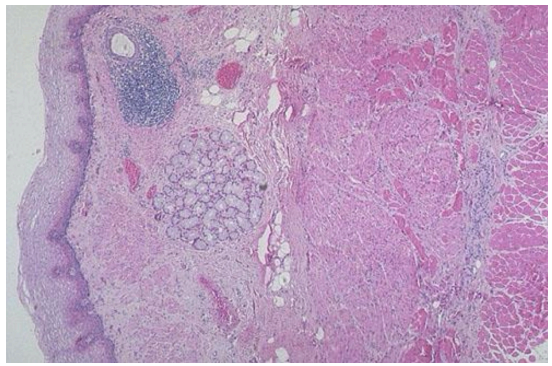
Gastrointestinal system pathology
-Midterm material-

Diseases of the esophagus

-The esophagus is a muscular tube that extends from the epiglottis to the gastroesophageal junction.

-The esophagus is lined by stratified squamous epithelium.



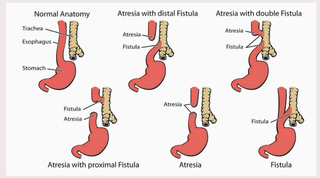
Obstructive diseases

Mechanical obstruction

Atresia

Thin,non-canalized cord replaces a segment of the esophagus,mostly near or at the tracheal bifurcation

Could be with or without fistula (upper or lower part of the esophagus pouches to a bronchus or trachea)



Clinical presentation :

Shortly after birth : regurgitation during feeding

Needs surgical management

If with fistula: aspiration,suffocation,pneumonia,water and electrolyte imbalance

Fistula

Duplication

Agenesis(rare)

Stenosis

Fibrous thickening of the submucosa and atrophy of muscularis propria due to inflammation and scarring

Could be acquired(mostly) or congenital

Causes:

Chronic gastroesophageal reflux disease (GERD)

Systemic sclerosis

Irradiation

Ingestion of caustic agents

Clinical presentation:

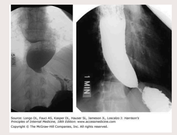
Progressive dysphagia (stats with solids and progresses to problems with liquids)

Functional obstruction

-Normally we need peristaltic contractions to deliver food and liquids to the stomach
-Dysmotility : discoordinated peristaltic contractions or spasm of muscularis

Achalasia

-Incomplete relaxation of the lower esophageal sphincter(LES)
-Increased LES tone
-Esophageal aperistalsis



Clinical presentation:

Difficulty in swallowing

Regurgitation

Chest pain (sometimes)

Could be primary(mostly) or secondary

Primary

Idiopathic

Degenerations of distal esophageal inhibitory neurons

Secondary

Loss of neural innervation due to damage in esophagus or vagus nerve or the distal motor nucleus of vagus

Chagas disease (Trypanosoma cruzi infection) causes distraction of myenteric plexus —>failure of the LES to relax —> esophageal dilation

Vascular diseases

Esophageal varices

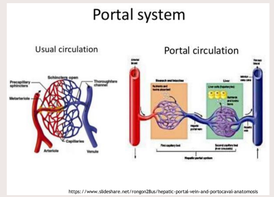
Tortuous dilated vein within the submucosa of the distal esophagus and proximal stomach

Diagnosis :

- Endoscopy
- Angiography

Pathogenesis :

- Portal circulation: blood goes from the GI tract to the liver for detoxification via portal vein ,then blood goes from the liver to the inferior vena cava and then the heart.
- Diseases that impede portal blood flow (like portal hypertension) result in esophageal varices
- Because of portal hypertension blood is redirected to collateral channels in distal esophagus —>shunt of blood from portal to systemic circulation—>dilated collaterals in distal esophagus—>varices
  - -Additional explanation : because of portal hypertension blood that comes from the GI tract finds another route to reach the heart this route is the collateral vessel within the wall of the esophagus,through this way the blood reaches the heart bypassing the liver.
- Distal esophagus is the site of Porto-systemic anastomosis



Causes of portal hypertension

- Liver cirrhosis(most common) , alcoholic liver disease
- Hepatic schistosomiasis(second most common)

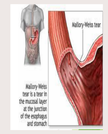
Clinical presentation:

- Often asymptomatic
- Rupture leads to massive hematemesis and death, 20% of patients die from the first bleed despite interventions
- Death due to hemorrhage,hepatic coma , and hypovolemic shock
- Rebleeding in 60% of patients

Esophagitis

Esophageal laceration

- Mallory Weiss tear
  - Cause: Severe retching or forceful prolonged vomiting
  - Clinical presentation : Hematemesis
  - Treatment : Heals quickly, no surgical intervention
  - -Superficial ,linear laceration,longitudinally oriented,cross the Gastroesophageal junction (GEJ)



Mucosal injury

- Chemical esophagitis
  - Damage to esophageal mucosa by irritant
  - Causes:
    - Alcohol and heavy smoking
    - Excessively hot fluids
    - Corrosive acids or alkalis
    - Medicinal pills (doxycycline and bisphosphonates)
    - Iatrogenic (chemotherapy,radiotherapy, graft vs host disease(GVHD))
  - Clinical presentation
    - Ulceration and acute inflammation
    - Self limited pain
    - Odynophagia(pain with swallowing)
    - Hemorrhage,stricture(may lead to stenosis),perforation in severe cases

Eosinophilic esophagitis

- -chronic immune mediated disorder
  -eosinophilic infiltration of squamous epithelium
- Symptoms
  - Food impaction and dysphagia in adults
  - Feeding intolerance or GERD-like symptoms in children
- Morphology
  - Rings in the upper and mid esophagus
  - Numerous eosinophils in epithelium
  - Far from gastroesophageal junction (GEJ)
- Management
  - Treatment
    - Corticosteroids (topical or systemic)
    - Dietary restrictions (cow milk and soy products)
  - -most patients are atopic (atopic dermatitis ,allergic rhinitis,asthma)or modest peripheral eosinophilia
    -refractory to proton pump inhibitors (will not response to PPI)

Infections

- -mostly in debilitated or immunosuppressed patients
- Etiology:
  - Viral
    - Herpes simplex virus
      - Punched out ulcer
        - On endoscopy
      - Epithelial cells show nuclear changes in the form of nuclear viral inclusions
      - Degenerating epithelial cells ulcer edge
      - Multinucleated epithelial cells (epithelial cells fuse to form one cell with many nuclei)
        - Histopathology
    - Cytomegalovirus
      - Shallow ulcer
        - On endoscopy
      - Nuclear and cytoplasmic inclusions in capillary endothelium and stromal cells(supportive connective tissue cells)
      - Mega cells(large cells)
        - Histopathology
  - Fungal
    - Candida (mostly)
      - Gray-white pseudo membranes
        - Adherent
      - Matted fungal hyphae
      - Inflammatory cells
        - Microscopically
    - Mucormycosis
    - Aspergillosis
  - Bacterial (less common 10%)

Reflux esophagitis

- -reflux of gastric content into the lower esophagus
  -most frequent cause of esophagitis
  -most common complaint by patients visiting outpatient clinics
  -squamous epithelium is sensitive to acids in gastric content
- Gastroesophageal reflux disease (GERD)
  - Protective forces:
    - Mucin and bicarbonate from submucosa glands
    - High lower esophageal sphincter(LES) tone
  - Causes:
    - Decreased LES tone
      - Alcohol and tobacco
      - Hiatal hernia
      - CNS depressants
    - An increase in abdominal pressure
      - Obesity
      - Pregnancy
      - Delayed gastric emptying
      - Increased gastric volume
    - Idiopathic
- Morphology
  - Macroscopic (endoscopy)
    - Depends on severity (unremarkable or simple erythema)
  - Microscopic
    - Eosinophils infiltration(early)
    - Neutrophils infiltration (more severe)
    - Basal zone hyperplasia
    - Elongation of lamina propria papillae
- Clinical presentation:
  - Most common over 40 years but may also occur in infants and children
  - Heartburn
  - Dysphagia
  - Regurgitation of sour tasting gastric content
  - Rarely: severe chest pain mistaken for heart disease
- Treatment
  - Proton pump inhibitors
- Complications:
  - Esophageal ulcers
  - Hematemesis
  - Melena(a sign of upper GI bleeding)
  - Strictures (stenosis)
  - Barrett esophagus

Barrett esophagus

-Complication of chronic GERD
-10% of patients with symptomatic GERD
-males>females , 40-60 years old

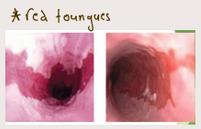
-Intestinal metaplasia—>direct precursor of esophageal adenocarcinoma
-0.2-1% / year develop dysplasia (precursor of adenocarcinoma)

Management

Periodic surveillance endoscopy with biopsy to screen for dysplasia

Interventions for high grade dysplasia and Intramucosal carcinoma

Morphology

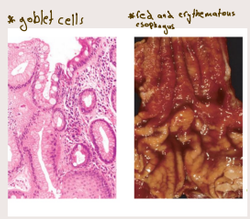


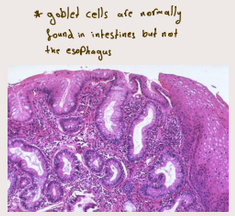
Endoscopy

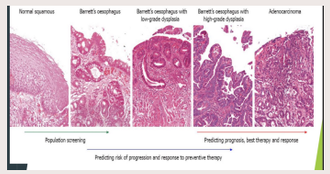
- Red tongues extending upwards from GEJ

Histology

- Intestinal metaplasia (presence of goblet cells)
- +-dysplasia(low grade or high grade)
- Intramucosal carcinoma : invasion into lamina propria





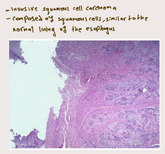


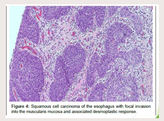
Esophageal tumors

Squamous cell carcinoma

- -Most common
  -more in rural areas and low resource countries
  -male : female (4:1)
- Risk factors
  - Alcohol and tobacco
  - Poverty
  - Caustic injuries
  - Achalasia
  - Plummer Vinson syndrome (iron deficiency,anemia,dysphagia, esophageal webs)
  - Very hot beverage
  - Previous radiation therapy
- Pathogenesis
  - In western — Alcohol and tobacco use
  - Other areas — Nutritional deficiencies,polycystic hydrocarbon,nitrosamines,fungus-contaminated foods
  - Human papilloma virus implemented in high risk regions
- Morphology
  - -Middle third (50% of cases)
    -polyploid, ulcerated , or infiltrative
    -esophageal wall thickening and lumen narrowing
    -invade surrounding structures (bronchi , mediastinum, pericardium, aorta)

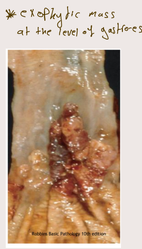
  - Microscopic
    - Pre-invasive: squamous dysplasia or carcinoma in situ
    - Well to moderately differentiated invasive squamous cell carcinoma
    - Intramural tumor nodules away from the main tumor
- Lymph node metastasis
  - Upper 1/3 : cervical lymph nodes
  - Middle 1/3 : mediastinalparatracheal lymph nodes ,tracheobronchial lymph nodes
  - Lower 1/3 : gastric and celiac lymph nodes
- Clinical features
  - Dysphagia , odynophagia , obstruction
  - Weight loss, debilitation
  - Impaired nutrition and tumor associated cachexia
  - Hemorrhage and sepsis if ulcerated
  - Aspiration via a tracheoesophageal fistula
  - Dismal prognosis : 5-year survival 10%

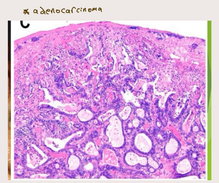




Adenocarcinoma

- On the rise, 1/2 of cases in developed countries
- -Background of Barrett esophagus and long-standing GERD
  -male : female (7:1)
  -geographic and racial variation (developed centuries)
- Risk is greater if:
  - Documented dysplasia
  - Smoking
  - Obesity
  - Radiotherapy
- Pathogenesis : -It's a multi-step process which is affected by many environmental factors
  -from Barrett esophagus to dysplasia to adenocarcinoma
  -acquisition of genetic and epigenetic changes
  -chromosomal abnormalities and TP53 mutation
- Morphology
  - Microscopy — Forms glands and mucin
  - Grossly
    - Distal third of the esophagus (the site of gastroesophageal reflux)
    - Early — Flat or raised patches
    - Late — Exophytic infiltrative masses
- Clinical features
  - Pain or difficulty swallowing
  - Progressive weight loss
  - Chest pain
  - Vomiting
  - Early stage at diagnosis — 5-year survival 80%
  - Late stage diagnosis (Advanced stage at diagnosis) — 5-year survival <25%





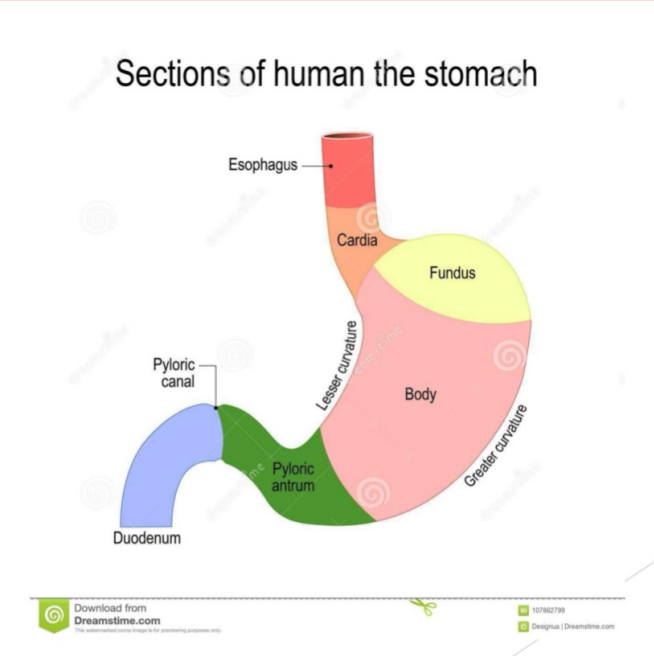
Gastric diseases

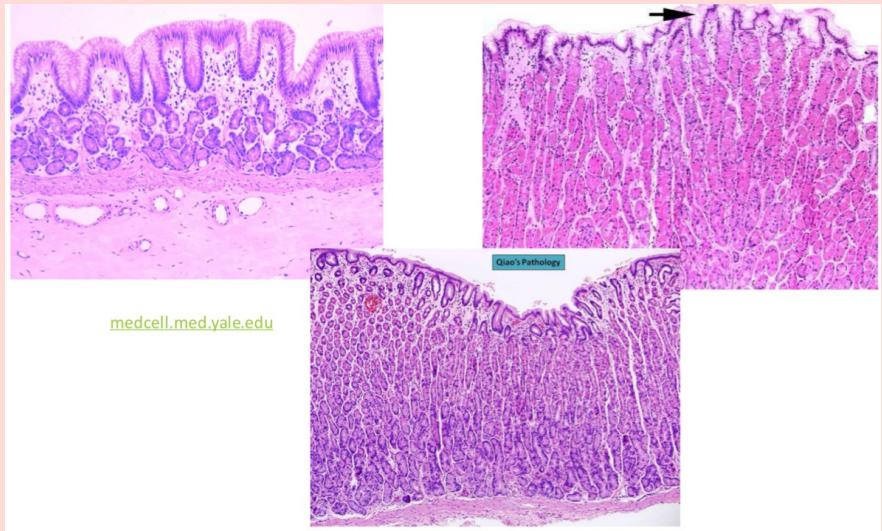
-the stomach is composed of four parts : cardia , fundus , body , antrum(pylorus)

-cardia : mucin secreting foveolar cells

-body and fundus : parietal cells (for HCL secretion and production of intrinsic factor) and chief cells (pepsin enzyme production)

-Antrum : neuroendocrine G cells (gastrin production)





-Gastric inflammatory conditions:

-acute gastritis
-chronic gastritis
-Acute gastric ulcer
-chronic peptic ulcer

Acute gastritis and gastropathy

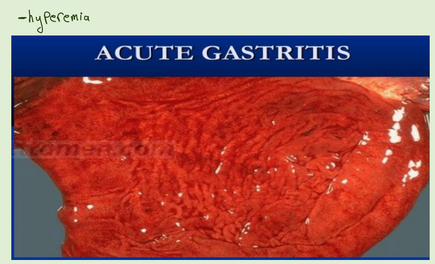
-acute gastritis : mucosal injury, neutrophils present (inflammation)
-gastropathy : regenerative , no/ rare inflammation

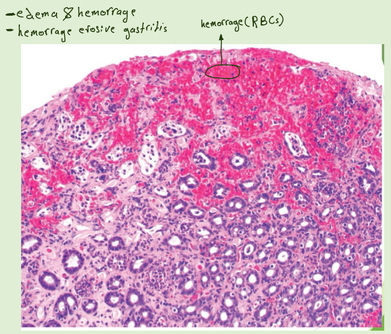
Causes of gastropathy :

- NSAIDs
- Alcohol
- Bile reflux
- Stress-included (physiological stress like trauma or in ICU)

Morphology

- Hyperemia (redness)
- Edema and slight vascular congestion
- Intact surface epithelium if mild
- Neutrophils, lymphocytes, plasma cells are not prominent (seen in gastritis but not gastropathy)
- Neutrophils: active inflammation (gastritis)
- Acute erosive hemorrhagic gastritis (advanced)





Pathogenesis

Prostaglandins E2 and I2

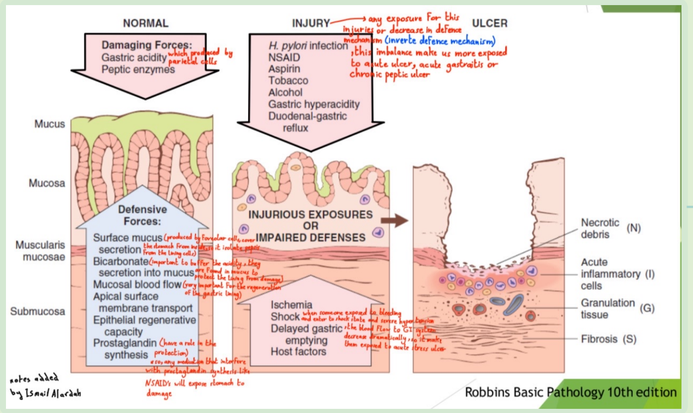
Stimulate nearly all the defense mechanisms including:

- Mucus and bicarbonate secretion
- Mucosal blood flow (caused by vasodilation)
- Epithelial restitution (regeneration)

Clinical features

- Asymptomatic
- Epigastric pain
- Nausea , vomiting
- In Severe cases : erosions , ulcers, hematemesis , melena

The pathogenesis of acute ulcers, acute gastritis and chronic peptic ulcers are the same



Pathogenesis of gastropathy , acute and chronic gastritis

Imbalance between protective and damaging forces

Main causes

- Inhibit prostaglandin synthesis especially E2 and I2 — NSAIDs (COX1 and COX2 inhibitors)
- Uremic patients (ammonia inhibit bicarbonate transport)
- H.pylori (urease produces ammonia)
- Aging(reduced mucin and bicarbonate secretion)
- Hypoxia (high altitude)
- Harsh chemicals (acids or bases) (direct epithelial injury)
- Alcohol, NSAIDs , radiation therapy (direct mucosal injury)
- Chemotherapy (inhibit DNA synthesis and interfere with cellular renewal)

Stress-related mucosal disease (acute ulcers)

-prophylaxis with proton pump inhibitors
-outcome depends on severity of the underlying cause

Clinical features

- Nausea , vomiting
- Melena(indicates upper GI bleeding)
- Coffee-ground hematemesis
- Perforation

Pathogenesis

-mostly due to ischemia caused by hypotension or decreased blood flow (splanchnic vasoconstriction)
-systemic acidosis (lower intracellular PH)
-COX2 expression is protective

The same Pathogenesis as gastritis and gastropathy

- Stress related injury
  - Direct vagal stimulation , acid hypersecretion
- CNS injury and Cushing ulcers

Severe physiologic stress :

- Trauma
- Extensive burns
- Intracranial disease (tumor, stroke)
- Major surgery
- Serious medical disease (ICU)
- Critically ill patients

All have the same microscopic presentation but different locations and associated features:

- Stress ulcers : critically ill patients with shock , sepsis or severe trauma
- Curling ulcers : proximal duodenum , severe burns or trauma
- Cushing ulcers : stomach , duodenum , esophagus , CNS injury as stroke , high risk of perforation

Morphology

- Spectrum (shallow to deep)
- Acute ulcers are rounded and typically <1 cm
- Ulcer base is brown to black
- Multiple , anywhere in stomach
- Normal adjacent mucosa
- No scarring
- Healing with complete epithelialization occurs days or weeks after removal of the injurious factor

Chronic gastritis

Causes

- H . Pylori associated gastritis (most common)
- Autoimmune atrophic gastritis (less than 10% of cases)
- Less common causes : NSAIDs , radiation injury , chronic bile reflux

Clinical features

- Nausea , vomiting
- Upper abdominal discomfort
- Hematemesis (uncommon)
- Less severe but more prolonged symptoms

Complications

- Peptic ulcer
- Mucosal atrophy
- Intestinal metaplasia
- Dysplasia

Helicopter pylori gastritis

-spiral or curved , gram negative , bacilli
-in almost all duodenal ulcers and majority of gastric ulcers or chronic gastritis
-discovery of the association between H . Pylori and peptic ulcer disease was a revolution

Treatment

Combination of antibiotics and proton pump inhibitors (triple therapy)

Diagnosis

Serological test : anti H . Pylori antibodies

Stool test for H . Pylori

Urea breath test

Gastric antral biopsy (rapid urease test during endoscopy)

Bacterial culture

PCR test for bacterial DNA

Morphology

Gastric antral biopsy : H . Pylori in mucus layer

Regenerative changes (hyperplastic polyps)

Neutrophils , plasma cells , lymphocytes , macrophages

Intestinal metaplasia (goblet cells)>>>> dysplasia >>>> increased risk of adenocarcinoma

Lymphoid aggregates >>> increased risk of MALT lymphoma

Epidemiology

Poverty , poor sanitation —> acquired in childhood and persists to adult-life

Acute infection is subclinical

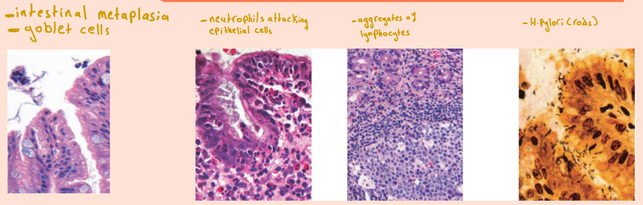
Pathogenesis

-non-invasive (doesn't enter inside the cell)
-adapted to live in the mucus layer (protected from acidic environment by certain virulence factors)

Virulence factors:

- Flagella : allow motility
- Urease : splits urea to ammonia , protects the bacteria from acidic PH
- Adhesins : bacterial adherence to foveolar cells
- Toxins : (cagA) mucosal damage

-It goes to the antrum (antral gastritis)—> stimulates G cells —>increases acid production—> peptic ulcer
-If severe it spreads to the body of the stomach with atrophy—> parietal cells damage
-intestinal metaplasia and increased risk of gastric cancer



Autoimmune gastritis

Pathogenesis

-Immune mediated loss of parietal cells >> reductions in acid and intrinsic factor secretion

Reductions in acid >> hyperplasia of antral G cells >> hypergastrinemia

Deficient intrinsic factor >> deficient ileal vit-B12 absorption >> pernicious anemia

Clinical features

60 years , slight female dominance

Often associated with autoimmune diseases

Dyspepsia

Anemia (vitamin B12 or iron deficiency)

-antibodies against parietal cells and intrinsic factor(vitamin B12 deficiency (pernicious anemia and neurologic changes))
-reduced serum pepsinogen I levels (damaged G cells that produce gastrin)
-antral endocrine cell hyperplasia (try to compensate)
-impaired gastric acid secretion (achlorhydria) -marked hypergastrinemia
-spares the antrum

Morphology

Damage of oxyntic (acid producing) mucosa

Diffuse atrophy , thinning of wall , loss of gastric folds

Intestinal metaplasia >>dysplasia >> carcinoma

G-cell hyperplasia >> carcinoids (neuroendocrine tumors)

Lymphocytes, plasma cells, macrophages, less likely neutrophils

Table 15.2 Characteristics of *Helicobacter pylori*–Associated and Autoimmune Gastritis

Feature	*H. pylori*–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to markedly increased	Markedly increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, lymphoma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease

Robbins Basic Pathology 10th edition

Peptic ulcer disease

Main factors

- H . Pylori (>70% of cases worldwide)
- NSAIDs (in USA , most cases are NSAIDs included , because of the increased use of low-dose aspirin in aged populations and the decline in H . Pylori infections)

Site

- Any portion of the GI tract exposed to acidic gastric juices
- Most common in gastric antrum and the first part of the duodenum
- Esophagus in gastroesophageal reflux disease or ectopic mucosa (within Meckel diverticulum)

Morphology

- Anterior duodenal wall or the stomach antrum (4:1 proximal duodenum:stomach)
- >80% solitary (only one ulcer)
- Round to oval , sharply punched-out ulcer
- Base of ulcer is smooth and clean
- Granulation tissue
- Complications : frank hemorrhage , iron deficiency anemia and perforation

Pathogenesis

- Only 5-10% of H . Pylori infected persons develop peptic ulcers (depending on host factors and bacterial strains)
- Hyperacidity is caused by:
  - H. Pylori
  - Parietal cell hyperplasia
  - Excessive secretory response (vagal)
  - Hypergastrinemia an in Zollinger-Ellison syndrome
    - Zollinger-Ellison syndrome : 1)caused by uncontrolled release of gastrin by a tumor (gastrinoma) and the resulting massive acid production 2)multiple peptic ulcerations in stomach, duodenum an even the jejunum
- Cofactors: smoking, chronic NSAIDs , high dose corticosteroids, alcoholic cirrhosis, COPD , chronic renal failure , hyperparathyroidism

Clinical features

- Epigastric burning or aching pain
- Nausea, vomiting, bloating, bletching
- Worst at night, relieved by alkali or food
- Pain 1 to 3 hours after meals daytime

Treatment

- Therapies are aimed at H . Pylori eradication
- Surgery for completions

Gastric polyps and tumors :

>>Gastric polyps :

1) inflammatory and hyperplastic polyps (totally benign)
2) gastric adenoma (polyp with dysplasia)

>>Gastric adenocarcinoma :

1) intestinal type
2) diffuse type

>>Lymphoma :

1) MALToma

>>Neuroendocrine (carcinoid) tumor

>>Gastrointestinal stromal tumor

Gastric polyps

Polyps : masses projecting above the level of adjacent mucosa

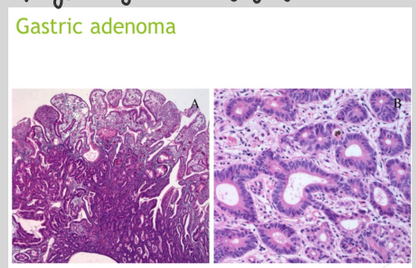
Inflammatory and hyperplastic polyps

- Benign
- 75% of all polyps
- Arise in a background of chronic gastritis
- Regress after H . Pylori eradication

Gastric adenoma

- 10% of cases
- Increases with age
- Male : female = 3 : 1
- Background: chronic gastritis , atrophy and intestinal metaplasia
- Dysplasia, low or high grade
- Risk of adenocarcinoma is related to size (greater if size is > 2 cm)
- Risk of carcinoma is higher than colonic adenoma
- 30% have concurrent carcinoma

*Polypoid growth carrying dysplasia



Gastric adenocarcinoma

-90% of all gastric cancers
-early symptoms mimic gastritis—> late diagnosis
-screening—>early detection
-background of mucosal atrophy and intestinal metaplasia
-peptic ulcer disease does not increase risk , except after surgery (because there is bile reflux in the stomach which is carcinogenic)

-Geographic variations (Japan , Costa Rica , Chile)
-in USA rates dropped >85% (due to drop in H.pylori) , but increased rate of cardia cancer due to obesity and gastroesophageal reflux disease

Two types according to Lauren classification : intestinal and diffuse

Pathogenesis

Genetic alterations (caused by H pylori associated chronic gastritis, and lesser extent EBV (Epstein-Barr virus)

Most cases are sporadic

Familial diffuse type	Gremlin mutation in CDH1 (E-Catherin)
Sporadic diffuse type	Somatic CDH1 mutation in 50%
Familial intestinal type	FAP , APC gene mutation
Sporadic intestinal type	Beta-catenin mutation
Sporadic cases	P53 mutation and HER2 amplification

Clinical features

Intestinal type

High risk areas

Develops from a precursor (adenoma , dysplasia associated with intestinal metaplasia)

Mean age is 55 years (old age)

M : F is 2 : 1

Diffuse type

Incidence is uniform across countries

No precursor lesion

M : F is 1 : 1

Young age

-most powerful prognostic factors : depth of invasion and extent of nodal and distant metastasis at the time of diagnosis
-incidences of both types are now similar in some regions
-the drop in gastric cancer incidence applies only to the intestinal type
-most cases are discovered at advanced stage
- 5-year survival is 90% to<30%for early and advanced tumors, respectively

<30%

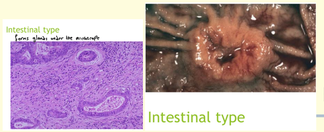
Morphology

Intestinal type

Bulky

Exophytic mass or ulcer

Form glands (under the microscope)



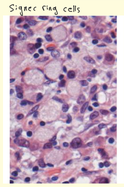
Intestinal type

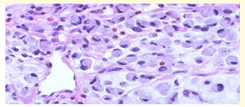
Diffuse type

Infiltrative growth pattern

Discohesive cells (signet ring cells : large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery)

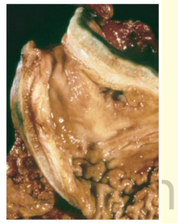
Desmoplastic reaction (stiffens wall , flat ruge , linitis plastica)





Diffuse type, signet ring cells

Linitis plastica



Treatment

Surgery

Chemotherapy

Targeted therapy (Anti-HER2)

Lymphoma

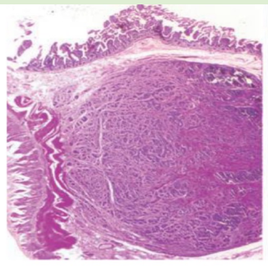
Stomach is the most common site of extranodal lymphoma

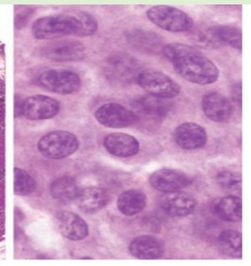
5% of all gastric malignancies

-Most common type : extranodal marginal zone B-cell lymphomas (MALToma)(indolent:slowly growing) -second most common lymphoma : diffuse large B-cell lymphoma (aggressive)

Neuroendocrine (carcinoid) tumor

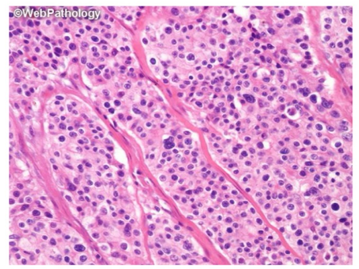
- Tumors arising from neuroendocrine-differentiated gastrointestinal epithelia (e.g , G cells)
- Slower growing than carcinomas
- Associated with endocrine cell hyperplasia, chronic atrophic gastritis and Zollinger-Ellison syndrome
- >40% occur in small intestines





Intramural or submucosal masses (small polypoid lesions)

Islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and salt and pepper chromatin.



- Carcinoid syndrome
  - Seen in 10% of cases
  - Due to vasoactive substances
  - Strongly associated with metastatic diseases
  - Cutaneous flushing , sweating, bronchospasm , colicky abdominal pain , diarrhea, right sided cardiac valvular fibrosis

Intestinal pathology

Intestinal obstruction

Mechanical obstruction

- Intussusception
- Hernias
- Adhesions
- Volvulus
- Tumors
- Diverticulitis
- Infarction

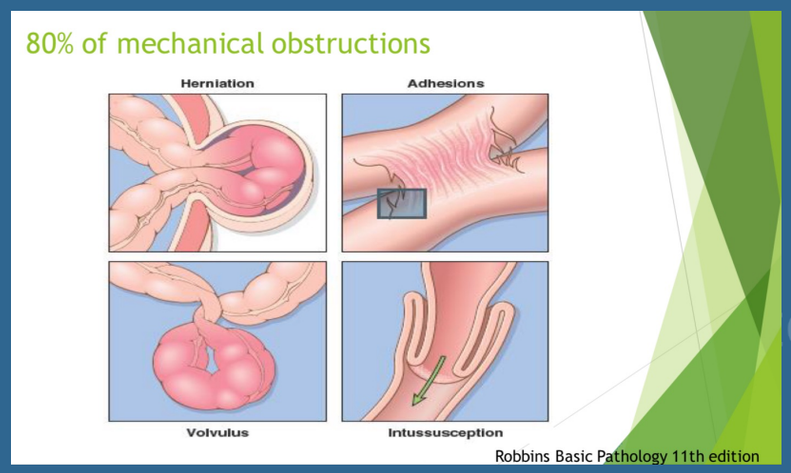
Non-mechanical obstruction

- Hurschsprung disease
- Neurological disorders
- Drugs

Could be acute or chronic

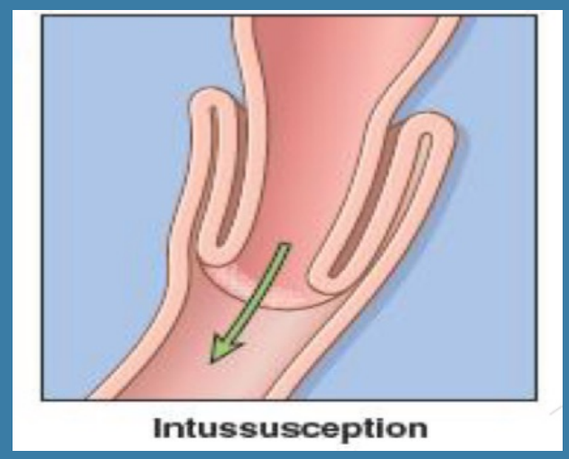
Clinical picture

- Abdominal pain
- Distention
- Vomiting
- Constipation



Intussusception

-segment of intestine constricted by peristalsis , telescopes into the immediately distal part
-once trapped, invaginated segment is propelled by peristalsis and pulls mesentery with it
-the most common cause of intestinal obstruction in children younger than 2 years of age
-if untreated it progresses to obstruction and infarction



Clinical features

- Pain
- Abdominal swelling
- Vomiting
- Currant jelly stool (stool mixed with blood and mucus)

Causes

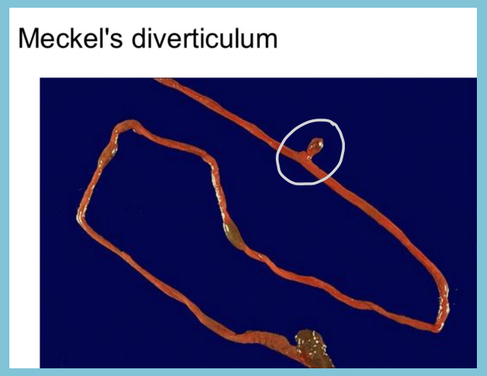
- Idiopathic (mostly)
- Peyer patches hyperplasia (caused by rotavirus vaccine or viral infections)
- Meckles diverticulum (ileum)
- In old children and adults: intramural mass or tumors

Management

- Contrast enemas in uncomplicated idiopathic cases (for diagnosis and therapy)
- Surgery (if complicated by infarction or if masses are the leading point)

Meckel’s diverticulum

-the most common congenital anomaly of the GI tract
-incomplete obliteration of the omphalomesenteric (vitelline) duct
-a true diverticulum (it is an out pouch)



Rule of 2

- About 2% of people have them
- Located 2 feet from the ileocecal valve
- 2 inches in length
- 2 types of heterotopic mucosa (gastric or pancreatic)
- The most common cause of lower GI bleeding before the age of 2

Clinical presentation

- Asymptomatic and discovered incidentally
- Ulceration , lower GI bleeding or perforation from ectopic gastric mucosa
- Bowel obstruction due to Intussusception , volvulus or adhesive band
- Can be confused with acute appendicitis

Hirschsprung disease

Morphology

- Extent is variable
- Rectum is always involved (most cases in rectosigmoid colon)
- Aganglionic region normal or contracted
- The segment proximal to the aganglionic region is progressively dilated

Complications

- Enterocolitis
- Peritonitis
- Perforation
- Fluid and electrolyte disturbances

Diagnosis

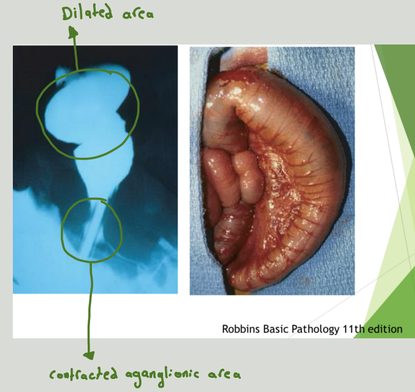
- Barium enema
- Biopsy (to confirm the absence of ganglion cells)

Treatment

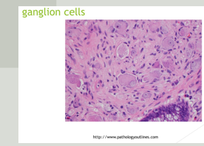
- Surgical resection of the aganglionic segment and anastomosis of normal segments

Pathogenesis

-congenital defect in colonic innervation
-congenital aganglionic megacolon (dilation and enlargement in colon)
-more common in males
-more severe in females
-risk increases in siblings



- During embryogenesis : disrupted migration of neural crest cells from cecum to rectum(they stop migrating at some point , so the distal part of the colon won't be innervated)
- Aganglionosis : distal part segment of colon lacks both Meissner submucosal plexus and Auerbach (myenteric) plexus
- Failure of coordinated peristaltic contractions
- -RET gene mutation : in familial cases and 15% of sporadic cases
  -other genes and environmental factors play a role
- More in Down syndrome



Typical presentation

- Neonatal failure to pass meconium(the first stool passed by the neonate)
- Later : obstructive constipation

Vascular disorders of bowel

1) ischemic bowel disease
2) angiodysplasia
3) hemorrhoids

Hemorrhoids

-Dilated anal and perianal collateral vessels that connect the portal with caval venous systems
-external hemorrhoid : below the anorectal line , inferior hemorrhoidal plexus
-internal hemorrhoid : above the anorectal line , superior hemorrhoidal plexus

Predisposing factors
- Constipation and straining
- Venous stasis of pregnancy
- Portal hypertension

Morphology
- Thin-walled , dilated , submucosal vessels beneath anal or rectal mucosa

Symptoms
- Bleeding (bright red)
- Pain (due to thrombosis and inflammation)

Treatment
- Sclerotherapy
- Rubber band ligation
- Infrared coagulation
- Hemorrhoidectomy

Angiodysplasia

- Malformed mucosal and submucosal blood vessels
- Most often in cecum and right colon
- 6th decade of life
- Less than 1% of adult population
- 20% of cases of lower GI bleeding
- Blood is bright red in color

Diarrheal disease

-diarrhea : increase in stool mass , frequency or fluidity
-dysentery : painful , bloody , small volume diarrhea
-types of diarrhea : secretory , osmotic , malabsorptive , exudative

Types of diarrhea according to response

Malabsorptive diarrhea

Malabsorptive diarrhea
- Pancreatic insufficiency
- Celiac disease
- Crohn’s disease
- Cystic fibrosis
- Lactase (disaccharidase) deficiency
- Abetalipoproteinemia

Infectious Enterocolitis

Ischemia

Inflammatory bowel disease

-defective absorption of fats , fat-soluble and water-soluble vitamins , proteins , carbohydrates , electrolytes , minerals and water
-chronic

Hallmark : steatorrhea (excessive fat , bulky , frothy , yellow , greasy stool)

Defect in one of the following :
- Intramural digestion
- Terminal digestion
- Transepithelial transport
- Lymphatic transport

Manifestations
- Weight loss , anorexia
- Flatus , abdominal distention
- Borborygmi (intestinal noise) , muscle wasting
- Anemia and mucositis (iron deficiency , pyridoxine(vitamin-B6) , folate or vitamin-B12 deficiency)
- Bleeding (vitamin-K deficiency)
- Osteopenia and tetany (calcium , magnesium or vitamin-D deficiency)
- Skin and endocrine disorders
- Neuropathy (vitamin A or B12 deficiency)

Cystic fibrosis

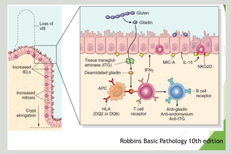
Caused by : mutations in cystic fibrosis transmemrane conductance regulator (CFTR) , defects in ion transport across intestinal and pancreatic epithelium , defect in intramural digestion

Thick viscous secretions (will cause obstruction of pancreatic duct and prevent pancreatic enzymes from reaching intestines)

-mucus pulgs in pancreatic ducts —> pancreatic insufficiency (in 80% of patients)

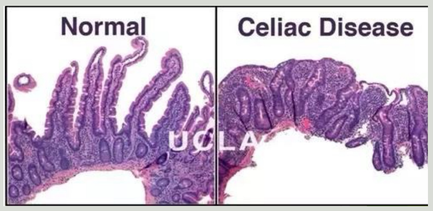
Meconium ileus in neonates (additional : it is a sticky meconium blocking the ileum)

Celiac disease

- -gluten sensitive enteropathy
  - immune mediated enteropathy
  -genetically predisposition , HLA-DQ2 or HLA-DQ8
  -Gluten is found in wheat , rye or barley
- Pathogenesis
  - 

  - Gluten >>gliadin>>deamidated by tissue transglutaminase (TTG)>>
    react with HLA-DQ2 or HLA-DQ8 on antigen presenting cells>>CD4+T
    cells activation >>cytokines>>tissue damage >>B cell activation >>antibodies
- Serology
  - Anti-tissue transglutaminase antibodies
  - Anti-gliadin antibodies
  - Anti-endomysial antibodies
- Treatment
  - Gluten free diet
- Morphology
  - 2nd portion of duodenum or proximal jejunum
  - Triad : intraepithelial lymphocytes (CD8+ T cells) , crypt hyperplasia and villous atrophy
  - Lamina propria : lymphocytes, plasma cells , eosinophils
  - Intraepithelial lymphocytes and villous atrophy are not pathognomonic (seen also in viral enteritis)
- Increased risk of :
  - Enteropathy associated T cell lymphoma
  - Small intestine adenocarcinoma
- Clinical features
  - Children (6-24 months)
    - Classical symptoms
      - Irritability
      - Abdominal distention
      - Anorexia
      - Diarrhea
      - Failure to thrive
      - Weight loss
      - Muscle wasting
    - Non-classical symptoms
      - Abdominal pain
      - Nausea, vomiting
      - Bloating
      - Constipation
  - Adults (30-60 years)
    - Anemia (iron deficiency)
    - B12 and folate deficiency : less common
    - Diarrhea, bloating, fatigue
  - Blistering skin lesion , dermatitis herpetiformis , in 10% of patients
    - 

- Diagnosis
  - Clinical , Histologic and serologic correlation
  - Non-invasive serologic tests
    - Most sensitive
      - Anti-tissue transglutaminase antibodies (IgA)
      - Anti-deamidated gliadin antibodies (IgA and IgG)
    - Most specific , less sensitive
      - Anti-endomysial antibodies
  - Invasive test
    - Small bowel biopsy
  - Missed diagnosis
    - Silent Celiac (positive serology and biopsy but asymptomatic)
- Associated with
  - Type I diabetes
  - Thyroiditis
  - Sjogren syndrome



Lactase deficiency

- Osmotic diarrhea
- Lactose will remain in gut lumen
- -Lactase is found at the apical brush border membrane
  -we get a normal biopsy findings
- Two types
  - Congenital
    - Rare
    - Autosomal recessive, genetic mutation
    - Explosive diarrhea, watery, frothy stool
    - Abdominal distention after milk ingestion
  - Aquired
    - Common
    - Downregulation of gene
    - After weaning
    - Affect 2/3 of worlds population (50% of USA population)
  - Transient
    - Caused by injury after infectious or inflammatory insult
    - Reversible

Abetalipoproteinemia

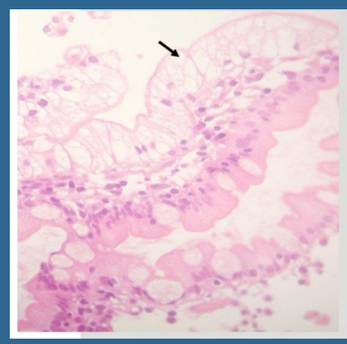
-inability of enterocytes to secrete triglyceride-rich chylomircons
-lack of absorption : transepithelial transport defect of lipoproteins , fatty acids and fat-soluble vitamins
-monoglycerides and triglycerides accumulate in epithelial cells

Autosomal recessive , rare

Clinical features

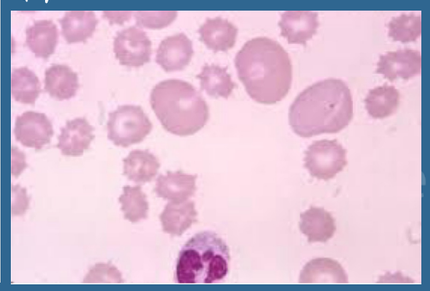
- Infants with failure to thrive
- Diarrhea
- Steatorrhea
- Vitamin K deficiency, skeletal, CNS and retinal abnormalities

-Lack of absorption of fats and fat-soluble vitamins
-spur cells in peripheral blood



Micrograph showing enterocytes with a clear cytoplasm (due to lipid accumulation) characteristic of abetalipoproteinemia.

*spur cells



Inflammatory intestinal disease

Chronic inflammatory bowel diseases

Pathogenesis

- Altered host interaction with intestinal microbiota
- Intestinal epithelial dysfunction
- Aberrant mucosal immune response
- -genetic predisposition
  -immune response to intestinal microbes -inappropriate mucosal damage

Epidemiology

- Adolescence & young adults , 2nd peak in 5th decade
- Geographic variation
- Hygiene hypothesis : childhood exposure to environmental microbes prevents excessive immune system reactions.....firm evidence is lacking

Divided into:

- Crohn's disease
- Ulcerative colitis

Colitis associated neoplasms

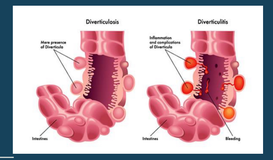
- -long standing Crohn's disease and ulcerative colitis
  -begins as dysplasia—> carcinoma
  -colonoscopy surveillance programs

Risk depends on:

- -Duration of the disease (increases after 8-10 years)
- -extent of involvement (more with pancolitis)
- -inflammation (frequency and severity of active disease with neutrophils)

Sigmoid diverticulitis

- -acquired pseudodivertivula
  -rare <30 years
  -common >60 years
  -multiple (diverticulosis)

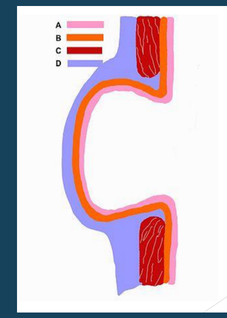


Pathogenesis

- Elevated intraluminal pressure
- Unique location (discontinuous muscle layer at points of nerves and vessels entry)
- Longitudinal muscle layer is discontinuous in colon (taeniae coil)
- Area of weakness: outward herniation of mucosa and submucosal
- Most common in sigmoid (narrowest part)
- Exaggerated peristaltic contractions
- Risk factors : Low fiber diet , constipation, sedentary lifestyle, obesity and smoking

Morphology

- Flask like outpouchings
- Between taeniae coli
- Thin wall (atrophic mucosa , compressed submucosa)
- Attenuated or absent muscularis propria
- Obstruction leads to diverticulitis
- Risk of perforation
- Recurrent diverticulitis leads to fibrosis (strictures)



Clinical features

- Asymptomatic (mostly)
- Intermittent lower abdominal pain
- Constipation or diarrhea

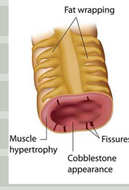
Treatment

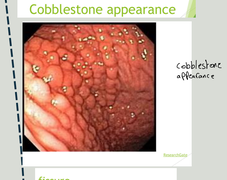
- High fiber diet
- Surgery
- Antibiotics (in diverticulitis)

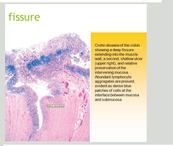
Chronic inflammatory bowel disease

Crohn's disease

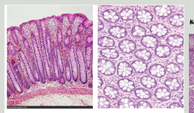
- Regional enteritis , frequent ileal involvement , affects any area of the GI tract, frequent transmural (the full thickness of the intestinal wall)
- Morphology
  - Macroscopic
    - Regional enteritis
    - Any area of the GI tract
    - Most common : terminal ileum , ileocecal valve and cecum
    - Small intestine alone 40%
      -colon only 30%
      -both small intestines and colon 30%
    - Skip lesions
    - Strictures (common)
    - Earliest lesion : aphthouse ulcers
    - Elongated , serpentine ulcers
    - Edema, loss of bowel folds
    - Cobblestone appearance
    - Toxic megacolon (before fibrosis)
    - Fissures (fistulas , perforations)
    - Creeping fat
    - Thick bowel wall (transmural inflammation , edema, fibrosis , hypertrophic MP)—> strictures
  - Microscopic
    - Neutrophils in active disease
    - Crypt abscesses
    - Ulceration
    - Mucosal atrophy
    - Paneth cell metaplasia in the left colon
    - Distortion of mucosal architecture (in repeated cycles)
    - Non-caseating granulomas (hallmark) only in 30% of cases. Anywhere

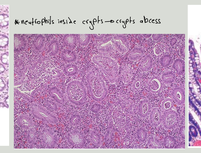


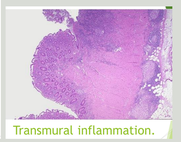


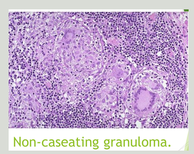


- Clinical features
  - Intermittent attacks of mild diarrhea, fever and abdominal pain
  - Acute right lower quadrant pain and fever (20%)
  - Bloody diarrhea and abdominal pain (colonic disease)
  - Asymptomatic intervals (weeks to months)
- Triggers
  - Physical or emotional stress
  - Specific dietary items
  - NSAIDs
  - Cigarettes smoking
- Complications
  - If lesions in colon : iron deficiency
  - If lesions in small bowel: hypoproteinemia , hypoalbuminemia , malabsorption of nutrients , vitamin-B12 and bile salt
  - Fistulas , strictures and peritoneal abscesses
  - Risk of colonic and small intestinal adenocarcinoma
- Extra intestinal manifestations
  - Uveitis
  - Migratory polyarthritis
  - Sacroiliitis
  - Ankylosing spondylitis
  - Erythema nodosum
  - Clubbing of fingerprints
  - Primary sclerosing cholangitis (more with ulcerative colitis)









Chronic inflammatory bowel disease

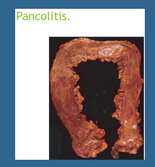
Ulcerative colitis

- Limited to the colon and rectum , restricted only to mucosa and submucosa

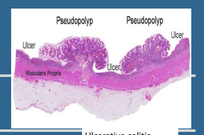
Morphology

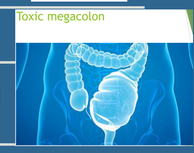
Macroscopic

- Rectum is always involved
- Extends proximally in a continuous pattern
- Pan colitis
- No skip lesions
- Occasionally focal appendiceal or cecal inflammation
- Limited diseases : ulcerative proctitis or ulcerative proctosigmoiditis
- Small intestine is normal (except mild backwash ileitis)



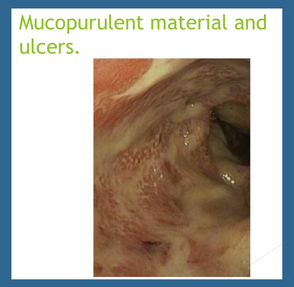
- Broad-based ulcers
- Pseudo polyps (regenerating mucosa)
- Mucosal atrophy in long standing
- Mural thickening absent
- Serosal surface normal
- No strictures
- Toxic megacolon (damage of MP , disturbed neuromuscular function)

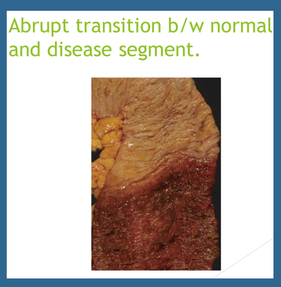




Microscopic

- Inflammatory infiltration
- Crypt abscesses
- Crypt architecture distortion
- Epithelial metaplasia
- Submucosal fibrosis
- Inflammation limited to mucosa and submucosa
- No skip lesions
- No granulomas



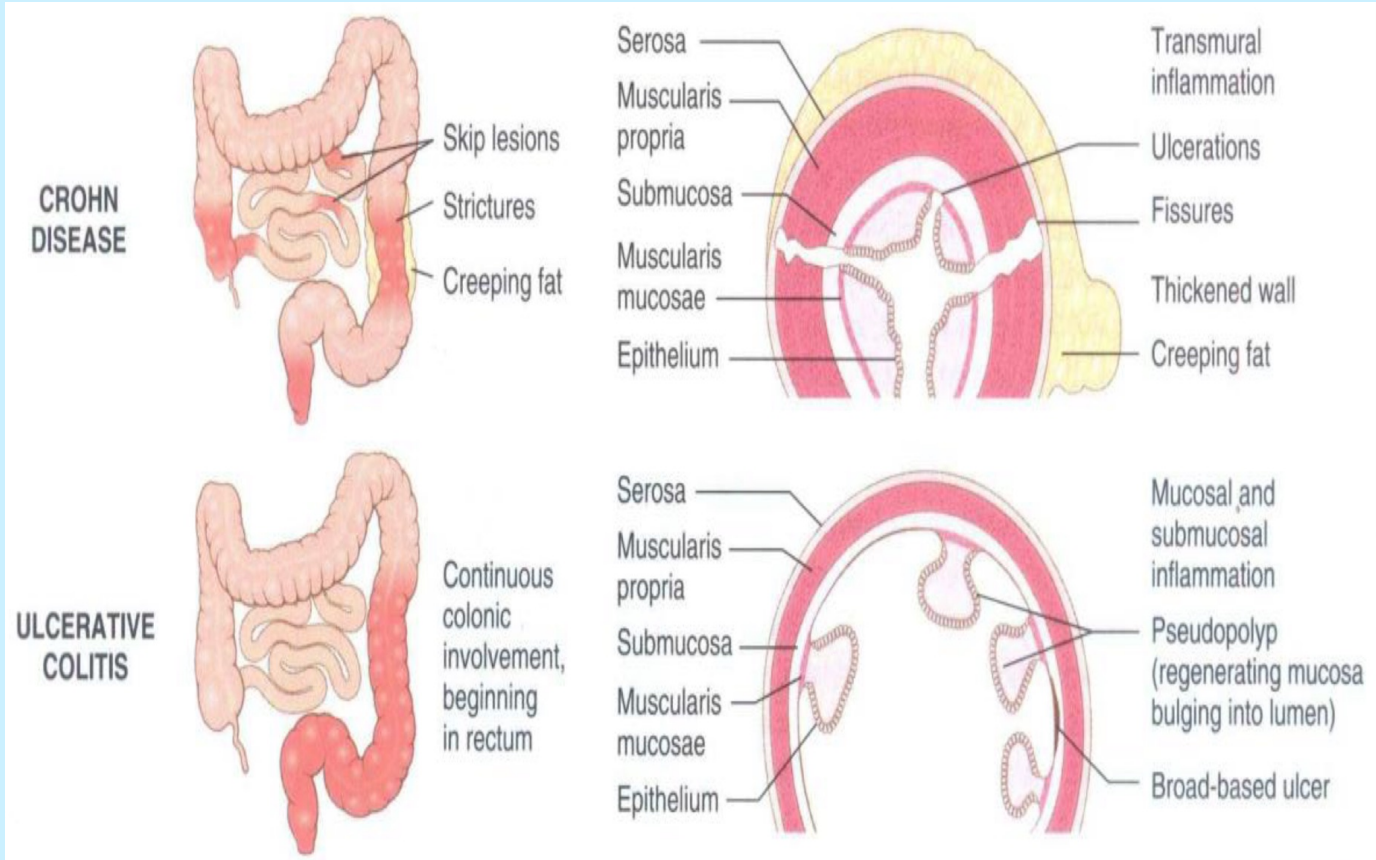


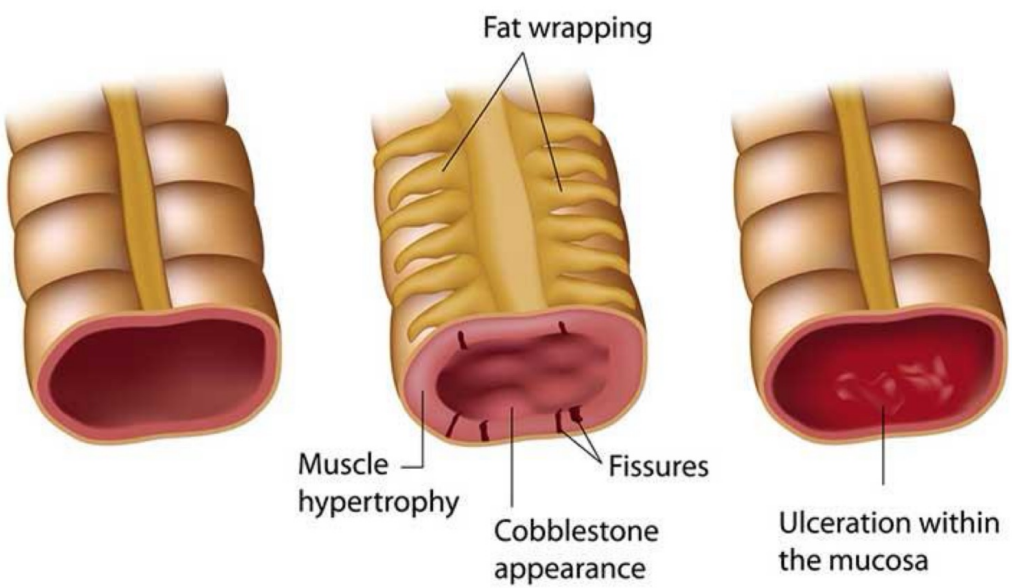
Clinical features

- Relapsing remitting disorder
- Attacks of bloody mucoid diarrhea and lower abdominal cramps
- Temporarily relieved by defection
- Attack last for days , weeks or months
- Asymptomatic intervals
- Infectious enteritis and cessation of smoking may trigger disease onset

Treatment

- Colectomy cures intestinal disease only
- Anti-inflammatory and biologic agents

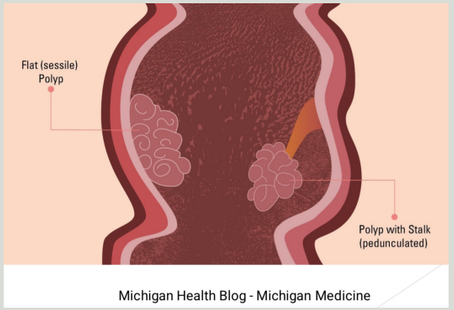




Robbins Basic Pathology 11th edition

Colonic polyps and neoplastic diseases

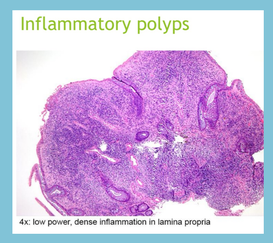
- Colon is the most common site of polyps
- Types
  - Sessile polyp — No stalk
  - Pedunculated polyp — Stalk
  - Neoplastic polyps — Adenoma
  - Non-neoplastic polyps — Inflammatory , hamartomatous , hyperplastic



Non-neoplastic polyps

Inflammatory polyps

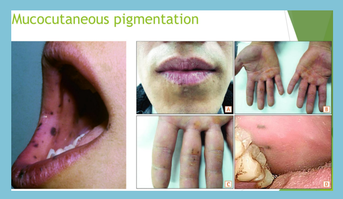
- -solitary rectal ulcer syndrome
  -recurrent abrasion and ulceration of the overlying rectal mucosa
  -the chronic cycles of injury and healing give a polyploid mass of inflamed and reactive mucosal tissue
  -impaired relaxation of the anorectal sphinctor
- Clinical Presentation
  - Rectal bleeding , mucus discharge and polyp

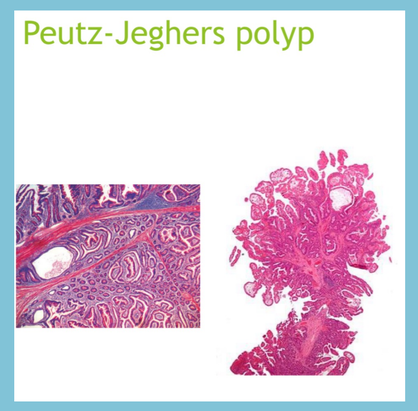


Hamartomatous polyps

- -Disorganized , tumor-like growth composed of mature cell types normally present at that site
  -sporadic or syndromic
- Hamartomatous polyposis syndromes
  - Juvenile polyps
    - -The most common hamartomatous polyp
    - Sporadic
      - Solitary (only one polyp)
      - <5 years of age
      - Rectum , bleeding
    - Syndromic (juvenile polyposis)
      - Dozens of polyps
      - <5 years of age
      - Autosomal dominant
      - Transforming growth factor beta (TGF-beta) signaling pathway germline mutation (SMAD4)
      - Increased risk of colonic adenocarcinoma and others
    - -Pedunculated polyp
      -reddish lesions
      -cystic spaces in cut sections
      -dilated glands filled with mucin and inflammatory debris
      -granulation tissue on surface

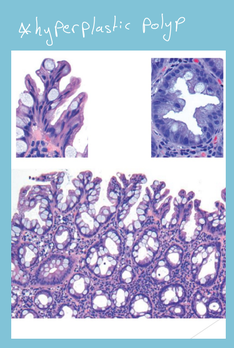
  - Peutz-Jeghers syndrome
    - Autosomal dominant, rare
    - Multiple gastrointestinal hamartomatous polyps
    - Mucocutaneous hyperpigmentation
    - Increased risk of several malignancies (colon , pancreas , breast , lung , ovaries , uterus and testes)
    - LKB1/STK11 germline mutation (tumor suppressor protein)
    - -mostly in small intestines
      -large , Pedunculated lobulated polyp
      -aborizing network of connective tissue, smooth muscles, lamina propria and glands
      -normal appearing intestinal epithelium
      -Christmas tree pattern





Hyperplastic polyps

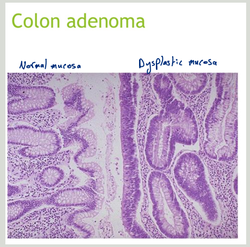
- -Common
  -6th-7th decades
  -decreased epithelial turnover and delayed shedding of surface epithelium—> pileup of goblet cells and epithelial overcrowding
  -no malignant potential
  -biopsy is important
- -left colon , recto-sigmoid
  -small (<5mm)
  -often multiple
  -crowding of goblet cells and absorptive cells
  -serrated surface

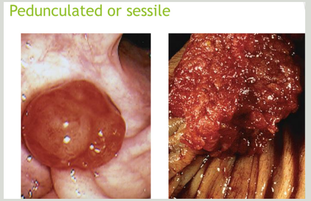


Neoplastic polyps (adenomas)

-most common and clinically important
-50% of adults >50 years (western world)
-precursor for majority of colorectal adenocarcinomas
-in USA screening colonoscopy starts at 45 years of age
-earlier screening with family history
-western diet and lifestyle increases risk

Colon adenoma





Hallmark : epithelial hyperplasia

Nuclear hyperchromasia , elongation , stratification , high nuclear/cytoplasmic ratio

-Size is most important correlate risk of malignancy (40% if >4cm)
-high grade dysplasia is a second factor

Architecture : tubular, villous , tubovillous

- Tubular adenoma
  - -Pedunculated
    -small tubular glands
- Villous adenoma
  - -long slender villi
    - large and sessile
    -more frequent invasive foci
- Tubovillous

Sessile serrated adenoma

Overlap with hyperplastic polyps

-malignant potential is similar to conventional adenomas
-lack dysplasia

-Serrated architecture throughout the full length of glands
-basal crypts dilation

Familial syndromes

-syndromes associated with colonic polyps and increased rates of colon cancer
-genetic basis

Hereditary nonpolyposis colorectal cancer (HNPCC) , Lynch syndrome

Autosomal dominant

-Inherited germline mutations in DNA mismatch repair genes (detection , resection and repair of errors in DNA replication)
-accumulation of mutations at 1000* higher rates in microsatellite DNA (short repeating sequences)>>microsatellite instability
-5 genes identified but majority of cases involve either MSH2 or MLH1

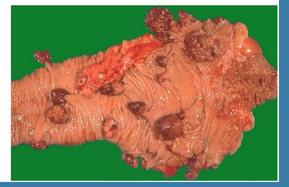
Colon cancer at younger age than sporadic cancers

Right colon , abundant mucin

Only few adenomatous precursors (typically sessile serrated adenomas)

Increased risk of : colorectum , endometrium , stomach , ovary , uterus , brain , small bowel , hepatobilary tract and skin cancers

Cecal polyps in HNPCC.



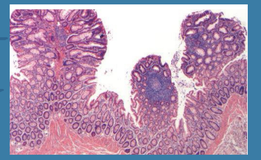
Familial adenomatous polyposis (FAP) syndrome

Autosomal dominant

Mutation in APC gene

-Numerous colorectal adenomas (teenage years)
-at least 100 polyps are necessary for the diagnosis of classical FAP

Morphology — Similar to sporadic adenomas



Standard therapy — Prophylactic colectomy

Risk of extraintesinal manifestations

100% of patients develop colorectal carcinoma, IF UNTREATED, often before the age of 30

Variants of FAP :

- Specific APC mutations — Intestinal polyps and osteomas (mandible, skull, long bones) ; epidermal cysts; desmoid and thyroid tumors and dental abnormalities
- Gardner syndrome
- Turcot syndrome — Intestinal adenomas and CNS tumors (medulloblastomas>>glioblastomas)

Colonic adenocarcinoma

-the most common malignancy of the GI tract (2nd cause of cancer related death after lung cancer)
-small intestine is uncommonly involved by neoplasia
-peak: 60-70 years , males>females , <20% before 50

Prognosis

Most important two prognostic factors:

- Depth of invasion (mucosa, submucosa, MP, serosa)
- Lymph node metastasis (needs radiotherapy and chemotherapy)

Poor differentiation and mucinous histology—> poor prognosis

Clinical features

-Early cancer is asymptomatic
-endoscopic screening—> prevention

-Cecal and right-side cancers : fatigue and weakness (iron deficiency anemia)
-iron deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise

Left sided carcinomas : occult bleeding, changes in bowel habits, cramping left quadrant discomfort

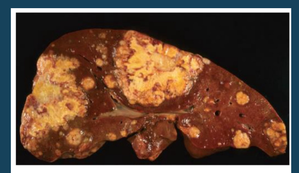
Prevention

- Dietary modification
- Pharmacologic chemoprevention
- Aspirin and NSAIDs have a protective effect (COX2 expressed in 90% of carcinomas , even adenomas, promotes epithelial proliferation)

Risk factors

- Smoking , alcohol
- Obesity , low intake of vegetable fiber and high intake of carbohydrates and fats +develop countries lifestyle and diet

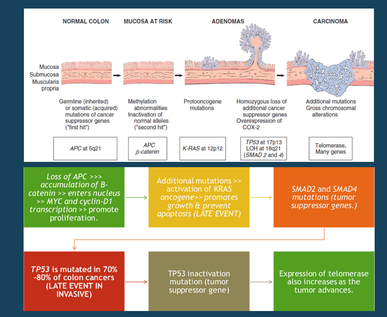
-distant metastasis to liver (most common) and lungs. Solitary metastasis can be resected
-tumors with microsatellite instability (immune checkpoint inhibitor therapy)



Liver metastasis.

Pathogenesis

-Sporadic >>> familial
-Heterotopic nuclear events (genetic and epigegetics)
-stepwise accumulation of multiple mutations

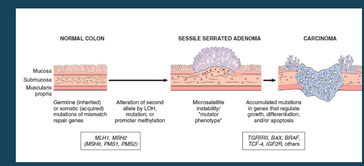


-classic adenoma carcinoma sequence
-80% of sporadic colon cancer
-mutation of APC tumor suppressor gene (early event)
-APC is a key negative regulator of B-catenin (promotes degradation) , a component of WNT signaling pathway
-both copies of APC should be inactivated for the adenoma to develop (first and second hits)
-chromosomal instability by deletion (hallmark)

Two pathways :

APC/B-catenin pathway : chromosomal instability >> increased WNT signaling

Microsatellite instability pathway (due to defects in DNA mismatch repair)



-DNA mismatch repair deficiency (loss of genes)
-mutations accumulates in microsatellite repeats (mostly non-coding)
-microsatellite instability
-silent if microsatellite located in a non-coding region
-uncontrolled cell growth if located in coding or promotor regions of genes involved in cell growth and apoptosis (TGF-B and BAX)
-BRAF mutations common. However, P53 and KRAS are absent

Morphology

Macroscopic

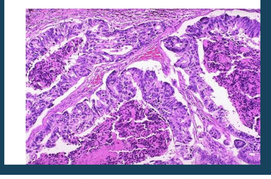
- Proximal colon tumors : polypoid , exophytic masses
- Proximal colon : rarely cause obstruction
- Distal colon : annular lesions(napkin ring) constriction and narrowing

Microscopic

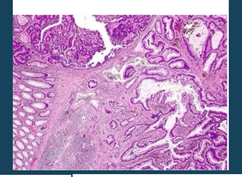
- Dysplastic glands with strong desmoplastic response (firm)
- Necrotic debris (dirty necrosis) are typical
- Some tumor give abundant mucin (poor prognosis) or form signet ring cells

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

Adenocarcinoma with necrosis



Invasive carcinoma



Napkin ring

Recto-sigmoid adenocarcinoma, napkin ring

Exophytic adenocarcinoma

Appendix diseases

-the appendix is a true normal diverticulum of the cecum

Acute appendicitis

-may occur at any age (most common in adolescents and young adults)
-difficult to confirm preoperatively , surgical emergency

Pathogenesis

Increased luminal pressure—> impaired venous drainage—> ischemic injury and stasis associated bacterial proliferation—> inflammatory response rich in neutrophils and edema

Luminal obstruction in 50-80% of cases by fecalith (small mass-like stone of stool) , less commonly: gallstones, tumor, worms

Diagnosis requires neutrophilic infiltration of muscularis propria

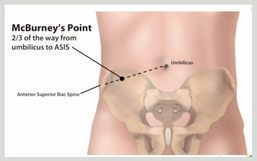
-Acute suppurative appendicitis >>more severe >>focal abscess within wall
-Acute gangrenous appendicitis >>gangrenous necrosis and ulceration>>rupture

Clinical features

Early acute appendicitis: periumbilical pain

Later: pain localized to the right lower quadrant

Nausea , vomiting , low grade fever , mildy leukocytosis



A classic physical finding is McBurney's sign (McBurney's point)

Signs and symptoms are often absent, creating a difficulty in clinical diagnosis

Rule out other causes of abnormal pain:

Mesenteric lymphadenitis

Acute salpingitis (additional: it's an inflammation of fallopian tube in childbearing age)

Ectopic pregnancy

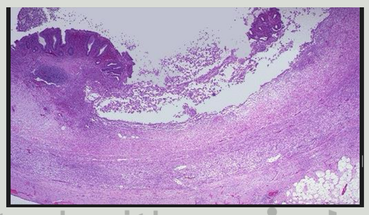
Mittelschmerz (pain associated with ovulation)

Ovarian cysts torsion

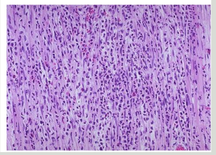
Rupture Meckel diverticulitis

Crohn disease


Normal appendix versus acute appendicitis



Acute appendicitis: neutrophils



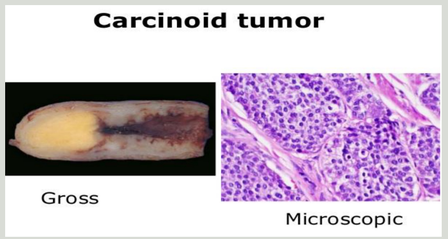
Tumors of the appendix

The most common tumor: carcinoid (neuroendocrine tumor)

Incidentally found during surgery or on examination of a resected appendix

Distal tip of the appendix

Nodal metastasis and distant spread are rare



Summarized by : Nasam Masadeh

Reference: Dr. Manar Hajeer's slides