcer - saucer shape.
 Napkin-ring: concentric; leads to obstruction
 Protuberant: polypoid
 Mucinous (colloid): grossly visible mucus; >50% mucus
 Rarely goes beyond macroscopic border; unlike stomach
 Rarely diffusely spreading; unlike stomach

- D. **Microscopic:**
 90% moderately or well differentiated, uniform, small amounts of mucus
 10% poorly differentiated
 Differentiation related to prognosis

- E. **Stage** - extent of spread; best indicator of prognosis:

TNM - Dukes Classification:	5 yr survival
I - A - in wall; not beyond muscularis propria	95%

II -	B - in pericolic tissue	60%
III-	C - in lymph nodes (regional)	45%
	1 - 3 nodes	60%
	> 3 nodes	35%
IV	distant metastasis	3%

Regional nodes are pericolic, perirectal, and along vessels: surgery based on lymphatic drainage; rectal can go to inguinal nodes
 Peritoneal membrane resists penetration; 10% have peritoneal spread.
 Venous spread: tumor in extramural veins, bad prognosis.
 Implantation, especially at suture line
 Metastases: liver 75%, lungs 15% of metastatic cases
 Pelvic recurrence - in rectal tumors

F. Non-neoplastic Complications

Obstruction - common; not an early sign
 Perforation - uncommon; poor prognosis
 Bleeding - important early sign if occult; adenomas and other polyps bleed but less than do carcinomas.
 Hemorrhoids - from low rectal tumors
 Appendicitis - from cecal tumors

G. Colorectal vs Gastric carcinoma (in general)

well localized good increasing "good"	poorly differentiated diffuse spread poor prognosis decreasing incidence poor nutrition
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H. Cancer incidence/100,000 = Connecticut | 5-year survival

	male	female	(all stages-SEER data) %
Esophagus	6	2	<10
Stomach	13	8	<20
Small Intestine	1	1	<30
Colon	39	41	55
Rectum	21	16	50

Colon and Rectum carcinoma: TNM classification

- T1 Submucosa
- T2 Muscularis propria
- T3 Subserosa, non-peritonealized
- T4 pericolic/perirectal tissues
Other organs or structures/visceral peritoneum
- N1 3 regional
- N2 >3 regional

ANAL REGION

An important site of inflammation and bleeding.

Anal canal: 3.5 cm; over internal sphincter area

Mid-point is pectinate (dentate) line

Anal glands enter at pectinate line

Above line: internal hemorrhoidal plexus; rectal mucosa and in lower 1 cm junctional (transitional, cloacogenic) mucosa

Below line: external hemorrhoidal plexus; squamous mucosa

Anal margin: below lower border of internal sphincter; perianal skin

I. INFLAMMATION

- A. Anal fissure: A common lesion with a triangular ulcer in posterior midline of lower anal canal. Probably due to fecal trauma and chronic inflammation.
- B. Anal fistula: A common lesion with communication between the anal canal via the orifice of an infected anal gland with the anal margin skin (common) or rectum (rare). Due to infected anal glands. Abscesses in ischioanal space deep to muscle may occur.
- C. Crohn disease: a common site is anal canal (lymphoid tissue). Deep fissures; difficult to diagnose if without granulomas (half the cases).
- D. Ulcerative colitis: superficial fissures more common than deep fissures of Crohn.
- E. Syphilis: primary lesion can resemble fissures and Crohn disease. Secondary syphilis can produce condyloma latum (warty papule).
- F. Pilonidal sinus: A chronic inflammatory lesion with abscesses due to ingrown hair shafts in the intergluteal crease.

- II. **HEMORRHOIDS:** dilatation of veins of the internal or external hemorrhoidal plexus in the anal canal and margin. Hemorrhage, thrombosis, prolapse and infection occur. Bleeding is never catastrophic. Pain and itching main symptoms. Higher venous pressure as in pregnancy or from a nearby tumor.

Fibrous polyp: end result of thrombosed hemorrhoid.

Cirrhosis can produce rectal varices; more serious blood loss than from hemorrhoids.

~~III. **CONDYLOMA ACUMINATUM:** warty squamous cell papillomatous perianal growth due to papilloma virus (HPV). Benign but can recur and burrow deeply. Can lead to anal squamous cell carcinoma.~~

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IV. TUMORS

Anal canal: Squamous cell carcinoma arising from the cloacogenic epithelium (cloacogenic carcinoma) can have squamous, basaloid, transitional and glandular components; arises above dentate line and tends to grow up into rectum. Carcinomas arising from lower anal canal (about 1/4 of total) are more purely squamous. Rarely, carcinomas arise from anal glands and ducts.

Malignant melanoma: uncommon but very malignant.

Carcinoma may arise in anorectal fistulae: usually mucinous.

Anal margin: carcinomas are of skin type, mostly squamous cell carcinomas, and have better prognosis than those of the anal canal.

Anal Canal Carcinoma: TNM classification

- T1 2 cm
- T2 >2 to 5 cm
- T3 >5 cm
- T4 Adjacent organ(s)
- N1 Perirectal nodes
- N2 Unilateral internal iliac/inguinal
- N3 Perirectal and inguinal, bilateral internal iliac/inguinal

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