

## Small Intestine

### DEVELOPMENTAL ANOMALIES

#### **1. Atresia**

- Complete failure of development of the intestinal lumen.
- May affect any segment of the small intestine, but *duodenal atresia is the most common.*

#### **2. Stenosis**

- Narrowing of the intestinal lumen with incomplete obstruction.

#### **3. Duplication**

- It takes the form of well-formed saccular to tubular cystic structures.
- It may or may not communicate with the lumen of the small intestine.

#### **4. Meckel diverticulum**

- It is the most common and innocuous of the anomalies.
- It results from failure of involution of the omphalomesenteric duct leaving a persistent blind-ended tubular protrusion as long as 5 to 6 cm.
- The diameter is variable.
- Site : ileum, about 80cm proximal to the ileocecal valve.
- It is composed of all layers of the normal small intestine.



Picture: The blind pouch (arrow) is located on the antimesenteric side of the small bowel.

#### • Clinical presentation

- Asymptomatic
- Syndrome similar to pernicious anemia when bacterial overgrowth depletes vitamin B12.
- Pancreatic rests that may be found in a Meckel diverticulum can get inflamed.
- In about 50% of the cases there are heterotopic islands of functioning gastric mucosa.
- Peptic ulceration in the adjacent intestinal mucosa sometimes is responsible for mysterious intestinal bleeding or symptoms resembling acute appendicitis

#### **5. Omphalocele**

- Is a congenital defect of the periumbilical abdominal musculature that creates a membranous sac into which the intestines herniate.
- In *gastroschisis*, extrusion of the intestines is caused by lack of formation of a portion of the abdominal wall

## **6. Malrotation**

- It can prevent the developing bowel from assuming their normal intra-abdominal positions.
- The cecum may be found anywhere in the abdomen, including the left upper quadrant.
- The large intestine is predisposed to volvulus
- Confusing clinical syndromes may arise when appendicitis presents as left upper quadrant pain.

## **Megacolon**

- Distention of the colon to greater than 6 or 7 cm in diameter.
- It occurs as:
  - a) **congenital**
  - b) **acquired**

### **7. Hirschsprung Disease**

- **Congenital megacolon** results when the migration of neural crest-derived cells along the alimentary tract arrests at some point before reaching the anus.
- *Aganglionic* segment is formed that lacks both the Meissner submucosal and Auerbach myenteric plexuses.
- This causes functional obstruction and progressive distention of the colon proximal to the affected segment.
- Ganglia are absent from the muscle wall and submucosa of the constricted segment but may be present in the dilated portion.

### **Pathogenesis**

- ~50% of familial cases result from mutations in *RET* genes and RET ligands, because this signaling pathway is required for development of the myoenteric nerve plexus and provides direction to migrating neural crest cells.
- Mutations in *endothelin 3 and endothelin receptors*.

### **Incidence**

- It occurs in ~ 1 in 5000- 8000 live births.
- M:F ratio is 4:1.
- It is much more frequent in those with other congenital anomalies such as hydrocephalus, ventricular septal defect, and Meckel diverticulum.

### **Clinical Features**

- Delay in the initial passage of meconium
- Vomiting in 48-72 hours.
- When a very short distal segment of the rectum alone is involved, the obstruction may not be complete and may not produce manifestations until later in infancy, in the form of alternating periods of obstruction and passage of diarrheal stools.

### **Complications**

- 1-Superimposed enterocolitis with fluid and electrolyte disturbances.
- 2-Perforation of the distended colon usually in the thin-walled cecum.

**Diagnosis:** By documenting the **absence of ganglion** cells in the **nondistended bowel** segment.

### Acquired megacolon

- 1) Chagas disease, in which the trypanosomes directly invade the bowel wall to destroy the plexuses
- 2) Organic obstruction of the bowel by a neoplasm or inflammatory stricture
- 3) Toxic megacolon complicating ulcerative colitis or Crohn disease
- 4) Functional psychosomatic disorder.

### Celiac disease

- Affects 1 in 300 persons both in Europe and in the United States.
- The basic disorder in celiac disease is immunological sensitivity to gluten, the component of wheat and related grains (oat, barley, and rye) that contains the water-insoluble protein gliadin.
- Gliadin peptides are efficiently presented by antigen-presenting cells in the lamina propria of the small intestine to CD4+ T cells, thereby driving an immune response to gluten.
- 95% of patients having an HLA-DQ2 haplotype and most of the remainder having HLA-DQ8.
- Early exposure of the immature immune system of the infant to high levels of gliadin is a prominent cofactor for manifestation of clinically overt celiac disease later in life.
- The effect of the immune response may be total flattening of mucosal villi (loss of surface area), affecting the proximal more than the distal small intestine.
- Lymphocytes and other inflammatory cells accumulate in the lamina propria.
- The age of presentation with symptomatic diarrhea and malnutrition varies from infancy to mid-adulthood
- Removal of gluten from the diet is met with dramatic improvement.
- There is a low long-term risk of malignant disease, with about a 2X increase over the usual rate.
- Intestinal lymphomas, especially T-cell lymphomas and other malignancies including GIT and breast carcinomas.
- In some patients with celiac disease there is an associated skin disorder called dermatitis herpetiformis.

## **Ischemic Bowel Disease**

- 1) Transmural infarction is caused by acute occlusion of a major mesenteric artery.
- 2) Mural or mucosal infarction results from either physiologic hypoperfusion or more localized anatomic defects.
  - Acute or chronic.
  - Mesenteric venous thrombosis is a less frequent cause of vascular compromise.

## **Predisposing factors**

### **1. Arterial thrombosis:**

- a. *Severe atherosclerosis* (usually at the origin of the mesenteric vessel)
- b. *Systemic vasculitis*
- c. *Dissecting aneurysm*
- d. *Angiographic procedures*
- e. *Aortic reconstructive surgery*
- f. *Surgical accidents*
- g. *Hypercoagulable states*
- h. *Oral contraceptives*

### **2. Arterial embolism:**

- a. *Cardiac vegetations* (as with endocarditis, or myocardial infarction with mural thrombosis)
- b. *Angiographic procedures*
- c. *Aortic atheroembolism*

### **3. Venous thrombosis:**

- a. *Hypercoagulable states induced by oral contraceptives or antithrombin III deficiency*
- b. *Intraperitoneal sepsis*
- c. *The postoperative state*
- d. *Vascular-invasive neoplasms(HCC) e- cirrhosis*
- e. *Abdominal trauma*

### **4. Nonocclusive ischemia:**

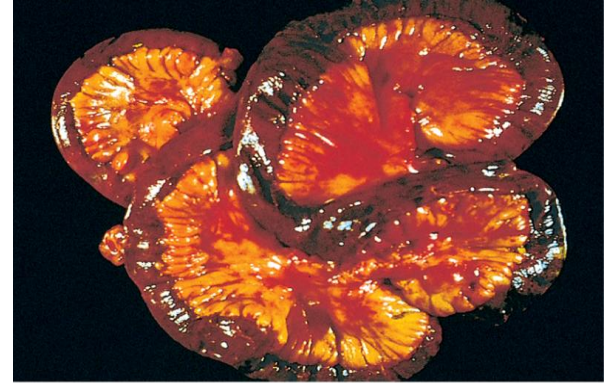
- a. *Cardiac failure*
- b. *Shock*
- c. *Dehydration*
- d. *Vasoconstrictive drugs* (e.g., digitalis, vasopressin, propranolol)

### **5. Miscellaneous:**

- a. *Radiation injury*
- b. *Volvulus*
- c. *Stricture*
- d. *Internal or external herniation*

### **Clinical Features**

- Ischemic bowel injury is most common in elderly.
  - With the transmural lesions, there is the sudden onset of abdominal pain, often out of proportion to the physical signs.
  - Bloody diarrhea.
  - The onset of pain tends to be more sudden with mesenteric embolism than with arterial or venous thrombosis.
  - It may progress to shock and vascular collapse within hours.
- 
- Picture: Infarcted small bowel, secondary to acute thrombotic occlusion of the superior mesenteric artery.



## **Angiodysplasia**

- Tortuous dilations of submucosal and mucosal blood vessels are seen most often in the cecum or Rt colon.
- It occurs after the 6<sup>th</sup> decade of life.
- *It account for 20% of significant lower intestinal bleeding.*
- The hemorrhage may be chronic and intermittent and only cause severe anemia, but rarely it is acute and massive.
- It can be part of a systemic disorder such as hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) or limited scleroderma, sometimes called the CREST syndrome (C<sup>alcinosis</sup>, R<sup>aynaud's</sup> phenomenon, E<sup>sophageal</sup> dysfunction, S<sup>clerodactyly</sup>, T<sup>elangiectasia</sup>).
- Isolated lesions thought to develop over decades as the result of mechanical influences operative in the colonic wall.
- As penetrating veins pass through the muscularis they are subject to intermittent occlusion during peristaltic contractions producing venous distention and ectasia.

## **Hemorrhoids**

- Hemorrhoids are variceal dilations of the anal and perianal submucosal venous plexuses.
- They are common after age 50 and develop in the setting of persistently elevated venous pressure within the hemorrhoidal plexus.

### **Common predisposing conditions are:**

1. Straining at stool in the setting of chronic constipation.
2. Pregnancy in younger women.
3. Cirrhosis and portal hypertension.

### **Types of hemorrhoids**

#### **A) Internal hemorrhoids**

- Varicosities in the superior and middle hemorrhoidal veins
- Appear above the anorectal line and are covered by rectal mucosa.

#### **B) External hemorrhoids**

- Dilations of the inferior hemorrhoidal plexus
- Appear below the anorectal line and are covered by anal mucosa.

### **Complications:**

- 1- Bleeding
- 2- Thrombosis
- 3- Prolapse of internal hemorrhoids during straining at stool may cause entrapment by the compressive anal sphincter leading to sudden extremely painful edematous hemorrhagic enlargement or strangulation.

## **COLONIC DIVERTICULOSIS**

***A diverticulum is a blind pouch that communicates with the lumen of the gut.***

### **Types:**

#### **1) Congenital Diverticula**

- Have all three layers of the bowel wall (mucosa, submucosa, and the muscularis propria).
- The prototype is *Meckel diverticulum*.

#### **2) Acquired**

- Herniation of mucosa & submucosa through muscularis and lack or have an attenuated muscularis propria.
- *May occur anywhere in the alimentary tract.*
- *The most common location is the colon.*
- The colon is unique in that the outer longitudinal muscle coat is not complete but is gathered into three equidistant bands (the taeniae coli).
- Focal defects in the muscle wall are created where nerves and arterial vasa recta penetrate the inner circular muscle coat alongside the taeniae.
- The connective tissue sheaths accompanying these penetrating vessels provide potential sites for herniations.

### **Pathogenesis**

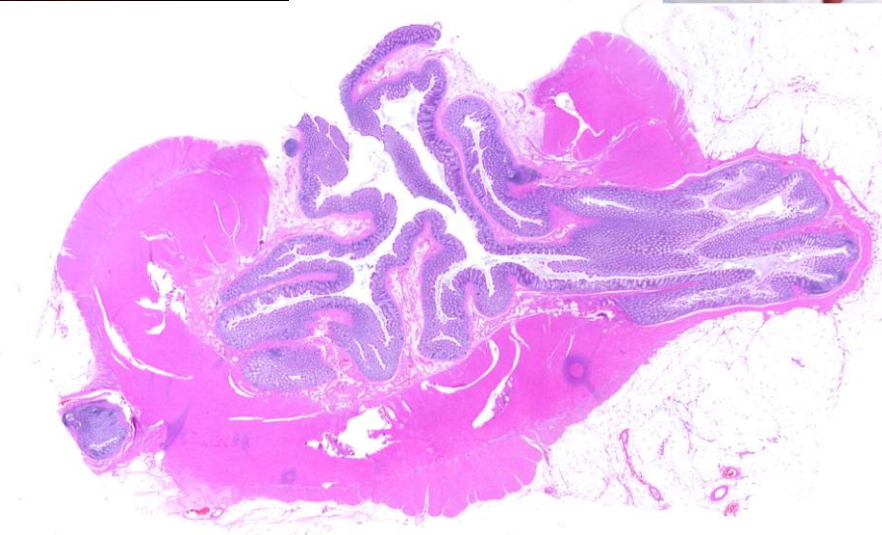
- Colonic diverticulosis is relatively infrequent in native populations of non-Western countries.
- In older age (> 60 yrs) the prevalence approaches 50%.
- This high prevalence is attributed to the consumption of a refined, low-fiber diet in Western societies, resulting in reduced stool bulk with increased difficulty in passage of intestinal contents.

### **Important factors in the genesis of diverticular protrusions:**

- a. *Exaggerated peristaltic contractions* with abnormal elevation of intraluminal pressure.
  - b. *Focal defects* peculiar to the normal muscular colonic wall.
- Sigmoid colon is involved in approximately 95% of patients.
  - Isolated cecal diverticula also occur.
  - The exaggerated peristalsis often induces muscular hypertrophy in affected segments with unusually prominent taenia coli and circular muscle bundles.



- **Pictures: Diverticulosis**



### **Complications**

- Inflammation (diverticulitis and peridiverticulitis)
- Perforation may lead to localized peritonitis or abscess formation.
- Fibrosis of bowel wall narrowing of the lumen producing a stricture.

### **Clinical Features**

- Asymptomatic and is discovered only at autopsy or by chance during a laparoscopy or barium enema for some other problem.
- Intermittent cramping or sometimes continuous left-sided lower quadrant discomfort in 20% of the cases.
- Sensation of never being able to completely empty the rectum.
- Left lower quadrant tenderness and fever.
- Minimal chronic intermittent bleeding or, rarely, brisk hemorrhage
- Perforation with pericolic abscess.
- Fistula formation.

## **INFLAMMATORY BOWEL DISEASE**

- Relapsing inflammatory disorders of unknown origin, collectively known as idiopathic inflammatory bowel disease (IBD), which share many common features.
- *They result from an abnormal local immune response against the normal flora of the gut, and probably against some self antigens, in genetically susceptible individuals.*

### **Etiology and Pathogenesis**

- The normal intestine is in a steady state of "physiologic" inflammation, representing a dynamic balance between:
  - i. Factors that activate the host immune system, such as luminal microbes, dietary antigens, and endogenous inflammatory stimuli;
  - ii. Host defenses that down-regulate inflammation and maintain the integrity of the mucosa.

### **The pathogenesis of IBD involves:**

1. Genetic susceptibility
2. Failure of immune regulation
3. Triggering by microbial flora

### **1) Genetic Predisposition**

- Genetic factors are important in the occurrence of IBD.
- First-degree relatives are 3-20 times more likely to develop the disease.
- 15% of persons with IBD have affected first-degree relatives.
- Ulcerative colitis has been associated with *HLA-DRB1*.
- ~ 30% of Crohn disease cases in North American white males are associated with *HLA-DR7* and *DQ4* alleles.
- A gene called *NOD2* (or *CARD15*) is mutated in as many as 25% of Crohn disease patients in some ethnic populations.
- The *NOD2* protein is an intracellular receptor for muramyl dipeptide, a component of the cell walls of many bacteria and is thought to play a role in host responses to these bacteria.
- The protein is expressed in Paneth cells.
- The disease-associated mutant form may be defective in responding to the bacteria thus allowing chronic infections to be established in the intestine and promoting inflammatory reactions by *NOD2*-independent pathways.
- The disease-associated form of *NOD2* may promote excessive host responses to intestinal bacteria.
- Mutation of the *IL-23 receptor (IL-23R)* gene in Crohn's disease and UC.
- *IL-23* is a cytokine that promotes the production of *IL-17* by T cells.

## 2) Immunologic Factors

- It is not known whether the immune responses in IBD are directed against self-antigens of the intestinal epithelium or to bacterial antigens.
- In both Crohn disease and ulcerative colitis the primary damaging agents appear to be CD4+ cells.
- Antineutrophil cytoplasmic antibodies (ANCA) and antitropomyosin antibodies detected in persons with ulcerative colitis do not seem to play a pathogenetic role.
- It has long been thought that Crohn disease is the result of a chronic delayed-type hypersensitivity reaction induced by IF $\gamma$ -producing TH1 cells.
- Inflammation may be the result of secretion of the cytokine IL-17 by a subset of CD4+ T-cells called the "TH17" subset.
- The inflammatory cytokine TNF may play an important pathogenic role in Crohn disease.

## 3) Microbial Factors

- The sites affected by IBD-the distal ileum and the colon-are a wash of bacteria.
- Microbes provide the antigenic trigger to a fundamentally dysregulated immune system.
- IBD develops in the presence of normal gut flora but not in germ-free mice.
  - **Inflammation** is the final common pathway for the pathogenesis of IBD.
- Both the clinical manifestations and the morphologic changes of IBD are ultimately the result of activation of inflammatory cells-neutrophils initially and mononuclear cells later in the course.
- The products of these inflammatory cells cause nonspecific tissue injury.
- Inflammation causes:
  - a. Impaired integrity of the mucosal epithelial barrier.
  - b. Loss of surface epithelial cell absorptive function.
- The inflammation ultimately causes outright mucosal destruction which leads to obvious loss of mucosal barrier and absorptive function.
- The most useful diagnostic tests is the detection of *perinuclear antineutrophil cytoplasmic antibodies(PANCA)* which are present in about 75% of persons with ulcerative colitis and 11% of individuals with Crohn disease.

## Crohn Disease

- This disease may affect any level of the alimentary tract, from mouth to anus, but most commonly located at the terminal ileum.
- The disease was thought to be limited to the ileum, and it was referred to as "terminal ileitis" or "regional enteritis."
- **Crohn disease is systemic inflammatory disease with predominant gastrointestinal involvement.**
- Active cases of the disease are often accompanied by *extra-intestinal complications* of immune origin, such as uveitis, sacroiliitis, migratory polyarthritis, erythema nodosum, bile duct inflammatory disorders, and obstructive uropathy with attendant nephrolithiasis.

### Crohn disease is characterized by:

1. Sharply limited transmural involvement of the bowel by an inflammatory process with mucosal damage.
2. Presence of noncaseating granulomas.
3. Fistula formation.

### Epidemiology

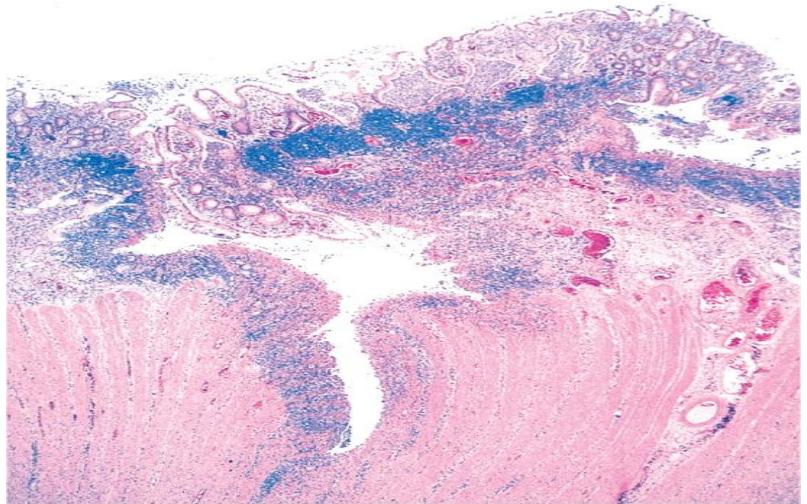
- Crohn disease is much more prevalent in the United States, Great Britain, and Scandinavia than in Central Europe
  - Rare in Asia and Africa.
  - The annual incidence in the United States is 3-5/100,000 population, which is slightly less frequent than the incidence of ulcerative colitis.
  - It occurs at any age.
  - The peak incidence is between the *2<sup>nd</sup> second and 3rd decades* of life, with a minor peak in the 6<sup>th</sup> and 7<sup>th</sup> decades.
  - F>M
  - Whites appear to develop the disease 2-5X more often than do nonwhites.
  - Crohn disease occurs 3-5 X more often among Jews than among non-Jews.
- 
- In Crohn disease there is gross involvement of the small intestine alone in about 30% of cases
  - Small intestine and colon in 40%
  - Colon alone in about 30%.
  - Crohn disease may involve the duodenum, stomach, esophagus, and even mouth, but these sites are distinctly uncommon.

### When fully developed, Crohn disease is characterized by:

- Transmural involvement of the bowel by an inflammatory process with mucosal damage.
- The presence of noncaseating granulomas in 40% to 60% of cases.
- Fissuring with formation of fistulae.

### **Morphological characteristics**

- a. *Creeping fat* the mesenteric fat wraps around the bowel surface
- b. The intestinal wall is *rubbery and thick*, the result of edema, inflammation, fibrosis, and hypertrophy of the muscularis propria.
- c. *String sign* on radiology
- d. *Strictures* may occur in the colon but are usually less severe.
- e. *Skip lesions* sharp demarcation of diseased bowel segments from adjacent uninvolved bowel.
- f. *Aphthous ulcer* - serpentine linear ulcers
- g. *Cobblestone appearance*
- h. *Fissuring ulcerations*
- i. *Adhesions* with adjacent loops of bowel
- j. *Fistula or sinus* tract formation
- k. *Transmural inflammation* with crypt abscesses
- l. *Chronic mucosal damage* in the form of architectural distortion, atrophy, and metaplasia (including rudimentary gastric metaplasia in the intestine)
- m. *Granulomas* may be present anywhere in the alimentary tract, even in individuals with Crohn disease limited to one bowel segment



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### **• Picture: Fissuring ulcerations**

### **Clinical Features**

- The dominant manifestations are recurrent episodes of diarrhea, crampy abdominal pain, and fever lasting days to weeks.
- Insidious onset but in some instances, particularly in young persons the pain is so abrupt and the diarrhea so mild that abdominal exploration is performed with a diagnosis of appendicitis.
- Melena is present in about 50% of cases with colon involvement (mild- massive).
- In 10-20% of persons with Crohn disease the symptom-free interval after the initial attack may last for decades and for a very fortunate few the first attack is the last.
- About 20% of patients experience continuously active disease following their diagnosis.

### Complications

- *Fistula* formation to other loops of bowel, the urinary bladder, vagina, or perianal skin.
- *Abdominal abscesses* or peritonitis.
- *Intestinal stricture* or obstruction.
- Massive intestinal bleeding.
- Toxic dilation of the colon.
- Carcinoma of the colon or small intestine.

- **Summary:**

<u><i>Crohn Disease (Small intestine)</i></u>	<u><i>Crohn Disease (colon)</i></u>	<u><i>Ulcerative Colitis</i></u>
Ileum ± colon	Ileum ± colon	Colon only
Skip lesions	Skip lesions	Diffuse
Stricture +	Stricture +/-	Rare
Thickened Wall +	+/-	Thin
No Dilation	Yes	Yes (toxic megacolon)
-	Pseudopolyps	Pseudopolyps
Deep linear Ulcers	Deep linear Ulcers	Superficial ulcers
Marked Fibrosis	Moderate fibrosis	Mild fibrosis
Granulomas (40-60%)	Granulomas (40-60%)	NO
Fistulas/sinuses	Fistulas/sinuses	NO



## Ulcerative Colitis

- Ulceroinflammatory disease affecting the colon.
- Limited to the mucosa and submucosa except in the most severe cases.
- Ulcerative colitis begins in the rectum and extends proximally in a continuous fashion sometimes involving the entire colon.
- Ulcerative colitis is a systemic disorder associated in some persons with migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, erythema nodosum, and hepatic involvement (pericholangitis and primary sclerosing cholangitis).

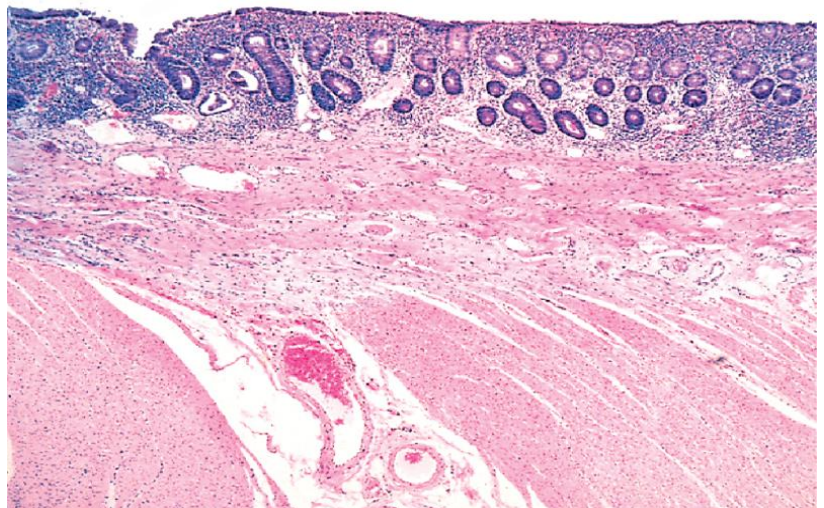
### Ulcerative colitis is characterized by:

- a. Absent well-formed granulomas
- b. No skip lesions
- c. Superficial mucosal ulcers
- d. Mild fibrosis
- e. No Mural thickening
- f. Normal serosal surface
- g. High risk of carcinoma development

### Epidemiology

- Ulcerative colitis is somewhat more common than Crohn disease in the United States and Western countries.
  - The incidence of around 7/100,000 population.
  - It is infrequent in Asia, Africa, and South America.
  - Whites > nonwhites
  - M=F
  - Peak incidence between ages 20 -25 years.
- 
- Ulcerative colitis has a familial association in about 20% of cases.
  - Individuals with ulcerative colitis and ankylosing spondylitis have an increased frequency of the *HLA-B27* allele, but this association is related to the spondylitis and not to ulcerative colitis.

- **Picture: Ulcerative colitis.**  
Marked chronic inflammation of the mucosa with atrophy of colonic glands, moderate submucosal fibrosis, and a normal muscle wall.







### **Clinical Features**

- Ulcerative colitis is a chronic relapsing disorder.
  - 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.
  - Presentation is usually insidious, with cramps, tenesmus, and colicky lower abdominal pain that is relieved by defecation.
  - Fever and weight loss.
- 
- In ~10% the first attack is the last.
  - Extra-intestinal manifestations, particularly migratory polyarthritis, are more common with ulcerative colitis than with Crohn disease.

### **Complications include:**

- Severe diarrhea and electrolyte derangements
- Massive hemorrhage
- Severe colonic dilation (toxic megacolon) with potential rupture
- Perforation with peritonitis
- Inflammatory strictures of the colorectum

## **TUMORS OF THE INTESTINES**

### **1. Non-neoplastic Polyps**

- Hyperplastic polyps
- Hamartomatous polyps
- Juvenile polyps
- Peutz-Jeghers polyps
- Inflammatory polyps
- Lymphoid polyps

### **2. Neoplastic Epithelial Lesions**

- Benign polyps (Adenomas)
- Malignant lesions
- Adenocarcinoma
- Squamous cell carcinoma of the anus

### **3. Other Tumors**

- Gastrointestinal stromal tumors
- Carcinoid tumor
- Lymphoma

## 1) Non-Neoplastic Polyps

- Non-neoplastic polyps represent about 90% of all epithelial polyps in the large intestine.
- 50% of cases present in age 60 years or older.

### Types :

- Hyperplastic polyps
- Juvenile polyps
- Retention polyps
- Peutz-Jegher syndrome

#### **a. Hyperplastic Polyps**

- Small (<5 mm in diameter).
- Single or multiple (hyperplastic polyposis).
- Rectosigmoid region in 50% of the cases.
- The vast majority of hyperplastic polyps have *no malignant potential*.
- Sessile serrated adenomas located on the right side of the colon may be precursors of colorectal carcinomas.

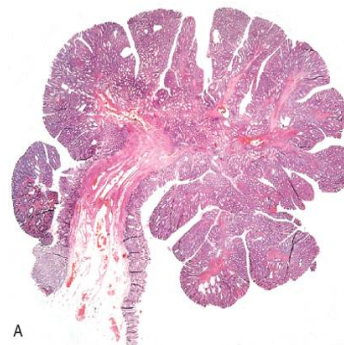
#### **b. Juvenile Polyps**

- Hamartomatous proliferations mainly of the lamina propria enclosing widely spaced dilated cystic glands
- Children younger than 5 years old
- Large in children (1-3 cm in diameter)
- Pedunculated( stalk as long as 2 cm)
- Single
- Rectum
- No malignant potential

## 2) Neoplastic Polyps

### Adenomas

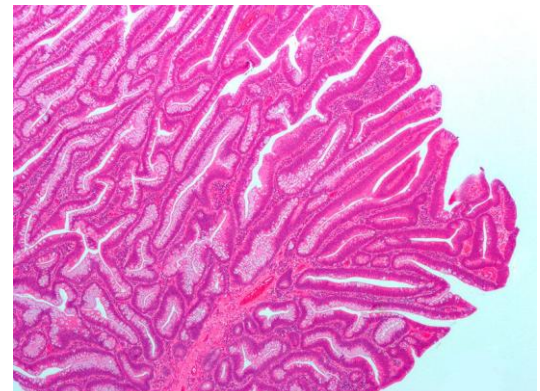
- Neoplastic polyps that range from small & pedunculated to large lesions that are usually sessile
- Rare in the small intestine
- The prevalence of colonic adenomas is
  - 20-30% before age 40
  - 40-50% after age 60
- M=F.
- There is a well-defined familial predisposition to sporadic adenomas(4X greater risk among first-degree relatives).
- 4X greater risk of colorectal carcinoma in any person with adenomas.
- Adenomatous polyps are divided into 4 subtypes on the basis of the epithelial architecture:
  - a. Tubular adenomas (most common) rectosigmoid
  - b. Villous adenomas (1%) rectum and rectosigmoid
  - c. Tubulovillous adenomas (5-10%)
  - d. Sessile serrated adenomas



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#### • **Picture (right): Villous adenoma**

- The malignant risk with an adenomatous polyp is correlated with:
  - Polyp size
  - Histologic architecture
  - Severity of epithelial dysplasia
- Cancer is rare in tubular adenomas smaller than 1 cm in diameter.
- Cancer risk is high (~40%) in sessile villous adenomas larger than 4 cm in diameter.
- Severe dysplasia is often found in villous areas.



- **Maximum diameter** is the chief determinant of the risk of an adenoma's harboring carcinoma.
- Architecture does not provide substantive independent information.

### **Features:**

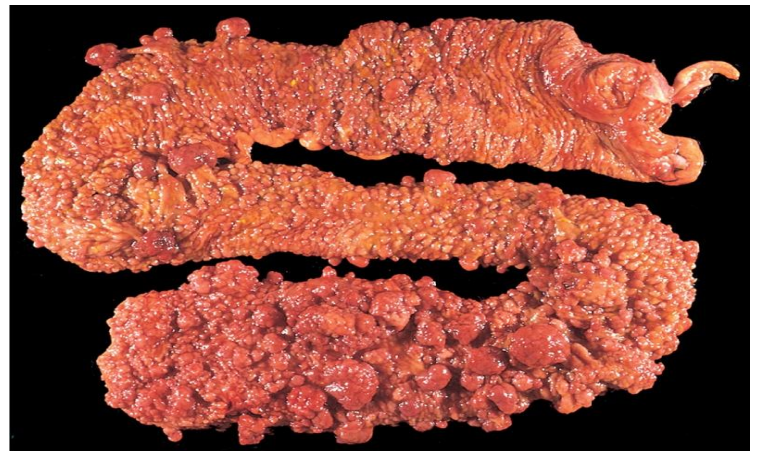
- Asymptomatic
- Anemia due to occult bleeding
- Villous adenomas are much more frequently symptomatic because of overt or occult rectal bleeding.
- The most distal villous adenomas may secrete sufficient amounts of mucoid material rich in protein and potassium to produce hypoproteinemia or hypokalemia.
- All adenomas regardless of their location in the alimentary tract are to be considered potentially malignant and should be excised.

## **Familial Polyposis Syndromes (FAP)**

- Uncommon autosomal dominant disorders.
- 500-2500 colonic adenomas may present in the mucosal surface.
- A minimum number of 100 is required for the diagnosis.
- Multiple adenomas may also be present elsewhere in the alimentary tract including almost a 100% lifetime incidence of duodenal adenomas.

### • **Picture: Familial Polyposis Syndromes**

- Most polyps are tubular adenomas.
- Occasional polyps are villous adenomas.
- Polyps usually become evident in adolescence or early adulthood.
- The risk of colonic cancer is virtually 100% by midlife unless a prophylactic colectomy is performed.
- The genetic defect underlying FAP has been localized to the *APC* gene on chromosome 5q21.



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- **Gardner syndrome** and **Turcot syndrome** seem to share the same genetic defect as FAP.
- These syndromes differ from FAP with respect to the occurrence of extra-intestinal tumors in the latter two (osteomas, gliomas, and soft tissue tumors).

- **Peutz-Jeghers syndrome**

- Peutz-Jeghers polyps are uncommon hamartomatous polyps.
- Autosomal dominant.
- Characterized in addition by melanotic mucosal and cutaneous pigmentation.
- This syndrome is caused by germ-line mutations in the **LKB1 gene** which encodes a serine threonine kinase.

- **Cowden syndrome**

- Is characterized by hamartomatous polyps in the GIT and by an increased risk of neoplasms of the thyroid, breast, uterus, and skin
  - This syndrome is caused by germ-line mutations in the **PTEN (phosphatase and tensin homologue) tumor suppressor gene**
  - PTEN gene is mutated in a large number of human cancers
  - It encodes a phosphatase that has the ability to regulate many intracellular signaling pathways.
  - It acts as a growth inhibitor by interrupting signals from several tyrosine kinase receptors (e.g EGFR) and by favoring apoptosis through the BAD/BCL2 pathways
- *Peutz-Jeghers and Cowden syndromes are associated with an increased risk of both intestinal and extraintestinal malignancies.*

## Colorectal Carcinoma

- 98% of all cancers in the large intestine are adenocarcinomas.
- 134,000 new cases per year and about 55,000 deaths (15% of all cancer-related deaths in the United States).

### Epidemiology

- 60-70 years of age.
- < 20% of cases occur before the age of 50 years.
- Males > females.
- Both genetic and environmental influences contribute to the development of colorectal cancers.
- *Hereditary nonpolyposis colorectal cancer syndrome (HNPCC, also known as Lynch syndrome)* caused by germ-line mutations of DNA mismatch repair genes are at a high risk of developing colorectal cancers.
- HNPCC patients are also at risk of developing other tumors such as cholangiocarcinomas.
- The highest incidence rates occurs in the USA, Canada, Australia, New Zealand, Denmark, Sweden, and other developed countries.
- Its incidence in India, South America, and Africa is lower by 30-folds.
- The incidence in Japan has now risen to the intermediate levels observed in the United Kingdom.
- Environmental influences, particularly dietary practices, are implicated in the striking geographic variation in incidence.

### The Dietary Factors Include:

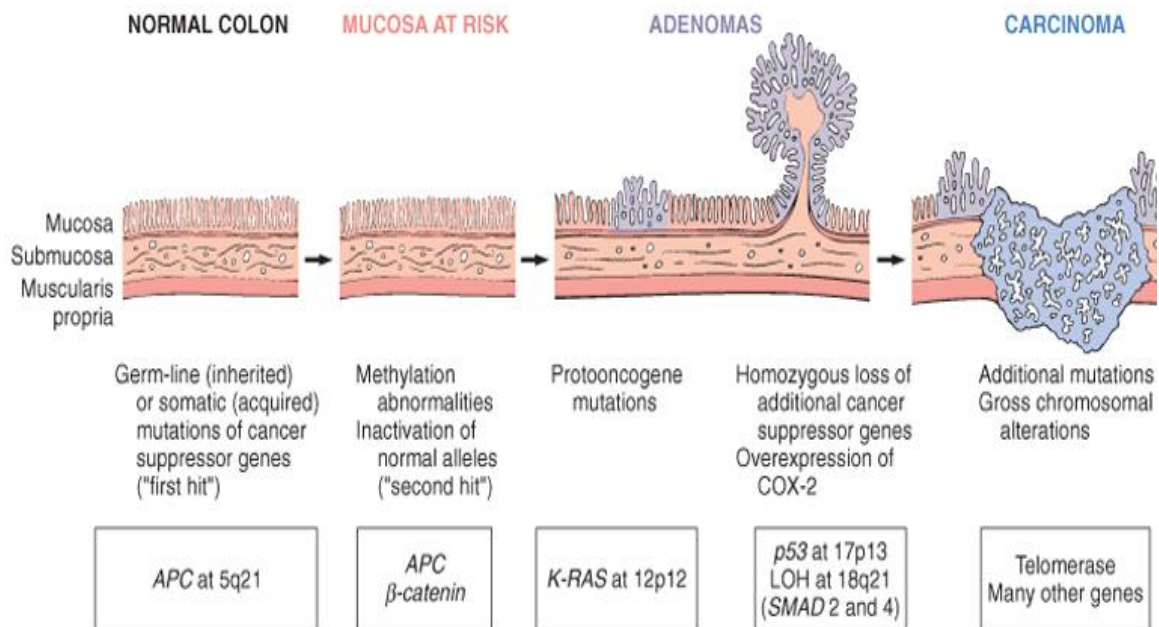
- a. A low content of unabsorbable vegetable fiber
  - b. High content of refined carbohydrates
  - c. High fat content (as from meat)
  - d. Decreased intake of protective micronutrients such as vit A, C, and E
- Reduced fiber content leads to decreased stool bulk, increased fecal retention in the bowel, and an altered bacterial flora of the intestine.
  - Potentially toxic oxidative byproducts of carbohydrate degradation by bacteria are therefore present in higher concentrations in the stool and are held in contact with the colonic mucosa for longer periods of time.
  - High fat intake enhances the synthesis of cholesterol and bile acids by the liver which in turn may be converted into potential carcinogens by intestinal bacteria.
  - Refined diets also contain less of vitamins A, C, and E, which may act as oxygen radical scavengers.

## **Adenoma-Carcinoma sequence**

- Populations that have a high prevalence of adenomas have a high prevalence of colorectal cancer and vice versa.
  - The distribution of adenomas within the colorectum is more or less comparable to that of colorectal cancer.
  - The peak incidence of adenomatous polyps antedates by some years the peak for colorectal cancer.
  - When invasive carcinoma is identified at an early stage surrounding adenomatous tissue is often present.
  - The risk of cancer is directly related to the number of adenomas.
  - Removal of adenomas reduces the incidence of colorectal cancer.
- ***There are two pathogenetically distinct pathways for the development of colon cancer:***
    - 1) *The APC/ $\beta$ -catenin (chromosome instability) pathway (80% of sporadic colon tumors )*
    - 2) *The mismatch repair (microsatellite instability) pathway*



**APC/ $\beta$ -catenin**  
**(chromosome instability) pathway**



- **APC** mutations are present in 60-80% of sporadic colon cancers.
- **K-RAS** is mutated in fewer than 10% of adenomas <1 cm.
- **K-RAS** is mutated in 50% of adenomas > than 1 cm.
- **K-RAS** is mutated in 50% of carcinomas.
- **18q21 deletion**
- *Loss of a suppressor gene on 18q21 has been found in 60-70% of colon cancers.*
- *Three genes have been mapped to this chromosome location:*
  - 1) *DCC (deleted in colon carcinoma)*
  - 2) *SMAD2*
  - 3) *SMAD4.*
- *The SMAD genes are considered to be the most relevant ones for colon carcinogenesis.*
- *They encode components of TGF- $\beta$  signaling pathway.*
- *The loss of these genes may allow unrestrained cell growth.*
- **Loss of p53**
- *Loss of this tumor suppressor gene is noted in 70-80% of colon cancers.*
- *Similar losses are infrequent in adenomas.*
- *Mutations in p53 occur late in colorectal carcinogenesis.*



### **DNA mismatch repair genes (MSI) pathway**

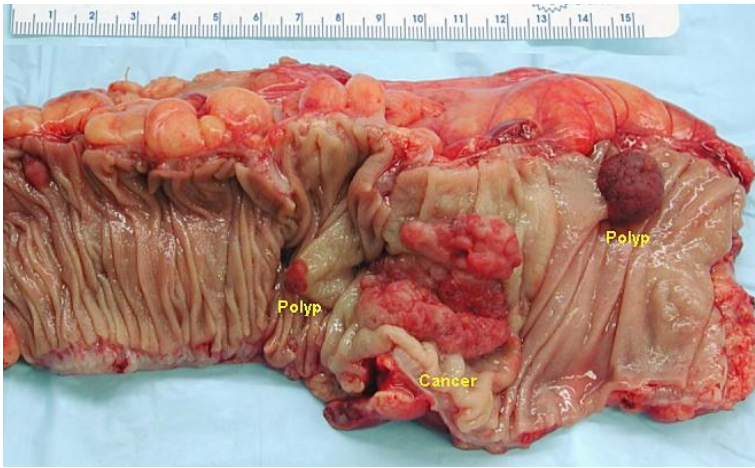
- It is involved in 10-15% of sporadic cases.
- There may be no detectable antecedent lesions or the tumors may develop from sessile serrated adenomas.
- Defective DNA repair caused by inactivation of DNA mismatch repair genes is the fundamental and the most likely initiating event in colorectal cancers that follow this path.
- Inherited mutations in one of five DNA mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, *PMS1*, and *PMS2*) give rise to the hereditary nonpolyposis colon carcinoma (HNPCC).
- *MLH1* and *MSH2* are the ones most commonly involved in HNPCC-derived and sporadic colon carcinomas.
- Loss of DNA mismatch repair genes leads to a hypermutable state in which simple repetitive DNA sequences called **microsatellites** leading to unstability during DNA replication giving rise to widespread alterations in these repeats
- Most microsatellite sequences are in noncoding regions of the genes.
- Some microsatellite sequences are located in the coding or promoter region of genes involved in regulation of cell growth.
- Such genes include:
  - i. Type II TGF- $\beta$  receptor gene
  - ii. *BAX* gene
- TGF- $\beta$  signaling inhibits the growth of colonic epithelial cells and the *BAX* gene product causes apoptosis.
- It has been noted that sessile serrated adenomas located on the right side of the colon display MSI and may be precancerous.
- Tumors that arise via the mismatch repair pathway do show some distinctive morphologic features including:
  - *Proximal colonic location*
  - *Mucinous histology*
  - *Infiltration by lymphocytes.*
- In general these tumors have a better prognosis than do stage-matched tumors that arise by the *APC*/ $\beta$ -catenin pathway.

**Location:**

- Cecum or ascending colon ( 25%)
  - Rectum and distal sigmoid (25%)
  - Descending colon and proximal sigmoid (25%)
  - Other (25%)
- 
- **Carcinomas in the distal colon tend to be annular encircling lesions that produce so-called napkin-ring constrictions of the bowel and narrowing of the lumen**
  
  - Almost all are adenocarcinomas that range from well-differentiated to undifferentiated, frankly anaplastic masses.
  - Many tumors produce mucin, which is secreted into the gland lumina or into the interstitium of the gut wall.
  - Secretions dissect through the gut wall and facilitate extension of the cancer and worsen the prognosis.
  - Cancers of the anal zone are predominantly squamous cell in origin.

- **Pictures: Carcinoma of the cecum**

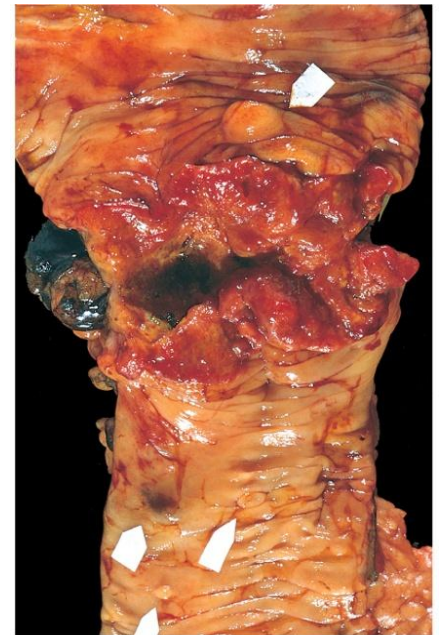
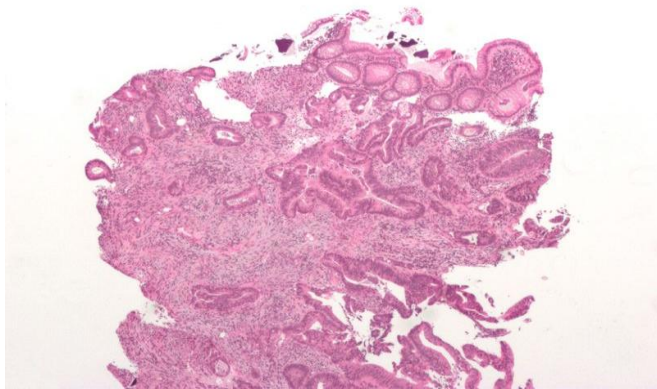
The exophytic carcinoma projects into the lumen not causing obstruction



- **Picture: Carcinoma of the descending colon.**

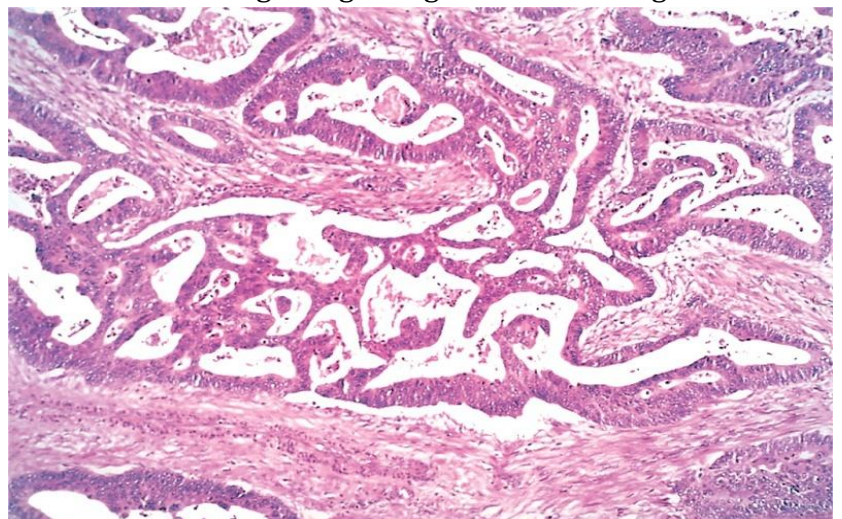
This circumferential tumor has heaped-up edges and an ulcerated central portion.

The arrows identify separate mucosal polyps.



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- **Pictures: Invasive adenocarcinoma of colon** showing malignant glands infiltrating the muscle wall.



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### **Clinical Features**

- Asymptomatic for years
- Cecal and right colonic cancers most often are called to clinical attention by the appearance of fatigue, weakness, and iron deficiency anemia.
- Left-sided lesions may produce occult bleeding, changes in bowel habit, or crampy left lower quadrant discomfort.
- *Iron deficiency anemia in an older man means gastrointestinal cancer until proved otherwise.*
- **Colorectal tumors spread by direct extension into adjacent structures and by metastasis through the lymphatics and blood vessels.**

the favored sites for metastasis are:

- *Regional lymph nodes*
  - *Liver*
  - *Lungs*
  - *Bones*
  - *serosal membrane of the peritoneal cavity.*
- **The single most important prognostic indicator of colorectal carcinoma is the extent (*stage*) of the tumor at the time of diagnosis:**

#### **Tumor (T)**

T0 = none evident

Tis = in situ (limited to mucosa)

T1 = invasion of lamina propria or submucosa

T2 = invasion of muscularis propria

T3 = invasion through muscularis propria into subserosa or nonperitonealized perimuscular tissue

T4 = invasion of other organs or structures

#### **Lymph Nodes (N)**

0 = none evident

1 = 1 to 3 positive pericolic nodes

2 = 4 or more positive pericolic nodes

3 = any positive node along a named blood vessel

#### **Distant Metastases (M)**

0 = none evident

1 = any distant metastasis

### **5-Year Survival Rates**

T1 = 97%

T2 = 90%

T3 = 78%

T4 = 63%

Any T; N1; M0 = 66%

Any T; N2; M0 = 37%

Any T; N3; M0 = data not available

Any M1 = 4%

## Neoplasms of the Small Intestine

- 1% of gastrointestinal malignancies.
- The most frequent benign tumors in the small intestine are stromal tumors of predominantly smooth muscle origin, adenomas, and lipomas, followed by various neurogenic, vascular, and hamartomatous epithelial lesions.
- Small intestinal adenocarcinomas and carcinoids have a roughly equal incidence.
- Adenomas of the small intestine may present with anemia or rarely intussusception or obstruction.
- Adenomas in the immediate vicinity of the ampulla of Vater may produce biliary obstruction causing jaundice.

### Adenocarcinoma of the Small Intestine

- Most small bowel carcinomas arise in the duodenum (including the ampulla of Vater).
- Cramping pain, nausea, vomiting, and weight loss are the common presenting signs and symptoms.
- Manifestations generally appear late in the course of these cancers.
- 5-year survival rate is about 70%.

### Gastrointestinal Stromal Tumors GIST

- Subdivided into:
- Tumors that show smooth muscle cell differentiation (the most common type)
- Tumors with neural differentiation (often called gastrointestinal autonomic nerve tumors)
- Tumors with smooth muscle/neural dual differentiation
- Tumors lacking differentiation toward these lineages.
  - GISTs constitute the majority of nonepithelial tumors of the stomach but can be present in the small and large intestine ∩
  - *Most GISTs have a somatic mutation in the c-KIT (CD117) gene, which encodes a tyrosine kinase receptor.*



### Gastrointestinal Lymphoma

- 40% of lymphomas arise in sites other than lymph nodes, and the gut is the most common extra-nodal location.
- 1-4% of all gastrointestinal malignancies are lymphomas.
- *By definition, **primary gastrointestinal lymphomas reveal no evidence of liver, spleen, or bone marrow involvement at the time of diagnosis.***
- Regional lymph node involvement may be present.
  
- Intestinal tract lymphomas can be of B- or T-cell origin.
- The most common form in Western countries is ***MALT lymphoma (B-cell NHL)***
- It affects adults, lacks a sex predilection, and may arise anywhere in the gut:
  - Stomach (55-60% of cases)
  - Small intestine (25-30%)
  - Proximal colon (10-15%)
  - Distal colon ( $\leq 10\%$ ).
  - The appendix and esophagus are only rarely involved.
  
- 1ry GIT lymphomas generally have a better prognosis than do those arising in other sites.
- About 50% of gastric lymphomas can regress with antibiotic treatment for *H. pylori*.
- Those that do not regress usually contain the t(11;18) translocation or other genetic abnormalities.
- Celiac disease is associated with a higher than normal risk of intestinal T-cell lymphomas.

### **Carcinoids**

- Tumors arising from the endocrine cells are called carcinoid tumors.
- They may develop in the pancreas or peripancreatic tissue, lungs, biliary tree, and liver.
- The term carcinoid is an old reference to "carcinoma-like."
  
- The peak incidence is in the 6<sup>th</sup> decade but they may appear at any age.
- *They compose less than 2% of colorectal malignancies but almost half of small intestinal malignant tumors.*
  
- Although all carcinoids are potentially malignant tumors, the tendency for aggressive behavior correlates with:
  - The site of origin
  - The depth of local penetration
  - The size of the tumor
  
- **Appendiceal and rectal carcinoids *almost never metastasize***
  
- 90% of ileal, gastric, and colonic carcinoids that have penetrated halfway through the muscle wall have spread to lymph nodes and distant sites at the time of diagnosis especially those larger than 2 cm in diameter.
- The cells of carcinoid tumors can synthesize and secrete a variety of bioactive products and hormones.
- Multiple hormones may be synthesized by a single tumor.
- It may secrete one type of hormone (e.g., gastrinoma, somatostatinoma, and insulinoma)

### **Clinical Features**

- Frequently asymptomatic including virtually all that arise in the appendix
- Only rarely do carcinoids produce local symptoms secondary to angulation or obstruction of the small intestine.
- The secretory products of some carcinoids can produce a variety of syndromes or endocrinopathies.
- Gastric, peripancreatic, and pancreatic carcinoids release their products directly into the systemic circulation and can produce the Zollinger-Ellison syndrome by excess elaboration of gastrin.
- Cushing syndrome caused by adrenocorticotrophic hormone secretion, hyperinsulinism
- These tumors may be less than 1.0 cm in size and extremely difficult to find even during surgical exploration.

- Some neoplasms are associated with a distinctive *carcinoid syndrome*.
- The syndrome occurs in about 1% of all patients with carcinoids and in 20% of those with widespread metastases.
- Most manifestations are thought to arise from elaboration of serotonin (5-hydroxytryptamine [5-HT]).
- Elevated levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) are present in the blood and urine of most individuals with the classic syndrome.
- 5-HT is degraded in the liver to functionally inactive 5-HIAA.

- **Vasomotor disturbances:**

Cutaneous flushes and apparent cyanosis (most patients)

- **Intestinal hypermotility:**

Diarrhea, cramps, nausea, vomiting (most patients)

- **Asthmatic bronchoconstrictive attacks:**

Cough, wheezing, dyspnea (about one-third of patients)

- **Hepatomegaly:**

Nodular, related to hepatic metastases (some cases)

- **Niacin deficiency** (due to shunting of niacin to serotonin synthesis)

- **Systemic fibrosis**

- **Cardiac involvement:**

- Pulmonic and tricuspid valve thickening and stenosis
- Endocardial fibrosis in right ventricle

- **Retroperitoneal and pelvic fibrosis**

- **Collagenous pleural and intimal aortic plaques**

- With gastrointestinal carcinoids, hepatic dysfunction resulting from metastases must be present for the development of the syndrome.
- The possibility that other secretory products such as histamine, bradykinin, and prostaglandins contribute to the manifestations of this syndrome has not been excluded.

- The 5-year survival rate for carcinoids (excluding appendiceal) is approximately 90%.