Lecture 6

SMALL & LARGE INTESTINES

Inflammatory diseases, & tumors, affect both small & large intestines, therefore, the two organs are considered together.

- **DEVELOPMENTAL ANOMALIES**

Atresia	No lumen = complete failure of development of the intestinal lumen, e.g., imperforated anus
Stenosis	is incomplete obstruction = narrowing of the intestinal lumen, may affect any segment of the small intestine, but duodenal atresia is the most common
Duplication	usually takes the form of well-formed saccular to tubular cystic structures, which may or may not communicate with the lumen of the small intestine
Omphalocele	is a congenital defect of the periumbilical abdominal musculature that creates a membranous sac, into which the intestines herniate
Gastroschisis	is extrusion of the intestines caused by lack of formation of a portion of the abdominal wall
Meckel diverticulum	Is the most common congenital anomaly {2% of births} It results from failure of involution of the omphalomesenteric duct, leaving a persistent blind-ended tubular protrusion as long as 5 to 6 cm (=2 Inches).
Malrotation	of the developing bowel can prevent the intestines from assuming their normal intra-abdominal positions, e.g., the caecum may be found anywhere in the abdomen, including the left upper quadrant, rather than in its normal position in the right lower quadrant. Confusion may arise when appendicitis presents as left upper quadrant pain. The large intestine is predisposed to volvulus
Hirschsprung Disease:	Megacolon is distention of the colon to greater than 6 or 7 cm in diameter, it occurs either as a congenital or acquired disorder.

- **Meckel diverticulum**

  The diameter is variable, sometimes approximating that of the small intestine itself.

  Located on the antimesenteric side of the small bowel, usually the ileum, about 2 feet proximal to the Ileocecal valve & are composed of all layers of the normal small intestine (i.e., Meckel is a true diverticulum).

  Generally are asymptomatic, except when they permit bacterial overgrowth that depletes vitamin B12, producing a syndrome similar to pernicious anemia.

  Rarely, pancreatic rests are found in it
  In 50% of 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.

  {Remember; in 2% of births, 2 Inches in length, & 2 feet proximal to ilio-caecal valve}

- **Hirschsprung Disease**

a. **Hirschsprung D** (congenital megacolon)
results when, during development, the migration of neural crest-derived cells along the GIT arrests at some point before reaching the anus.

Hence, an aganglionic segment is formed that lacks both the Meissner submucosal & Auerbach myenteric plexuses. This causes functional obstruction & progressive distention of the colon proximal to the affected segment.

Ganglia are absent from the muscle wall & submucosa of the constricted segment but may be present in the dilated portion.

Hirschsprung D occurs 1 in 5000 to 8000 live births; It predominates in males, M/F is 4:1.

It is much more frequent in those with other congenital anomalies like hydrocephalus, VSD, & Meckel diverticulum.

H :
the critical lesion in Hirschsprung disease is the lack of ganglion cells, & of ganglia, in the submucosa & muscle wall of the affected collapsed segment (aganglionic segment)

the diagnosis is established by documenting the absence of ganglion cells in the nondistended bowel segment.

GROSSLY :
(1) It is the proximal, properly innervated, ganglionic segment that undergoes dilation.
When only the distal colon is aganglionic, the proximal colon becomes massively distended up to a diameter of 15 to 20 cm.
The dilated wall may be thinned by distention, or, is thickened by compensatory muscle hypertrophy.

(2) The mucosal lining of the distended portion may be intact or have shallow, so-called stercoral ulcers produced by impacted, inspissated feces.

Clinically :
in most cases a delay occurs in the initial passage of meconium, followed by vomiting in 48 to 72 hours.

When a very short distal segment of the rectum alone is involved, the obstruction may not be complete & may not produce manifestations until later in infancy, in the form of alternating periods of obstruction & passage of diarrheal stools.

The principal threat to life is superimposed enterocolitis with fluid & electrolyte disturbances.

b. **Acquired megacolon may result from**
(1) Chagas disease, in which the trypanosomes directly invade the bowel wall to destroy the plexuses; the other forms of megacolon are not associated with any deficiency of mural ganglia, including:
(2) Organic obstruction of the bowel by a tumor or inflammatory stricture,
(3) Toxic megacolon complicating ulcerative colitis or Crohn disease
(4) A functional psychosomatic disorder.

VASCULAR DISORDERS

Ischemic Bowel Disease

- Depending on the vessel or vessels involved, ischemic lesions may be restricted to the small or large intestine or, both.

- Acute occlusion of one of the three major supply trunks of the intestines:
  1. Celiac 2. superior 3. inferior mesenteric arteries-may lead to infarction of extensive segments of intestine.

- However, insidious loss of one vessel may be without effect, Thanks God for the rich vascular anastomoses.

- Lesions within the end-arteries that penetrate the gut wall produce small, focal ischemic lesions.

- **The severity ranges from:**

(1) Transmural infarction involving all gut layers, always caused by acute occlusion of a major mesenteric artery, to
(2) Mural infarction of the mucosa & submucosa, sparing the muscular wall, to
(3) Mucosal infarction, if the lesion extends not deeper than the muscularis mucosae,

- Both mural & mucosal infarctions are more often results from either physiologic hypoperfusion or more localized anatomic defects, & may be acute or chronic.

- Mesenteric venous thrombosis is a less frequent cause of vascular compromise.

- **The predisposing conditions for all three infarctions are:**
  1. Arterial thrombosis: severe atherosclerosis (usually at the origin of the mesenteric vessel), systemic vasculitis, dissecting aneurysm, angiographic procedures, aortic reconstructive surgery, surgical accidents, hypercoagulable states, & oral contraceptives

  2. Arterial embolism: cardiac vegetations (as with endocarditis), or MI with mural thrombosis, angiographic procedures, & aortic Atheroembolism.

  3. Venous thrombosis: hypercoagulable states induced, for example, by oral contraceptives or antithrombin III deficiency, intraperitoneal sepsis, the postoperative state, cancerous invasion of veins (particularly hepatocellular ca), cirrhosis, & abdominal trauma

  4. Nonocclusive ischemia: cardiac failure, shock, dehydration, vasoconstrictive drugs (e.g., digitalis, vasopressin, propranolol),

  5. Miscellaneous: radiation injury, volvulus, stricture, & internal or external herniation

- **Clinical Features** :

  Ischemic bowel injury is most common seen in the elderly.

  With the transmural lesions, there is sudden severe abdominal pain, sometimes accompanied by bloody diarrhea.
  Because this condition may progress to shock & vascular collapse within hours, the diagnosis must be made promptly, & making it requires a high index of suspicion in the appropriate context (e.g., recent major abdominal surgery, atrial fibrillation, or vegetative endocarditis or recent MI).

- **GROSSLY** :

	Characteristic:	H:	Prognosis
Transmural intestinal infarction	may involve a short or long segment, depending on the particular vessel affected & the patency of the anastomotic supply. Whether the occlusion is arterial or venous, the infarction always has a dark red hemorrhagic appearance because of reflow of blood into the damaged area. The ischemic injury usually begins in the mucosa & extends outward; within 18 to 24 hours there is a thin, fibrinous exudate over the serosa. With arterial occlusion the demarcation from adjacent normal bowel is fairly sharply defined, but with venous occlusion the margins are less distinct	the Transmural infarction changes are typical of ischemic coagulative necrosis with marked edema, interstitial hemorrhage, & sloughing of the mucosa. Within 24 hours intestinal bacteria produce gangrene & sometimes perforation of the bowel.	mortality rate approaches 90% largely because of the short time between onset of symptoms & perforation caused by gangrene
Mural & Mucosal infarctions	are recognized by multi-focal lesions interspersed with spared areas. Their location depends in part on the extent of preexisting atherosclerotic narrowing of the arterial supply; lesions can be scattered over large regions of the small or large intestines. Affected foci may or may not be visible from the serosal surface, because by definition the ischemia does not affect the entire thickness of the bowel. When the bowel is opened, hemorrhagic edematous thickening of the mucosa, sometimes with superficial ulcerations, is seen.	there is hemorrhage, edema, & outright necrosis of the affected tissue layers. Inflammation develops at the margins of the lesions, & an inflammatory fibrin-containing exudate (pseudomembrane), usually secondary to bacterial superinfection, may coat the affected mucosa. Alternatively, chronic vascular insufficiency may produce a chronic inflammatory& ulcerative condition, mimicking IBD.	mural & mucosal ischemia may appear only as unexplained abdominal distention or GIT bleeding, sometimes accompanied by the gradual onset of abdominal pain or discomfort. Suspicion is raised if the individual has experienced conditions that favor acute hypoperfusion of the bowel, i.e., episode of cardiac failure or shock. Mucosal & mural infarctions are not by themselves fatal, &, indeed, if the cause of hypoperfusion can be corrected, the lesions may heal

- **Angiodysplasia**
  Tortuous dilations of mucosal & submucosal BV are seen most often in the cecum or right colon, usually only after the 6th decade of life.

  They are prone to rupture & bleed into the lumen, accounting for 20% of significant lower intestinal bleeding. The hemorrhage may be chronic & intermittent & only, causing severe anemia; but rarely is it acute & massive.

  Most often, these lesions are isolated, but sometimes they are part of a systemic disorder such as hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).

- **Hemorrhoids**
  are variceal dilations of the anal & perianal submucosal venous plexuses.

  They are common after age 50 & develop in the setting of persistently elevated venous pressure within the hemorrhoidal plexus

  Common predisposing conditions are straining at stool in the setting of chronic constipation & the venous stasis of pregnancy in younger women.

  More rarely, hemorrhoids may reflect portal hypertension, usually resulting from liver cirrhosis.

  Hemorrhoids 2 types are

Internal hemorrhoids	are varicosities in the superior & middle hemorrhoidal veins, appearing above the anorectal line & are covered by rectal mucosa. Prolapse with strangulation of the internal hemorrhoids may occur during straining at stool & then become trapped by the compressive anal sphincter, leading to sudden, extremely painful, edematous hemorrhagic enlargement	Both 1 & 2 are thin-walled, dilated vessels that commonly Bleed, {sometimes masking bleeding from far more serious malignant proximal lesions}. Sometimes they may become Thrombosed, particularly when subject to trauma from passage of stool.
External hemorrhoids	are those that appear below the anorectal line, representing dilations of the inferior hemorrhoidal plexus & are covered by anal mucosa	

- **COLONIC DIVERTICULOSIS**

A diverticulum is a blind pouch that communicates with the lumen of the gut.
Congenital {Meckel} diverticula have all three layers of the bowel wall (mucosa, submucosa, & muscularis propria) & are distinctly uncommon.

Virtually all other diverticula are acquired & either without, or, having an attenuated muscularis propria.

Acquired diverticula may occur anywhere in the GIT, but by far, the most common location is the colon, giving rise to diverticular disease of the colon (diverticulosis); 95% of which are in the sigmoid 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 & 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.

Colonic diverticulosis is relatively infrequent in native populations of non-Western countries. Although unusual in Western adults younger than 30 years of age, in those older than the age of 60 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.

Exaggerated spastic contractions of the colon result in segmentation (isolate segments of the colon in which the intraluminal pressure becomes markedly elevated), with consequent herniation of the bowel wall through the anatomic points of weakness.

Thus, two influences are important in the genesis of diverticular protrusions:
(1) Exaggerated peristaltic contractions with abnormal elevation of intraluminal pressure
(2) Focal defects of the normal muscular colonic wall.

- **GROSSLY** :
  Most colonic diverticula are small, flasklike or spherical outpouchings, usually 0.5 to 1 cm in diameter, located in the sigmoid colon in 95% of patients.

  The exaggerated peristalsis often induces taenia coli & circular muscular hypertrophy in the affected segments.

  Diverticula frequently dissect into the appendices epiploicae & therefore may be inapparent on external inspection

  In the uninflamed state the walls are usually very thin, made up largely of mucosa & submucosa enclosed within fat or an intact peritoneal covering.

  Inflammatory changes may supervene to produce both diverticulitis & peridiverticulitis; perforation of which may lead to localized peritonitis or abscess formation.

  When many closely adjacent diverticula become inflamed, the bowel wall may be encased by fibrous tissue, with narrowing of the lumen, producing a remarkable resemblance to a malignant stricture..

- **Clinically** :
  diverticular disease is mostly, asymptomatic. In 20% of patients there is intermittent cramping or discomfort.

- **Complications** : superimposed

(1) diverticulitis accentuates the symptoms & produces left lower quadrant tenderness & fever. Other rare complications include brisk
(2) hemorrhage,
(3) perforation with pericolic abscess, or fistula formation.

- **Treatment** is by a high-fiber diet, recommended on the theory that the increased stool bulk & ↓ the exaggerated peristalsis.

BOWEL OBSTRUCTION

- Although any part of the gut may be involved, because of its narrow lumen, the small bowel is most commonly affected.

- 4 major Causes of Intestinal Obstruction are mechanical :

{internal or external Hernias + Adhesions + Intussusception + Volvulus}, accounting for at least 80% of the cases

- **The four major causes of intestinal obstruction:**

(1) Herniation of a segment in the umbilical or inguinal regions,
(2) Adhesions between intestinal loops,
(3) Intussusception,
(4) Volvulus.

- **Less Frequent Causes :**
  Tumors, Inflammatory strictures, Obstructive gallstones, fecaliths, foreign bodies, Congenital stricture or bands, atresias, imperforate anus, Meconium in cystic fibrosis.

Hernias	Adhesions	Intussusception	Volvulus
-when there is a weakness or defect in the wall of the peritoneal cavity, it may permit protrusion of a pouchlike, serosa-lined sac of peritoneum, which is called a hernial sac. -The usual sites of weakness are: anteriorly at the inguinal & femoral canals + at the umbilicus + in surgical scars. -Segments of viscera, mostly small bowel loops, or portions of omentum or large bowel frequently intrude & become trapped in hernias (external herniation), particularly in the inguinal hernias, which have narrow orifices & large sacs. -Pressure at the neck of the hernial sac may Impair venous drainage of the trapped viscus causes stasis & edema, ↑ the bulk of the herniated loop, leading to 1. incarceration, i.e.; permanent trapping which further compromise its blood supply & drainage leading to 2. strangulation of the trapped segment, i.e.; Infarction. -Surgical procedures, infection, & even endometriosis often cause localized or general peritonitis. With healing.	-may develop between the bowel segments or with the abdominal wall or the operative site. -These fibrous bridges can create closed loops (rings) through which the intestines may slide & become trapped (internal herniation) -The sequence of events is the same as with external hernias	-means telescoping of a proximal segment of the bowel into the immediately distal segment. -In infants & children, intussusception sometimes occurs without apparent cause. -While in adults, such telescoping often points to an intraluminal mass (e.g., tumor) that becomes trapped by a peristaltic wave & pulls its point of attachment along with it, into the distal segment. Not only does intestinal obstruction ensue, but the vascular supply may be so compromised as to cause infarction of the trapped segment.	-refers to 360 degree twisting of a loop of bowel (or other structure e.g., ovarian cyst or tumor) about its base of attachment, -constricting the venous outflow & sometimes the arterial supply as well. -Volvulus affects the small bowel most often & rarely the redundant sigmoid. -Intestinal obstruction & infarction may follow.

Malabsorption Syndrome

- Is defective absorption of fats, fat-soluble & other vitamins, proteins, carbohydrates, electrolytes & minerals, & water.
- The most common presentation is chronic diarrhea; the ® hallmark of malabsorption syndromes is steatorrhea (excessive fat content of the feces).

Table 15-9 shows the Major Malabsorption Syndromes.

- The most common malabsorptive disorders encountered in the US are pancreatic insufficiency, celiac disease, & Crohn disease.

- Basically, malabsorption is the result of **disturbance of at least one of these normal digestive functions**:

Intraluminal digestion	in which carbohydrates, proteins, & fats are enzymatically broken down. The process begins in the mouth with saliva, receives a major boost from gastric peptic digestion, & continues in the small intestine, assisted by pancreatic enzyme secretion & the emulsive action of bile
Mucosal absorption	in which water, electrolytes, & nutrients are absorbed & transported into the cell. Absorbed fatty acids are converted to triglycerides & are assembled with + cholesterol & + apoprotein B into = chylomicrons. Disturbances can be caused by (1) primary mucosal cell abnormalities (2) reduced small intestinal surface area or (3) from mucosal infections.
Nutrient delivery	involving the delivery of nutrients from the intestinal cells into the lymphatics. Disturbances may be caused by congenital defects, or be secondary to tuberculosis or retroperitoneal fibrosis

- **The Major Malabsorption Syndromes**

Defective Intraluminal Digestion	Digestion of fats & proteins: Pancreatic insufficiency, due to pancreatitis or cystic fibrosis Zollinger-Ellison syndrome, with inactivation of pancreatic enzymes by excess gastric acid secretion Solubilization of fat, due to defective bile secretion, hepatic dysfunction, Biliary obstruction, resulting in cessation of bile flow, Ileal dysfunction or resection, with ↓ bile salt uptake, Nutrient preabsorption or modification by bacterial overgrowth Distal ileal resection or bypass, Total or subtotal gastrectomy
Primary Mucosal Cell Abnormalities:	Defective terminal digestion Disaccharidase deficiency (lactose intolerance) Bacterial overgrowth, with brush-border damage Defective transepithelial transport Abetalipoproteinemia
Reduced Small Intestinal Surface Area	Celiac disease , Crohn disease , Short-gut syndrome, after surgical resections
Infections	Acute infectious enteritis , Parasitic infestation , Tropical sprue , Whipple disease
Lymphatic Obstruction	Lymphoma , Tuberculosis & tuberculous lymphadenitis

Defects of Intraluminal Digestion

- Typical features of defective intraluminal digestion are an osmotic diarrhea from undigested nutrients, & steatorrhea (excess output of undigested fat in the stool).
- The latter can arise either from inadequate action of pancreatic lipases or from inadequate solubilization of fat by hepatic bile secreted into the gut lumen.

- **The most common causes are :**
  pancreatic insufficiency associated with chronic alcoholism & Crohn disease.
  Other causes are intestinal bacterial overgrowth, cholestatic liver disease, & surgical procedures such as extensive ileal resection & gastrojejunostomy.

Defects of Mucosal Absorption

1. Lactose intolerance

- is caused by the deficiency of disaccharidase (lactase).
- The inherited form is rare but is of great consequence, because in infants it produces milk intolerance, leading to diarrhea, weight loss, & failure to thrive.
- The acquired deficiency is common among adults, particularly North American blacks. Aside from the need to avoid milk products, the disorder is of minimal consequence.
- The intestinal mucosa is morphologically normal.
- **Diagnosis** :
  is made by measurement of breath hydrogen level, which reflects bacterial overgrowth in the presence of excess intraluminal carbohydrate.

2. Deficiency of apolipoprotein B

- Apolipoprotein B is the protein is required for the assembly of dietary lipids into chylomicrons, which are then secreted into intestinal lymphatics, In the case of abetalipoproteinemia , the mucosal epithelial cell is unable to export lipid.
- In this disease, mucosal absorptive cells contain vacuolated lipid inclusions, but the mucosa is otherwise normal.
- This deficiency causes diarrhea & steatorrhea in infancy & significant failure to thrive.

3. Celiac disease (Gluten-sensitive enteropathy)

- Is a noninfectious cause of malabsorption resulting from a reduction in small intestinal absorptive surface area.
- Celiac disease is believed to be quite common, affecting about 1 in 300 persons both in Europe & in the US (1 Million in US), & many patients have subclinical disease.

- The basic disorder in celiac disease is immunological sensitivity to gluten, the component of wheat & related grains (oat, barley, & 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.

- There is hence a strong genetic susceptibility, with 95% of patients having an HLA- DQ2 haplotype & the remainder having HLA-DQ8.
- When the small intestinal mucosa exposed to gluten, it accumulates intraepithelial CD8+ T cells & large numbers of lamina propria CD4+ T cells sensitized to gliadin.

- The intestinal pathology may result from epithelial cell stress, perhaps induced by gliadin sensitivity, & CD8+ T cell-mediated killing of these epithelial cells.

- The effect of the immune response is :
  Total flattening of mucosal villi (& hence loss of surface area), affecting the proximal more than the distal small intestine, with lymphocytic & plasma cell infiltration in the lamina propria.

- Age of presentation, with symptomatic diarrhea & 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 twofold increase over the usual rate of Intestinal lymphomas and other malignancies include GI & breast carcinomas.
- In some patients with celiac disease there is an associated skin disorder called dermatitis herpetiformis.

4. Tropical sprue

- Resembles celiac disease in symptomatology, but occurs almost exclusively in persons living in or visiting the tropics.
- No specific causal agent has been clearly identified, but the appearance of malabsorption within days or few weeks of an acute diarrheal enteric infection strongly implicates an infectious process, as does the
- Prompt response to broad-spectrum antibiotic therapy!
- Small intestinal changes vary: from near normal to severe diffuse enteritis with villus flattening. In contrast to celiac disease, injury is seen at all levels of the small intestine, proximal and distal.

5. Whipple disease

- Is a rare systemic infection that may involve any organ of the body but principally affects the intestine, CNS, & joints.
- The hallmark of Whipple disease is a small intestinal mucosa laden with distended PAS-positive macrophages in the lamina propria.
- The causal organism is a gram-positive & culture-resistant actinomycete, Tropheryma whippelii.
- Affecting principally males in the 4th to 5th decades of life,
- Whipple disease causes a malabsorptive syndrome.
- Response to antibiotic therapy is usually prompt, but relapses are common.

- **CLINICALLY :**
  All the malabsorption syndromes resemble each other:
  Steatorrhea, the passage of abnormally bulky, frothy, greasy, yellow or gray stools is a prominent feature of malabsorption, accompanied by weight loss, anorexia, abdominal distention, borborygmi & flatus, & muscle wasting.

- **The consequences of malabsorption affect many organ systems:**

Hematopoietic system	*anemia → from iron, pyridoxine, folate, or vitamin B12 deficiency (vitamin B12 is normally absorbed in the ileum) *bleeding → from vitamin K deficiency (a fat-soluble vitamin).
Musculoskeletal system	*osteopenia & tetany → from defective calcium, magnesium, vitamin D, & protein absorption
Endocrine system	*amenorrhea, impotence, & infertility → from generalized malnutrition; & *hyperparathyroidism → from protracted calcium & vitamin D deficiency
Skin	*purpura & petechiae →from vitamin K deficiency *edema → from protein deficiency *dermatitis & hyperkeratosis → from deficiencies of vitamin A (fat soluble), zinc, essential fatty acids, & niacin *mucositis → from vitamin deficiencies
Nervous system	*peripheral neuropathy → from vitamin A & B12 deficiencies

INFLAMMATORY BOWEL DISEASE (IBD)

- Crohn's disease (CD) & Ulcerative colitis (UC) are chronic relapsing inflammatory disorders of unknown (idiopathic) origin, collectively known as idiopathic inflammatory bowel disease (IBD), which share many common features.
- IBD result from an abnormal local immune response against the normal flora of the gut & probably against some self antigens, in genetically susceptible individuals.
- CD may affect any portion of the GIT from esophagus to anus, but most often involves the ileum (terminal ileitis); 50% of cases exhibit noncaseating granulomatous inflammation.
- UC is a nongranulomatous disease limited to the colon.
- CD & UC differ in many respects, including the disease natural history, pathological aspects, treatment & responses to treatment.
- Before considering these diseases separately, the pathogenesis of both CD & UC will be considered.

- **Etiology & Pathogenesis of both CD & UC :**

The normal intestine is in a steady state of "physiologic" inflammation, representing a dynamic balance between

(1) Factors that activate the host immune system, such as luminal microbes, dietary antigens, & endogenous inflammatory stimuli; &

(2) Host defenses that down-regulate inflammation & maintain the integrity of the mucosa.

- The search for the causes of loss of this balance in CD & UC has revealed many parallels, but the origins of both diseases remain unexplained (thus their designation as idiopathic).

- **Genetic Predisposition** :

-There is little doubt that genetic factors are important in the occurrence of IBD.
-First-degree relatives are 3 to 20 times more likely to develop the IBD, & 15% of persons with IBD have affected first-degree relatives.
-In keeping with an underlying immunologic dysfunction, both CD & UC have been linked to specific major histocompatibility complex class II alleles.
-UC has been associated with HLA-DRB1, whereas HLA-DR7 & DQ4 alleles are associated with 30% of CD cases in North American white males.

- **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 CD & UC, the primary damaging agents appear to be CD4+ cells.
-The inflammatory cytokine TNF may play an important pathogenic role in CD; this is suggested by the effectiveness of treatment with TNF antagonists in CD.

- **Microbial Factors** :

-The sites affected by IBD-the distal ileum & the colon-are awash {covered by tides} in bacteria.
-While there is no evidence that these diseases are caused by microbes, it is quite likely that microbes provide the antigenic trigger to a fundamentally dysregulated immune system.
-This concept is strengthened by the observations that in murine models, IBD develops in the presence of normal gut flora but not in germ-free mice.

- The Final Common Pathway for the Pathogenesis of IBD is Inflammation, which is ultimately, the result of activation of inflammatory cells (neutrophils initially & mononuclear cells later) in the course, causing mucosal destruction & the intermittent bloody diarrhea that is characteristic of IBD.

- Most current therapeutic interventions act entirely or partly through nonspecific down-regulation of the immune system.
- Among **diagnostic tests**, the most useful is the detection of perinuclear antineutrophil cytoplasmic Abs, which are present in 75% of persons with UC & only 11% of individuals with CD.

1. Crohn's Disease (CD)

- **Epidemiology** :

*Worldwide in distribution, CD is much more prevalent in the US, GB, & Scandinavia than in Central Europe, & is rare in Asia & Africa.

*The incidence & prevalence of CD has been steadily raising in the US & Western Europe, with annual incidence in the US of 4 per 100,000 populations (12000 new cases/Year)

*It occurs at any age, from young childhood to advanced age, but peak incidence is between the 2nd & 3rd decades of life.

*Females are affected slightly more often than males.

*Whites appear to develop the disease 2 to 5 times more often than do nonwhites. In the US, CD occurs 3 to 5 times more often among Jews than among non-Jews.

*CD may affect any level of the GIT, from mouth to anus, but most commonly located at the terminal ileum. At first, the disease was thought to be limited to the ileum, & that is why it was referred to as "terminal ileitis" or "regional enteritis".

*BUT, CD must be viewed as a systemic inflammatory disease with predominant GIT 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, & obstructive uropathy.

- **GROSSLY** :

Site: In CD there is gross involvement of the small intestine alone in 30% of cases, of both small intestine & colon in 40%, & of the colon alone in about 30%.

CD disease may involve the mouth, esophagus, stomach, & duodenum, but these sites are distinctly uncommon.

Fully developed CD characterized by:

1. Classically, sharply limited, & demarcated diseased bowel segments from adjacent uninvolved bowel.
2. Transmural inflammation involving all the bowel wall, with
3. Mucosal damage Fissuring Fistula formation
4. Noncaseating granulomas in 50% of cases,

The intestinal wall is rubbery & thick, the result of edema, inflammation, fibrosis, & hypertrophy of the muscularis propria. As a result, the lumen is almost always narrowed; in the small intestine this is seen radiographically as "string sign," a thin stream of barium passing through the diseased segment.

In diseased segments, the serosa becomes granular & dull gray & often the mesenteric fat wraps around the bowel surface ("creeping fat").
When several bowel segments are involved, the intervening bowel is essentially normal ("skip" lesions).

- In the intestinal mucosa, early disease shows focal mucosal.

- **Ulcers** → resembling aphthous ulcers, edema, & loss of the normal mucosal texture.
  Later, ulcers coalesce into long, serpentine linear ulcers, which tend to be oriented along the axis of the bowel.
  Because the intervening mucosa tends to be relatively spared, it acquires a coarsely textured, **cobblestone appearance**.

- **Fissures** → develop between the folds of the mucosa, often penetrating deeply through the bowel wall all the way to the serosa. This may lead to:

- **Adhesions** with adjacent loops of bowel. Further extension of fissures leads to:

- **Fistula or sinus tract formation** to adherent viscera, to the outside skin, or into a blind cavity to form a localized abscess.

- {Summary: Cobblestone & Ulcers →Fissures →Adhesions →Sinus →Fistula →Abscess}.

- **H** :

mucosa show characteristic features :
(1) Inflammation, with neutrophilic infiltration into the epithelial layer (cryptitis) & accumulation within crypts to form crypt abscesses;
(2) Ulceration,
(3) Chronic mucosal damage, distortion & atrophy.

- Granulomas may be present any-where in the GIT, even in individuals with CD limited to one bowel segment. However, the absence of granulomas does not exclude the diagnosis of CD.

In diseased segments, the muscularis mucosae & muscularis propria are usually markedly thickened, & fibrosis affects all bowel layers (Transmural inflammation).

Lymphoid aggregates scattered through the full intestinal wall & in the extramural fat are characteristic.

- Particularly important in persons with long-standing chronic CD are dysplastic changes appearing in the mucosal epithelial cells. These may be focal or widespread, tend to increase with time, & predispose to a X 5-6 folds increased risk of carcinoma, particularly of the colon.

- **Clinically** :

the presentation of CD disease is highly variable & unpredictable.
(1) The dominant manifestations are recurrent episodes of diarrhea & crampy abdominal pain.
(2) In most patients, after an initial attack, the manifestations remit either spontaneously or with therapy, but characteristically they are followed by relapses, & intervals between successive attacks grow shorter.
(3) Superimposed on this course are the potential development of malabsorption & some of the extra-intestinal manifestations mentioned earlier.

- **The debilitating consequences of CD include**

(1) Fistula formation to other loops of bowel, urinary bladder, vagina, or perianal skin;
(2) Abdominal abscesses or peritonitis;
(3) Intestinal stricture or obstruction.

- **Rare devastating events are**

1. massive intestinal bleeding,
2. toxic dilation of the colon,
3. ca of the colon or small intestine. Although the increased risk for ca is significant, it is substantially less than that associated with UC.

2. Ulcerative Colitis (UC)

- UC is an inflammatory-ulcerative disease affecting the colon only, which is limited to the mucosa & submucosa, except in the most severe cases.
- Like CD, UC is a systemic disorder associated in some persons with migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, erythema nodosum, & hepatic involvement (pericholangitis a & primary sclerosing cholangitis).

- **There are several important differences between UC & CD:**
  the most important are:
  ➔ In UC:
  1. Superficial colonic mucosal ulcers, rarely extend below the submucosa & there is surprisingly little fibrosis, which means ...
  2. Serosal surface is completely normal.
  3. No Mural thickening; there are
  4. No granulomas, &
  5. No skip lesions, there appears to be a
  6. High risk of carcinoma development in the colon.

- **Epidemiology** :
  *UC is slightly more common (Double) than CD in the US & Western countries, with an incidence of around 7 per 100,000 populations, but it is infrequent in Asia & Africa.
  *As with CD, the incidence of UC has risen in recent decades.

  *In the US it is more common among whites than among nonwhites & exhibits no particular sex predilection.

  *UC may arise at any age, with a peak incidence between ages 20 & 25 years.

  *UC has a familial association; 20% of persons with the UC have affected relatives.
  Individuals with UC & ankylosing spondylitis have an increased frequency of the HLA-B27 allele, but this association is related to the spondylitis & not to UC.

- **GROSSLY** :
  UC usually involves the rectum & sigmoid & much less frequently involves the entire colon

  Colonic involvement is continuous from the distal colon, so that skip lesions are not encountered.

  Active UC denotes ongoing inflammatory destruction of the mucosa, with gross hyperemia, edema, granularity with friability & easy bleeding,

  In severe UC there is extensive & broad-based ulceration of the mucosa in the distal, or the whole colon aligned along its long axis. Isolated islands of regenerating mucosa bulge upward to create pseudopolyps

In rare cases, the muscularis propria is so compromised as to permit perforation & pericolonic abscess formation.

Exposure of the muscularis propria & neural plexus to fecal material also may lead to complete shutdown of neuromuscular function. When this occurs, the colon progressively swells & becomes gangrenous (toxic megacolon).

The **pathologic features of UC** are those of mucosal inflammation, ulceration, & chronic mucosal damage.
*A diffuse, predominantly mononuclear inflammatory infiltrate in the lamina propria is almost universally present,

*Neutrophilic infiltration of the epithelial layer may produce collections of neutrophils in crypt lumina (crypt abscesses), which are not specific for UC & may be observed in CD or any active inflammatory colitis.
*Unlike CD, there are no granulomas

*Further destruction of the mucosa leads to outright ulceration, extending into the submucosa.

*With remission of active disease, granulation tissue fills in the ulcer craters, followed by regeneration of the mucosal epithelium.

*Submucosal fibrosis & mucosal architectural disarray & progressive mucosal atrophy leads to a flattened & attenuated mucosal surface, which remain as residua of healed disease

- The most serious complication of UC is the development of colon carcinoma.
- Two factors govern the risk: duration of the disease & its anatomic extent.

- It is believed that with 10 years of UC limited to the left colon the risk is minimal, & at 20 years the risk is on the order of 2%.

- With pancolitis, the risk of carcinoma is 10% at 20 years & 15% to 25% by 30 years.
- Overall, the annual incidence of colon cancer in persons with UC of more than 10 years' duration is 1%.

- **Clinical Features of UC** :
  UC is a chronic relapsing disease marked by attacks of bloody mucoid diarrhea that may persist for days, weeks, or months & then subside, only to recur later.

  Presentation is usually insidious, with cramps, tenesmus, & colicky lower abdominal pain that is relieved by defecation.

  Grossly bloody stools are more common with UC than with CD, & the blood loss may be considerable. Extra-intestinal manifestations, particularly migratory polyarthritis, are more common with UC than with CD.

  Uncommon but life-threatening complications include
  *severe diarrhea & *electrolyte derangements, *massive hemorrhage, *severe colonic dilation (toxic megacolon) with *potential rupture, *perforation & *peritonitis.

  Diagnosis can usually be made by endoscopic examination & biopsy.
  Specific infectious causes must always be ruled out.

TUMORS OF THE SMALL AND LARGE INTESTINES

- **Colorectal cancer is**:
  the 1st commonest cancer in Jordanian males & the 2nd in females since 2004.
  In the US, it ranks 2nd to bronchogenic ca among the cancer killers
  about 5% of Americans will develop colorectal cancer & 40% of them will die from it & it represent 70% of all GIT malignancies.

- **Tumors of the Small & Large Intestines**

Non-neoplastic Polyps	Hyperplastic + Hamartomatous {Juvenile} + Peutz-Jeghers + Inflammatory + Lymphoid polyps.
Neoplastic Epithelial Lesions	Benign polyps: Adenomas Malignant: Adenocarcinoma (98%) & SCC of the anus
Other Tumors	Gastrointestinal stromal tumors (GIST), Carcinoid tumor & Lymphoma.

- **NB** :
  *Some polypoid lesions may be caused by submucosal or mural tumors.
  *However, as with the stomach, the term polyp:
  In the GIT, polyp (P) refers to protruding mass arising from the mucosal epithelium.
  *P may be sessile, i.e., without a stalk, But traction on the mass may create a stalked, so it is pedunculated

  *P may be formed as the result of abnormal mucosal inflammation, maturation, or architecture.
  These P are non-neoplastic & do not have malignant potential.

  *P that arise as result of epithelial proliferation & dysplasia are termed adenomatous P or adenomas and are true neoplastic lesions & are precursors of carcinoma.

  *Hyperplastic P are the most common polyps of the colon & rectum.
  When single, they do not have malignant potential.

  *However, sessile serrated adenoma lesion, which has some similarities with hyperplastic P, may have malignant potential.

- **Non-Neoplastic Polyps** :
  Majority of intestinal P occurs sporadically, particularly in the colon, & ↑ in frequency with age.
  Non-neoplastic P represent about 90% of all epithelial P in the large intestine & are found in more than 50% of persons older than 60y.

- **Hyperplastic polyps** :
  Are the commonest non-neoplastic P of the colon & rectum.
  Are small (<5 mm in□), nipple-like, hemispherical, smooth protrusions of the mucosa, 50% found in the rectosigmoid area.
  May occur singly, but are more often multiple.

  ***H** :
  -they contain abundant crypts lined by well-differentiated goblet or absorptive epithelial cells, separated by a scant lamina propria.
  Vast majority of hyperplastic polyps have no malignant potential.
  BUT some, either solitary or multiple ("hyperplastic polyposis") so-called sessile serrated adenomas, which are located on the right side of the colon, may be precursors of colorectal ca.
  These P show microsatellite instability & can give rise to ca by the mismatch repair pathway.

- **Juvenile (Rectal) polyps** :

*Are essentially hamartomatous proliferations of the lamina propria, enclosing widely spaced, dilated cystic glands.
*Occur mostly in children younger than 5 years old, but also may be in found in adults of any age.
*Occur singly, in the rectum, 1-3 cm in diameter; rounded, smooth, or slightly lobulated & sometimes pedunculated.
*May cause rectal bleeding
*May become twisted on their stalks (torsion) to undergo painful infarction.
*Because they are hamartomatous, they have no malignant potential.

- **Adenomas** :

*Adenomas are neoplastic P that range from small pedunculated to large sessile tumors.
*Prevalence of colonic adenomas is 20% -30% before age 40, rising to 50% after age 60.
*M/F ratio is 1:1
*All adenomatous lesions arise as a result of epithelial proliferation & dysplasia, which may range from mild to so severe as to represent transformation to carcinoma.

*There is a well-defined familial predisposition to sporadic adenomas, accounting for about a X4 fold greater risk for adenomas among first-degree relatives, & also a X4 fold greater risk of colorectal ca in any person with adenomas.
*There is strong evidence that most sporadic invasive colorectal adenocarcinomas arise in preexisting adenomatous lesions.

❖ **The 4 subtypes of adenomatous P base on their epithelial architecture are:**

1. Tubular adenomas	90%; mostly small & pedunculated; showing tubular glands, recapitulating mucosal topology
2. Villous adenomas	1% - villous projections, tend to be large & sessile
3. Tubulovillous adenomas	5% -10% - a mixture of the above
4. Sessile serrated adenomas	serrated epithelium lining the crypts

- **The malignant risk with an adenomatous P is correlated with 3 interdependent features :**
  1. polyp size 2. histologic architecture 3. severity of epithelial dysplasia

- Cancer is rare in tubular adenomas smaller than 1 cm in diameter.
- Cancer risk is high (approaching 40%) in sessile villous adenomas larger than 4 cm in diameter.
- Severe dysplasia, is often found in villous areas.
- Among these variables, maximum diameter is the chief determinant of the risk of an adenoma's harboring ca.

1. Tubular adenomas

- May arise anywhere in the colon, however, 50% are found in the rectosigmoid area.
- 50% of tubular adenomas are single, in the other 50%, two or more are present.
- Small tubular adenomas are sessile, while Larger ones are pedunculated; having stalk & with raspberry-like heads.
- **H** :

  the stalk of tubular adenomas is covered by normal colonic mucosa, but the head is composed of neoplastic epithelium, forming branching glands lined by hyperchromatic, tall cells, which may/may not show mucin secretion.
  In the clearly benign lesion, the branching glands are well separated by lamina propria, & the level of dysplasia or cytologic atypia is slight.

However, all degrees of dysplasia may be encountered, ranging up to cancer confined to the mucosa (intramucosal carcinoma) or invasive carcinoma extending into the submucosa of the stalk.

A frequent finding in any adenoma is superficial erosion of the epithelium, the result of mechanical trauma.

- **Clinically** :
  the smaller adenomas are usually asymptomatic, until such time that occult bleeding (much more frequently from villous adenomas) leads to clinically significant anemia

2. Villous adenomas :

- (1%) are larger, tend to occur in older persons, most commonly in the rectum & rectosigmoid, but they may be located elsewhere
- are sessile, up to 10 cm in diameter, cauliflower-like masses projecting above the surrounding mucosa.
- **H** :
  there is frond-like (finger-like) villiform projections of the mucosa covered by dysplastic, piled-up, columnar epithelium.
  All degrees of dysplasia may be encountered, & invasive carcinoma is found in as many as 40% of these lesions, the frequency being correlated with the size of the P

- Villous adenomas may secrete sufficient amounts of mucoid material rich in protein & potassium to produce hypoproteinemia or hypokalemia.

3. Tubulovillous adenomas :

- (5-10%) are composed of mix tubular & villous areas.
- They are intermediate between the tubular & the villous lesions in their frequency of, been pedunculated or sessile, their size, the degree of dysplasia, & the risk of harboring intramucosal or invasive carcinoma.

- All adenomas, are to be considered potentially malignant; therefore, prompt & adequate excision is mandated.

Familial Polyposis Syndromes

- The importance of this uncommon, autosomal dominant disorders, called familial polyposis syndromes, lies in the propensity (tendency) for malignant transformation.

- Familial adenomatous polyposis (FAP) individuals typically develop 500 to 2500 {a minimum of 100 is required for the diagnosis} colonic adenomas that carpet the mucosal surface

- Multiple adenomas may also be present elsewhere in the GIT, including almost a 100% lifetime incidence of duodenal adenomas.

- Most polyps are tubular adenomas; an occasional P have villous features.
- 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.

Gardner syndrome & the much rarer Turcot syndrome	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, & soft tissue tumors, to name a few.
Peutz-Jeghers polyps	are uncommon hamartomatous polyps that occur as part of the rare autosomal dominant Peutz- Jeghers syndrome, characterized in addition by melanotic mucosal & cutaneous pigmentation. (This syndrome is caused by germ-line mutations in the LKB1 gene, which encodes a serine threonine kinase).
Cowden syndrome	is also characterized by hamartomatous polyps in the GIT & by an ↑ risk of tumors of the thyroid, breast, uterus, & skin. This syndrome is caused by germ-line mutations in the PTEN (phosphatase & tensin homologue) tumor suppressor gene

- Peutz-Jeghers & Cowden syndromes, like the other familial polyposis syndromes, are associated with an ↑ risk of both intestinal & extraintestinal malignancies.

Colorectal Carcinoma (Ca)

- is the 1st commonest cancer in Jordanian males & the 2 nd in females since 2004.
- Adenocarcinomas comprise 98% of all colonic cancers (2% SCCa anal channal).
- It represent prime challenges to the medical profession, because they almost always arise in adenomatous polyps that are generally curable by resection .

- **Epidemiology** :
  Peak incidence for colorectal ca is 60 to 70 years of age
  fewer than 20% of cases occur before the age of 50 years.
  M/F ratio is 1.2:1.
  Adenomas are the presumed precursor lesion for most of the tumors;
  The frequency of colorectal cancer arises de novo from flat colonic mucosa remains undefined, but appears to be low

- Both genetic & environmental influences contribute to the development of colorectal ca.

- **When colorectal cancer is found in a young person** :
  1. preexisting ulcerative colitis
  2. one of the polyposis syndromes must be suspected.
  3. individuals with hereditary nonpolyposis colorectal cancer syndrome {HNPCC, also known as Lynch syndrome, also at risk of developing other tumors, such as cholangiocarcinomas}
     caused by germ-line mutations of DNA mismatch repair genes, are at a high risk of developing colorectal cancers.

- Colorectal ca has a worldwide distribution, with the highest incidence rates in the US, Canada, Australia, New Zealand, Denmark, Sweden, & other developed countries.

  Its incidence is substantially lower, up to 30-fold less, in India, Africa, & South America.

- Environmental influences, particularly dietary practices, are implicated in the striking geographic variation in incidence.

- **The dietary factors receiving the most attention are a:**

(1) Low contents of unabsorbable vegetable fiber
(2) High contents of refined carbohydrates
(3) High fat content (as from meat)
(4) Decreased intake of protective micronutrients such as vitamins A, C, & E.

- **It is theorized that**:

a) reduced fiber content leads to ↓ stool bulk
b) fecal retention in the bowel
c) an altered bacterial flora of the intestine.
d) Potentially toxic oxidative byproducts of carbohydrate degradation by bacteria are therefore present in higher concentrations in the stool & are held in contact with the colonic mucosa for longer periods of time.
e) Moreover, high fat intake enhances the synthesis of cholesterol & bile acids by the liver, which in turn may be converted into potential carcinogens by intestinal bacteria.
f) Refined diets also contain less of vitamins A, C, & E, which may act as oxygen radical scavengers.

- **Intriguing as these scenarios are, they remain unproven!**

- Epidemiologic studies suggest that use of aspirin & other NSAIDs exerts a protective effect against colon cancer.
- In the Nurses' Health Study, women who used 4 to 6 tablets of aspirin daily for 10 years or more had a ↓ incidence of colon ca

- **The development of ca from adenomatous lesions is documented by the following general observations:**
  - Populations that have a high prevalence of adenomas have a high prevalence of colorectal ca, & vice versa.
  - The distribution of adenomas within the colorectum is more or less comparable to that of colorectal ca.
  - The peak incidence of adenomatous polyps antedates by some years the peak for colorectal cancer.
  - When invasive ca is identified at an early stage, surrounding adenomatous tissue is often present
  - The risk of cancer is directly related to the number of adenomas, & hence the virtual certainty (100%) of cancer in persons with Familial Polyposis Syndromes.
  - Programs that carefully follow persons for the development of adenomas, & remove all that are identified reduce the incidence of colorectal cancer.

Colorectal Carcinogenesis

- It is now believed that there are two pathogenetically distinct pathways for the development of colon cancer, the

(A) APC/β-catenin pathway (or adenoma-carcinoma sequence)
(B) Mismatch repair (or microsatellite instability) pathway.

Both of these pathways involve the stepwise accumulation of multiple mutations, but the genes involved & the mechanisms by which the mutations accumulate are different.

(A) **The first pathway** :

- variously called the adenoma- carcinoma sequence, the APC/β-catenin pathway, or the chromosome instability pathway,
- is characterized by chromosomal instability associated with stepwise accumulation of mutations in a number of oncogenes & tumor suppressor genes.
- The molecular evolution of colon cancer along this pathway occurs through a series of morphologically identifiable stages.
- Initially, there is localized epithelial proliferation, followed by formation of small adenomas, progressively enlarge & to be more dysplastic, & ultimately develop invasive ca.
- Such adenoma-carcinoma sequence, accounts for about 80% of sporadic colon tumors.
- **The genetic correlates of this pathway are as follows:**

I. Loss of the APC tumor suppressor gene, present in 60% to 80% of sporadic colonic ca.
This is believed to be the earliest event in the formation of adenomas.
Recall that in the FAP & Gardner syndromes, germ-line mutations in the APC gene give rise to hundreds of adenomas that progress to form ca.

II. Mutation of K-RAS. Seen n 10% of adenomas less than 1 cm, in 50% of adenomas larger than 1 cm, in 50% of ca.

III. 18q21 deletion. Loss of a putative cancer suppressor gene on 18q21 has been found in 60% to 70% of colon cancers.
Three genes have been mapped to this chromosome location: DCC (deleted in colon carcinoma), SMAD2, & SMAD4

IV. Loss of p53. Loss of this tumor suppressor gene is noted in 70% to 80% of colon cancers, yet similar losses are infrequent in adenomas, suggesting that mutations in p53 occur late in colorectal carcinogenesis

V. Alterations in the methylation level of tumor suppressor genes occur in the development of colorectal tumors in the adenoma-carcinoma pathway.

(B) The second pathway :

- of colorectal carcinogenesis is characterized by genetic lesions in DNA mismatch repair genes.
- It is involved in 10% to 15% of sporadic cases.
- As in the APC/β-catenin schema, there is accumulation of mutations, but the involved genes are different.
- 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 & 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, & PMS2) give rise to the hereditary nonpolyposis colon carcinoma (HNPCC).

- Loss of DNA mismatch repair genes leads to a hypermutable state in which simple repetitive DNA sequences, called microsatellites, are unstable during DNA replication, giving rise to widespread alterations in these repeats.

- The resulting Micro Satellite Instability (MSI) is the molecular signature of defective DNA mismatch repair, & hence this pathway is often referred to as the MSI pathway.
- Sessile serrated adenomas located on the right side of the colon display MSI & may be precancerous.
- Fully developed T that arise via the mismatch repair pathway do show some distinctive morphologic features, including proximal (Rt) colonic location, mucinous histology, & infiltration by lymphocytes.

- **Generally** :
  these T have a better prognosis than do stage- matched tumors that arise by the APC/β-catenin pathway.

- **Morphology of colorectal ca** :
  - Site:
  25% @ cecum & ascending colon,
  25% @ descending colon & proximal sigmoid;
  25% @ distal sigmoid & rectum.
  25% @ remainder are scattered elsewhere.

  Most often ca occur singly & have frequently obliterated their adenomatous origins.
  When multiple carcinomas are present, they are often at widely separated from each other.

- **Grossly** :
  ca in the proximal {cecum & ascending colon} tend to grow as polypoid, exophytic masses.
  Obstruction is uncommon.

  Distal colon ca tend to be annular stenosing , encircling lesions that produce so-called napkin-ring constrictions of the bowel & narrowing of the lumen; the margins of the ulcerating napkin ring are classically heaped up.

  Some ca are ulcerative.

  With time, all colorectal carcinomas directly penetrate bowel wall & appearing as firm masses on the serosa.

- **H** :
  all are adenocarcinomas, 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 where it dissect through it, facilitating the extension of cancer & worsen the prognosis.

  Cancers of the anal zone are predominantly SCCa.

- **Clinically** :
  colorectal ca remain asymptomatic for years; symptoms develop insidiously & late.

  Cecal & right colonic ca most often present with fatigue, weakness, & iron deficiency anemia.

  ® Rule: Although anemia in females may arise from gynecologic causes, the rule is: iron deficiency anemia in an older man means GIT cancer until proved otherwise.

  Left-sided ca may produce occult bleeding, changes in bowel habit, or crampy left lower quadrant discomfort.

- All colorectal carcinomas invade & spread directly into adjacent structures & by metastasis through the lymphatics & BV.

- **In order of preference, the favored sites for metastasis are the :**
  regional LN → liver → lungs → bones.

- Generally, the ca spreads beyond curative surgery in 25% to 30% of patients.
- The challenge is to discover the neoplasm when curative resection is possible.

- Ca of the anal region are locally invasive & metastasize to regional LN & distant sites.
- Almost 80% of cancers of the anal canal are SCCa.

- **Diagnosis** of colorectal T rely on :
  *digital per-rectal (PR) examination
  *fecal testing for occult blood loss
  *endoscope
  *confirmatory biopsy for diagnosis, & Barium enema
  *CT & other X-ray studies are used to assess metastatic spread.
  *Serum markers for T, such as elevated blood levels of CEA, are of little diagnostic value, because they reach significant levels only after the cancer has achieved advanced stage.

- Because APC mutations occur early in most colon cancers, molecular detection of APC mutations in epithelial cells, isolated from stools, is being evaluated as a diagnostic test (400$).

- The single most important prognostic indicator of colorectal ca is the tumor stage (TNM) at the time of diagnosis.

Tumors (T) of the Small Intestine

- Whereas the small bowel represents 75% of the length of the GIT, its T account for only 3% to 6% of GIT T, with a slight preponderance of BT.
- The most frequent benign T in the small intestine are stromal tumors of predominantly smooth muscle origin, adenomas, & lipomas, followed by various neurogenic, vascular, & hamartomatous epithelial lesions.

- Small intestinal adenomas may present with obstruction, anemia, or intussusception.
- Adenomas adjacent to the ampulla of Vater may produce biliary obstruction, with jaundice.
- Small intestinal adenoca & carcinoids have equal incidence.

1. Adenocarcinoma of the Small Intestine

- Rare T, grow in a annular-stenosing pattern or as polypoid fungating T.
- Most ca arise in the duodenum (including the ampulla of Vater).
- **Clinically** :
  colicky pain, nausea, vomiting, & weight loss are the common presenting S&S , but generally appear late.
  By the time of diagnosis, most T have already penetrated the bowel wall, invaded the mesentery, spread to regional LN, & metastasized to the liver or more widely.
  Despite these problems, wide en bloc excision of these ca yields a 5-year survival rate of about 70%.

2. Gastrointestinal Stromal Tumors (GISTs)

- GISTs classified on the basis of a common (CD117) molecular marker & with the use of immunohistochemical markers
- **GISTs are now subdivided into tumors with:**

(a) SMC differentiation (most common type)
(b) Neural differentiation (GI autonomic nerve tumors)
(c) Both SMC/neural dual differentiation
(d) Lacking differentiation toward these lineages.

- GISTs, mostly occur in adults, constitute the majority of nonepithelial T of the stomach, but can be present in the small & large intestine.
- The preferred sites for metastases of the malignant T are the liver, peritoneum, & lungs.
- Metastases can appear more than 20 years after removal.

- All GISTs have a somatic mutation in the c-KIT (CD117) gene, which encodes a tyrosine kinase receptor.
- Mutations in this receptor lead to consitutive signaling from the receptor, without the need for a ligand.
- The tyrosine kinase inhibitor {imatinib mesylate}, shown to be highly effective in the treatment of individuals with chronic myeloid leukemia (CML), has been used very successfully in the treatment of GISTs that have a c-KIT mutation.

3. Gastrointestinal Lymphoma

- Any segment of the GIT may be involved secondarily by systemic dissemination of non-Hodgkin lymphomas.
- However, 40% of lymphomas arise in extra-nodal sites, & the gut is the most common extra-nodal location;
- 1% to 4% of all GI malignancies are lymphomas.

- By definition, primary GI lymphomas reveal no evidence of liver, spleen, or bone marrow involvement at the time of diagnosis; regional LN involvement may be present.
- GIT lymphomas can be of B- or T-cell origin.

- The most common form in West is a sporadic lymphoma that originates in B cells of the Mucosa-Associated Lymphoid Tissue (MALT) of the GIT, i.e., MALT lymphoma.
- **MALT lymphoma** :
  *usually affects adults, lacks a sex predilection, & may arise anywhere in the gut: stomach (55% of cases), small intestine (25%), & colon (20%).
  *The appendix & esophagus are rarely involved.

  ***Gastric MALT lymphomas arise in the setting of:**
  1. H. pylori-associated chronic gastritis, in which there is an
  2. intense mucosal lymphoid activation of T & B cells leading to
  3. polyclonal B-cell hyperplasia & eventually, the emergence of
  4. a monoclonal B-cell lymphoma.

  *About 50% of gastric lymphomas can regress with antibiotic treatment for H. pylori.
  Those that do not regress usually contain the t(11;18) or other genetic abnormalities.

  MALT lymphoma cells are CD5 & CD10 negative, & a t(11;18) translocation is common (the translocation creates a fusion gene between the apoptosis inhibitor BCL-2 gene in chromosome 11 & the MLT gene in chromosome 18).

- Primary GI lymphomas have a better prognosis than do those arising in other sites, because combined chemotherapy, surgery, & radiation therapy offer reasonable hopes of cure.
- Celiac disease is associated with a higher than normal risk of intestinal T- cell lymphomas.

4. Carcinoids

- Cells generating peptide & nonpeptide hormones are normally dispersed along the length of the GIT mucosa & have a major role in coordinated gut function.

- Most tumors (T) that develop from endocrine cells in the body arise in the gut, such T are called {carcinoid T}.
- Carcinoid is an old term, refer to "carcinoma-like," which has persisted through the decades.

- Carcinoids develop in the pancreas or peripancreatic tissue, lungs, biliary tree, & liver.
  The peak incidence of these T is in the 6th decade, but they may appear at any age.

- Carcinoids compose 50% of small intestinal malignant T , but less than 2% of colorectal malignant T.

- All carcinoids are potentially malignant T, but the tendency for aggressive behavior correlates with the site of origin, the depth of local penetration, & the size of the T .

- Appendiceal & rectal carcinoids rarely metastasize, even though they may show extensive local spread.

- By contrast, 90% of gastric, ileal, & colonic carcinoids that have penetrated 50% of the muscle wall {especially those larger than 2 cm in diameter} have spread to LN & distant sites, including the liver at the time of diagnosis,.

- The 5-year survival rate for carcinoids (excluding appendiceal) is approximately 90%.
- The secretory products of some carcinoids can produce a variety of syndromes.
  When a T secretes a predominant product to cause a clinical syndrome, it may be called by that name (e.g., gastrinoma, somatostatinoma, & insulinoma).

- The appendix is the most common site of GI carcinoid T {where it appear as bulbous swellings of the tip, which frequently obliterate the lumen}, followed by the small intestine (primarily ileum), rectum, stomach, & colon.

- Other gastrointestinal carcinoids appear as intramural or submucosal T that create small, polypoid, or elevations less than 3 cm in diameter

- The overlying mucosa may be intact or ulcerated, & the T may infiltrate the bowel wall & invade the mesentery.

- Carcinoids of the stomach & ileum are frequently multicentric, but the remainder tends to be solitary.

- Carcinoids may be small, less than 1.0 cm in diameter & are extremely difficult to find, even during surgical exploration!

- **Carcinoids characteristic feature**
  C/S is the solid, yellow- tan appearance.
  They are exceedingly firm because of desmoplasia
  when they invade small bowel mesentery they may cause angulation or kinking with obstruction.
  Rectal & appendiceal carcinoids almost never metastasize.

- **H** :
  the T cells may form discrete islands, trabeculae, strands, glands, or undifferentiated sheets.
  They are monotonously similar, with minimal pleomorphism, having a scant, pink granular cytoplasm & a round-to-oval stippled nucleus & mitoses are usually absent
  By EM
  most T cells contain cytoplasmic, membrane-bound secretory granules with osmophilic centers (dense-core granules).

- Most carcinoids can be shown to contain chromogranin A, synaptophysin, & neuron-specific enolase.

- All appendiceal (& most other) carcinoids are frequently asymptomatic.
- 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 endocrinopathies or syndromes.
- Gastric, peripancreatic, & pancreatic carcinoids release their products directly into the systemic circulation & can produce the Zollinger-Ellison syndrome by excess elaboration of gastrin, Cushing syndrome caused by ACTH secretion, hyperinsulinism, & others.

- Some carcinoids are associated with a distinctive carcinoid syndrome,occuring in 1% of all patients with carcinoids & in 20% of those with widespread metastases.

- **The most important features of which are :**
  Cutaneous flushes & apparent cyanosis, Intestinal hypermotility, Diarrhea, cramps, nausea, vomiting (most patients), bronchoconstrictive asthmatic attacks, Cough, wheezing, dyspnea (1/3 of patients)

- Most manifestations arise from the elaboration of serotonin (5-hydroxytryptamine [5-HT]); which is degraded in the liver to functionally inactive 5-hydroxyindoleacetic acid {5-HIAA}.

  Elevated levels of 5-HT & its metabolite 5-HIAA are present in the blood & urine of most individuals with the classic carcinoid syndrome.

  Thus, with GI carcinoids, hepatic dysfunction resulting from metastases must be present for the development of the syndrome.

APPEDIX

- Appendicitis is the most common cause of acute abdomen.
- 10% of US & Western countries populations develop appendicitis (Like PU!). It can occur at any age, with peak incidence in the 2nd & 3rd decades, & M/F ratio of 1.5:1.
- **Pathogenesis** :
  Appendicitis associated with obstruction in 50% to 80% of cases
  usually in the form of a fecaliths (hard fecal mass) &, less commonly, a gallstone, tumor, or ball of worms (Oxyuriasis vermicularis).

  With continued secretion of mucinous fluid, the buildup of intraluminal pressure, presumably, is sufficient to cause collapse of the draining veins.
  Obstruction & ischemic injury then favor bacterial proliferation, additional inflammatory edema & exudation further compromising the blood supply.

Nevertheless, 20% to 50% of inflamed appendices have no demonstrable luminal obstruction, & the pathogenesis of the inflammation remains unknown!

- **Morphology of appendicitis** :
  - ➔ Initially, a scant neutrophilic exudate may be found throughout the mucosa, submucosa, & muscularis propria.
    Subserosal vessels becomes congested, with a modest perivascular neutrophilic infiltrate, transforming the normal glistening serosa into a dull, granular, red membrane; signifies early acute appendicitis for the operating surgeon.
  - ➔ Later, a prominent neutrophilic exudate generates a fibrinopurulent exudate reaction over the serosa, along with foci of necrosis & mucosal ulcerations; abscess formation within the wall,
    This is acute suppurative appendicitis.
  - ➔ More severe inflammation leads to large areas of hemorrhagic mucosal ulceration, & green-black gangrenous necrosis through the wall extending to the serosa, creating acute gangrenous appendicitis that is quickly followed by rupture, perforation & suppurative peritonitis
  - ➔ The essential histologic criterion for the diagnosis of acute appendicitis is neutrophilic infiltration of the muscularis propria.

- **Clinically** :
  classical case of appendicitis is marked by pain in the right lower abdomen & Rt Iliac Fossa (RIF) tenderness & rigidity, associated with nausea, vomiting, fever & leukocytosis.
  Regrettably, a large number of cases are not classic (specially with retrocaecal appendicitis) & some cases are remarkably silent, particularly in the aged.

- It is generally conceded (accepted) that it is better to occasionally resects a normal appendix than to risk the morbidity & mortality (<2%) of appendiceal perforation.

Tumors of the appendix

- The most common tumor of the appendix is carcinoid.
  Other important lesions are mucocele of the appendix & mucinous tumors.

- **Mucocele** :
  is dilation of the lumen of the appendix by mucinous secretion.
  It is caused by non-neoplastic obstruction (e.g., fecaliths) of the lumen, permitting the slow accumulation of sterile mucinous secretions, which eventually induces atrophy of the mucin-secreting mucosal cells, which stop the secretion.
  This condition is usually asymptomatic; rarely, mucocele ruptures, spilling innocuous (harmless) mucin into the peritoneum.

- **Mucinous tumors** :
  range from the benign mucinous cystadenoma, to mucinous cystadenocarcinoma, which may invades & permeate the wall, allowing tumor cells to implant throughout the peritoneal cavity, which becomes filled with mucin to a form disseminated intraperitoneal cancer called pseudomyxomatous peritonei.