Pathology

Second Year Students
UJ-GIG GI Booklet

Table of Contents

The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pathology

Esophageal diseases 1&2

Written by: Nour Alhaj Qassim

Edited by: Rawan Fratekh

Reviewed by: Yazeed Alajlouni

[Overview]

➔ **Outline of Esophageal diseases we will cover:**

1) **Obstructive diseases**
   - Mechanical diseases
   - Functional diseases

2) **Vascular diseases**
   - Esophageal varices

3) **Inflammatory diseases**
   - Esophageal lacerations
   - Esophagitis (chemical & infectious)
   - Gastroesophageal Reflux Disease (GERD)

4) **Tumors**
   - Esophageal Cancer

[Obstructive Diseases]

- **Obstructive diseases** affecting the esophagus are divided into **mechanical** (physical blockage that prevents passage of contents) **vs. functional** (the esophagus is not blocked, but it fails to move due to loss of normal motility)

➔ **Mechanical causes:**
   - Esophageal atresia, agenesis, and stenosis
   - Tracheoesophageal fistula and associated diseases

➔ **Functional causes:**
   - Achalasia

➔ Mechanical diseases:

[Esophageal atresia and Tracheoesophageal fistula]

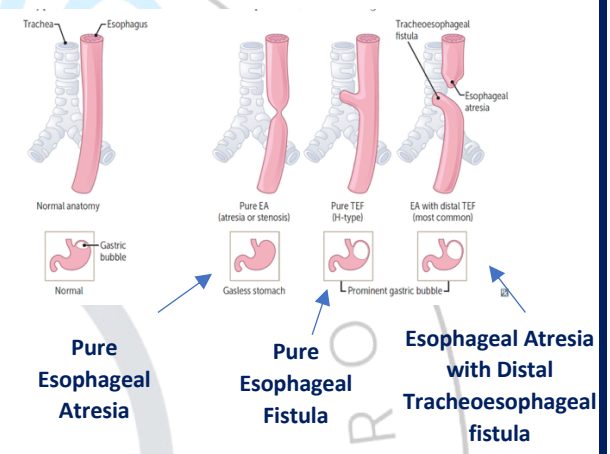
➔ **Definitions:**

- **Atresia** = A congenital condition where a hollow organ ends blindly because it failed to form an open lumen (i.e., it's closed or absent)

- **Fistula** = An abnormal connection between two epithelialized surfaces (e.g., the esophagus and trachea)

- **Esophageal atresia** = A **congenital** defect where a non-canalized cord replaces a segment of the esophagus ➔ esophagus ends in a blind pouch and does not connect to the stomach ➔ it is usually associated with a **Tracheoesophageal fistula** (fistula between the trachea and esophagus)

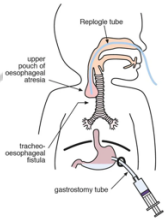
➔ **Location and Types?**
   - **Most common location:** at or near the tracheal bifurcation
   - May be pure atresia (without fistula) OR atresia + fistula



➔ **Clinical Presentation?**

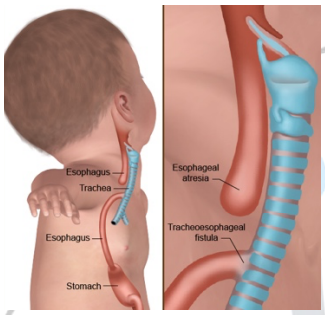
- Shortly after birth, the newborn develops regurgitation during feeding, Pooling of secretions (excessive secretions at the mouth), choking, drooling (because the esophagus is blocked and food can't pass through the esophagus)

- If we try to place a feeding tube, the feeding tube cannot pass through the esophagus to the stomach.



- **Most common type: proximal esophageal atresia with distal fistula** ➔ presents with
   1) **Polyhydramnios** (increased amniotic fluid around the fetus)**:** fetus can't swallow amniotic fluid ➔ fluid accumulates

2) **Vomiting/regurgitation:** blind proximal esophagus ➔ milk has nowhere to go ➔ comes back up
3) **Aspiration:** pooled saliva/milk + connection to trachea ➔ enters airway
4) **Abdominal distension:** air from trachea ➔ passes through fistula ➔ fills stomach



- A condition that is incompatible with life without intervention. It requires prompt surgical correction (re-anastomosis of the affected segment) to allow the baby to feed and swallow normally.

➔Complications of fistula:

1) **Aspiration:** Milk, saliva, and gastric contents can pass through the fistula into the airway, resulting in aspiration during feeding.
2) **Suffocation اختناق:** because of the pooling of secretion in the airway
3) **Pneumonia:** occurs due to aspiration of oropharyngeal secretion into the lungs
4) **Severe fluid and electrolyte imbalance:** because of the inability to eat and dehydration

[Esophageal stenosis]

➔ **Definition**: Narrowing or restriction of the lumen of the esophagus that leads to impedance of food flow through the esophagus and swallowing difficulties.

➔ **Pathophysiology**: Fibrous thickening of the submucosa & atrophy of the muscularis propria due to chronic inflammation and scarring (anything that may cause inflammation in the esophagus may lead to scarring and stenosis)

➔ **Types**:
1) Congenital
2) Acquired (most common)

➔ **Possible acquired causes:**

1) **Chronic GERD:** regurgitation of stomach acid into the esophagus ➔ chronic acid reflux-induced inflammation ➔ fibrotic healing resulting in scar formation and permanent luminal narrowing.
2) **Systemic sclerosis:** autoimmune-mediated smooth muscle atrophy and fibrosis by dense collagen.
3) **Irradiation:** mucosal injury, vascular ischemia, and fibrotic healing due to radiation exposure ➔ lead to luminal narrowing
4) **Ingestion of caustic agents مواد كيميائية كاوية:** acids and alkaline can cause chemical esophagitis that ends with fibrosis.

➔ **Clinical presentation:**

- **Progressive dysphagia**: Difficulty swallowing solids that progresses to problems with liquids (so starts with solids and with time progresses to difficulty in swallowing liquids)

➔ Functional diseases:

- Functional obstruction occurs when no physical lesion is seen to block the passage of food, but abnormal innervation or neuromuscular coordination prevents effective transit.

- Efficient transport of food and fluid from the esophagus to the stomach requires coordination, sequential peristaltic contraction, and appropriate relaxation of the lower esophageal sphincter (LES).

[Achalasia]

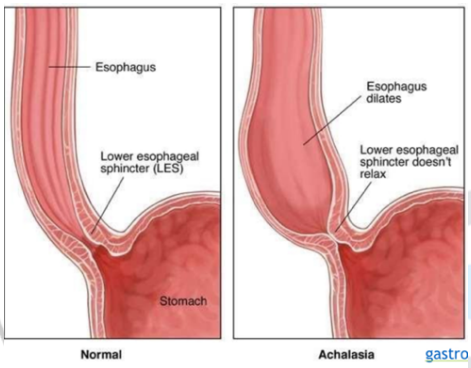
➔ **Definition:** Disordered esophageal motility with inability to relax the lower esophageal sphincter (LES), results in **triad of:**

1) Incomplete LES relaxation
2) Increase LES tone
3) Esophageal aperistalsis (lack of peristalsis)

➔ **Pathophysiology:**

Due to damaged ganglion cells (neurons) in the myenteric plexus

- Ganglion cells of myenteric plexus are located between the inner circular and outer longitudinal layers of the muscular layer of the esophagus and are important for regulating bowel motility and relaxing the LES.
- Damage to ganglion cells can be idiopathic or secondary to a known insult.
- **Result:** failure of LES to relax + esophageal dilation proximal to LES ➔ so food accumulates in the esophagus and can't pass to the stomach



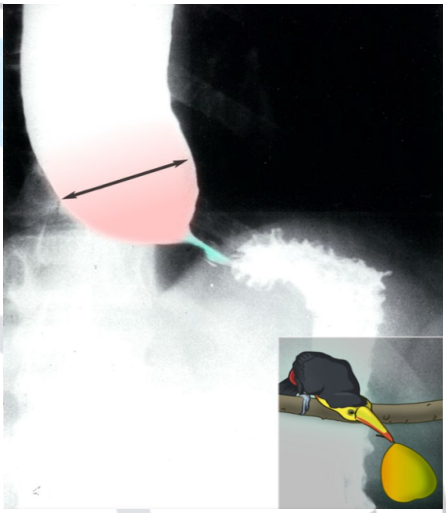
➔ **Types:**

1) **Primary** (most common): idiopathic, caused by degeneration of distal esophageal inhibitory neurons, increasing the tone of LES.
2) **Secondary**: acquired loss of myenteric plexus, which is responsible for the peristaltic movement, due to damage either to the esophagus or vagus nerve

   Example: Chagas disease ➔
   Trypanosoma cruzi Infection > destruction of the myenteric plexus > failure of LES relaxation > esophageal dilatation.

➔ **Clinical presentation:**

- **Dysphagia** (difficulty in swallowing) ➔ to both solids and liquids that can be progressive (while mechanical obstruction usually manifests as dysphagia to solids only, and with time may develop dysphagia to liquids)
- **Regurgitation of food** (ارتجاع الأكل)
- **Chest pain**

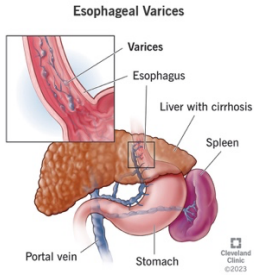


- The above image is an X-ray of the esophagus using contrast ➔ **Notice:** Smooth, funnel-shaped tapering (green overlay) in the region of the lower esophageal sphincter is accompanied by a widening (double-headed arrow) of the esophagus (red overlay). ➔ The appearance of the esophagus in achalasia is referred to as the **"bird-beak sign"** (illustration).
- **Increases the risk for esophageal squamous cell carcinoma**

[Vascular diseases]

[Esophageal varices]

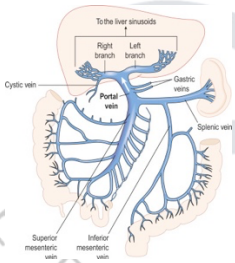
➔ **Definition:** Dilated submucosal veins in the lower esophagus



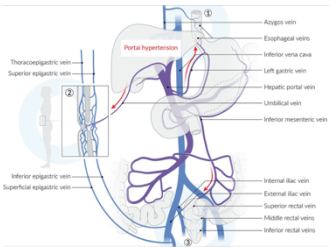
➔ **Pathophysiology:**

- **Portal Circulation**: a specialized vascular system in which blood collected from the gastrointestinal tract does not drain directly into the systemic circulation. Instead, it follows this pathway: GIT → Portal vein → Liver (detoxification & metabolism) → Hepatic veins → Inferior vena cava (IVC).

- This arrangement allows the liver to metabolize nutrients and detoxify substances absorbed from the gut before they enter the systemic circulation.

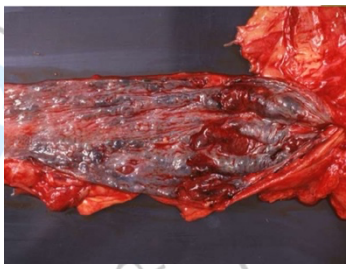


- **Portal hypertension**: any disease that causes resistance to blood flow through the portal vein or liver, resulting in diverting the blood from the portal circulation to the systemic circulation through portosystemic anastomoses.



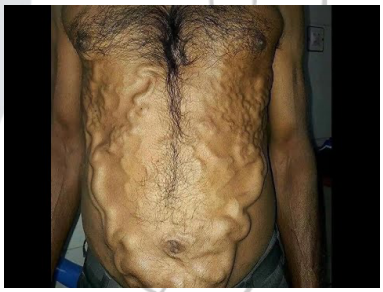
- **How esophageal varices develop?**
  They arise secondary to portal hypertension

1) Portal blood flow is obstructed
2) Portal hypertension
3) Blood is shunted through porto-systemic collateral channels
4) Collateral veins in the distal esophagus become dilated, resulting in esophageal varices.



- The same principle leads to development of

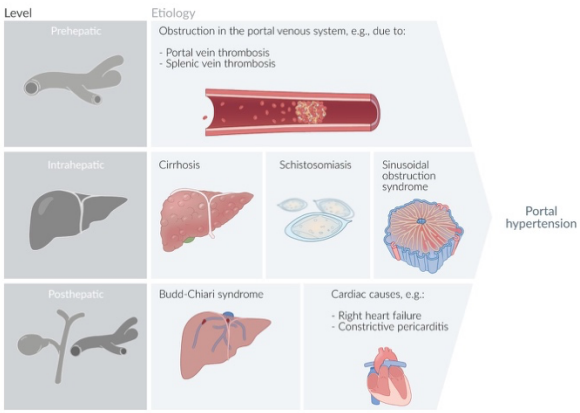
1) **Caput Medusae:** Dilated, tortuous veins radiating from the umbilicus due to portal hypertension ➔ blood is diverted from the portal system to superficial abdominal veins



2) **Internal Hemorrhoids:** Dilated veins of the rectum

➔ **Causes of portal hypertension:**

Main idea: Anything that causes resistance to blood flow



- **Cirrhosis** is the **MOST COMMON** cause: which is defined as fibrosis of the liver parenchyma (usually irreversible) in response to hepatic injury ➔ ↑ resistance to blood flow in the hepatic sinusoids (due to hepatic fibrosis) → ↑ hydrostatic pressure in the hepatic sinusoids → ↑ pressure in the portal vein and its tributaries ➔ **many possible causes:** examples include, chronic hepatitis C, chronic alcohol use disorder, metabolic dysfunction associated with steatotic liver disease, hereditary hemochromatosis, Wilson's disease, and autoimmune conditions (we will talk more about these in the liver lectures)

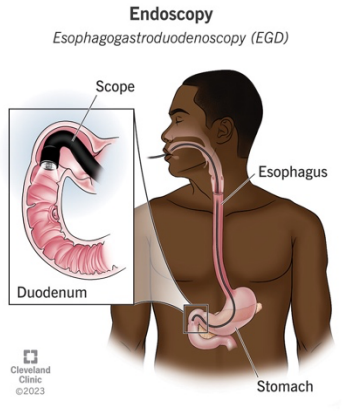
- **Hepatic schistosomiasis** (liver infection by the helminth Schistosoma) is the second most common cause worldwide

➔ **Clinical presentation:**

- Often asymptomatic (discovered during screening endoscopy in patients diagnosed with cirrhosis)
- Rupture leads to **massive painless hematemesis** (vomiting of blood) and death ➔ most common cause of death in cirrhosis
- 20% of patients die from the first bleed despite interventions.
- Death due to hemorrhage, hepatic coma, and hypovolemic shock
- Rebleeding rate is 60%.

➔ **Diagnosis:**

It is diagnosed by **Upper Endoscopy (تنظير علوي)** ➔ we can see the dilated veins

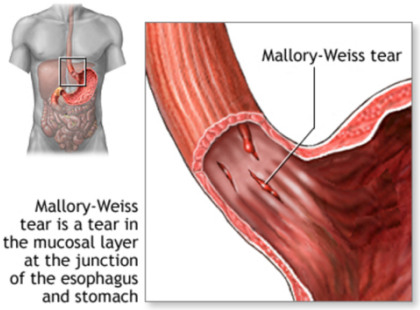


[Inflammatory diseases]

[Esophageal laceration]

➔ **Definition:** a tear in the lining (mucosa) of the esophagus

- Most common cause is **Mallory-Weiss tear**: linear laceration, longitudinal oriented, cross Gastro-esophageal junction, superficial, and heals quickly without surgical intervention.



➔ **Pathophysiology:**

- Sudden and severe rise in the esophageal intraluminal pressure results in tearing of the esophageal mucous membrane, as well as the submucosal arteries and veins ➔ **Precipitating factors:**
  Severe vomiting (most important): a large amount of gastric content will pass through the esophagus, causing distention and stretching of the esophagus, leading to a tear.

➔ **Clinical presentation:**

- Painful hematemesis (vomiting of blood)

[Esophagitis]

Esophagitis: inflammation of the esophageal linin ➔ can be due to many causes:

- **Reflux:** acid irritation (GERD) **MOST COMMON CAUSE**
- **Infections**
- **Chemical** (medications, acids/alkalis etc..)
- **Eosinophilic:** allergic/immune-mediated

[Chemical esophagitis]

Damage to esophageal mucosa by irritants, causing ulceration and acute inflammation:

1) Alcohol
2) Corrosive acids or alkalis
3) Excessively hot fluids
4) Heavy smoking
5) Medicinal pills (doxycycline and bisphosphonates) ➔ this is why we ask the patient to drink plenty of water and be in an upright position while taking these drugs
6) Iatrogenic (chemotherapy, radiotherapy)

➔ **Clinical presentation:**

- **Usually only:** Pain and odynophagia (pain with swallowing).
- May develop Hemorrhage, stricture, or perforation in severe cases

[Infectious esophagitis]

Infections of the esophagus are not common in healthy people ➔ they mostly occur in **immunocompromised** patients

➔**Infectious causes:**

1) Viral (HSV, CMV)
2) Fungal (candida, mucormycosis, aspergillosis)
3) Bacterial (less common) and can be secondary to viral or fungal infection

➔ **Clinical presentation:**

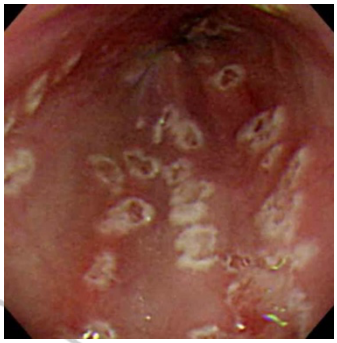
- Pain and odynophagia

➔ **Diagnosis:** we differentiate the different infections through:

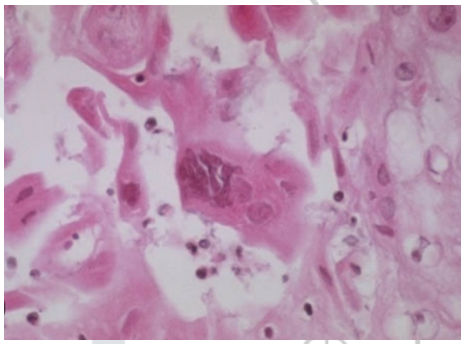
- Endoscopy ➔ mucuosal changes
- Biopsy

#1: Herpes viruses (HSV)

- **Endoscopy**: **circular punched-out** ulcers

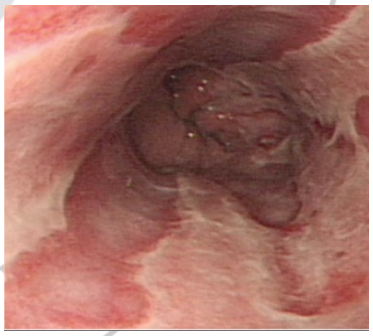


- **Histopathological features:**
  1) Nuclear viral inclusion
  2) Degeneration of epithelial cells at ulcer edge
  3) Multi-nucleated epithelial cells

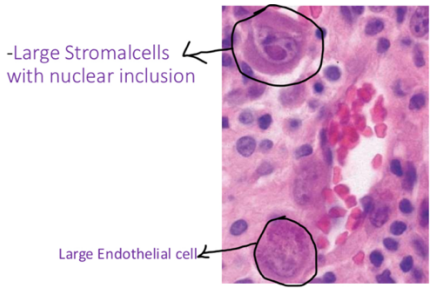


#2: Cytomegalovirus (CMV)

- **Endoscopy**: shallower, **linear** ulcerations

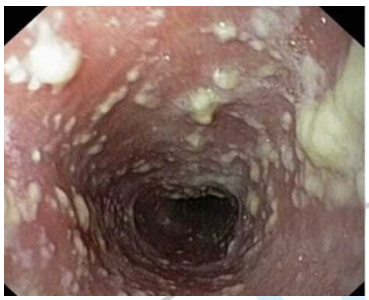


- **Histopathological features:** nuclear and cytoplasmic inclusions in capillary endothelium and stromal cells

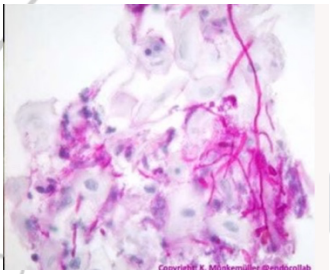


#3: Candida "candidiasis"

- **Endoscopy**: adherent, **gray-white** pseudo-membranes.



- **Histopathology features:** fungal hyphae and inflammatory cells.



[Gastroesophageal reflux disease GERD, and reflux esophagitis]

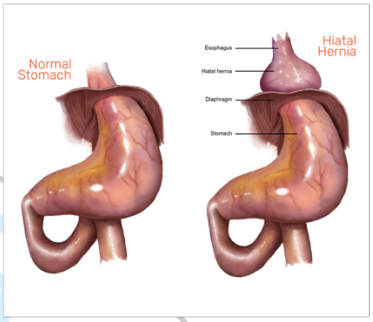
➔ **Definitions:**

- **Gastroesophageal reflux disease:** regurgitation of stomach contents into the esophagus causing troublesome symptoms and/or esophageal injury
- **Reflux esophagitis:** inflammation of the esophagus that results from exposure of the esophageal mucosa to gastric content, mainly acid and pepsin

➔ **Pathophysiology:**

Imbalance between intragastric and lower esophageal sphincter (LES) pressures ➔ Reflux occurs when the intragastric pressure is higher than that created by the LES.

1) **Decrease lower esophageal sphincter tone** ➔ risk factors include:
   - Alcohol
   - Smoking
   - CNS depressants
   - Certain foods (e.g. coffee)
   - **Hiatal hernia**: where part of the stomach herniates through the diaphragm and enters the thoracic cavity, leading to a decrease in LES tone and increased reflux of contents into the lower esophagus.



2) **Increase intra-abdominal pressure** ➔ Reflux occurs when the intragastric pressure is higher than that created by the LES, such as in:
   - Obesity
   - Pregnancy
   - Delayed gastric emptying and increased gastric volume

3) **Idiopathic** (unknown cause)

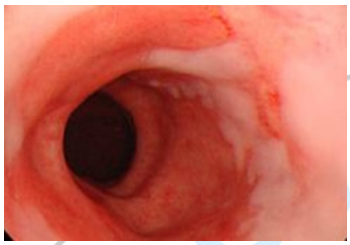
➔ **Clinical presentation:**

- Most common over 40 years (but may occur in infants and children)
- **Heartburn** (Burning sensation and pain in the chest) ➔ increased by lying down shortly after meals
- Rarely: severe **chest pain**, mistaken for heart disease (acute myocardial infarction, MI), particularly when patients present to the emergency room.
- **Dysphagia** (difficulty in swallowing)
- **Regurgitation of sour-tasting gastric contents** (which may reach the mouth, causing sour taste)
- **Cough** (regurgitation fluid enters airway and caused irritation)

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

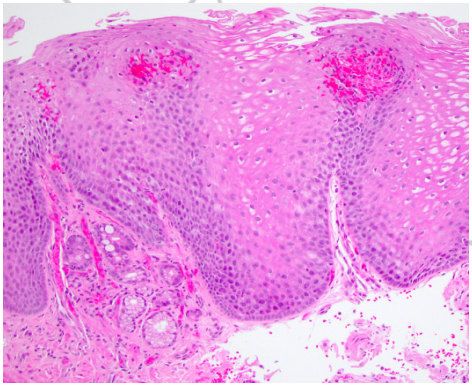
- Depends on severity:
  Mild GERD ➔ usually normal with no changes
  More severe GERD ➔ erythema (redness) due to the inflammation
  May see complications of GERD (see complications below)



#2: Microscopic appearance

1) **Eosinophilic** infiltration of the squamous epithelium (Earliest Manifestation)
2) Followed by neutrophil infiltration later (in more severe cases).
3) Basal zone hyperplasia of the basal squamous epithelial cells.
4) Elongation of lamina propria papillae, due to chronic injury and regeneration, where these papillae reach the upper 2/3 of the epithelium or even the surface to increase the blood supply and support for the regeneration of the epithelium.
5) **May develop: Barret Esophagus** ➔ metaplastic transformation of squamous epithelium into columnar epithelium

- Biopsy of Gastro-esophageal junction with scattered inflammatory cells.



➔ **Treatment:**

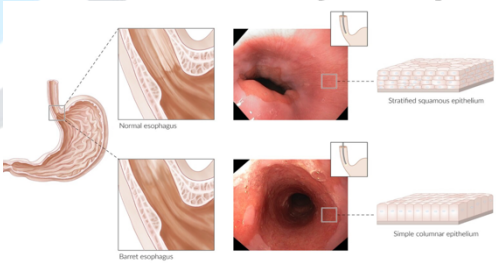
Drugs that decrease acidity of the stomach ➔ Most effective: **Proton pump inhibitors PPIs** (you will study these drugs in detail in pharmacology)

➔ **Complications**:

- **Esophageal ulceration**
- **Hematemesis** (vomiting of blood)
- **Melena** (black stool) ➔ when blood from upper gastrointestinal bleeding passes through the stomach, where it is altered by stomach acid, resulting in black, tarry stools.
- **Strictures** (narrowing of the esophagus that makes swallowing difficult) can develop in patients with recurrent and long-standing reflux esophagitis, as the healing of chronic inflammation may involve fibrosis, leading to narrowing of the esophagus.
- **Barrett's esophagus** ➔ see below

[Barrett esophagus]

➔ **Definition:** Intestinal metaplasia occurs when the normal squamous epithelium of the esophagus is replaced by intestinal-type epithelium (simple columnar epithelium with goblet cells)

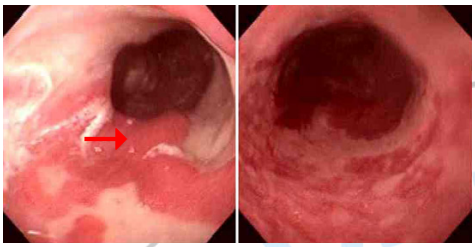


- Occurs in 10% of individuals with symptomatic, long-standing GERD.
- Affects males > females, 40-60 yrs
- It's important to establish the diagnosis of Barrett's esophagus because it's a **direct precursor of esophageal adenocarcinoma.** ➔ The annual risk of developing dysplasia in patients with intestinal metaplasia (Barrett's esophagus) is approximately 0.2-1% /year. ➔ so, it is **Precancerous**

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

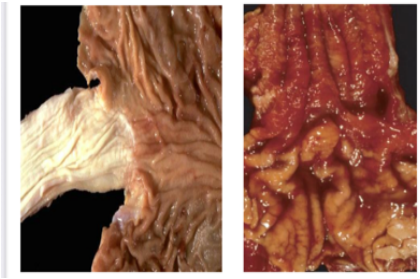
- Red tongues extending upward from the GEJ.



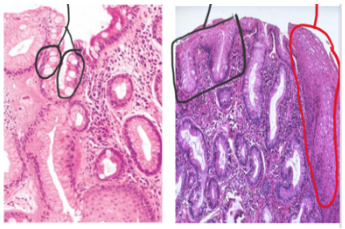
#2: Microscopic appearance

- **Intestinal metaplasia** (defined by simple columnar epithelium with goblet cells))
- +/- Dysplasia: low-grade or high-grade, disordered growth of epithelium is characterized by abnormally frequent mitotic figures and loss of cell orientation and uniformity (size, shape).
  ➔ It can progress to irreversible malignancy, but it is reversible if not all epithelial layers are involved
- Intramucosal carcinoma (early carcinoma) ➔ may progress to cancer
- **VERY IMPORTANT NOTE:** Barrett's esophagus can only be diagnosed in the presence of intestinal metaplasia. Therefore, biopsy is essential for diagnosis and monitoring the progression of metaplasia or the potential development of dysplasia & cancer

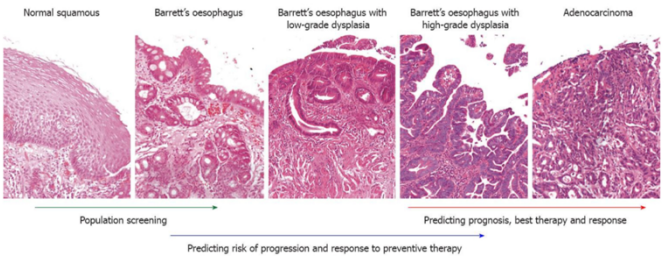
The images below show normal esophagus morphology compared to the erythematous mucosa of Barrett's esophagus.



The histology slides show goblet cells (in black), which are the hallmark of intestinal metaplasia, compared to normal mucosa (red).



Barret esophagus progression:
normal squamous mucosa ➔ intestinal metaplasia ➔ low-grade dysplasia ➔ high-grade dysplasia ➔ adenocarcinoma.



➔ **Treatment:**
- PPI therapy and Periodic surveillance endoscopy with biopsy to screen for dysplasia.
- If high-grade dysplasia and intramucosal carcinomas developed, the patient will need intervention (example: resection of the lesions)

[Eosinophilic esophagitis]

➔ **Definition:** It is an **Allergic** condition characterized by chronic immune-mediated inflammation of the esophagus, leading to extensive inflammatory infiltration of the squamous epithelium

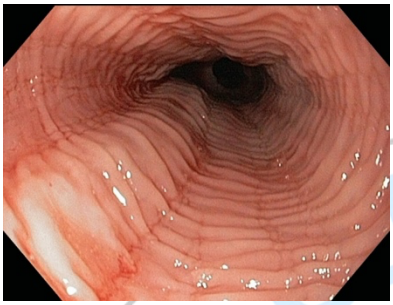
➔ **Pathophysiology:** it is an allergic reaction

- Most patients are **atopic** (having a genetic tendency to develop allergic reactions) and typically exhibit other atopic manifestations, such as atopic dermatitis (eczema), allergic rhinitis, or asthma and may also have modest peripheral eosinophilia.

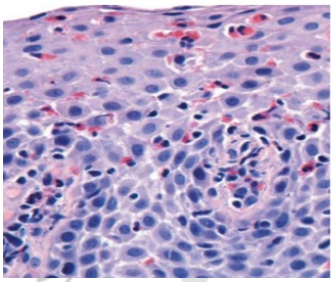
➔ **Clinical presentation:**
- Food impaction and dysphagia in adults
- Feeding intolerance or GERD-like symptoms in children

➔**Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance ➔ Rings in the upper and mid esophagus



#2: Microscopic appearance ➔ Numerous eosinophils in the epithelium: the cardinal histologic feature is epithelial infiltration by many eosinophils, particularly in the superficial layers and at sites distant from the gastroesophageal junction, which helps to differentiate between GERD and eosinophilic esophagitis.



➔ **Treatment:**

- **Dietary restrictions ➔** focus on eliminating foods that provoke symptoms, such as cow's milk (particularly in children) and soy products.
- Topical or systemic corticosteroid
- It is refractory to PPI (PPIs aren't beneficial)

Feature	Eosinophilic Esophagitis (EoE)	Gastroesophageal Reflux Disease (GERD)
Clinical Presentation	- Dysphagia (especially solids) - Food impaction - History of atopy (asthma, eczema, allergic rhinitis) - Affects young males commonly - Poor response to PPIs alone	- Heartburn (burning sensation) - Regurgitation of sour-tasting gastric contents -Most common over 40 years. May occur in infants and children - Usually improves with PPIs
Endoscopic Findings	- Rings ("trachealization" of esophagus) - Linear furrows - White exudates (eosinophilic microabscesses) - Narrow-caliber esophagus	- May appear normal or show signs of erosive esophagitis - Mucosal erythema or ulcers - Hiatal hernia may be present - Less likely to have rings or furrows
Histologic Findings	- ≥15 eosinophils per high-power field (HPF) - Eosinophilic microabscesses - Superficial layering of eosinophils - Inflammation often patchy	- Usually <15 eosinophils/HPF - Basal zone hyperplasia and elongation of papillae - Mild eosinophilia may be present - More diffuse inflammation pattern

[Esophageal cancer]

➔ **Types**: 2 different types

1) **Squamous cell carcinoma** (the most common worldwide)
2) **Adenocarcinoma** (most common type in developed countries)

➔ **Clinical presentation:**

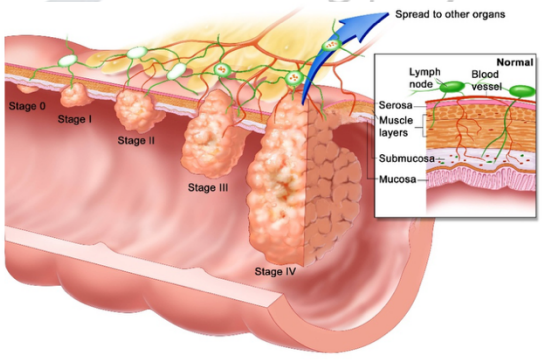
Esophageal carcinoma presents late (poor prognosis)

- **Dysphagia** and **odynophagia** (occur due to the exophytic tumor obstructing the esophageal lumen)
- Progressive **unintentional weight loss** (may result from tumor-induced cachexia and reduced oral intake due to dysphagia)
- Chest pain
- Vomiting
- Occasionally, squamous cell carcinoma of the upper and mid esophagus presents with symptoms caused by a**spiration of food via a tracheoesophageal or tracheobronchial fistula.**

➔ **Lymph node metastases:**

According to the site of the tumor in the esophagus

1) **Upper 1/3:** cervical lymph nodes
2) **Middle 1/3:** mediastinal paratracheal and tracheobronchial lymph nodes.
3) **Lower 1/3:** gastric and celiac lymph nodes.



[Adenocarcinoma]

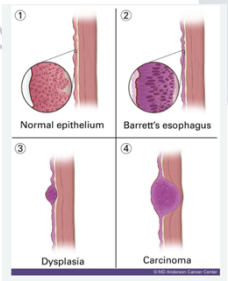
- Malignant proliferation of glands, that arises from **preexisting Barrett esophagus**

- Usually affects the **lower third of the esophagus**

- Male: female ratio of (7:1) with a high rate in developed countries, partly due to higher obesity prevalence ➔ Obesity increases the risk of GERD, which is strongly associated with the development of Barrett's esophagus.

➔**Pathophysiology:**

- Barrett esophagus ➔ dysplasia ➔ adenocarcinoma (by acquiring genetic and epigenetic changes, with Chromosomal abnormalities and TP53 mutation)



➔ **Risk factors:** same as risk factors for GERD (because this type of cancer arises from barret esophagus which is caused by GERD)

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

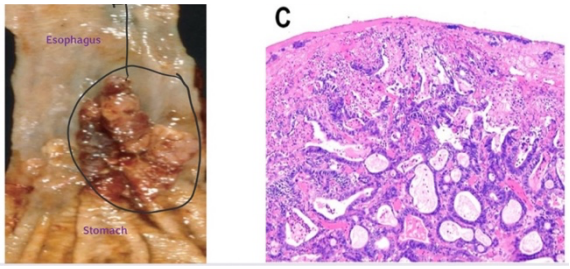
#1: Gross (Macroscopic) appearance

- Early morphologic changes of the lesion may present as: flat or raised patches

- **Later:** exophytic infiltrative masses ➔ meaning a mass that protrudes into the esophageal lumen and may cause luminal obstruction. Additionally, they begin to infiltrate the esophageal wall with longitudinal spread, extending both proximally and distally along the esophagus.

#2: Microscopic appearance

- Microscopically, these tumors are adenocarcinomas, characterized by the **formation of glandular structures** and the production of mucin.



[Squamous cell carcinoma]

- Malignant proliferation of squamous cells

- Male: female (4:1) and more common in rural, low-resource countries.

- Usually affects the **middle third of the esophagus**

➔ **Pathophysiology:**
Anything that might irritate and damage the esophageal epithelium

➔ **Risk factors:**

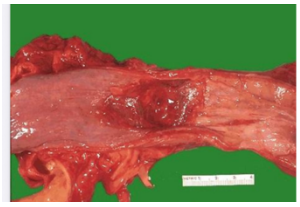
1) Alcohol
2) Tobacco use (with alcohol, mainly in Western countries)
3) Poverty (nutritional deficiencies)
4) Exposure to polycyclic hydrocarbons, nitrosamines, and fungus-contaminated foods.
5) Caustic injury, including exposure to acidic or alkaline substances.
6) HPV infection has been implicated in squamous cell carcinoma in high-risk regions, particularly as part of upper digestive tract malignancies.
7) Achalasia
8) **Plummer-Vinson syndrome** (a triad of iron deficiency Anemia, dysphagia, and esophageal webs)
9) Frequent consumption of very hot beverages
10) Previous radiation Tx.

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

- **Polypoid, ulcerated, or infiltrative** masses that lead to esophageal wall thickening and luminal narrowing, resulting in progressive dysphagia.

- Invade surrounding structures (bronchi, mediastinum, pericardium, aorta).



#2: Microscopic appearance

- **Pre-invasive**: the precursor lesion is squamous dysplasia & carcinoma-in-situ (abnormal cells confined to the epithelium).
- **Invasive**: well to moderately differentiated invasive SCC.

Very nice summary table

Adenocarcinoma	Squamous Cell Carcinoma
Most common in the US	Most common worldwide
History of long-standing GERD & Barrett's esophagus	Alcohol, tobacco, diet (nitrites), Plummer-Vinson
Lower third of the esophagus	Upper and middle thirds of the esophagus
Squamous cell carcinoma clusters with circular keratinization. Lymphocytic infiltration between the clusters.	Gland-forming tumors with different possible growth patterns (tubular, papillary, tubulopapillary)

The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pathology

Gastric Pathology

Written by: Mohammad Talal Harahsheh

Edited by: Bdour Abdallat

Reviewed by: Yazeed Alajlouni

[Overview]

➔ **Gastric diseases are common clinical conditions and are broadly classified into two main groups** (These two categories account for the majority of stomach pathology)

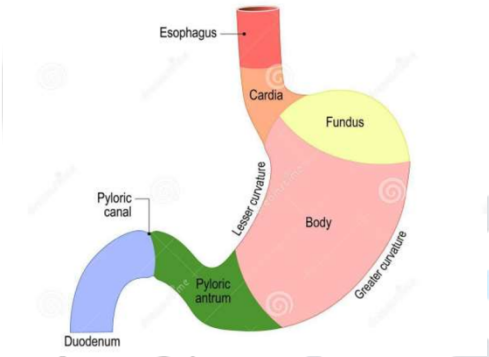
1) **Inflammatory gastric diseases**
   - Acute gastritis
   - Chronic gastritis
   - Acute gastric ulcer
   - Chronic peptic ulcer

2) **Neoplastic gastric diseases**
   Many types ➔ will be discussed in this lecture

[Normal Gastric Anatomy & Histology]

➔ **The stomach is divided into four main parts:**

1. **Cardia**
2. **Fundus**
3. **Body**
4. **Antrum (pylorus)**



➔ **Each region has characteristic cell types:**

- **Cardia:** contains mucin-secreting **foveolar cells**, which provide mucosal protection
- **Body and fundus:** contain **parietal cells** that secrete hydrochloric acid (HCl) and **chief cells** that secrete pepsin
- **Antrum:** contains neuroendocrine **G cells**, which secrete gastrin

[Inflammatory Conditions]

1) Acute gastritis
2) Chronic gastritis
3) Acute gastric ulcer (stress related mucosal disease)
4) Chronic peptic ulcer

[Acute Gastritis and Gastropathy]

➔ **Definitions:**
#1: Acute Gastritis:
Mucosal injury with neutrophil infiltration

#2: Gastropathy: Cell injury and regeneration without significant inflammation

Both result from: ➔ acidic damage caused by imbalance between mucosal defenses and acid secretion

➔ **Pathogenesis:**

Main principle: imbalance between protective mechanisms and damaging forces

Protective mechanisms include
- Mucus layer from surface foveolar cells ➔ barrier against acid & food particles
- Bicarbonate secretion ➔ neutralizes acid at epithelial surface
- Rich mucosal blood flow ➔ supplies nutrients and removes back-diffused H^+

#1: Things that decrease mucosal defense

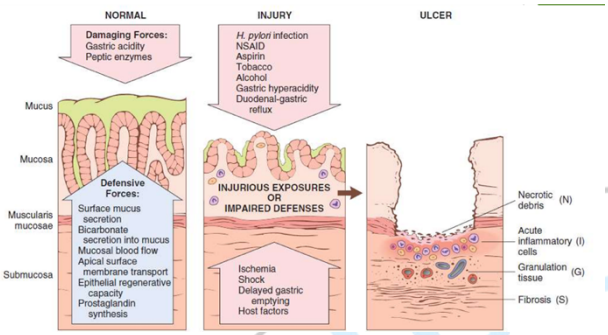
- **NSAIDs** "Nonsteroidal anti-inflammatory drugs" e.g. Apirin ➔ inhibit COX-1 & COX-2 ➔ reduce prostaglandins E2 & I2 ➔ weaken mucosal defense by impaired mucus, bicarbonate, blood flow and epithelial repair (prostaglandins are protective to the mucous)
- **H. pylori** infection ➔ this bacteria causes ammonium production which inhibits bicarbonate secretion (which usually protects the mucosa)

#2: Things that injure the mucous
- Alcohol consumption ➔ direct epithelial injury
- Bile reflux (bile from the intestine goes back to the stomach and causes injury)
- Direct injury: harsh chemicals, chemotherapy, radiation
- Stress-induced injury (See below)

Result: Injury results in superficial inflammation, erosion (loss of superficial epithelium), or ulcer (loss of mucosal layer)

****Note:** Additional Risk Factors

- Aging → decreased mucin & bicarbonate secretion
- Hypoxia (high altitudes) → increased susceptibility



****Very important note:**
Protective Role of Prostaglandins

- Prostaglandins E2 & I2
- Stimulate nearly all gastric defense mechanisms:
  - Mucus & bicarbonate secretion
  - Mucosal blood flow
  - Epithelial restitution
- They are synthesized by COX enzymes ➔ **COX-1** is more important than COX-2, but both contribute to mucosal protection

➔ **Clinical Features:**

- Often asymptomatic
- Epigastric pain, nausea, vomiting
- **Severe cases:** Mucosal erosion or ulceration, which may lead to:
  1- **Hemorrhage** ➔ hematemesis (vomiting blood) OR melena (black stool due to upper GI bleeding)
  2- **Perforation**

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

- **Gastropathy**:
  - Hyperemia (redness), edema, slight vascular congestion
- **Gastritis:**
  - Features of inflammation
  - **Mild**: intact surface epithelium
  - **Severe / erosive:** superficial epithelium lost (ulcer), hemorrhage present

#2: Microscopic appearance

- **Gastropathy**:
  - Rare neutrophils, lymphocytes, or plasma cells
- **Acute gastritis:**
  - Neutrophil infiltration → hallmark of active inflammation

[Stress-Related Mucosal Disease]

➔ **Definition:** Damage and ulceration of gastric mucosa due to severe physiologic stress, including:

- Trauma
- Extensive burns
- Intracranial disease
- Major surgery
- Serious medical illness
- Critically ill patients

Fact: >75% of critically ill patients develop visible gastric lesions within the first 3 days of illness

➔ **Types of Stress Ulcers:**

1) **General stress ulcers:** critically ill patients with shock, sepsis, or severe trauma
2) **Curling ulcers:**
   - Proximal duodenum
   - Associated with severe burns or trauma ➔ hypovolemia (causing hypotension) leads to decreased blood supply
3) **Cushing ulcers:**
   - Esophagus, Stomach, duodenum
   - Associated with CNS injury (e.g., stroke) ➔ increased stimulation of vagus nerve leads to increased acid production
   - High risk of perforation

➔ **Pathogenesis:**

Main cause is **local ischemia** due to:

- Systemic hypotension (curling ulcer)
- Splanchnic vasoconstriction (stress-induced vasoconstriction of GI blood vessels, causing decreased blood flow)

Others:

- Systemic acidosis ➔ lowers intracellular pH
- **Cushing ulcers:** direct vagal stimulation ➔ acid hypersecretion

➔ **Clinical Features:**

- **Common presenting symptoms:**
  Nausea, vomiting
  Melena (black stool due to upper GI bleeding)
  Coffee-ground hematemesis (vomiting blood that looks dark, granular like coffee grounds ➔ blood has been partially digested by gastric acid, suggesting a slower or less active upper GI bleed)

- Bleeding requiring transfusion in 1–4% of patients
- Rare complications: perforation

****Very important notes:**

- Healing with complete epithelialization occurs days or weeks after removal of injurious factors
- Outcome depends mostly on the severity of the underlying condition
- **Prevention:** giving proton pump inhibitors (PPIs) to patients with underlying critical diseases
-

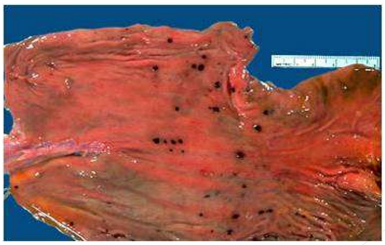
➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

- Ranges from shallow erosions ➔ deep mucosal ulcers

[Features of acute ulcers]

- Rounded, <1 cm, brown to black base (digested blood)
- Often multiple, can appear anywhere in the stomach
- Adjacent mucosa appears normal (unlike chronic peptic ulcers) ➔ Little inflammation, no scarring or vessel thickening
- Some blood suffusion and mild inflammation possible



[Chronic Gastritis]

➔ **Definition:** chronic inflammation of stomach mucosa

- **Divided into two main types based on underlying etiology:**
  1) **Chronic H pylori gastritis** (most common, ~90%)
  2) **Autoimmune atrophic gastritis** (<10%)

- **Less common causes:**
  1) Chronic NSAID use
  2) Radiation injury
  3) Chronic bile reflux (long-term backflow of **bile from the duodenum into the stomach** ➔ Leads to irritation and inflammation of the gastric lining)

➔ **Clinical Features:**

- Less severe but more persistent symptoms than acute gastritis
- Epigastric pain and upper-abdominal discomfort
- Nausea and vomiting may occur
- Hematemesis is uncommon (more common in acute gastritis)

[H. pylori Gastritis]

- **Helicobacter Pylori (H.Pylori)** is a spiral-shaped, curved, **gram-negative** bacilli

- Infection usually acquired in childhood and may persist lifelong.

- More common in settings of poverty and poor sanitation.

- Acute infection is often subclinical (no symptoms) ➔ chronic gastritis brings patient to medical attention

- **Most common Location:** Antrum of stomach (may extend to involve rest of stomach)

> **Note:** In addition to being responsible for most cases of Chronic gastritis ➔ H.pylori is found in:
> - **Almost all duodenal ulcers**
> - **Most gastric ulcers**
>
> See Peptic Ulcer disease below

➔ **Pathogenesis:**

Bacteria lives in the mucus layer of stomach (it does NOT invade the epithelium)

Virulence factors
- **Flagella:** motility in viscous mucus
- **Urease:** an enzyme that breaks down urea to generate ammonia ➔ ammonia protects bacteria from acid
- **Adhesins:** adherence to foveolar cells
- **Toxins (CagA):** contribute to mucosal damage, ulcers, cancer

Disease progression:
- **Starts as**: antral gastritis ➔ stimulates G cells to ↑ acid production ➔ duodenal/peptic ulcers
- **If severe:** May extend to body/fundus ➔ parietal cell atrophy ➔ ↓ acid ➔ hypergastrinemia (gastrin secretion increases in reaction to low acid)
- **Intestinal metaplasia** (metaplastic change of gastric epithelium to intestinal type epithelium due to chronic inflammation) ➔ ↑ risk of gastric adenocarcinoma

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

Inflammation +/- ulcers

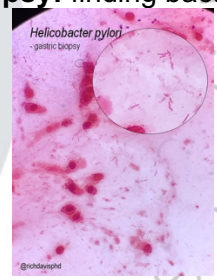
#2: Microscopic appearance

Antral biopsies preferred; bacteria usually absent from acid-producing body

- Organisms concentrated in mucus overlying surface epithelium
- **Inflammatory infiltrate:** neutrophils (intraepithelial & lamina propria), plasma cells, lymphocytes, macrophages
- **Pit abscesses**: neutrophils in gastric pits
- **Lymphoid aggregates (MALT) "Mucosa associated lymphoid tissue"**
- **Intestinal metaplasia:** metaplastic change of gastric epithelium to intestinal type epithelium (goblet + columnar cells) due to chronic inflammation → ↑ risk of adenocarcinoma

Diagnosis of the presence of H.Pylori infection
➔ there are multiple options to test for the presence of infection:

1) **Serology**: anti-H. pylori antibodies in the blood
2) **Stool antigen test**
3) **Urea breath test** (a noninvasive test to detect Helicobacter pylori infection ➔ Patient drinks urea labeled with carbon → if H. pylori is present, its urease breaks it down → releases labeled CO_2 → detected in breath)
4) **Gastric biopsy:** finding bacteria on biopsy



➔ **Treatment:**
- **Triple therapy:** Multiple antibiotics + proton pump inhibitors
- After treatment must confirm eradication of infection ➔ **How?** via negative urea breath test or stool antigen

[Autoimmune Gastritis]

- Autoimmune destruction of gastric parietal cells, which are in the stomach body and fundus
- **Stomach location affected:** Usually spares antrum, affects body/fundus

➔ **Pathogenesis:**

Immune-mediated destruction of parietal cells ➔ ↓ production of acid and intrinsic factor ➔ RESULT:

- Gastric inflammation (from the immune attack)
- Vitamin B12 deficiency (due to decreased intrinsic factor production, which is important for B12 absorption)
- Antral G-cell hyperplasia ➔ hypergastrinemia (low gastric acid leads to reactive G-cell hyperplasia)

➔ **Clinical features:**

- Same as chronic gastritis features discussed above but also:
  1) Vitamin B12 deficiency → pernicious anemia, neurologic changes
  2) Slight female predominance; median age ~60
  3) Often associated with other autoimmune diseases

➔ **Laboratory findings:**

- Antibodies to parietal cells & intrinsic factor
- ↓ pepsinogen
- Hypergastrinemia (due to antral G-cell hyperplasia)

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

- Diffuse damage of oxyntic mucosa (body/fundus)
- Rugal folds lost, wall thinning

#2: Microscopic appearance

- **Inflammatory infiltrate:** lymphocytes, plasma cells, macrophages (neutrophils rarely)
- Extensive parietal/chief cell loss ➔ achlorhydria (lack of hydrochloric acid)
- **Intestinal metaplasia** (metaplastic change of gastric epithelium to intestinal type epithelium due to chronic inflammation) ➔ ↑ risk of gastric adenocarcinoma
- Antral G-cell hyperplasia ➔ risk of gastric carcinoid tumor (see below)

Comparison of H.pylori vs 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

[Complications of Chronic Gastritis]

In both H.pylori and autoimmune

- Intestinal Metaplasia ➔ can transform to adenocarcinoma

In H.pylori only

- Peptic ulcers
- MALT lymphoma (Mucosa associated lymphoid tissue lymphoma)

In Autoimmune only

- Pernicious anemia (from B12 deficiency)
- G cell carcinoid tumor

[Peptic Ulcer Disease (PUD)]

➔ **Definition:** A mucosal ulcer caused by acid–peptic injury**, most commonly** involves:

- Proximal duodenum (≈ 90%)
- Distal stomach (≈ 10%)

- Very common worldwide.
- In the United States:
  - 3 million patients treated annually
  - ~190,000 hospitalizations
  - ~5,000 deaths per year

Lifetime risk:

- Males: ~10%
- Females: ~4%

➔ **Sites of Involvement:**

Any part of the gastrointestinal tract exposed to gastric acid:

- Gastric antrum
- First part of the duodenum
- Esophagus (GERD)
- Small intestine with ectopic gastric mucosa (e.g. Meckel diverticulum ➔ a congenital pouch in the small intestine that may contain **ectopic gastric mucosa** ➔This gastric tissue secretes

acid → causes **ulceration and bleeding** in adjacent intestine)

➔ **Etiology and pathogenesis:**

Core mechanism

- Imbalance between mucosal defensive factors and damaging forces
- Gastric acid is essential for ulcer development ➔ examples of causes of hyperacidity:
  1) H. pylori infection
  2) Parietal cell hyperplasia
  3) Excessive vagal stimulation
  4) Hypergastrinemia

Major causes

1) **Helicobacter pylori infection** ➔ same mechanism as chronic gastritis (see above)

   - 70% of PUD cases are associated with H. pylori infection
   - Only 5-10% of infected individuals develop ulcer ➔ **WHY?** host factors and bacterial virulence play a role

2) **NSAIDs** "Nonsteroidal anti-inflammatory drugs" e.g. Apirin ➔ inhibit COX-1 & COX-2 ➔ reduce prostaglandins E2 & I2 ➔ weaken mucosal defense by impaired mucus, bicarbonate, blood flow and epithelial repair (prostaglandins are protective to the mucous)

3) **Zollinger–Ellison (ZE) syndrome:**
   - A condition caused by a gastrin-secreting tumor (gastrinoma)
   - Leads to excess gastric acid
   - Causes multiple peptic ulcers in the stomach, duodenum, jejunum

4) Bile reflux (gastric ulcers)

**Duodenal ulcer is almost always due to H pylori (> 95%); rarely, may be due to ZE Syndrome

**Gastric ulcer is usually due to H pylori (75%); other causes include NSAIDs and bile reflux.

****Note:** In the USA, most cases are NSAID induced (as H. Pylori infection is falling and increased use of low-dose aspirin in aged population)

Cofactors in Ulcer Formation
(Things that increase risk)

- Cigarette smoking
- High-dose corticosteroids
- Alcoholic cirrhosis
- Chronic obstructive pulmonary disease (COPD)
- Chronic renal failure
- Hyperparathyroidism ➔ hypercalcemia stimulates gastrin release ➔ increased acid production

➔ **Clinical features:**
Main symptom: Epigastric pain

- Increases with food (gastric ulcer)
- Decreases with food (duodenal ulcer)

Other:

- Nausea and vomiting
- Bloating and belching

➔ **Complications:**

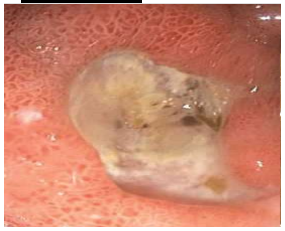
- Bleeding (may be life-threatening)
- Perforation (surgical emergency)
- Iron deficiency anemia (from chronic small bleeding)

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Gross (Macroscopic) appearance

- >80% are solitary (single lesions)
- **Shape:** Round to oval, Sharply punched-out
- **Size:**
  <0.3 cm → shallow
  0.6 cm → deep
- **Ulcer base:** Smooth and clean + Composed of vascular granulation tissue

Example



#2: Microscopic appearance

- Duodenal ➔ Ulcer with hypertrophy of Brunner glands
- Gastric ➔ Biopsy done to differentiate benign vs malignant

➔ **Treatment**: ACCORDING TO CAUSE

- H.pylori ➔Eradication of H. pylori with triple therapy
- NSAIDS ➔ stop drugs
- Surgery; reserved for complications (uncontrolled bleeding or perforation)

** For symptom relief ➔ Gastric acid suppression (proton pump inhibitors)

[Duodenal Ulcer]

- Accounts for ~90% of PUD

➔ **Etiology:**

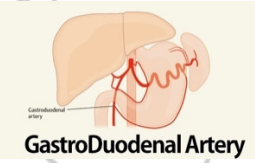
- H. pylori (>95%)
- Rarely, Zollinger–Ellison syndrome

➔ **Clinical Features:**

- Epigastric pain relieved by meals
- Worse at night

➔ **Location:**

- Usually located in the **anterior wall** of the **first part** of duodenum
- If it occurs in posterior wall ulcers ➔ Risk of bleeding from the gastroduodenal artery (remember from anatomy that this artery runs behind the posterior wall of the first part of the duodenum)



➔ **Endoscopic biopsy findings:**

- Ulcer with hypertrophy of Brunner glands

➔ **Malignancy risk:**

- Almost never malignant (Duodenal carcinoma is extremely rare)

[Gastric Ulcer]

- Accounts for ~10% of PUD

➔ **Etiology:**

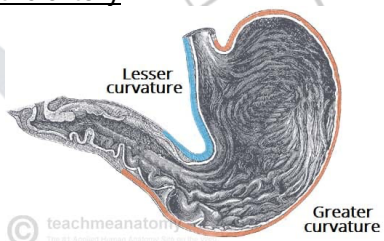
- H. pylori (~75%)
- NSAIDs
- Bile reflux

➔ **Clinical Features:**

- Epigastric pain that worsens with meals
- May be associated with weight loss (patient avoids food because it increases the pain)

➔ **Location:**

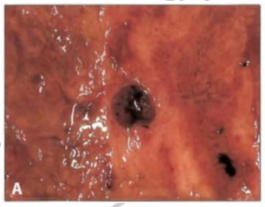
- Typically located on the **lesser curvature of the antrum**
- Rupture may cause bleeding from the left gastric artery



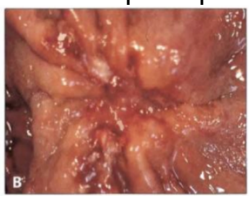
➔ **Malignancy risk:**

- Gastric ulcers can be caused by gastric carcinoma (intestinal subtype)

- Benign peptic ulcers are usually:
  1) Small (< 3 cm)
  2) Sharply demarcated ("punched-out"),
  3) Surrounded by radiating folds of mucosa



- Malignant ulcers are:
  1) Large
  2) Irregular with heaped up margins



However, Biopsy is required for definitive diagnosis

[Gastric Polyps and Tumors]

****Quick note before studying this part:**
Tumors/cancers are usually a very complicated topic to study, so no need to spend time on understanding it in detail, just know a few details about each type, and RELAX ;)

➔ **Classification of gastric tumors:**

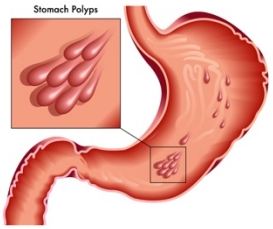
- Gastric polyps
  1) Gastric adenoma
  2) Inflammatory and Hyperplastic Polyps
  3) Fundic gland polyps

- Gastric adenocarcinoma
  1) Intestinal type
  2) Diffuse type

- Lymphoma (MALToma)
- Neuroendocrine (carcinoid) tumor
- Gastrointestinal stromal tumor (GIST)

[Gastric Polyps]

➔ **Definition:** polyps are nodules or masses projecting above the level of surrounding gastric mucosa



- They are detected in up to 5% of upper GI endoscopies.

➔ **Types:**

1) Inflammatory and hyperplastic polyps
2) Fundic gland polyps
3) Gastric adenomas

<u>They are differentiated based on HISTOLOGY</u>

[Inflammatory and Hyperplastic Polyps]

- Most common type (~75%)
- Occur mainly between 50–60 years

- Arise in a background of chronic gastritis ➔ so, commonly associated with H. pylori infection and may regress after H. pylori eradication

- Risk of dysplasia increases with size ➔ Significant when >1.5 cm

[Fundic gland Polyps]

- Occur sporadically OR in familial adenomatous polyposis <u>(a genetic disease where patients have hundreds of colonic polyps with 100% chance of developing colon cancer)</u>
- Sporadic type associated with proton pump inhibitor use

- **Mechanism**: ↓ acid ➔ ↑ gastrin ➔ glandular hyperplasia

- Usually asymptomatic and incidental
- Located in body and fundus

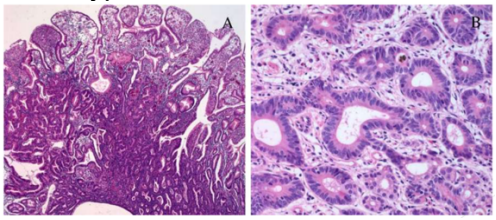
- Multiple, well-circumscribed
- Rarely progress to malignancy

[Gastric Adenoma]

- Account for ~10% of gastric polyps
- Incidence increases with age
- Age: 50-60 years
- M:F of 3:1

- **Pathogenesis**: occur in the background of
  1) Chronic gastritis
  2) Gastric atrophy
  3) Intestinal metaplasia

- **Histology:**
  Dysplastic glandular epithelium (precancerous) ➔Crowded, irregular glands with loss of normal architecture with cellular atypia



- Always show epithelial dysplasia (Low-grade or high-grade)

- **Malignant Potential:** Risk of adenocarcinoma increases with size ➔ Highest if >2 cm

- **Malignant potential greater than colonic adenomas** ➔ Carcinoma present in up to 30% of gastric adenoma

[Gastric Adenocarcinoma]

➔ **Definition:** Malignant proliferation of surface epithelial cells

- Accounts for >90% of gastric malignancies

➔ **Epidemiology:**

Marked geographic variation

- High incidence: Japan, Chile, Costa Rica, Eastern Europe
- More common in lower socioeconomic groups
- In USA rates dropped > 85% (but rising incidence of cardia cancer due to GERD and obesity)

➔ **Risk factors:**

- Chronic gastritis
- Intestinal metaplasia
- H. pylori infection
- EBV (Epstein bar virus) infection (~10%)
- Nitrosamines (chemicals found in smoked foods)
- Blood group A
- Partial gastrectomy (gastric stump carcinoma, meaning cancer at site of surgery due to chronic inflammation)

****VERY IMPORTANT NOTE: ALL these risk factors:** increase risk of intestinal type adenocarcinoma NOT diffuse type

➔ **Pathogenesis:**

Most cases are sporadic (not familial) ➔ Generally, fall under the umbrella of molecular/genetic alterations

Diffuse type

- **Familial:** germline CDH1 (E-cadherin) mutation
- **Sporadic:** somatic CDH1 mutation

Intestinal type

- **Familial**: FAP (APC mutation)
- **Sporadic:** β-catenin, TP53, HER2 amplification

➔ **Types (Lauren classification):**

#1: Intestinal Type

- More common

Arises from precursor lesions: such as ➔

- Dysplasia
- Adenoma
- Intestinal metaplasia

Associated with:

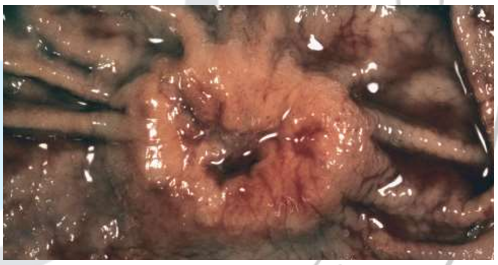
- H. pylori
- Dietary nitrosamines
- Smoking
- Achlorhydria

Common location:

- Lesser curvature of the antrum (just like gastric ulcers)

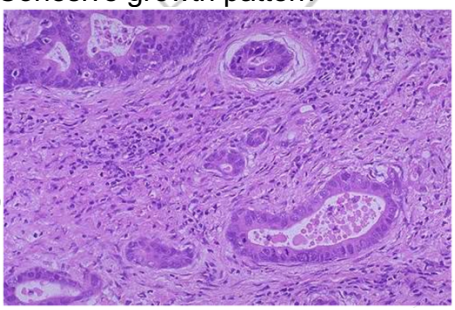
Gross appearance:

- Exophytic mass or ulcer (Irregular ulcer with heaped-up margins)



Microscopic appearance:

- Forms glands
- Cohesive growth pattern

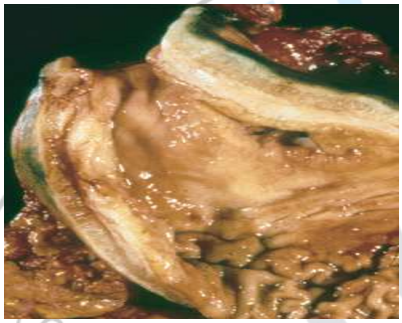


#2: Diffuse Type

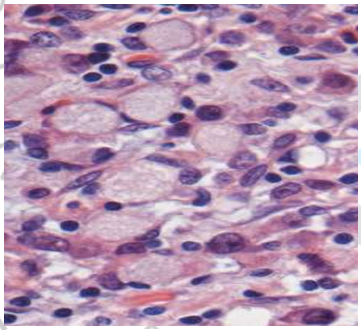
No precursor lesion

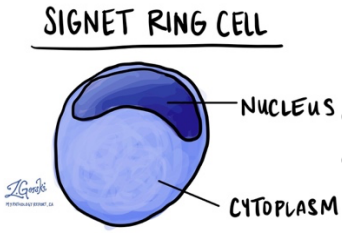
NOT associated with:
- H. pylori
- Intestinal metaplasia
- Nitrosamines

Gross appearance:
- Thickened, rigid stomach wall ➔ described as **Linitis plastica** (leather bottle stomach)



Microscopic appearance:
- **Signet ring cells: Mucin-filled cytoplasm + Peripheral nucleus** (large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery)



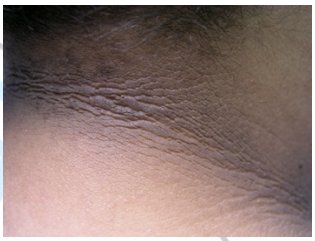


- Diffusely infiltrate the gastric wall (Poorly cohesive cells)
- Marked **desmoplasia** (proliferation of fibroblasts and collagen) ➔ this is responsible for wall thickening
- Loss of E-cadherin (CDH1 mutation)

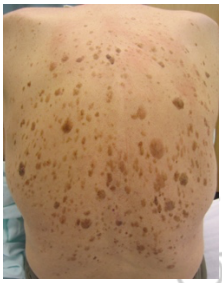
➔Clinical Features:
- Late presentation is common
- Symptoms include: Weight loss, Abdominal pain, Early satiety, Anemia

- **Paraneoplastic signs (rare):**

1) **Acanthosis nigricans:** Dark, velvety thickening of skin (usually neck/axilla) ➔ Commonly due to insulin resistance, but if sudden/severe → can be a paraneoplastic sign of gastric cancer



2) **Leser–Trélat sign:** Sudden appearance of multiple seborrheic keratoses (benign skin tumors)



➔ Spread and Metastasis:

Lymphatic
- **Virchow node** (spread to left supraclavicular)

Hematogenous
- Liver (most common)

Peritoneal
- Sister Mary Joseph nodule (periumbilical)
- Krukenberg tumor (bilateral ovarian metastasis)
- Blumer shelf (rectouterine pouch)

➔ Prognosis:

Prognostic Factors
- Depth of invasion (more deep = worse prognosis)
- Lymph node involvement (lymphatic spread = worse prognosis)
- Distant metastasis (metastasis = worse prognosis)

Survival

- Early gastric cancer: >90% 5-year survival
- Advanced cancer: <20–30%

➔ **Treatment:**

- Surgical resection
- Chemotherapy
- Targeted therapy (e.g. anti-HER2)

[Gastric Lymphoma]

- A type of **Extranodal lymphoma (**lymphoma that **arises outside lymph nodes** in organs/tissues) ➔ Stomach is the most common site of extranodal lymphoma
- Accounts for ~5% of gastric malignancies
- **Most common type: Extranodal marginal zone B-cell lymphoma (MALToma)**
- **Second most common:** Diffuse large B-cell lymphoma

[Neuroendocrine (Carcinoid) Tumors]

Origin: Arise from neuroendocrine-differentiated GI epithelial cells (e.g., G cells)

Features:

- 40% occur in the small intestine
- Slower growing than carcinomas

Associated with:

- Endocrine cell hyperplasia
- Chronic gastritis
- Zollinger–Ellison syndrome

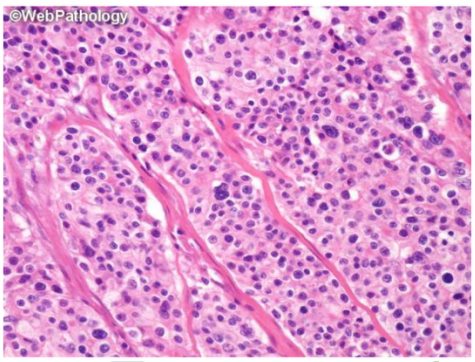
Carcinoid syndrome

- A syndrome of symptoms that occurs when neuroendocrine tumors (carcinoids) secrete vasoactive substances (mainly serotonin) into systemic circulation.
- **Why it happens?** Normally, serotonin from GI tumors is metabolized in the liver (so they don't reach the circulation and nothing happens) ➔ When there are liver metastases, substances bypass metabolism ➔ enter circulation ➔symptoms appear

- **Main features:**
  1) **Flushing:** episodic, red/pink face
  2) **Watery diarrhea:** due to ↑ intestinal secretion/motility
  3) **Bronchospasm:** wheezing (asthma-like)
  4) **Right-sided heart disease:** fibrosis of tricuspid & pulmonary valves

Morphology & Histopathology

- Intramural or submucosal masses
- Small polypoid lesions
- Under the microscope, uniform cells with pink granular cytoplasm and **salt-and-pepper chromatin** are seen



The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pathology

Intestinal diseases 1&2

Written by: Nour Alhaj Qassim

Edited by: Ghada T. Alzoubi

Reviewed by: Yazeed Alajlouni

[Overview]

➔ **Outline of intestinal diseases we will cover:**

1) **Obstructive diseases**
   - Mechanical
   - Non-mechanical

2) **Vascular diseases**
   - Ischemic bowel disease
   - Angiodysplasia
   - Hemorrhoids

3) **Diarrhea disease**
   - Secretory
   - Osmotic
   - Malabsorptive
   - Exudative

4) **Inflammatory disease**
   - Sigmoid diverticulitis
   - Inflammatory bowel disease

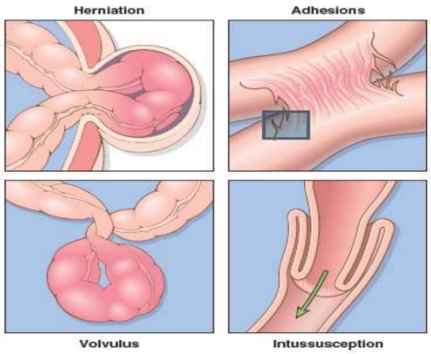
5) **Polyps and neoplastic disease**

[Intestinal obstruction]

- **Obstructive diseases** affecting the intestines are divided into **Mechanical** (physical blockage that prevents passage of contents) **VS non-mechanical** (the intestines is not physically blocked, but it fails to move due to loss of normal motility)

➔ **Mechanical causes:**
- Adhesions (most common cause)
- Hernias (second most common cause)
- Intusseption
- Volvulus
- Tumors
- Diverticulosis
- Infarction

80% of causes



➔ **Non mechanical causes:**
- Neurological disorders (Hirschsprung disease)
- Drugs (drugs that inhibit affecting peristalsis movement)

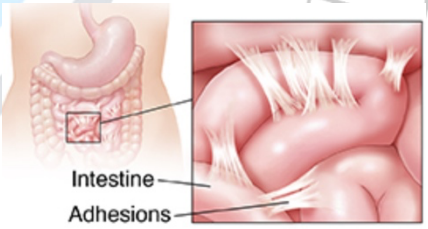
➔ **General Clinical features** (regardless of the cause)**:**

1) **Constipation** (most important feature, most common in patients with chronic obstruction): Nothing can pass beyond the blockage ➔ SO stool and gas are trapped
2) **Vomiting** (in patients with acute obstruction): Contents accumulate ➔ pressure increases ➔ bowel tries to relieve pressure by reverse peristalsis ➔ leads to vomiting
3) **Abdominal pain**
4) **Abdominal distention:** obstruction causes Gas + fluid accumulation

➔ Causes of mechanical obstructions:

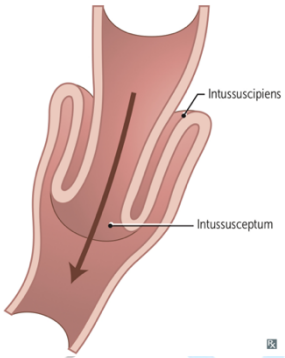
1) Adhesions: fibrotic connections between bowels loops, so this will affect the peristaltic movement.

➔**Why do they happen?**
- If the patient had a previous surgical procedure in the abdomen (Cesarean section, previous ulcer perforated, previous perforation of the bowel, etc…)



2) Intussusception: Telescoping of proximal segment of bowel forward into distal segment ➔ Segment of the intestine constricted by peristalsis, telescopes into the immediately distal segment

- Trapped segment pulls mesentery with it, which may compress the blood supply to the intestine ➔ may lead to bowel ischemia



- **Most common cause of intestinal obstruction in children aged between (3m-3y) years of age.**

➔Pathophysiology:

- Development of a **lead point**: an intestinal **lesion or abnormality** of the intestinal wall that enables the proximal bowel to **be pulled by peristalsis into the distal bowel**

- Peristalsis moves the lead point distally ➔ invagination or so-called "**telescoping**" of a portion of intestinal bowel **(intussusceptum)** into the distal adjacent bowel loop **(intussuscipiens)**

- Invaginated bowel leads **to mechanical bowel obstruction**

- Impaired lymphatic drainage and increasing pressure in intussusceptum bowel wall → venous impairment → congestion of mesenteric vessels → ischemia of intussusceptum bowel wall → sloughing of bowel mucosa (earliest feature of bowel ischemia since it is the furthest from the arterial supply) → transmural necrosis and perforation with prolonged ischemia.

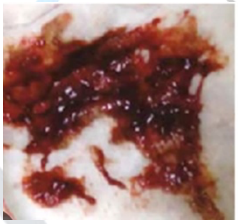
➔Etiology:

- **Idiopathic:** most common
- **Pathological lead points:**

***Adults:** intraluminal mass or tumors
*** Children:**
Meckel diverticulum
Peyer patches hyperplasia after viral infection or vaccine.

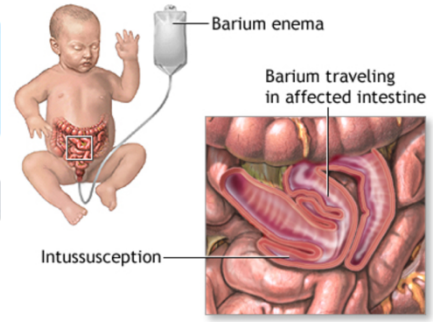
➔Clinical features:
Same common intestinal obstruction features but since it affects children mainly, you will notice**:**

- Irritable, crying child
- Passage of **currant jelly stool** (stool mixed with blood and mucus)



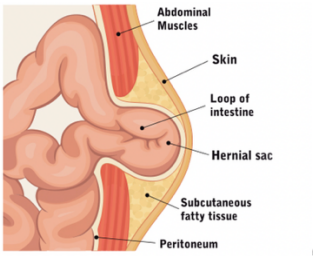
➔Management:

- Barium enemas (diagnostic and therapeutic) in uncomplicated idiopathic
- Surgery if complicated by infarction or if masses are the leading point.



Note: **What is Barium enema?** a heavy, radio-opaque dye, is administered through the rectum, fills the bowel, and allows for visualization of the bowel by x-rays. This procedure is sometimes successful in correcting the problem - the weight of the barium itself in the bowel frequently reduces the telescoped bowel. If intussusception is diagnosed and not corrected by barium enema, surgery is necessary IMMEDIATELY to prevent complications such as obstruction, gangrenous bowel and peritonitis.

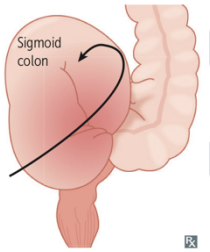
3) Herniation: protrusion of visceral contents (bowel) through a congenital or acquired defect in the peritoneum or mesentery within the abdominal wall



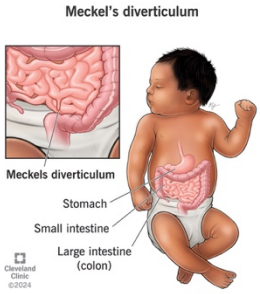
- It can be **reducible** (content like bowel reduced especially if the hernia hiatus is wide) OR **irreducible** (neck is small, so bowel is trapped inside the hernia ➔ start to have ischemic changes due to the pressure on the venous return ➔ if we don't treat these herniations, hemorrhagic infarction of the bowel could be developed

4) Volvulus

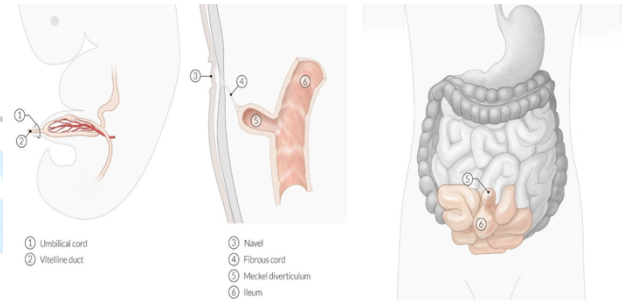
- **Twisting** of a loop of bowel on its mesentery
- Results in obstruction and disruption of the blood supply with infarction
- Most common locations are **sigmoid** colon (elderly) and **cecum** (young adults).



5) Meckel's diverticulum: Outpouching of all three layers of the bowel wall (true diverticulum)



- Arises due to failure of the **vitelline duct** (an embryologic tube connecting the midgut to the yolk sac. ➔ Normally obliterates in the fetus ➔ If it persists ➔ Meckel diverticulum)
- **Most common congenital anomaly of GI tract**



Meckel diverticulum

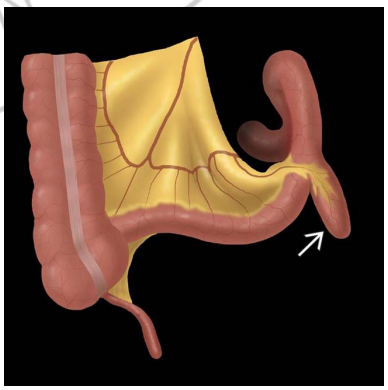
The Meckel diverticulum is a remnant of the omphalomesenteric duct. The omphalomesenteric duct connects the yolk sac to the alimentary tract in the embryo (left image). The duct is normally obliterated by the 6th week of intrauterine life. However, incomplete obliteration leads to the development of a diverticulum located approx. 2 feet proximal to the ileocecal valve (right image). The Meckel diverticulum is often connected to the navel via a fibrous cord, which is the obliterated part of the omphalomesenteric duct (middle image).

➔**Remember (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) ➔ means: it contains epithelium not of intestinal type but may be GASTRIC or PANCREATIC
- Most common cause of lower GI bleeding before age of 2.

➔ **Clinical presentation:**

1) Can be asymptomatic and discovered incidentally.
2) Ulceration, lower GI bleeding or perforation (due to ectopic gastric mucosa ➔ secretes acid ➔ acid causes mucosal damage)
3) Bowel obstruction (may cause intussusception, volvulus or adhesive band)
4) Acute inflammation (diverticulitis) ➔ Can be confused with acute appendicitis



➔ Causes of non mechanical obstruction:

1) Hirschsprung disease **"congenital aganglionic megacolon"**: an inherited disorder that primarily affects newborns. It is characterized by the absence of ganglion cells (neurons) in the distal colon, leading to functional obstruction.

- More common in males
- More severe in females
- Risk increase in siblings
- **RET** gene mutation: in familial cases and 15% of sporadic
- More common in **Down syndrome**

➔ Pathogenesis:

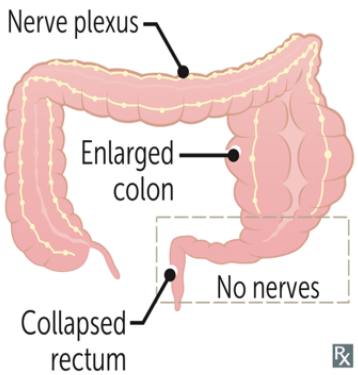
- During embryogenesis: disrupted migration of neural crest cells from cecum to rectum ➔ **Aganglionosis**: Distal intestinal segment lacks both: Meissner submucosal plexus and the Auerbach (myenteric) plexus ➔ **Failure of coordinated peristaltic contractions.**

➔ Clinical presentation:

- Neonatal failure to pass meconium (meconium is the first stool passed by the baby)
- Later: Intestinal obstruction features

➔ Morphology:

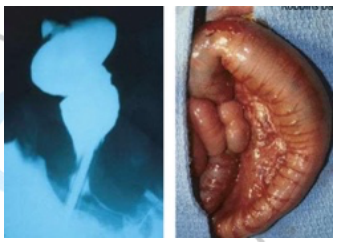
- Rectum always involved
- Extent is variable (may involve entire colon but most cases in rectosigmoid)
- **Aganglionic region**: normal or contracted. ➔ **Normal proximal part:** progressively dilated



➔ Diagnosis:

- **Barium enema** ➔ helps us to identify the transitional area ➔ the barium will give white color in the x-ray. The lower part in the figure, which is contracted, this is the aganglionic region, upper part dilated in both pictures due to the accumulation of stool.

So, this patient will come with abdominal distension and risk of perforation if it's not treated.



- **Rectal Biopsy** (to confirm absence of ganglion cells)

➔ Complications:

- Enterocolitis (GI infection)
- Fluid and electrolyte disturbances, due to vomiting
- Perforation
- Peritonitis (peritoneal inflammation caused by perforation and entry of stool into peritoneum)

➔ Treatment:

Surgical resection of aganglionic segment and anastomosis (re-attachment) of normal segments

[Vascular disorders]

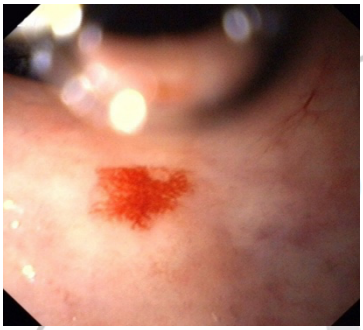
1) Ischemic Bowel disease: occurs if bowel perfusion cannot meet the metabolic demands of the intestine. This relative hypoperfusion may be the result of:

- **Atherosclerosis** (Build-up of **lipid-rich plaques in arterial walls** → narrowing and stiffening of arteries → ↓ blood flow and risk of ischemia)
- **Thromboembolic** disease (Formation of a blood clot that blocks blood vessel → causes sudden ischemia)
- Severe systemic **hypotension**.

Clinical features include ➔ abdominal pain, bloody diarrhea

2) Angiodysplasia: Malformed submucosal and mucosal blood vessels

- Most often in **cecum** and **right colon**
- Mainly affects elderly
- Less than 1% of adult population.
- Presents with Lower GI bleeding (20% of cases of lower GI bleeding) ➔ Bleeding from rectum (blood bright red in color)



3) Hemorrhoids: Dilated anal and perianal collateral vessels that connect the portal and systemic venous systems

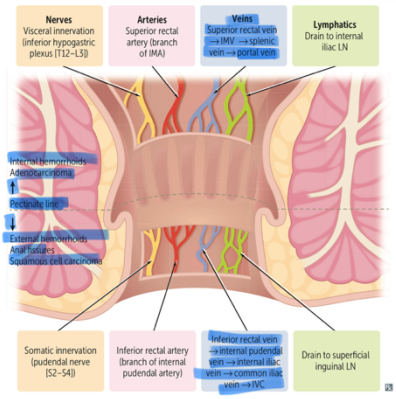
➔ **Types:**

#1: Internal hemorrhoids:

- Abnormal distention of anal venous plexus ABOVE dentate line (superior hemorrhoidal plexus)
- Receive **visceral innervation** ➔ therefore not painful

#2: External hemorrhoids:

- Abnormal distention of anal venous plexus BELOW dentate line (inferior hemorrhoidal plexus)
- Receive **somatic innervation** (inferior rectal branch of pudendal nerve) ➔ therefore painful if thrombosed

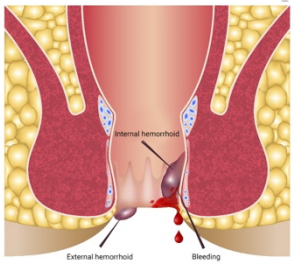


➔ **Predisposing factors:**

1- Portal Hypertension
The anus has an anastomosis between the systemic venous circulation and portal venous circulation, so anything that elevates the portal pressure will lead to dilation of these BV, which results in hemorrhoids.

2- Chronic Constipation and straining
3- Venous stasis of pregnancy (happens commonly due to the pressure of the uterus on pelvic veins)

➔ **Morphology:** Thin walled, dilated, submucosal vessels beneath anal or rectal mucosa (Thin walled so risk of rupture is high, so bleeding occurs fast)



➔ **Clinical presentation:**

- Bleeding in lower GIT (bright red), (mostly painless)
- Pain due to thrombosis and inflammation (or infection of the hemorrhoid).

➔ **Treatment:** Hemorrhoid removal (Many options: sclerotherapy, rubber band ligation, infrared coagulation and Hemorrhoidectomy)

[Diarrheal Disease]

Diarrhea: increase in stool mass, frequency or fluidity (≥ 3 loose or watery stools per day OR more frequent passage than is normal for the individual OR > 200 g/day)
Dysentery: painful, bloody, small volume diarrhea (mostly with infections)

➔**Types:**

1) Malabsorptive
2) Secretory
3) Osmotic
4) Exudative

[Malabsorptive diarrhea]

➔ **Definition:** diarrhea caused by defective absorption of nutrients (fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes, minerals and water)

- Unabsorbed substances stay in the lumen → draw water osmotically → diarrhea
- Often associated with:
  1) Weight loss (due to malabsorption)
  2) **Steatorrhea** (excessive fat in stool causing bulky, frothy, yellow, greasy, foul-smelling stool)
  3) Nutritional and Vitamin deficiencies

➔**Pathophysiology:**
Defect in any of the steps of digestion & absorption, including:

- Intraluminal digestion (e.g. pancreatic enzymes deficiency)
- Terminal digestion like lactase deficiency (remember that this was a brush border enzyme, meaning it is attached to the surface of epithelial cells)
- Transepithelial transport
- Lymphatic transport (e.g. lymphatic obstruction)

➔ **Clinical presentation:**

1) Weight loss (due to malabsorption of nutrients)
   - **Includes:** Muscle wasting, especially in children and mostly seen in the gluteus region + Failure to thrive (growth impairment in children)
2) **Steatorrhea** (excessive fat in stool causing bulky, frothy, yellow, greasy, foul-smelling stool)
3) Flatus (gas production) and Abdominal distention ➔ due to the action of microflora on the nutrients that are not absorbed (fermentation) which leads to gas production in the intestine
4) Borborygmi (intestinal noise)
5) Nutritional and Vitamin deficiencies, examples include:
   - Iron, Pyridoxine (B6), Folate (B9), or vitamin B12 deficiency ➔ Anemia and mucositis (inflammation of mucosa)
   - Vitamin K deficiency ➔ Bleeding
   - Calcium, Magnesium, or Vitamin D deficiency ➔ Osteopenia and tetany or rickets
   - Vitamin A or B12 deficiency ➔ Neuropathy
   - Skin and endocrine disorders (e.g. iodine deficiency may lead to hypothyroidism, which is decreased function of the thyroid gland)

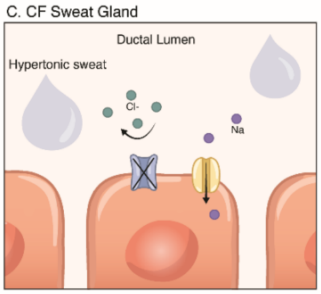
#1: Cystic fibrosis: hereditary autosomal recessive disorder caused by defective **CFTR** (cystic fibrosis transmembrane conductance regulator) protein due to mutation in the CFTR gene located on the long arm of **chromosome 7** (deletion at F508)

➔ **Pathophysiology:**

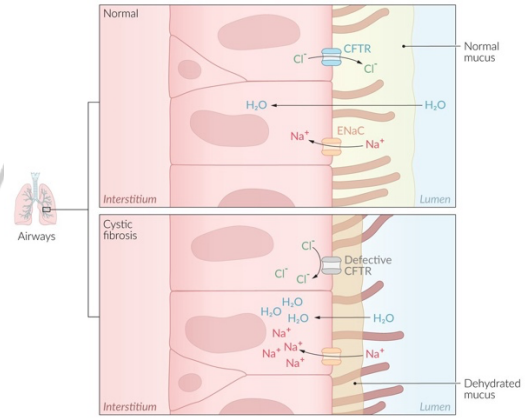
- The CFTR gene encodes the CFTR protein, which is an important component of the ATP-gated chloride channel in cell membranes.

- Mutated CFTR gene → misfolded protein → degraded of the defective protein in the rough endoplasmic reticulum (rER) → **absence of ATP-gated chloride channel on the cell surface of epithelial cells throughout the body** (e.g., intestinal and respiratory epithelia, sweat glands, exocrine pancreas, exocrine glands of reproductive organs).

- **In sweat glands:** the chloride channel is responsible for transporting Cl- from the lumen into the cell (**reabsorption**) ➔ Defective ATP-gated chloride channel → inability to reabsorb Cl- from the lumen of the sweat glands → reduced reabsorption of Na+ and H2O → **excessive loss of salt and elevated levels of NaCl in sweat.**

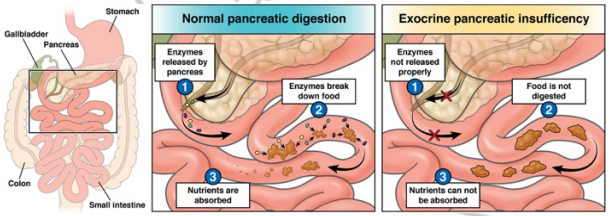


- **In all other epithelial surfaces** (e.g., in the GI tract or lungs): The chloride channel is responsible for transporting Cl- from the cell into the lumen (**secretion**) ➔ Defective ATP-gated chloride channel → inability to transport intracellular Cl- across the cell membrane → reduced secretion of Cl- and H2O → accumulation of intracellular Cl- → ↑ Na+ reabsorption → ↑ H2O reabsorption → **formation of hyperviscous mucus → accumulation of secretions and blockage of small passages of affected organs → chronic inflammation and remodeling → organ damage**



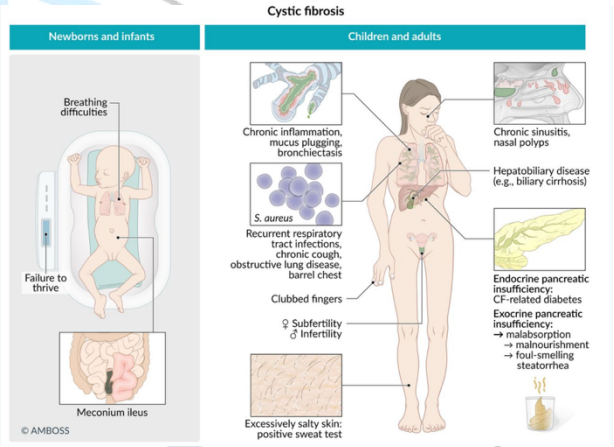
Examples of organs involved

- **Mucus plugs in pancreatic ducts** ➔ blockage of pancreatic ducts ➔ inability to secrete pancreatic enzymes ➔ **Exocrine pancreatic insufficiency** (A condition in which the pancreas fails to produce or secrete sufficient digestive enzymes, leading to impaired digestion and absorption of nutrients) ➔ Malabsorption



[**Note:** Treatment of pancreatic insufficiency includes providing patients with an oral medication containing these enzymes]

- **Mucus plugs in the intestines** ➔ thick Meconium (first stool after birth) ➔ Meconium ileus in neonates (delayed passage of the thick meconium so it stays in the bowel and result in obstruction)
- **Mucus plugs in the bronchi** → thick, sticky mucus → impaired mucociliary clearance → mucus retention in airways → bronchial obstruction → recurrent infections and inflammation



#2: Celiac disease (gluten sensitivity enteropathy): maladaptive immune response to gluten (a protein found in many grains e.g., wheat, rye, barley) ➔ leads to immune-mediated damage of small bowel villi

- The disease often occurs in patients with other autoimmune illnesses (as both are associated with HLA variants "human leukocyte antigens" which encode immunoregulatory proteins that cause pathologically increased immune responses) ➔ **DM type1, thyroiditis**

- **Genetic predisposition: HLA-DQ2 OR HLA-DQ8 genes**

➔**Pathogenesis:**

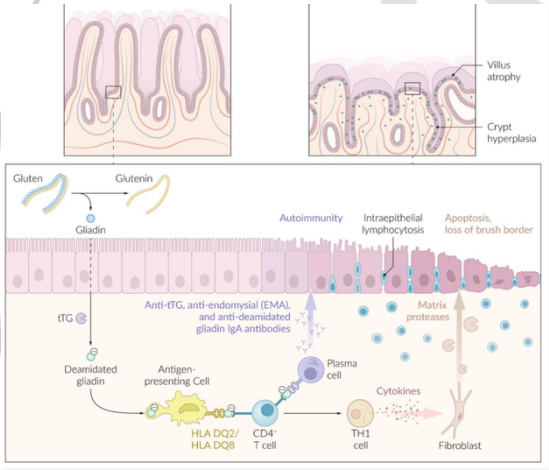
1- **Gluten** is present in wheat and grains ➔ its most pathogenic component is **Gliadin**
2- Once absorbed, gliadin enters between enterocytes to the submucosa and is deamidated by **tissue transglutaminase (tTG)**

3- Deamidated gliadin reacts with **HLA-DQ2 or HLA-DQ8** on antigen-presenting cells ➔ CD4+ T cells (helper T cell) activation ➔ they will induce a strong inflammatory reaction in the small bowel ➔ tissue damage

4- The strong inflammatory reaction leads to **B** cell activation ➔ antibody formation (anti-gliadin, anti-endomysium, & anti-TTG present in the serum of the patient).

- **Serology** (antibodies found in the serum of patients with celiac disease):
  1) **Anti-tissue transglutaminase antibodies**
  2) **Anti-gliadin antibodies**
  3) **Anti-endomysial antibodies**

5- **End result:** Mucosal damage which causes defective absorption



➔ **Morphology:**

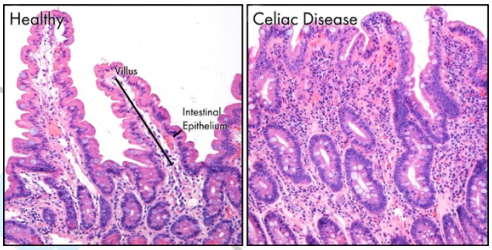
- Affects mainly the second portion of the duodenum or proximal jejunum ➔ these are important sites for iron absorption so patients can present with iron deficiency as the only manifestation (B12 and folate deficiency are less common because they are absorbed in the ileum)

- Histologic features:

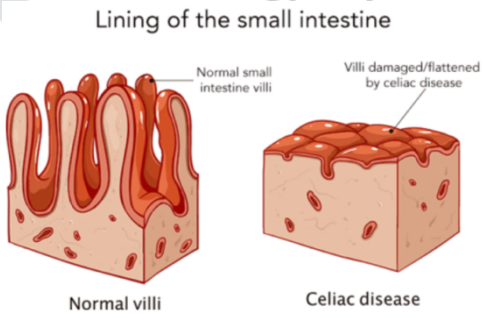
Triad of

1) **Intraepithelial lymphocytosis** (lymphocytes inside the epithelium)
2) **Crypt hyperplasia** (intestinal crypt epithelial cells undergo excessive growth "hyperplasia")

3) **Villous atrophy** (Flattening or loss of the intestinal villi) ➔ the most important and leads to a decrease in the surface area and impaired nutrient absorption (Remember: Intestinal Villi are responsible for increasing the surface are available for absorption)



Other histological feature: Lamina propria ➔ lymphocytes, plasma cells, eosinophils



➔**Clinical features:**

- **Children before 6 months of age**: cannot get diagnosed because at this age they only drink milk (they are not exposed to food that contains gluten like wheat, rye, or barley)
- **Children 6-24 months:** classical or non-classical symptoms
- **Older children and adults:** classical symptoms

Classical Symptoms

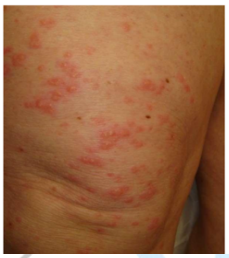
- **Features of malabsorption discussed previously:** Abdominal distention, diarrhea, weight loss, failure to thrive or muscle wasting, iron deficiency.

Non-classical Symptoms

- Abdominal pain
- Nausea and vomiting
- Bloating
- Constipation

- **Dermatitis Herpetiformis:** Skin blisters similar in appearance to herpes virus infection (its name comes from its similarity with herpes virus, but it's immune mediated) ➔ occurs in 10% of patients

Dermatitis herpetiformis.



Missed diagnosis

- Cases where the disease is present but not recognized or diagnosed, often because symptoms are mild or absent
- **Silent celiac** ➔ positive serology and biopsy but asymptomatic)

Possible complications

- Increased risk of:
  1) **Enteropathy associated small intestinal T cell lymphoma** (Chronic inflammation from celiac disease → damages intestinal lining → over time, immune cells (T-cells) become malignant → form an aggressive lymphoma in the small bowel)
  2) **Small intestinal adenocarcinoma**

➔**Diagnosis:**

#1: Noninvasive serologic tests:
Most sensitive:

- Anti tissue transglutaminase antibody IgA
- Anti deamidated gliadin antibodies IgA & IgG

Most specific, but less sensitive:

- Anti-endomysial antibody

#2: Invasive tests: small bowel biopsy (findings seen in biopsy as described above)

****Very important note:** Intraepithelial lymphocytosis & villous atrophy are not pathognomonic (**which means:** not specific to celiac disease and they can occur in other conditions **like viral gastroenteritis**) ➔ So? celiac disease cannot be diagnosed based on these features only especially if the biopsy is taken from the first portion of the duodenum as the villous atrophy can be from gastric acid secretions not celiac disease. Biopsy should be taken from the second portion of the duodenum)

- **So, diagnosis needs:** Clinical, histologic and serologic correlation

➔ **Treatment:** gluten free diet

#3: Abetalipoproteinemia: Autosomal recessive disease characterized by deficiency of apolipoproteins that manifests as Inability of enterocytes to secrete triglyceride-rich chylomicrons ➔ Resulting in **Lack of absorption of FATS an FAT SOLUBLE VITAMINS ONLY** (Transepithelial transport defect of lipoproteins, FAs and fat-soluble vitamins)

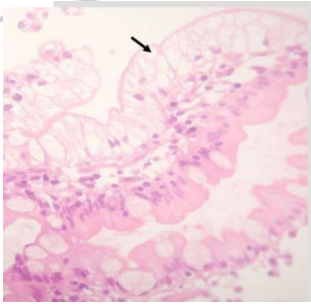
Reminder from physiology

Normal lipid absorption:

Dietary fats → digested inside the intestinal lumen → absorbed by enterocytes → re-assembled inside the cells → packaged with apolipoprotein B-48 → form chylomicrons → secreted into lymphatics

Abetalipoproteinemia: → deficiency of apolipoproteins (especially ApoB) → failure to form chylomicrons → lipids accumulate inside enterocytes → lipids cannot enter circulation → malabsorption

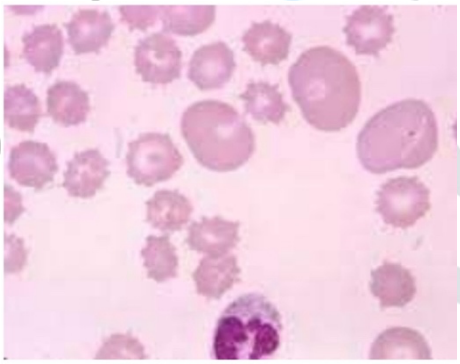
➔ **Microscopic findings:**
White / foamy cytoplasm of enterocytes (due to accumulation of: Monoglycerides and Triglycerides)



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

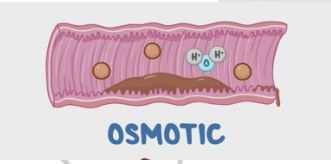
➔ **Clinical presentation:**
Usually affects infants (since its GENETIC!)

- Failure to thrive (growth failure)
- Chronic diarrhea
- Steatorrhea (bulky, greasy stools due to fat malabsoprtion)
- ADEK deficiency (fat soluble vitamins deficiency) ➔ this causes skeletal, CNS and retinal abnormalities.
- **Spur cells "acanthocytes"** (Red blood cells with irregular, spiky projections on their surface) **on peripheral blood smear:** Fatty acids are required to form phospholipids of RBC membranes **SO** Defective lipid transport → abnormal RBC membrane



[Osmotic Diarrhea]

➔ **Definition:** diarrhea caused by non-absorbable osmotically active substances in the intestinal lumen → Unabsorbed solutes draw water into the bowel → osmotic water retention → diarrhea



➔ **Clinical features:**

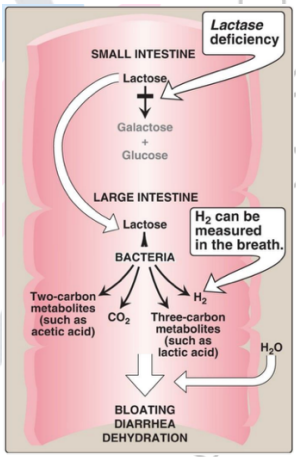
- Watery diarrhea
- Decreases or stops with fasting (key feature) ➔ When you fast: No new osmotic substances enter the gut ➔The lumen becomes "clean" of solutes → No osmotic pull → diarrhea stops
- Abdominal bloating and flatulence (due to fermentation of unabsorbed carbs and production of gases)
- No significant weight loss

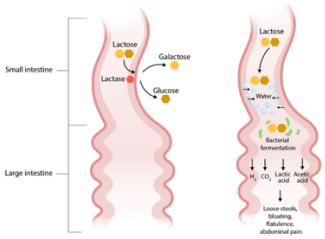
#1: Lactose Intolerance (Lactase deficiency):

Lactose intolerance: inability to tolerate eating lactose (milk containing foods) due to lactase deficiency ➔ **WHY?** low levels of lactase enzyme in the small intestine ➔ Lactase deficiency prevents the digestion of lactose in the small intestine ➔ So, lactose can NOT be absorbed

Unabsorbed Lactose consequences?

Lactose Remains inside the intestinal lumen ➔ draws in water into the lumen by the principle of osmosis (unabsorbed lactose acts as an osmotically active substance)
So, **diarrhea**!!
+
Normal Intestinal bacteria ferment lactose (degrade it to produce H2 gas/ CO2 / acids)
So,
(انفاخ و غازات!) **flatulence/bloating**





- If we do intestinal biopsy ➔ NORMAL

Very important reminder:
Lactase as a **brush border enzyme** (located on the apical (brush border) surface of enterocytes not inside the cells)

Why biopsy is normal: In lactase deficiency, the intestinal structure is intact → only the enzyme activity is reduced → mucosa looks normal on biopsy (no villous damage)

➔**Possible causes:** 3 possible causes of lactase deficiency:
1) Congenital: Autosomal recessive, genetic mutation ➔ this type is RARE

2) Acquired Lactase non-persistence:
- Very common: almost 2/3 of the world's population
- Age dependent loss of lactase enzyme activity ➔ due to downregulation of lactase gene (Lactase is present but in decreased amount, so if patient consumes more milk than the amount of enzyme they have, they will experience symptoms)
- Thought to be an evolutionary phenomenon in which people used to drink milk products only in infancy so no need for the enzyme in adult so its activity decreases!

3) Transient deficiency: caused by injury after infectious or inflammatory insults (reversible) ➔ injury to intestinal epithelium ➔ loss of lactase enzyme (remember it is found in the epithelial cell membrane) ➔ lactase deficiency (The patient will experience symptoms for a short period of time that is until the brush border regenerates)

[Secretory Diarrhea]

➔ **Definition:** diarrhea caused by increased secretion of electrolytes and water into the intestinal lumen ➔ Active secretion of Cl^- and water → large-volume watery diarrhea

➔ **Examples of causes:**
- Enterotoxins of infections (e.g. Vibrio cholerae)
- Hormonal causes (e.g. Carcinoid syndrome)
- Some drugs/laxatives

[Inflammatory / Exudative diarrhea]

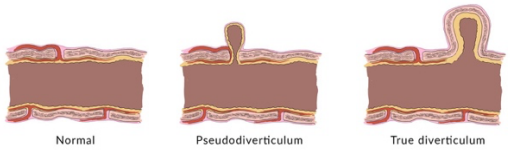
➔ **Definition:** diarrhea caused by intestinal mucosal inflammation, leading to exudation of blood, mucus, and proteins into the lumen ➔ leading to pain, fever, and bloody diarrhea (blood and inflammatory cells are present in the stool)

➔ **Examples of causes:**
- **Infections**: e.g., Shigella, Salmonella, Campylobacter
- **Inflammatory bowel disease**: Crohn's disease, ulcerative colitis

[Inflammatory Intestinal Diseases]

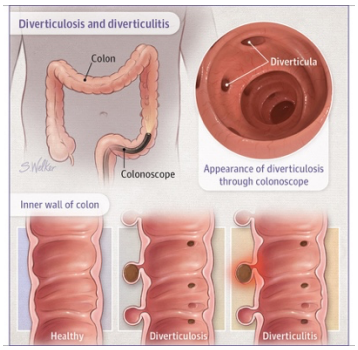
[Sigmoid diverticulosis & Diverticulitis]

➔ **Definitions:**
- **Diverticula:** blind pouches that protrude from the gastrointestinal wall and communicate with the lumen ➔
  2 types:
  1) **True diverticulum:** a type of diverticulum that affects **all layers of the intestinal wall** ➔ only example you should know: Meckel diverticulum (we studied this above)
  2) **False diverticulum "Pseudo-diverticulosis":** a type of diverticulum that involves **only the mucosa and submucosa** and does not contain muscular layer or adventitia ➔ most GI diverticula are of this type



- **Diverticulosis:** the presence of **multiple colonic diverticula** without evidence of infection ➔ usually affects Sigmoid colon (hence, the name sigmoid diverticulosis)
- **Diverticulitis:** Inflammation or infection of colonic diverticula

➔ **Some facts:**
- Common condition > 60 years age
- Most commonly affected site: **Sigmoid Colon**

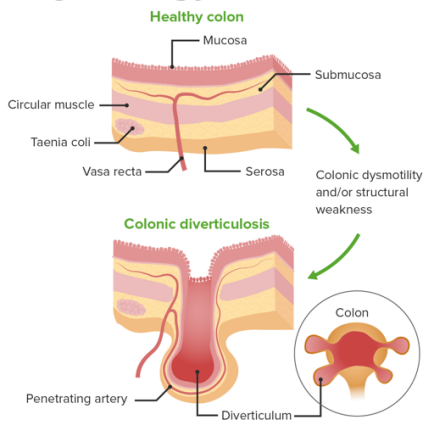


** **Note**: Sigmoid diverticula differ from Meckel's diverticulum in several ways: they are pseudodiverticula involving herniation of the mucosa and submucosa through the muscularis propria, are typically acquired rather than congenital, usually appear after the age of 60, and are often multiple rather than solitary.

➔Pathogenesis:

Related to wall stress (Increased intraluminal pressure inside the colon) ➔ pressure on the colon wall pushes the wall outwards and produces the "outpouchings"

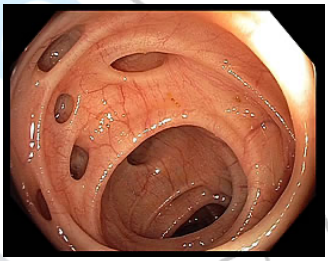
- Associated with constipation, straining, obesity, and low-fiber diet (all increase wall stress)
- Commonly seen in older adults (risk increases with age due to weakness of intestinal wall)
- Arise **where the vasa recta traverse the muscularis propria** (weak point in colonic wall) ➔ Physiological gaps in the intestinal wall, **which occur where blood vessels penetrate**



➔ Morphology:

- Flask-like outpouchings
- Present between taeniae coli (Three distinct longitudinal bands of smooth muscle on the outer surface of the colon that help maintain its tone and form the haustra by their partial contraction)
- Thin wall (atrophic mucosa, compressed submucosa)
- Attenuated or absent muscularis propria.

Appearance on colonoscopy



➔Clinical presentation:

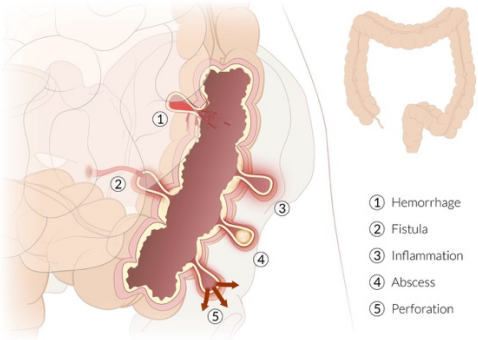
Mostly asymptomatic (unless complications develop) ➔ Patients usually do not experience symptoms from diverticulosis itself, they rather complain from constipation (which is the cause of the disease)

May have:

- Intermittent lower abdominal pain
- Constipation or diarrhea.

➔ Possible complications:

1) **Bleeding:** Painless, usually large-volume rectal bleeding due to erosion of a vessel in the diverticular wall
2) **Diverticulitis:** Inflammation of a diverticulum, causing localized pain (often Left lower quadrant), fever, and leukocytosis (elevated WBC count)
3) **Abscess:** Localized collection of pus around an inflamed diverticulum, may cause tenderness and palpable mass
4) **Fistula:** Abnormal connection between the colon and adjacent organs (e.g., bladder) due to chronic inflammation.
5) **Perforation:** Rupture of a diverticulum leading inflammation of the peritoneum



➔ **Treatment:**

- If no complications ➔ High fiber diet (to treat constipation)
- Diverticulitis ➔ antibiotics
- In certain cases ➔ Surgery

[Chronic Inflammatory Bowel Disease]

➔ **Definition:** A group of conditions characterized by chronic inflammation of the intestine due to autoimmune attack to the intestine (possibly due to abnormal immune response to intestinal microbiome) ➔ resulting in mucosal damage

➔ **Epidemiology:**

- **Most commonly affected population:** Adolescence & young adults (2nd peak in fifth decade, although it is uncommon)
- There is **Geographic variation** (more common in the west) ➔ proposed explanation: **Hygiene hypothesis:** suggests that reduced exposure to infections and microbes in early life leads to an undertrained immune system, increasing susceptibility to inappropriate intestinal inflammation seen in IBD

➔ **Pathogenesis:**

Exact cause is **UNKNOWN;** it is a **MULTIFACTORIAL** disease ➔ Combined effect of:

- Genetic predisposition (runs in families)
- Altered host interaction with intestinal microbiota.
- Intestinal Epithelial dysfunction
- Abnormal mucosal immune responses (this means that even commensal or low virulence organisms can trigger an immune response, due to the abnormal immune reactivity seen in inflammatory bowel disease)

➔ **Clinical presentation:**

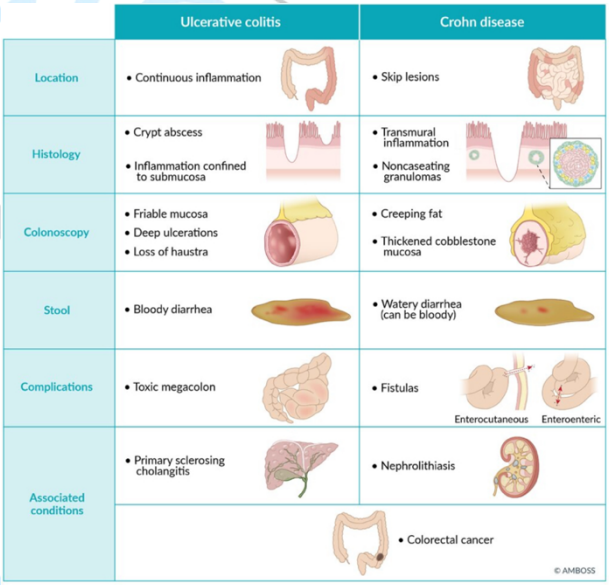
Main symptoms: Abdominal pain + Diarrhea

- Diarrhea is usually Bloody in Ulcerative Colitis and Non-bloody in Crohn's

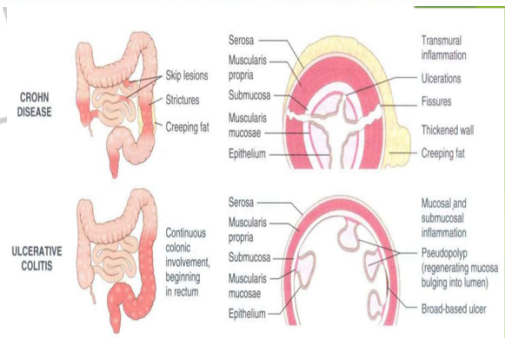
Patients may have other symptoms (see below)

➔ **Classification:** IBD has 2 subtypes (which have distinct features)

1) **Crohn's disease**
2) **Ulcerative colitis**



	ULCERATIVE COUTIS (UC)	CROHN DISEASE
Wall Involvement	Mucosal and submucosal ulcers	Full-thickness inflammation with knife-like fissures
Location	Begins in rectum and can extend proximally up to the cecum (involvement is continuous, Fig. 10.21A); remainder ofthe GI tract is unaffected.	Anywhere from mouth to anus with skip lesions; terminal ileum is the most common site, rectum is least common.
Symptoms	Left lower quadrant pain (rectum) with bloody diarrhea	Right lower quadrant pain (ileum) with non-bloody diarrhea
Inflammation	Crypt abscesses with neutrophils (Fig. 10.21B)	Lymphoid aggregates with granulomas (40% of cases)
Gross Appearance	Pseudopolyps; loss of haustra ('lead pipe' sign on imaging, Fig. 10.21C)	Cobblestone mucosa (Fig. 10.22A), creeping fat, and strictures ('string-sign' on imaging, Fig. 10.22B)
Complications	Toxic megacolon and carcinoma (risk is based on extent ofcolonic involvement and duration of disease; generally not a concern until > 10 years of disease)	Malabsorption with nutritional deficiency, calcium oxalate nephrolithiasis, fistula formation, and carcinoma, if colonic disease is present
Extraintestinal Manifestations	Arthritis (peripheral joints, ankylosing spondylitis, sacroiliitis, migratory polyarthritis), uveitis, erythema nodosum (Fig. 10.22C), pyoderma gangrenosum, primary sclerosing cholangitis, and p-ANCA	
Smoking	Protects against UC	Increases risk for Crohn disease

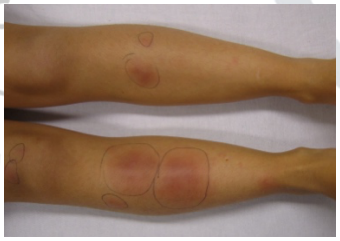


ملاحظة مهمة: هذه الجداول تحتوي على أهم الفروقات التي يجب معرفتها بين المرضين

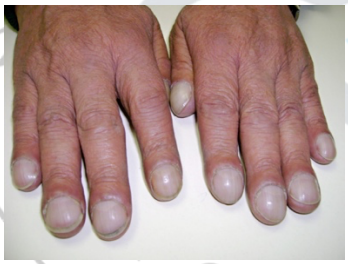
➔ **Extra-intestinal manifestations:**
Patients with IBD may develop symptoms outside the GI tract (hence the name "**extra-intestinal manifestations**")

- All are considered immune-mediated symptoms

1- **Uveitis** (inflammation of the uvea, which is the second layer of the eye)
2- **Migratory polyarthritis**
   - **"Polyarthritis"** → affects multiple joints.
   - **"Migratory"** → joints affected change locations, rather than all being swollen at once.
3- **Sacroiliitis** (arthritis of sacroiliac joint)
4- **Ankylosing spondylitis** (immune mediated rheumatological disorder affecting the spine)
5- **Erythema nodosum:** inflammation of subcutaneous tissue of the legs ➔ tender (painful with touch) red elevated regions on the legs



6- **Clubbing** of the fingertips ➔ It refers to an increased convexity of the nail at the fingertips.



7- **Primary sclerosing cholangitis** ➔ autoimmune inflammation of the bile ducts in the liver (more common with Ulcerative Colitis than Crohn's)

[Crohn's disease]

➔ **Definition:** an inflammatory bowel disease characterized by:

- May affect any part of the GI tract (from mouth to anus) ➔ Most common affected sites: **right side of the bowel, terminal ileum, ileocecal valve, and cecum**
- Spares the rectum (never involves the rectum)
- **Segmental involvement with skip lesions** ➔ means:
   - **Segmental involvement:** the inflammation affects discrete sections of the intestine, not the entire length continuously.
   - **Skip lesions:** There are normal areas of bowel in between inflamed segments, so the disease "skips" parts of the intestine
- **Transmural** inflammation ➔ means inflammation affecting all 4 layers of the bowel wall (mucosa, submucosa, muscularis, serosa)

➔ **Affected parts of GI tract:**

- Small intestine alone (40% of cases)
- Small intestine and colon (30% of cases)
- Colon only (30% of cases)

➔ **Clinical features:**

- **Main symptoms:** Intermittent attacks of mild diarrhea, fever, and abdominal pain ➔ Asymptomatic intervals between attacks (weeks to months)

- In approximately 20% of Crohn's disease cases, the disease involves the terminal ileum, ileocecal region, and cecum, presenting with symptoms that mimic acute appendicitis, such as acute right lower-quadrant pain and fever (20%)

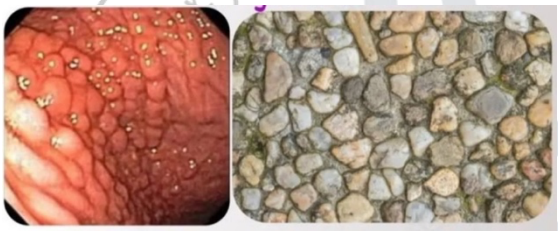
- Diarrhea is usually non-bloody ➔ but if colonic involvement patient may have bloody diarrhea

- Possible triggers of symptoms: Infections, physical or emotional stress, specific dietary items, NSAID use, and cigarette smoking

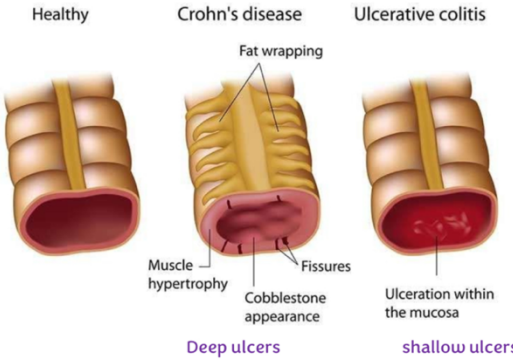
➔ **Diagnostic findings:** changes can be seen both GROSSLY (on endoscopy) and MICROSCOPICALLY (by biopsy)

#1: Macroscopic findings:

- **Earliest lesion:** Superficial aphthous ulcer ➔ then elongated, deep serpentine ulcers
- Regional enteritis (segmental inflammation as noted above) ➔ Edema, loss of bowel folds.
- Strictures
- **Cobblestone** appearance: refers to the appearance of the intestinal lining where deep ulcers and inflamed tissue create a patchy, bumpy pattern that looks like cobblestones.

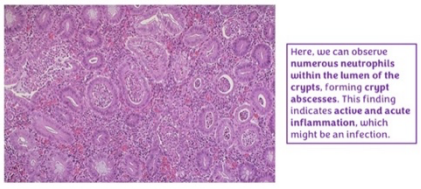


- Fissures (small tear or crack)
- Thick bowel wall (transmural inflammation with edema)
- **Creeping fat** ➔ fat from outside the intestine (mesenteric fat) wraps around the inflamed bowel



#2: Microscopic findings:

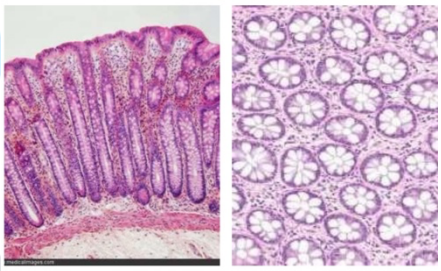
1- Neutrophils (in active disease, which indicates acute active inflammation)



2- Crypt abscesses (accumulation of neutrophils within the lumen of an intestinal crypt)

3- Ulceration.

4- **Distortion of mucosal architecture** (happens with repeated cycles of inflammation, which means with chronic disease) ➔ This is the most important feature to observe, as the diagnosis of chronic inflammatory bowel disease requires evidence of **chronicity**, such as architectural distortion of the crypts.

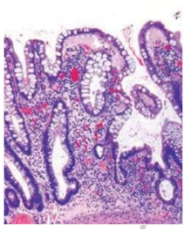


Normal colon

In a **normal colon**, the **crypts are closely packed, organized rounded**, and aligned vertically, extending **down to the muscularis mucosae**.

Haphazardly arranged crypts

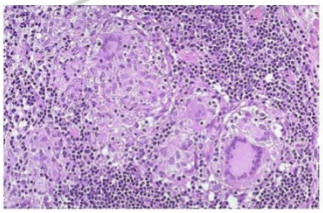
- In **chronic inflammatory bowel disease**, the **crypts of the colonic mucosa appear haphazardly arranged.**
- This feature is **characteristic and supportive** of IBD.



5- **Paneth cell metaplasia in left colon** ➔ Normally, Paneth cells are found in the small intestine and extend only up to the transverse colon. If Paneth cells are seen in a rectal or sigmoid biopsy, this indicates chronic inflammation, as they are not normally present in this region.

6- Mucosal atrophy.

7- **Non-caseating granulomas (they are a hallmark feature)** ➔ **BUT** only in 35% of cases.



Non-caseating granuloma.

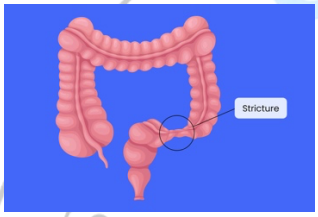
A **granuloma** is a collection of **epithelioid histiocytes**, often containing **multinucleated giant cells**. In **Crohn's disease**, these granulomas are typically **non-caseating**.
Reminder: The presence of a **caseating granuloma** should raise suspicion for **tuberculosis**.

➔**Complications:**

- Colonic involvement: Iron-deficiency anemia (happens due to ulcerations and bleeding)

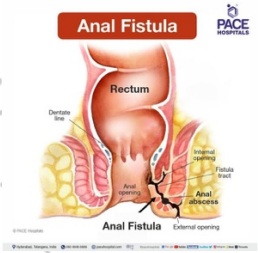
- Small bowel involvement: malabsorption ➔ Hypoproteinemia and hypoalbuminemia (due to malabsorption of proteins), malabsorption of nutrients, vitamin B12, folate and bile salts

- Strictures: narrowed segment of the intestine (common) ➔ they develop when transmural inflammation is followed by fibrotic healing, which leads to narrowing of the affected bowel segment ➔ bowel obstruction



- Fistula: deep mucosal ulcer can extend and perforate, forming a fistula ➔ and abnormal connection between two bowel loops (enteroenteric) or between the bowel and other structures, such as the **skin** (perianal fistula).

- Perianal fistulas are particularly common in Crohn's ➔ any patient presenting with one should be evaluated for Crohn's disease.



- Abscess: A peritoneal abscess may form if a fissure or ulcer perforates and leaks bowel contents into the peritoneal cavity

****Very important note:** fistula, perforation, abscess ➔ These complications do not occur in ulcerative colitis (as its inflammation is limited to the mucosa and submucosa)

- **Cancer**: Risk of **colonic and small intestinal Adenocarcinoma**, usually after 8-10 years of diagnosis ➔ VERY IMPORTANT TO KNOW

[Ulcerative colitis]

➔ **Definition:** an inflammatory bowel disease characterized by:

- Only affects the colon ➔ starts from the rectum and extends proximally

  Proctitis: only rectum involved
  Proctosigmoiditis: Rectum + sigmoid
  Pancolitis: entire colon involved (most severe form)

- Rectum ALWAYS involved
- **Continuous involvement with no skip lesions** ➔ means: the inflammation affects the colon in an uninterrupted, continuous manner, starting from the rectum and extending proximally to varying lengths of the colon without any normal segments in between.
  - **Example:** If the rectum and sigmoid colon are inflamed, every part of the rectum and sigmoid shows inflammation ➔ there are no healthy patches
- **Mucosal and submucosal** inflammation ONLY➔ means: not all 4 layers are affected

** **Important note:** Although as mentioned above, UC only affects the colon ➔ In some patients with pancolitis, the inflammation may also involve the terminal ileum, a condition known as **backwash ileitis**

➔ **Clinical features:**

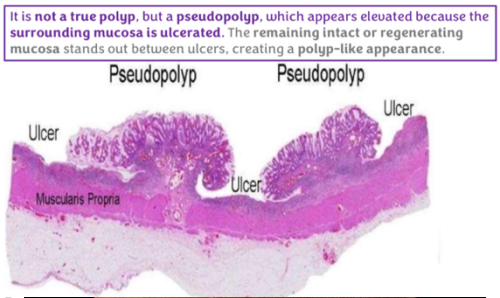
- **Main symptoms:** Intermittent attacks of BLOODY diarrhea, fever, and abdominal pain ➔ Asymptomatic intervals between attacks (weeks to months)
  (Keep in mind: It is often difficult to differentiate clinically between Crohn's disease and ulcerative colitis, as both can present with similar symptoms)

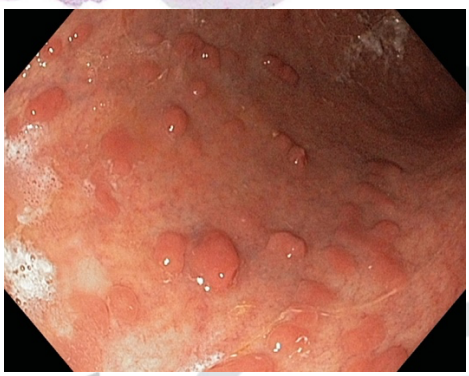
- Malabsorption is not a feature of ulcerative colitis (as the small intestine is not involved)

➔ **Diagnostic findings:** changes can be seen both <u>GROSSLY</u> (on endoscopy) and <u>MICROSCOPICALLY</u> (by biopsy)

#1: Macroscopic findings:

- As opposed to Crohn's disease: No fissures, fistulas, perforations, strictures, granulomas or transmural inflammation
- Broad-based ulcers.
- **Pseudo polyps** (Raised areas of normal mucosal tissue that result from repeated cycles of ulceration and healing)





- Mucosal atrophy in long standing disease
- Serosal surface normal (NO creeping fat)

Abrupt transition b/w normal and disease segment.

#2: Microscopic findings:

<u>SAME as Crohn's but with the following differences:</u>

- Inflammation limited to mucosa and submucosa (in Crohn's it is transmural)
- No granulomas (Only in Crohn's disease)

➔ **Treatment:**

1- Drugs that inhibit the immune system ➔ decrease immune attack on intestine (biologic agents and immune-modulating drugs like steroids)

2- Surgery (e.g. colectomy which is surgical removal of the colon) ➔ performed for complications such as toxic megacolon, dysplasia, or carcinoma

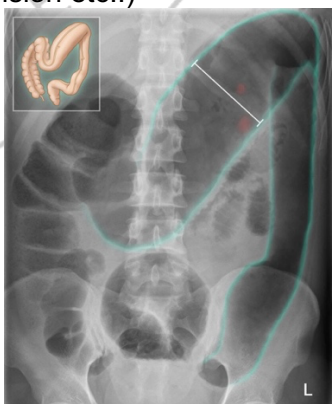
<u>Important idea:</u>
Surgical cure in ulcerative colitis:

- Colectomy (removal of entire colon) can **cure the intestinal disease** because ulcerative colitis is **limited to the colon**. ➔ However, **extraintestinal manifestations may persist** since they are **immune-mediated and not solely dependent on colonic inflammation**.

Surgery is not curative in Crohn's because the disease can affect any part of the GI tract and often recurs after resection

➔ **Complications:**

- **Toxic megacolon:** a life-threatening, acute dilation of the colon associated with systemic toxicity (fever, hypotension etc..)



Very important idea:

Colon cancer risk in IBD

- Occurs in long standing UC and CD
- Begins as **dysplasia** ➔ transforms to **carcinoma** with time

- Ulcerative colitis: Always increases colorectal cancer risk because the disease always involves the colon.

- **Crohn's disease:** Increases risk only if the colon is affected (some people don't have colonic involvement)

- Risk depends on:

1) **Duration of disease:** increase after 8-10 years.
2) **Extent of involvement:** higher risk with pancolitis.
3) **Inflammation:** frequency & severity of active disease with neutrophils (more inflammation = higher risk)

- Screening recommendation: Colonoscopy starting 8–10 years after diagnosis for patients with colonic involvement.

The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pathology

Intestinal pathology 3+4

Written by: Mohammad Talal Harahsheh

Edited by: Ghada T. Alzoubi

Reviewed by: Yazeed Alajlouni

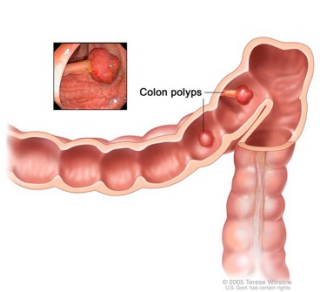
[Overview]

In these lectures (Intestinal Diseases 3&4) we will cover:

- **Colonic Polyps** (with their various types)
- **Colon cancer**
- **Diseases of the Appendix** (appendicitis and tumors of the appendix)

[Colonic Polyps]

Polyp = raised protrusions of colonic mucosa



- **Colon is most common site for polyps in the GI tract** (Polyps can also occur in the esophagus, stomach, and small intestine, but the colon remains the main site)

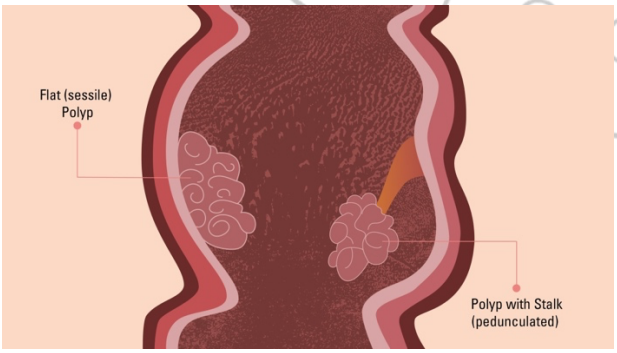
➔ **Definitions:**

- **Sessile polyp:** Broad-based, flat lesion that arises directly from the mucosa ➔ **NO stalk**

(As sessile polyps enlarge, traction and proliferation of adjacent mucosa may eventually form a stalk)

- **Pedunculated polyp:** Polyp attached to the mucosa by a narrow stalk ("peduncle"), resembling a mushroom ➔ Has a **stalk**

(Pedunculated polyps represent these evolved lesions with a stalk connecting them to the mucosa)



- **Neoplastic polyps:** polyps characterized by epithelial dysplasia with cytologic atypia and architectural complexity

Main example: Adenoma

These polyps are **Premalignant ➔** carry potential to progress to malignancy (colorectal cancer)

- **Non-neoplastic polyps:** polyps that lack dysplasia; show mature, non-atypical epithelium with preserved architecture

Examples:

1) Inflammatory
2) Hamartomatous
3) Hyperplastic

In general: NOT premalignant (although usually benign, these polyps may cause bleeding, obstruction, or serve as markers for syndromes with cancer risk)

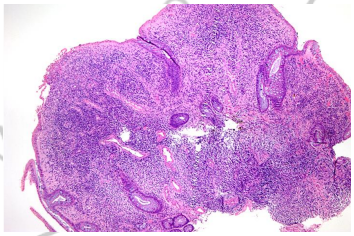
[Inflammatory Polyps "Pseudopolyps"]

Inflammatory polyp: a non-neoplastic mucosal projection formed by regenerative and inflamed residual mucosa (composed histologically of granulation tissue, inflammatory infiltrate, and distorted but non-dysplastic epithelium)

- Typically seen in **chronic inflammation (e.g., IBD)**
- **Other cause (rare):** Solitary rectal ulcer syndrome

- **Histology:** dense inflammatory infiltrate

-



Solitary rectal ulcer syndrome: disorder of the rectum caused by abnormal defecation leading to repeated mucosal trauma and inflammatory poly formation

- Represents purely inflammatory polyps arising in the rectum from chronic mucosal injury

- Caused by impaired relaxation of anorectal sphincter ➔ This creates abnormal angles in the rectum, causing repeated trauma ➔ Recurrent abrasion and ulceration of the overlying rectal mucosa
- Chronic injury stimulates reactive epithelial proliferation ➔ Chronic cycles of injury and healing give a polypoid mass of inflamed and reactive mucosal tissue

- **Symptoms:** Triad

1) Rectal bleeding
2) Mucus discharge
3) Polyp in the rectum

These clinical features correspond to the triad seen in solitary rectal ulcer syndrome

[Hamartomatous Polyps]

Hamartomatous polyps: a non-neoplastic polyp composed of a disorganized, tumor-like growth composed of mature cell types normally present at that site (Growth is structural, not neoplastic, but abnormal organization can mimic neoplasia)

➔ **Types:**

1) **Sporadic:**
   - Hamartomatous polyps that occur in isolation without an underlying genetic syndrome
   - Typically, **single lesion**
   - Minimal malignant risk
   - No associated extraintestinal features

2) **Syndromic**
   - Occur as part of **inherited polyposis syndromes** (associated with inherited germline mutations) ➔ they are rare, we will talk about 2 in this lecture:
   1) Juvenile polyposis syndrome
   2) Peutz-Jeghers syndrome

   - Usually **multiple**

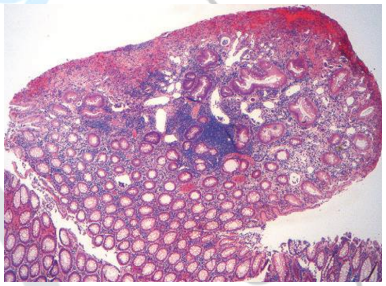
   - There is increased cancer risk ➔ similar to gastric polyps, syndromic lesions require surveillance (follow-up) due to neoplastic potential

   - May have extraintestinal manifestations

[Juvenile Polyps]

- Most common type of hamartomatous polyp
- Often in children < 5 years (hence the name "juvenile"
- **Macroscopic appearance:**
  - Pedunculated
  - Reddish lesions

- **Microscopic appearance:**
  - Cystic spaces on cut sections
  - Dilated glands filled with mucin and inflammatory debris are characteristic
  - Granulation tissue on surface



- May be **SPORADIC** or **SYNDROMIC**

Sporadic

- Usually **single**
- Age < 5 years
- Located in the **rectum** (sometimes they may prolapse out of the rectum through the anus)
- **Usual presentation:** Painless rectal bleeding
- Cancer risk is low

Syndromic

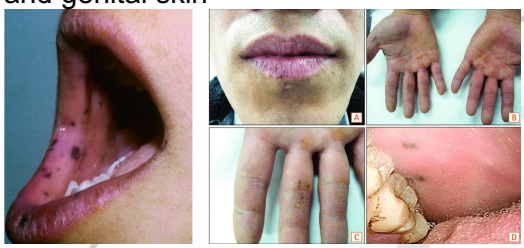
"Juvenile polyposis syndrome"

- Usually **multiple** polyps
- Age <5 years
- Polyps in **colon + stomach**
- Autosomal dominant
- **Genetic mutations:** Transforming growth factor-β (TGF-β) signaling pathway germline mutation (SMAD4) ➔ Mutations in TGF-β signaling ➔ contribute to abnormal mucosal proliferation.

- Carry significant cancer risk (increased risk for colonic adenocarcinoma and cancer in other site in the GI tract)

[Peutz-Jeghers Syndrome]

- Autosomal dominant syndrome characterized by:
  1) Many Hamartomatous polyps throughout GI tract (occur mostly in the small intestine, but also colon and stomach)
  2) Mucocutaneous hyperpigmentation (freckle-like spots) on lips, oral mucosa, and genital skin



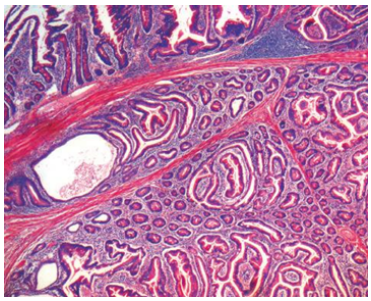
**Nice note: Early recognition of these hyperpigmented spots helps identify Peutz-Jeghers syndrome early to guide surveillance for polyps and cancer risk

- **Genetic mutations:** Autosomal dominant, Germline LKB1/STK11 mutation affects cellular metabolism and growth

- **Increased risk for several malignancies:** colon, pancreas, breast, lung, ovaries, uterus, and testes (Reflects systemic cancer risk associated with abnormal cellular proliferation from LKB1/STK11 germline mutation which is a tumor suppressor protein)

- **Macroscopic appearance:**
  - Large pedunculated

- **Microscopic appearance:**
  - Arborizing network (مثل الشجرة)of connective tissue, smooth muscle, lamina propria, and glands
  - Histologic hallmark; resembles normal epithelium but structurally abnormal.
  - Normal-appearing intestinal epithelium
  - Christmas tree pattern



[Hyperplastic Polyps]

Hyperplastic polyps: non-neoplastic polyp defined as a benign epithelial proliferation (hyperplasia of glands)

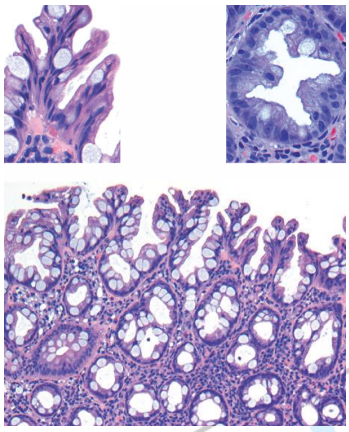
- **Most common in elderly (**6–7th decades)
- Usually arise in the **left colon (rectosigmoid)** ➔ Small <5 mm and often multiple

- **Pathogenesis:** Decreased epithelial turnover and delayed shedding of surface epithelium → pileup of goblet cells & epithelial overcrowding

- **No malignant potential** (VERY IMPORTANT) ➔ Unlike sessile serrated adenomas, which mimic hyperplastic polyps but may progress to cancer

- **Biopsy is important ➔ WHY**? On colonoscopy, hyperplastic and adenomatous polyps look identical. Hence, all polyps are removed and examined microscopically. To differentiate hyperplastic polyps from adenomas (which have malignant risk)

- **Microscopic findings:**
  - Crowding of goblet & absorptive cells
  - Classically **Serrated** surface (Refers to a **saw-tooth–like infolding of the epithelium)**



[Adenomas (Adenomatous polyps)]

Adenomas: benign neoplastic proliferation of glands

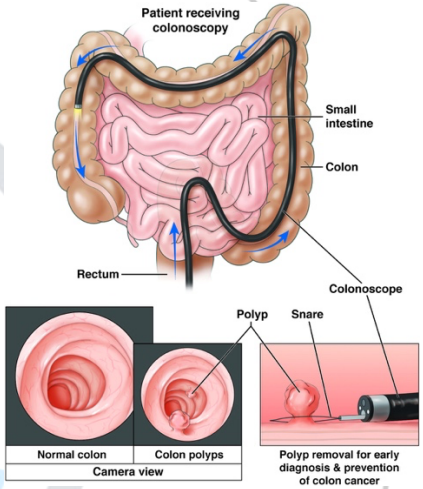
- Most common type of polyp ➔ Most important clinically, because they are **premalignant** (can transform to cancer)
- Most common in elderly
- >50% of adults > 50 years have adenomas in the western world (Frequency is lower in Asia but increasing with Western diets and lifestyles)
- Western diets and lifestyles increase risk (High-fat, low-fiber diets and sedentary lifestyles contribute to adenoma formation)
- Most cases are ASYMPTOMATIC (sometimes they may bleed)

➔ **Malignancy potential:**

- Adenomas are benign tumors, but premalignant ➔ may progress to adenocarcinoma via the **adenoma-carcinoma sequence** (see below)
- Adenomas give rise to most colorectal adenocarcinomas
- However, **most adenomas do not progress to cancer**

➔ **Screening:**

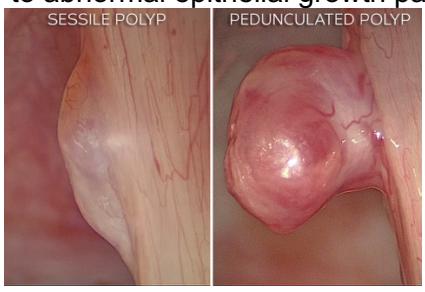
- **Concept of screening:** screening is the testing of asymptomatic people to detect disease early, before symptoms or complications appear (It is usually done in high-risk groups and aims to prevent disease or catch it at an early, treatable stage)
- **Screening for Adenomas:** adenomatous polyps are important because they are premalignant lesions—over years, they can develop into colorectal cancer. ➔ By detecting and removing these polyps early, we can prevent cancer before it develops
- **How is screening done? Colonoscopy** تنظير سفلي



- **Goal:** remove adenomas before they progress to cancer
- USA: screening colonoscopy starts at 45 yrs in ALL people
  - Screening starts earlier if family history (of colon cancer) exists ➔ screening typically started 10 years before the youngest affected relative

➔ **Macroscopic appearance:**

- May be Pedunculated or sessile
- Typical adenomas range from 0.3 to 10 cm
- **Velvet or raspberry surface texture** Due to abnormal epithelial growth patterns



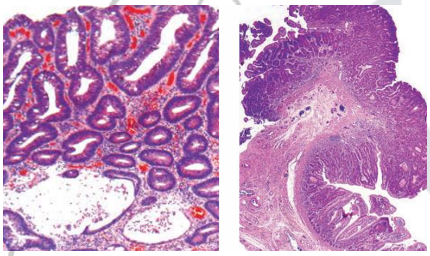
➔ **Microscopic appearance:**

- **Hallmark:** epithelial dysplasia

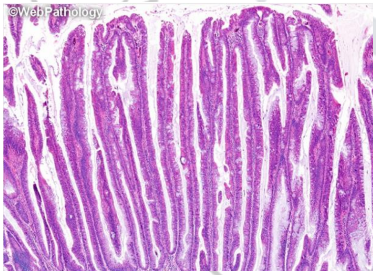
- Cytologic features:
  - Nuclear hyperchromasia
  - Elongation
  - High Nucleus/Cytoplasmic ratio

- **4 Histological subtypes:**

1) **Tubular Adenoma:** small tubular glands (rounded or tubular glands lined by dysplastic epithelium)
- Most common type
- Usually small, easier to remove
- Usually pedunculated

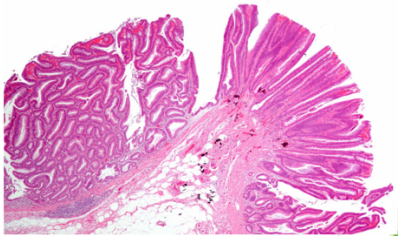


2) **Villous Adenoma:** long slender villi (finger like projections) ➔ villous architecture increases surface area
- Large and sessile
- Higher likelihood of foci of invasion than tubular adenomas (higher likelihood of malignancy)



3) **Tubulovillous Adenoma:**

- Mixture of tubular and villous elements
- Risk of malignancy is intermediate between tubular and villous types



4) **Sessile Serrated Adenoma:**
- Overlap in appearance with hyperplastic polyps
- Malignant potential similar to conventional adenomas

- **Serrated architecture affects the full gland length** (including crypt base) ➔ Distinguishes sessile serrated adenomas from hyperplastic polyps, where serration is only at the surface
- Most common in right colon (hyperplastic polyps are more common in the left colon)

➔ **Features associates with higher malignancy risk:**

1) **Size**: as size increases, risk of malignancy increases (most important correlate with risk for malignancy) e.g. 40% if > 4 cm
   Cancer is extremely rare in adenomas <1 cm; risk rises significantly in lesions >4 cm
2) **Degree of dysplasia** ➔ High-grade dysplasia increases risk of malignancy
3) **Histological Architecture:**
   Risk: Villous > Tubulovillous > Tubular

[Colorectal Carcinoma]

➔ **Definition:** carcinoma arising from colonic or rectal mucosa

➔ **Epidemiology:**
- Most common malignancy of the gastrointestinal tract
- Second most common cause of cancer-related death after lung cancer (among all cancer types)
- Most common in the elderly
- Peak incidence: 60–70 years (only < 20% of cases occur before age 50)
- Males > Females
- More common in developed countries (due to diet and lifestyle influence)
- Sporadic cases >>> Familial

- **Note**: The small intestine is rarely affected by neoplasia despite representing ~75% of GI length

➔ **Risk factors:**

1) Low intake of indigestible vegetable fiber
2) High intake of refined carbohydrates and fat
3) Obesity
4) Smoking
5) Alcohol
6) Family history

➔ **Protective factors:**

- Dietary modification (high fiber diet)
- **NSAIDs / Aspirin:** they Inhibit COX-2, which is expressed in most carcinomas and many adenomas and promotes epithelial proliferation (especially during injury or inflammation)

➔ **Pathogenesis:**

- Colorectal carcinogenesis involves heterogeneous genetic and epigenetic events
- Sporadic cases far outnumber familial cases

2 pathways have been described that lead to the development of colorectal cancer:

1- **Adenoma-carcinoma sequence** (most cases arise from this pathway)
2- **Microsatellite instability (MSI) pathway**

- Both progress through stepwise accumulation of multiple mutations
- Epigenetic changes (especially methylation) may accelerate progression in either pathway

[Adenoma-carcinoma sequence]

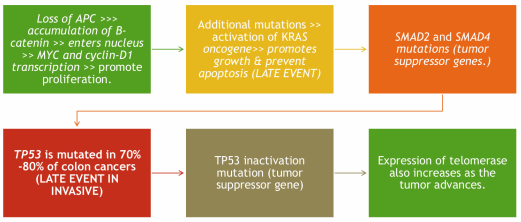
Describes the molecular progression from normal colonic mucosa to adenomatous polyp to carcinoma.

- **Other name:** APC / β-catenin pathway → ↑ WNT signaling (chromosomal instability)
- Accounts for **~80%** of sporadic tumors

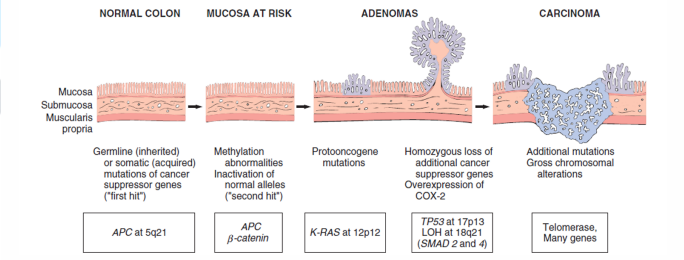
1) **APC (adenomatous polyposis coli gene)** mutations (sporadic or germline) are the earliest event
2) **K-ras** mutation promotes growth and prevents apoptosis ➔ leads to formation and growth of polyp.
3) **p53 mutation** and increased expression of **COX** allow for progression to carcinoma

- **Earliest event: APC mutation** ➔ Both APC alleles must be inactivated (two-hit mechanism) ➔ **Result:**
  - APC normally promotes degradation of β-catenin
  - Loss of APC → β-catenin accumulates → enters nucleus → activates MYC and Cyclin-D1 → drives proliferation

- **Additional mutations develop over time:**
  - KRAS (late event) → promotes growth and prevents apoptosis (clinically, more frequent in larger adenomas)
  - SMAD2 / SMAD4 (TGF-β signaling suppressors)
  - TP53 (70–80% of cancers) — late event in invasive cancer
  - Increasing telomerase expression accompanies advanced lesions



- **Hallmark:** chromosomal deletions and chromosomal instability



[Microsatellite Instability Pathway]

- **Microsatellites** are repeating sequences of noncoding DNA; integrity of sequence (stability) is maintained during cell division.

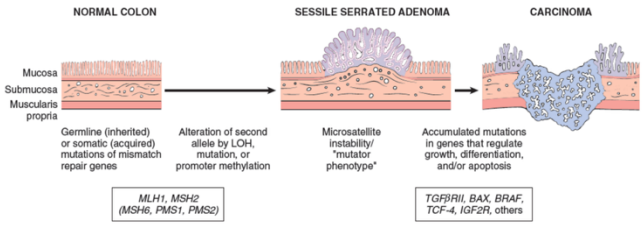
- Instability indicates defective DNA copy mechanisms (e.g., DNA mismatch repair enzymes).

- Almost <20% of sporadic cancers

- **What happens?**
  - Loss of DNA mismatch repair (MMR) genes
  - Errors accumulate in microsatellite repeats → microsatellite instability

- **Consequences?**
  - If instability involves non-coding DNA → often silent
  - Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth and apoptosis (e.g. TGF-B and BAX genes)

- **Genetic features:**
  - BRAF mutations are common
  - KRAS and TP53 are usually absent
  - CIMP Subtype: Hypermethylation of CpG islands (often the MLH1 promoter) → reduced MMR
  - **Signature pattern:** microsatellite instability + BRAF mutation + MLH1 methylation



Summary table:

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

➔ **Clinical Features:**
- Carcinoma can develop anywhere along entire length of colon.
- Early cancers are frequently asymptomatic

1) **Left-sided carcinoma** (descending/sigmoid) usually grows as a **'napkin-ring'** lesion ➔ presents with:
   - Decreased stool caliber
   - Left lower quadrant pain,
   - Blood-streaked stool
   - Change in bowel habits

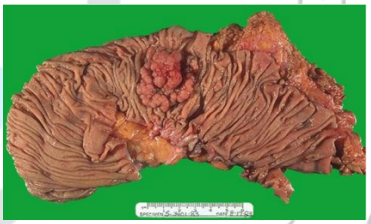
2) **Right-sided carcinoma** (cecum / ascending colon) usually grows as a **raised lesion** ➔ presents with:
   - Iron- deficiency anemia (fatigue, weakness) ➔ due to occult bleeding (small amounts of blood loss in the gastrointestinal tract that is not visible in stool but can be detected by laboratory tests)

** **Important rule:** An older adult (older man or postmenopausal women) with iron deficiency anemia has colorectal carcinoma until proven otherwise.
- Left-sided (descending/sigmoid)
- Occult bleeding
- Change in bowel habits
- Cramping left lower-quadrant discomfort

➔ **Diagnostic findings:** changes can be seen both GROSSLY (on colonoscopy) and MICROSCOPICALLY (by biopsy)

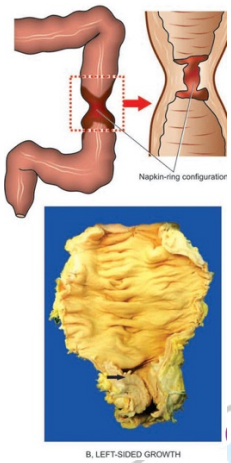
➔ **Gross (Macroscopic) features:**

- **Right (proximal) colon:**
  - Polypoid, exophytic masses
  - They rarely obstruct the lumen



- **Left (distal) colon:**
  - Annular "napkin-ring" lesions
  - Higher risk of narrowing and possible obstruction

Napkin ring



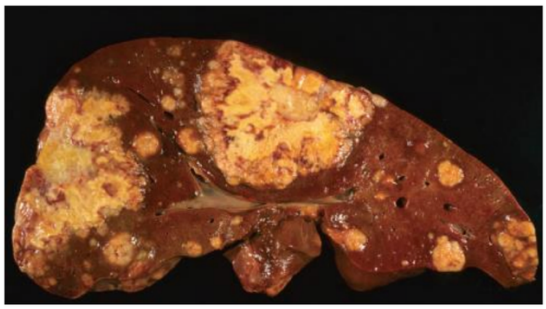
➔ **Microscopic features:**
- Dysplastic glands resembling adenomas
- Prominent desmoplastic stromal reaction (abundant collagen and connective tissue) ➔ firm tumors
- Dirty necrosis (necrotic debris) is typical
- **Some tumors:**
  - Produce abundant mucin (poorer prognosis)
  - Contain signet-ring cells (as in diffuse type gastric cancer)

➔ **Staging**
1) **T - depth of invasion;** tumors limited to the mucosa generally do not spread due to lack of lymphatics in the mucosa.
2) **N - spread to regional lymph nodes**
3) **M - distant spread ➔ most commonly** involves the **liver** (due to portal circulation: blood from GIT first passes to liver)
   - Lung metastasis is also common

- **CEA** (Carcinoembryonic antigen): a protein that is secreted by cancer cells and blood levels increase in patients with colon cancer ➔ is a serum tumor marker that is useful for assessing treatment response and detecting recurrence

➔ **Prognosis:**
- Poor differentiation on histology and mucinous tumors → worse outcomes
- **Most important prognostic factors:**
  - Depth of invasion (mucosa → submucosa → muscularis propria → serosa)
  - Lymph node metastasis (often requires radiation/chemotherapy)
- Some solitary metastases can be resected with good prognosis in select cases
- Tumors with microsatellite instability may respond to immune checkpoint inhibitor therapy (something complicated, no need to know details)

Liver metastasis



➔ **Prevention:**
- **Risk factor modification:** dietary modification, taking Aspirin/NSAIDs
- **Screening colonoscopy ➔ Goal:**
  1) Detect and remove adenomas before they progress to cancer
  2) Detect early stage cancer and treat it before it becomes advanced (early cancer is asymptomatic)

[Familial Cancer Syndromes]

- Inherited familial syndromes associated with colonic polyps and increased rates of colon cancer ➔ genetic basis
- These inherited conditions explain a significant portion of **early-onset cancers**

- **2 important syndromes:**
  1) **Familial Adenomatous Polyposis (FAP)**
  2) **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)** ➔ Also called **Lynch syndrome**

[Familial Adenomatous Polyposis (FAP)]

Autosomal dominant disorder characterized by development of 100s to 1000s of adenomatous colonic polyps in early life (hence the name)

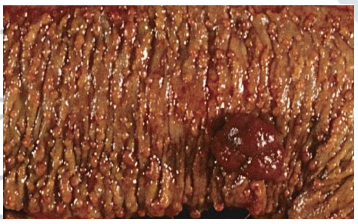
➔ **Genetics**:
- **Inherited APC mutation** (chromosome 5) ➔ increases propensity to develop adenomatous polyps throughout colon and rectum

- Single inherited mutation ➔ second mutation is acquired (not inherited) occurs later
- For cancer to develop the 2 APC genes need to be mutated (1 inherited + 1 acquired)
- What is the effect of APC mutation? See adenoma-carcinoma sequence above!

- Different mutation sites correlate with clinical variants and severity

- **Note:** A small subset of patients with multiple adenomas may instead carry MUTYH (base-excision repair) mutations — a related polyposis condition

➔ **Clinical features:**
- Numerous colorectal adenomas in youth (hundreds to thousands may eventually form) ➔ **At least 100 polyps are necessary for a diagnosis of classic FAP**



- **If polyps are not removed ➔ 100% risk of progression to cancer** (often before age 30)

➔ **Macroscopic and microscopic appearance of polyps:**
- Morphologically similar to sporadic adenomas (as discussed before) ➔ They look the same — the difference is the number and the inherited defect

➔ **Management:**
Cancer prevention is the goal! ➔ HOW?
Prophylactic Colectomy (surgical removal of the colon)

➔ **Variants of FAP:**
#1: Gardner syndrome: Represents FAP with prominent bone/soft-tissue lesions and dental changes
colonic polyps + osteomas (benign bone tumors in the mandible, skull, and long bones)

Also: epidermal cysts; desmoid and thyroid tumors; and dental abnormalities.

#2: Turcot syndrome:
intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)

[HNPCC "Lynch Syndrome"]

Hereditary cancer syndrome that leads to increased risk for multiple cancers (including colorectal, ovarian, and endometrial carcinoma) **ii.**

➔ **Genetics**:
- **Autosomal dominant**
- **Inherited mutations in DNA mismatch repair enzymes ➔ Result:**
  - Accumulation of mutations at 1000x higher rates in microsatellite DNA (short repeating sequences)
  - Resulting in microsatellite instability ➔ This molecular signature is used for diagnostic testing

- **5** genes identified but Majority of cases involve either **MSH2 or MLH1**

- Single inherited mutation ➔ second mutation is acquired (not inherited) occurs later
- For cancer to develop the 2 genes need to be mutated (1 inherited + 1 acquired)

➔ **Clinical features:**
- **Increased risk of the following cancers:**
  1) **Colorectal cancer**
  2) **Endometrial cancer** (females)
  3) **Ovarian cancer** (females)
  4) Other: Stomach, Ureters, brain, small bowel, hepatobiliary tract, and skin cancers

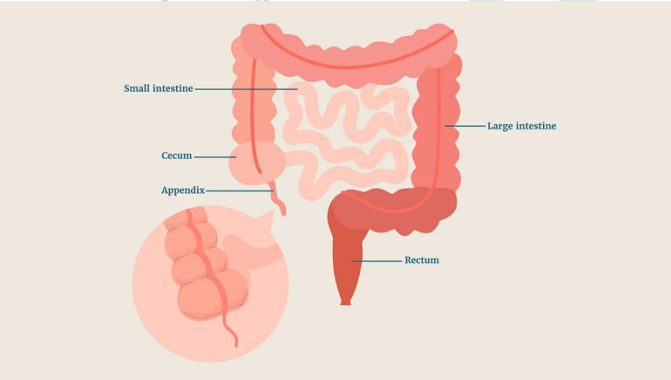
- **Colorectal carcinoma:**
  - arises de novo (Polyposis is not typical — cancer develops despite relatively few lesions ➔ So, not from adenomatous polyps)
  - cancer at a relatively early age
  - usually right sided
  - Mucinous histology may be prominent

** **Concept link:** Understanding mismatch-repair errors in HNPCC helped explain the pathogenesis of many sporadic colorectal cancers that also show microsatellite instability

[Appendix Diseases]

➔ **Reminder of Anatomy:**

- Small, tube-like organ attached to the cecum near the ileocecal valve
- **Normal true diverticulum** of the cecum (An outpouching that includes all layers of the bowel wall)
- Usually 6–9 cm long, lined with mucosa, muscle, and lymphoid tissue.
- Common positions: behind the cecum (retrocecal) or in the pelvis.
- **Function**: part of the immune system (lymphoid tissue).



[Acute Appendicitis]

➔ **Definition:** Acute inflammation of the appendix

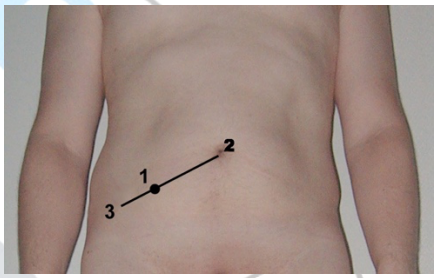
- Most common in adolescents and young adults (Peak incidence is in the 2nd–3rd decades)
- But, may occur at any age

➔ **Pathogenesis:**

- Related to obstruction of the appendix ➔ Luminal obstruction in 50–80% of cases by fecalith (small mass-like stone of stool), less commonly: gallstone, tumor, worms….
- Obstruction ➔ Increased luminal pressure ➔ impaired venous drainage ➔ ischemic injury & stasis associated bacterial proliferation ➔ inflammatory response rich in neutrophils & edema <u>(Obstruction causes swelling; swelling compromises blood flow, leading to inflammation)</u>

➔ **Clinical features:**

1) **Abdominal pain:**
   Early acute appendicitis: periumbilical pain (Pain starts vague because it is visceral in origin) ➔ this is referref pain
   Later: pain localizes to the right lower quadrant (Localization reflects parietal peritoneal irritation)
   - A classic physical finding is **McBurney's sign (Tenderness at McBurney's point ➔** <u>located one-third of the distance from the anterior superior iliac spine (ASIS) to the umbilicus on the right side</u>**)**



2) **Nausea and vomiting**
3) **Fever**
4) **Leukocytosis** (elevated WBC count)

****Note:** Atypical presentations are common in children and elderly)

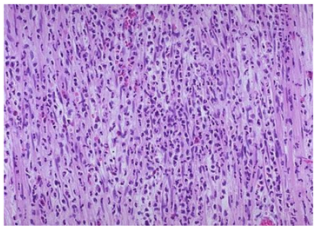
Rupture results in release of inflammatory cells into the peritoneum ➔ **peritonitis

➔ **Diagnostic evaluation:**

- Difficult to confirm preoperatively ➔ it is a surgical emergency (we remove the appendix) ➔ Histological evaluation of the appendix:

Acute appendicitis: neutrophils present in appendix (Presence of neutrophils within the wall is the key microscopic feature) ➔ Diagnosis requires neutrophilic infiltration of the muscularis propria <u>(Without neutrophils in the muscle layer, the diagnosis should not be made)</u>

Acute appendicitis: neutrophils



➔ **Treatment:**
Appendectomy (surgical removal of appendix)

- Delay in treatment increases risk of perforation and peritonitis

- **ملاحظة: لما حدا يحكي "عملت عملية الزايدة" يعني صار عنده التهاب في الزايدة و شالوها

➔ **Differential diagnosis of of acute Appendicitis:**

Any disease that may cause right lower quadrant abdominal pain ➔ many! (no need to understand them now)

- Mesenteric lymphadenitis
- Acute salpingitis
- Ectopic pregnancy
- Mittelschmerz (pain associated with ovulation)
- Ovarian cysts torsion
- Rupture Meckel diverticulitis
- Crohn disease

➔ **Complicated cases:**

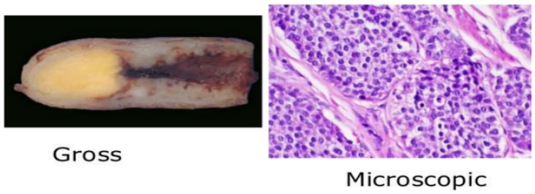
- **Acute suppurative appendicitis ➔** more severe inflammation with focal abscess within wall
- **Acute gangrenous appendicitis ➔** gangrenous necrosis and ulceration ➔ rupture

[Tumors of the Appendix]

The most common tumor of the appendix:
carcinoid (neuroendocrine tumor)

- usually Incidentally found during surgery or on examination of a resected appendix
- Found in distal tip of the appendix
- Lymph node metastases & distant spread are rare
- Appendiceal carcinoids are usually small and behave indolently)

Carcinoid tumor



Gross

Microscopic

The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pathology

Liver diseases 1&2

Written by: Nour Alhaj Qassim

Edited by: Momen Alfawadel

Reviewed by: Ahmad Al Laham

[lecture outlines]

1) Foundations

- Overview & function of the liver
- Hepatic injury (patterns & mechanisms)
- Hepatic failure

2) Common Clinical Diseases

3) Hepatitis

4) Genetic & Metabolic Diseases

5) Biliary Diseases

6) Vascular Disorders

7) Special / Miscellaneous Conditions

8) Tumors

[Overview and functions]

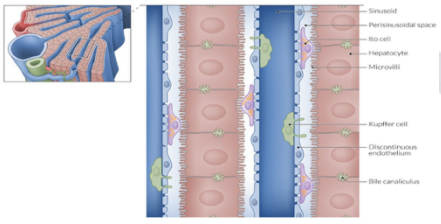
1) Basic Facts

- Weight: **1400–1600 g** (~2.5% of body weight)

2) Blood Supply

- **Portal vein:** 60–70% → nutrient-rich, low oxygen
- **Hepatic artery:** 30–40% → oxygen-rich

➔Both mix in the sinusoids



Hepatic microstructure: sinusoids, perisinusoidal space, and hepatocytes

From the sinusoids, plasma can enter the perisinusoidal space through the highly fenestrated endothelium. Microvilli on the basolateral surface of the hepatocytes increase the surface area for efficient substance exchange. The apical surfaces of adjacent hepatocytes form the bile canaliculi, which drain into the peripherally located interlobular bile ducts.

© AMBOSS

Parenchyma:

- **Structure:**
  - Liver is mainly composed of **hepatocytes**
    - ➢ Rich in smooth endoplasmic reticulum (SER)
      → important for detoxification
- **Polarity of hepatocytes**
  - Basolateral surface → faces sinusoids (blood)
  - Apical surface → faces bile canaliculi (bile)

  ➔This explains opposite flow directions:
  - Blood flow: portal triad → central vein
  - Bile flow: hepatocytes → canaliculi → bile ducts → duodenum
- **Bile Flow**
  - Hepatocytes secrete bile into canaliculi
  - Flows → intrahepatic ducts → common bile duct → duodenum
  - Flow is opposite to blood flow
- **Hepatic Sinusoids**
  - Specialized capillaries:
    - ➢ **Highly fenestrated endothelium**
    - ➢ Allow exchange between blood and hepatocytes
  - Blood drains into the **central vein**

Histological zones:

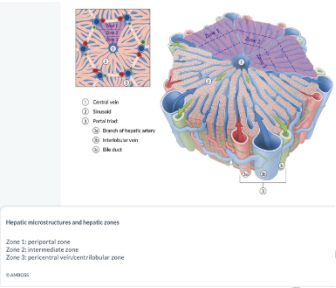
- **Classic Lobule**(It is the basic structural unit of the liver consists of):
  - Hexagonal structure
  - Central vein in the middle
  - Portal triads at the corners

- **Hepatic Acinus**(functional unit of the liver, organized based on blood supply and oxygenation) → Divided based on oxygen supply:

  - Zone 1 – Periportal (closest to the portal vein, closest to blood supply)
    - ➢ Highest oxygen Concentration
    - ➢ First exposed to:
      - Toxins from blood
      - Viruses(Viral hepatitis)
    - ➢ Most resistant to ischemia
  - Zone 2 – Intermediate
    - ➢ Features between zones 1 and 3
    - ➢ Less clinically emphasized
  - Zone 3 – Centrilobular (near central vein)
    - ➢ Lowest oxygen concentration
    - ➢ Most vulnerable to:
      - Ischemia
      - Metabolic toxins
    - ➢ Examples:

- Ethanol
- Acetaminophen
- CCl_4
- Halothane

➢ Contains highest cytochrome P450 activity



Liver functions:

Energy metabolism	Glycolysis, lipid metabolism, amino acids degradation, beta-oxidation, breakdown of serotonin, breakdown of fructose
Synthesis	Gluconeogenesis, production of ketone, synthesis of plasma proteins, cholesterol and fatty acid synthesis, bile acid synthesis, clotting factors, albumin
Storage	Glycogen, lipoprotein, iron and copper, fat soluble vitamins (A D E K), folate and B12
Detoxification	Drug, hormones, Urea cycle, cytochrome p450 system, breakdown ethanol
Excretion	Bile

[Hepatic injury]

- **Key pathological changes and its consequences:**
  - **Inflammation (hepatitis)**
  - **Ballooning degeneration**

➢ Irregularly clumped cytoplasm showing large, clear spaces.

➢ Substances may accumulate in viable hepatocyte(not injured), including fat, iron, copper and retained biliary materials.

- **Steatosis (fatty changes)**

➢ Microvesicular(Many small fat droplets inside the cell): ALD, Reye syndrome, acute fatty change of pregnancy

➢ Macrovesicular(One large fat droplet in the cell): DM, obese

- **Necrosis**

➢ **Depending on the type:**
  - ➔ Coagulative necrosis
  - ➔ Lytic necrosis

➢ **Depending on the cause:**
  - ➔ Ischemic
  - ➔ Toxic

➢ **Depending on location**
  - ➔ Centrilobular necrosis
  - ➔ Mid zonal
  - ➔ Periportal: interface hepatitis
  - ➔ Focal: Piece meal necrosis, bridging necrosis
  - ➔ Diffuse: massive & submassive necrosis

- **Regeneration**

➢ Definition
  - The liver's ability to replace damaged hepatocytes through cell proliferation, restoring normal structure and function.

➢ Evidenced by increased mitosis or cell cycle markers.

➢ The cells of canal of hering are the progenitors of hepatocyte and bile duct cells.

- **Fibrosis**

➢ Definition:
  - Excess deposition of collagen (scar tissue) in the liver due to chronic injury.

➢ Patterns of fibrosis:
  - portal or periportal fibrosis(around the portal vein)
  - pericentral- around the central vein.
  - pericellular fibrosis or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes
  - bridging fibrosis(links portal and central areas)

- **Cirrhosis**

➢ Definition
  - End-stage liver disease characterized by diffuse fibrosis and regenerative nodules, leading to distorted liver architecture and impaired function.

➢ Patterns of Cirrhosis
  - Micronodular (lots of tiny, evenly sized lumps in the liver)
  - Macronodular (bigger, irregular lumps)

- **Ductular proliferation**
  - Definition
    - It is the increase in number of small bile duct–like structures in the liver, usually as a response to injury or obstruction.

[Hepatic failure]

➔Definition

- Hepatic failure is a clinical condition that occurs when 80–90% of liver functional capacity is lost, leading to inability of the liver to maintain normal metabolic, synthetic, and detoxification functions.

➔ Causes:

1-Massive hepatic necrosis:

- Definition:
  - A severe form of acute liver injury characterized by extensive destruction of hepatocytes over a short period of time, leading to acute liver failure (often with loss of >80–90% of liver functional capacity).
- Fulminant viral hepatitis
- Drugs & chemicals (acetaminophen, halothane, anti TB drugs, CCL4 poisoning, Mushroom poisoning)

2-Chronic liver disease

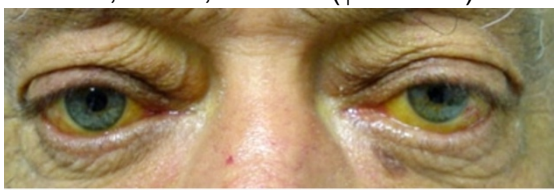
3-Hepatic dysfunction without overt cirrhosis

- Definition
  - A state of significant liver functional impairment causing clinical features of liver failure, but without established cirrhosis (no diffuse fibrotic architectural distortion of the liver)
- Reye's syndrome
- Tetracycline toxicity
- Acute fatty liver of pregnancy

➔Clinical features:

1)Features of Liver Dysfunction:

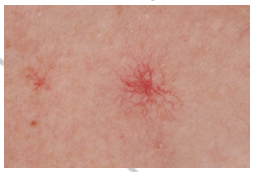
- Jaundice → yellow discoloration of skin, sclera, mucosa (↑ bilirubin)



- Hypoalbuminemia → edema
- Hyperammonemia → neurotoxicity

2)Hormonal Effects (Endocrine imbalance)

- Due to impaired hepatic metabolism of sex hormones → ↑ estrogen levels:
  - Palmar erythema
  - Spider angiomas



  - Hypogonadism
  - Gynecomastia

3)Characteristic breath odor

- Fetor hepaticus → musty / sweet-sour smell

Pathophysiology of Hormonal changes:

- Changes in the hepatic metabolization of sex hormones (eg. estrogen) causes an imbalance in the estrogen-androgen ratio, resulting in a marked increase in systemic estrogen levels, which causes Palmar erythema, Spider angiomas, and feminization in men (eg. Hypogonadism & gynecomastia).

➔ Consequences:

1) Multiple organ failure, advanced liver failure can lead to dysfunction of multiple systems, including CNS, CVS, renal and pulmonary.
2) Coagulopathy → bleeding, due to impaired hepatic synthesis of clotting factors II, VII, IX, X (vitamin K dependent).
3) Hepatic encephalopathy, caused by accumulation of neurotoxin (ammonia), leading to=
   - ↓level of consciousness (coma)
   - Rigidity(Abnormally increased muscle tone causing stiffness and resistance to movement of muscles.)
   - Hyperreflexia(Exaggerated or overactive reflex responses when testing deep tendon reflexes.)
   - Seizures
   - Asterixis (flapping tremors)

4) Hepatorenal syndrome: Renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure, caused by systemic circulatory dysfunction.

[Alcoholic Liver Disease]

➔Definition

- Alcoholic liver disease is a spectrum of liver injury caused by chronic excessive alcohol consumption, ranging from fatty liver (steatosis) → alcoholic hepatitis → cirrhosis.

➔Overview

- Alcohol is the most widely abused agent
- It is the 5th leading cause of death in USA due to accidents, Cirrhosis.

➔Dose–Effect Relationships

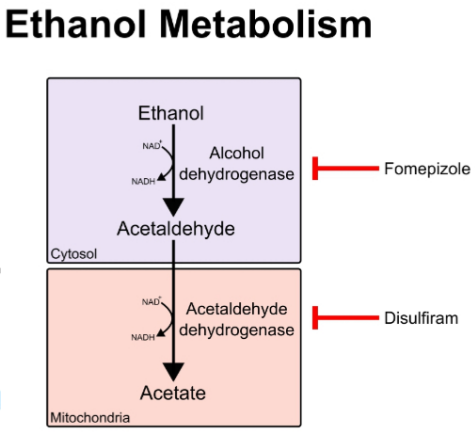
- Fatty liver threshold
  - ~80 g/day ethanol (short-term intake)→ causes hepatic steatosis (fatty change)

- Blood alcohol concentration (BAC) in non-habitual drinkers
  - 200 mg/dL → coma
  - 300–400 mg/dL → respiratory failure → death

- **Legal intoxication limit**
  - 80–100 mg/dL → legal driving limit
    - Equivalent to ~44 mL ethanol in a 70 kg adult

- **Alcohol Tolerance (Habitual Drinkers)**
  - Can tolerate very high BAC levels (up to ~700 mg/dL)
    - Due to 5–10× induction of hepatic microsomal enzymes
- **Enzyme Induction Mechanism CYP2E1 (MEOS system)**
  - Chronic alcohol use induces CYP2E1 leading to:
    - ↑ ethanol metabolism
    - ↑ metabolism of other drugs:
      - Acetaminophen (paracetamol) → ↑ hepatotoxicity risk
      - Cocaine → altered metabolism and toxicity

➔ Ethanol metabolism:



- **Distribution & elimination:**
  - After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level
  - less than 10% of absorbed ethanol is excreted unchanged in urine sweat & breathe
- **Gastric metabolism (sex difference)**
  - Women have lower levels of gastric alcoholdehydrogenase activity than men & they maydevelop higher blood Levels than men after drinking the same quantity of ethanol

- **Genetic variation (ALDH polymorphism)**
  - **Defintion:**
    - Genetic variation: Differences in DNA sequences among individuals in a population that lead to variation in traits or biological responses.
    - Polymorphism: A type of genetic variation where two or more common variants (alleles) exist in a population (each usually present in ≥1% of individuals).

- There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism e.g 50% of chinese , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme. → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation

➔**Pathogenesis of alcoholic liver disease:**

- **Dose-Time relationship**
  - Short term exposure
    - Short term ingestion of 80gm of ethanol/day (8beers) → mild reversible hepatic changes(fatty liver)
  - Long term& borderline exposure:
    - Long term ingestion (10-20yrs) of 160gm of ethanol per day → severe hepatic injury
    - 50 – 60gm/day → borderline effect, may produce mild or borderline liver effects
- **Sex susceptibility**
  - Women are more susceptible to hepatic injury due to ↓gastric metabolism of ethanol .
- **Progression to cirrhosis**
  - Only 8 – 20% of alcoholics develop cirrhosis

➔ **Mechanism of ethanol toxicity:**

1) Fatty Liver (Steatosis)
Core problem: Imbalance of fat metabolism → fat accumulates in liver
- ↑ NADH / NAD ratio (from ethanol metabolism)
  → shifts metabolism toward lipid synthesis
  → ↓ fatty acid oxidation
- ↑ peripheral fat breakdown
  → ↑ free fatty acids (FFA) delivered to liver
- Acetaldehyde forms adducts with tubulin
  → disrupts microtubules
  → ↓ lipoprotein (VLDL) export from liver
- ↓ mitochondrial β-oxidation of fatty acids
  → further fat accumulation

2) Acetaldehyde Toxicity (Direct Cellular Injury)
- Lipid peroxidation
- Protein modification (acetaldehyde adducts)
  → hepatocyte dysfunction
  → antigen formation → immune attack

3) Oxidative Stress Injury
- Induction of CYP2E1 (cytochrome P450 system)
  → ↑ reactive oxygen species (free radicals) → damage to:
  - Lipids
  - Proteins
  - Cell membranes

4) Drug Toxicity (Enzyme Induction Effect)
- CYP2E1 induction enhances drug metabolism to toxic products
- Example:
  - Acetaminophen → ↑ toxic metabolites → hepatotoxicity

5) Direct Cellular & Organelle Damage
- Alcohol directly impairs:
  - Microtubules
  - Mitochondria
  - Membrane fluidity

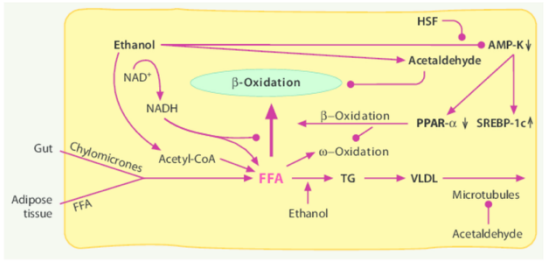
6) Immune-Mediated Injury
- Acetaldehyde-modified hepatocytes become antigenic → immune system attacks liver cells Key cytokines:
  - TNF (major mediator)
  - IL-6
  - IL-8
  - IL-18

7) Gut–Liver Axis (Endotoxin Injury)
- Alcohol increases intestinal permeability → bacterial endotoxins (LPS) enter portal circulation
  → liver inflammation

8) Hypoxic Injury
- Alcohol → ↑ endothelin release (vasoconstrictor) → ↓ hepatic

sinusoidal blood flow → regional liver hypoxia

9) Infection Synergy
- Hepatitis C virus (HCV) accelerates liver damage
- Present in ~30% of alcoholics



7 Development of alcoholic fatty liver (AFL). Various factors contribute to the fat accumulation in the liver: (1) Ethanol oxidation results in the generation of NADH which overfl oods the hepatocytes and shifts all redox partners into their reducing intermediate , favouring fatty acid-and tryglyceride synthesis and inhibiting mitochondrial ß-oxidation of fatty acids. (2) The hepatic infl ux of free fatty acids from adipose tissue and of chylomicrons from the intestinal mucosa is enhanced by ethanol. (3) Ethanol inhibits adenosine monophosphate activated kinase (AMP-K) resulting in a decrease of peroxisome proliferating-activated

➔ **Forms of alcoholic liver disease:**

1) Hepatic steatosis (90-100% of drinkers)
2) Alcoholic hepatitis (1- 35% of drinkers)
3) Cirrhosis (14% of drinkers)
- Steatosis & hepatitis may develop independently

1) Hepatic steatosis

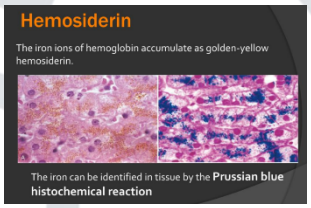
➔**Definition**
- is the abnormal accumulation of fat (mainly triglycerides) within hepatocytes, leading to a fatty liver, which is usually reversible if the underlying cause is removed.

➢ Can occur following even moderate intake of alcohol in form of microvesicular steatosis
➢ Chronic intake → diffuse steatosis
➢ Liver is large (4 – 6 kg) soft yellow & greasy
➢ Continued intake →fibrosis
➢ Fatty change is **reversible** with complete abstention from further intake of alcohol

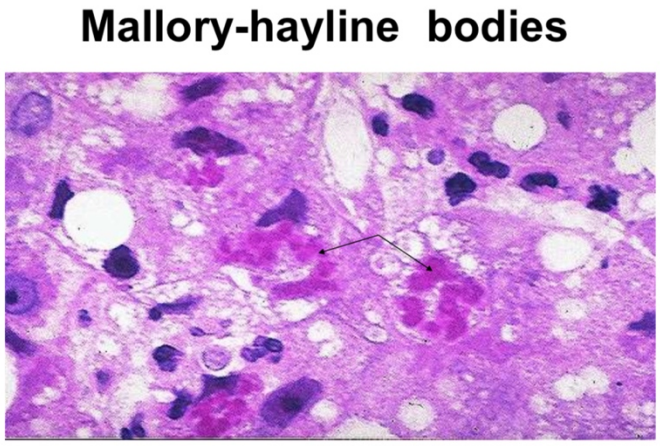
➔ **Clinical features:** ↑ liver enz.
Severe hepatic dysfunction is unusual

2) Alcoholic hepatitis

➔ **Hepatocyte swelling & necrosis**
- Accumulation of fat & water & proteins
- Cholestasis
  - ➢ (impairment or cessation of bile flow, resulting in accumulation of bile within the liver and/or reduced delivery of bile to the intestine.)
- Hemosiderin(insoluble iron-storage complex derived from the breakdown of ferritin and hemoglobin, which appears as golden-brown granular pigment in cells) deposition in hepatocytes & kupffer cells.



➔ **Mallory-hayline bodies**
- **Definition**
  - ➢ eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other protein
- Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease, they are also seen in:
  1-Primary biliary cirrhosis
  2-Wilson disease
  3-Chronic cholestatic syndromes
  4-Hepatocellular carcinoma
  5-Neutrophilic reaction
  6-Fibrosis, Sinusoidal & perivenular, Periportal
  7-Cholestasis
  8-Mild deposition of hemosiderin in hepatocytes and Kupfer cells.



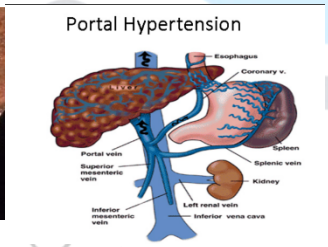
➔ **Clinical features**:
- Non-specific symptoms, malaise, anorexia, wt. loss
- ↑ liver & spleen
- ↑ LFT
- Each bout of hepatitis →10-20% risk of death

3) Alcoholic cirrhosis

- **Overview**
  - Definition: Chronic liver disease caused by long-term alcohol use
  - Usually, it develops slowly
  - It can develop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs)
- **Gross Morphology**
  - Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < l kg in wt.
- **Microscopic Features**
  - Initially micronodular cirrhosis
  - Progresses to mixed micro- and macronodular cirrhosis
  - Fibrous scar tissue formation (Laennec cirrhosis)
- **Histologic Findings**
  - Bile stasis
  - Mallory bodies are only rarely evident at this stage

-Key point is that it is Irreversible condition once cirrhosis is established because by the time it is established, the liver architecture has been permanently destroyed and replaced by scar tissue.

➔ Clinical features: portal hypertension



➔Causes of death in alcoholic liver Disease:

1) **hepatic failure**
2) **Massive GI bleeding**
3) **Infections**
4) **Hepatorenal syndrome**
5) **HCC in 3-6% of cases**

[Cirrhosis]

➔Definition:

- It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules.

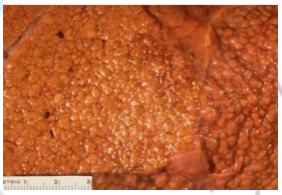
➔Main characteristics:

1) Bridging fibrous septae
2) Parenchymal nodules encircled by fibrotic Bands
3) Diffuse architecture disruption

➔ Types:

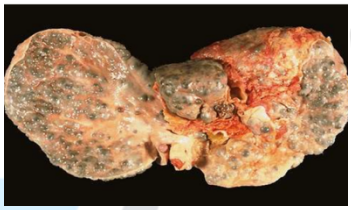
1) Micro-nodules < 3mm in diameter

Micronodular cirrhosis



2) Macro nodules > 3 mm in diameter

Macronodular cirrhosis



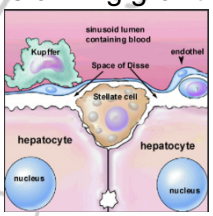
➔ Causes of cirrhosis:

1) Chronic alcoholism
2) Chronic viral infection HBV & HCV
3) Biliary disease
4) Hemochromatosis
5) Autoimmune hepatitis
6) Wilson disease
7) α-1- antitrypsin deficiency
8) Rare causes: Galactosemia, Tyrosinosis, , Glycogen storage disease III &IV, Lipid storage disease, Hereditary fructose intolerance, Drug induced e.g methyldopa
   - **Cryptogenic(**Cirrhosis in which no clear underlying cause is identified**) cirrhosis in 10%**

➔ Pathogenesis of cirrhosis:

- The mechanism of cirrhosis involves:
  - Hepatocellular death
  - Regeneration
  - Progressive fibrosis
  - Vascular changes

- Cell death should occur over a long period of time & accompanied by fibrosis
- In normal liver the ECM collagen (types I, III, V& XI) is present only in: Liver capsule, Portal tracts, around central vein
- delicate framework of type IV collagen & other proteins lie in space of Disse
- **In cirrhosis types I & III collagen & others are deposited in the space of Disse**
- The major source of collagen in cirrhosis is the **perisinusoidal stellate cells (Ito cells) which lie in space of Disse,** Perisinusoidal stellate cells act normally as storage cells for vit A & fat**,** upon stimulation myofibroblast- like cells**,** transforming growth factor β (TGF-β)



- The stimulus for the activation of stellate cells & production of collagen are:
  1) reactive oxygen species
  2) Growth factors
  3) cytokines TNF, IL-I, lymphotoxins

- The vascular changes include:
  1) Loss of sinusoidal endothelial cell fenestration
  2) development of vascular shunts as:

➔ Portal vein- hepatic vein

Blood from the portal vein flows directly into the hepatic vein

➔ Hepatic artery – portal vein

Blood from the hepatic artery enters the portal vein

- Both types of shunts bypass the liver causing defect in liver function
- Loss of microvilli from hepatocytes →↓ transport capacity of the cells
- Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
- the movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and the plasma is markedly impaired.
- These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell

➔ **Clinical features of cirrhosis:**

1) Silent
2) Anorexia, wt loss, weakness

- **Complications**:

1) Progressive hepatic failure
2) Portal hypertension
3) Hepatocellular carcinoma

Portal hypertension:

➔**Definition**

- **↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules**

- Arterial – portal anastomosis develops in the fibrous bands →increase in the blood pressure in portal venous system

- Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension by imposing arterial pressure on the normally low-pressure portal venous system.

- Fibrous bands in cirrhosis create abnormal artery-to-portal connections, increasing blood inflow into an already obstructed portal system → causing portal hypertension.

- **Causes of portal hypertension:**

➔ **Pre hepatic:**

1) Portal vein thrombosis
2) Massive splenomegaly

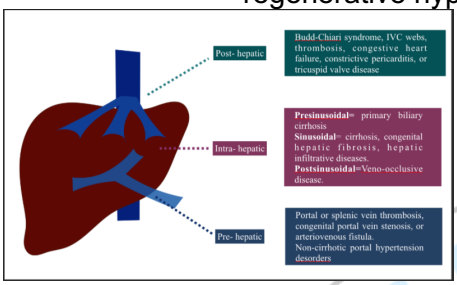
➔ **Post hepatic:**

1) Severe Rt.- sided heart failure
2) Constrictive pericarditis
3) Hepatic vein out flow obstruction

➔ **Hepatic:**

1) Cirrhosis
2) Schistosomiasis

3) Massive fatty change
4) Diffuse granulomatosis as sarcoidosis, TB
5) Disease of portal microcirculation as nodular regenerative hyperplasia



- **Clinical consequences of portal hypertension:**

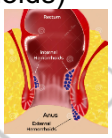
1) Ascites: Collection of excess fluid in peritoneal cavity, it becomes clinically detectable when at least 500 ml have accumulated.
   - Pathogenesis: Sinusoidal ↑ Bp + Hypoalbuminemia= Leakage of hepatic lymph into the peritoneal cavity, Renal retention of Na+ & water due to 2ry hyperaldosteronism.
   - Features: Serous fluid, contains as much as 3g/ml of protein (albumin), It has the same concentration as blood of glucose, Na+, & K+, Mesothelial cells & lymphocytes
   - Neutrophils found → infection

RBCs found → disseminated cancer

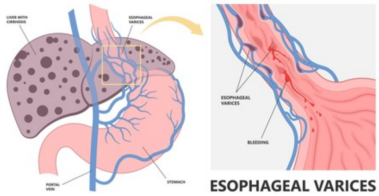
2) Portosystemic shunts: ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds.

- Sites:

1) Around and within rectum (hemorrhoids)



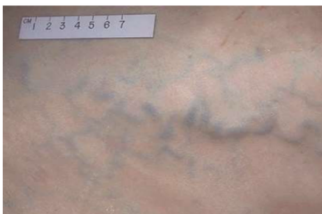
2) Gastroesophageal junction (varices)



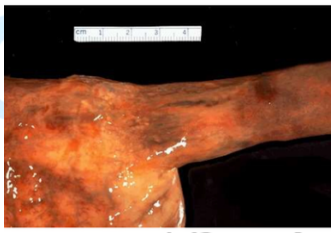
3) Retro peritoneum
4) Falciform ligament of the liver (periumbilical and abdominal wall collaterals) lead to Caput medusae

- Gastroesophageal varices appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1

caput medusae



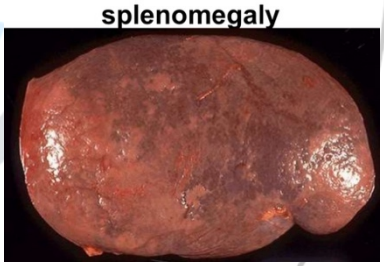
Esophageal varicies



bleeding

3) Splenomegaly, usual 500-1000 g (normal <300g)
   - Not necessarily correlated with other features of portal ↑Bp
   - May result in hypersplenism and thrombocytopenia

splenomegaly



4) hepatic encephalopathy:
   - It is a complication of acute & chronic hepatic failure
   - Disturbance in brain function ranging from behavioral changes to marked confusion & stupor to deep coma & death
   - The changes may progress over hrs. or Days

- Neurological signs:
  1)Rigidity
  2)Hyper-reflexia
  3)Non – specific EEG
  4)Seizures
  5)Asterixis (non-rhythmic rapid extension flexion movements of head & extremities.
  6)Brain shows edema & astrocytic reaction

➔ **Pathogenesis:** Physiologic factors important in development of hepatic encephalopathy: -

1) Severe loss of Hepatocellular function
2) Shunting of blood around damaged liver
3) Exposure of Brain to toxic metabolic products
4) High NH3 level in blood → generalized brain edema impaired neuronal function

[Drug induced liver disease]

➔**Definition**

- Liver injury caused by exposure to a medication, herbal product, or chemical agent, in the absence of an alternative cause of liver disease.

➔ **Drug reaction:**

1) Predictable drug reactions depend on the dose(dose-dependent).

Example: Acetaminophen, Tetracycline, Antineoplastic agents, CCL4, Alcohol

2) Unpredictable drug reactions depend on:

- The immune response of the host to the antigenic stimulus
- The rate at which the host metabolizes the agent
- Examples: Chlorpromazine, Halothane, Sulfonamides, Methyldopa, Allopurinol

- **Time course**
  - The injury maybe immediate or takes weeks to months.
- Drug-induced chronic hepatitis is clinically & histologically Indistinguishable from chronic viral or autoimmune hepatitis.
- **Morphology:**
  - Massive necrosis → 500 – 700 gm liver
  - Submassive necrosis
  - Patchy necrosis

➔**Mechanism of drug injury:**

1) Direct toxic damage, like: acetaminophen, CCL4, mushrooms toxins
2) Immune mediated damage

➔ **Patterns of injury:**

1) Hepatocellular necrosis
2) Cholestasis
3) Steatosis
4) Steatohepatitis
5) Fibrosis
6) Vascular lesion
7) Granuloma
8) Neoplasms benign and malignant

➔**Drug that may cause acute liver failure:**

1) Acetaminophen(most common)
2) Halothane
3) Antituberculosis drugs (rifampin, isoniazid)
4) Antidepressant monoamine oxidase inhibitors
5) Toxins as CCL4 & mushroom poisonin

[Fulminant Hepatitis]

➔**Definition**

- Hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy in 2-3 wks
  - Sub fulminant (up to 3 mon)

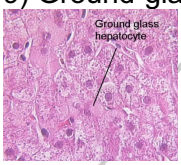
- **Causes:**
  1) Viral hepatitis 50 – 65%, HBV 2x > HCV
  2) Drugs & chemical 25- 50%, e.g Isoniazid, halothane, methyldopa & acetaminophen
  3) Obstruction of hepatic vein
  4) Wilson's disease
  5) Acute fatty change of pregnancy.
  6) Massive tumor infiltration
  7) Reactivation of chronic hepatitis B
  8) Acute immune hepatitis

[chronic hepatitis]

- **Definition**
  - Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease for more than 6 months with histologically documented inflammation & necrosis
- **Nature of the disease**
  - Progressive or non progressive
- **Common causes**
  - HBV, HCV, HBV-HDV

➔ **Morphology of chronic hepatitis:**

1) portal inflammation
2) Lymphoid aggregate
3) Necrosis of hepatocytes-councilman bodies
4) Bile duct damage
5) Steatosis
6) Interface hepatitis(Inflammation at the junction between the portal tract and the hepatic parenchyma (hepatocytes))
7) Bridging necrosis & fibrosis
8) Fibrosis
9) Ground-glass appearance



10) Sanded nuclei
11) Lobular disarray

[Autoimmune Hepatitis]

➔**Definition**

- Chronic hepatitis with immunologic abnormalities

➔**Histology**

- Histologic features are similar to chronic viral hepatitis

➔**Clinical course**

- Indolent or severe course

➔**Treatment response**

- Dramatic response to immunosuppressive therapy

➔ **Features:**

1) Female predominance (70%)
2) Negative serology for viral Ags.
3) ↑serum Ig (>2.5 g/dl)
4) High titers of autoantibodies (80% of cases)
   - **Types of autoantibodies:**
     1) Anti-smooth muscle antibodies (anti-actin, anti-troponin, anti-tropomyosin)
     2) liver/kidney microsomal antibodies (anti-cytochrome P-450 components, anti UDP-glucuronosyl transferases)
     3) Anti – soluble liver / pancreas antigen
   - presence of other autoimmune diseases as RA, thyroiditis, sjoger syndrome, UC in 60% of the case

➔**Outcome:**

- Mild to severe chronic hepatitis
- Full remission is unusual
- Risk of cirrhosis is 5% which is the main cause of death.

[Nonalcoholic fatty liver disease]

➔**Definition**

- progressive form of non-alcoholic fatty liver disease (NAFLD) characterized by: Hepatic steatosis (fat accumulation) + hepatocellular injury + inflammation, occurring in patients with little or no alcohol consumption.

➔ **Types:**

1) Steatosis (Fatty liver)
2) Steatohepatitis
   - hepatocyte destruction
   - parenchymal inflammation
   - progressive pericellular fibrosis

➔**Predisposing factors:**

1) Type 2 DM
2) Obesity: body mass index > 30 kg /m2 in caucasians, > 25 kg /m2 in Asians
3) Dyslipidaemia (↑ TG, ↑LDL, ↓HDL)

➔ **Pathogenesis:**

- Metabolic syndrome: Insulin resistance, Obesity, Dyslipidaemia
- Mechanism of fatty accumulation

1.Impaired oxidation of fatty acids
2.Increased synthesis & uptake of FFA
3.Decreased hepatic secretion of VLDL
- ↑TNF, IL6, chemokine →liver inflammation & damage

➔ **Clinical features:**

- NAFLD is the most common cause of incidental ↑ in transaminases
- Most pts. are asymptomatic
- Non-specific symptoms (Fatigue, malaise, RUQ discomfort)
- Severe symptoms
- Liver Bx is required for dx.
- NAFLD maybe a significant contributor to cryptogenic cirrhosis

[Hemochromatosis]

➔**Definition**

- Excessive accumulation of body iron (liver & pancreas)

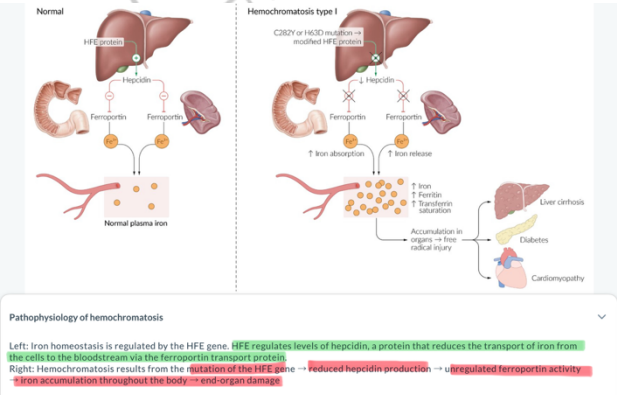
➔ **Causes:**

1) **Genetic:** 4 variants, the most common form is aut. Recessive disease of adult onset caused by mutation in the HFE gene on chromosome 6
2) **acquired:**

- multiple transfusions
- ineffective erythropoiesis (thalassemia)
- increased iron intake (Bantu sidrosis)
- chronic liver disease

➔ **Pathogenesis:**

- primary defect in intestinal absorption of dietary iron.
- Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes
- In disease >**50gm Fe accumulated → 1/3 in liver**
- In hereditary hemochromatosis **there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 gm/yr**
- The gene responsible is HFE gene located on chr.6 close to HLA gene complex
- **HFE gene regulates the level of hepcidin hormone synthesized in liver**
- **Hepcidin → inhibit Fe. absorption from Intestine**
- **HFE gene deletion causes iron overload**



- **Two mutations can occur:**

1) Mutation at 845 nucleotide leads to tyrosine substitution for cystine at AA 282 (C282 Y)
2) Aspartate substitution for histidine at AA63 (H63D)
3) 10% of patients have other mutation

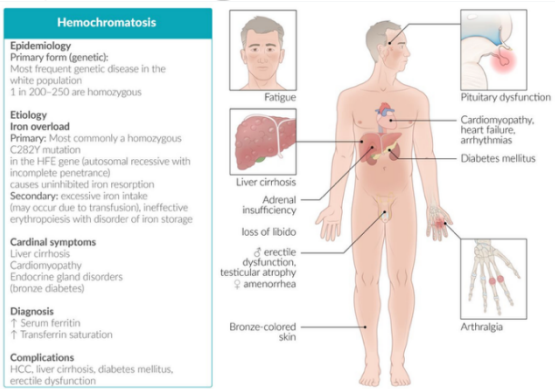
- Carrier rate for C282Y is 1/70
- Homozygosity is 1/200
- 80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation
- 10% of pts. are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation
- Excessive Fe deposition → toxicity of the tissues:
  1. Lipid peroxidation
  2. Stimulation of collagen formation
  3. DNA damage

➔ **Feature and clinical presentation:**

- **Deposition of hemosiderin in different organs:**

1) Micro nodular cirrhosis (all patients)
2) Liver---Hepatomegaly, Abdominal pain, cirrhosis and HCC 200* increased risk
3) Pancreas--- D.M (75 – 80%)
4) skin pigmentation (75-80%)
5) Myocardium---cardiomegaly
6) joints --- polyarthritis, pseudogout, synovitis
7) Pituitary gland--- hypogonadism, Testicular atrophy, amenorrhea
8) Adrenal gland
9) Thyroid and parathyroid gland
10) high serum ferritin

- symptoms appear 5th to 6th decade, not before 40
- M: F ratio is 5-7:1

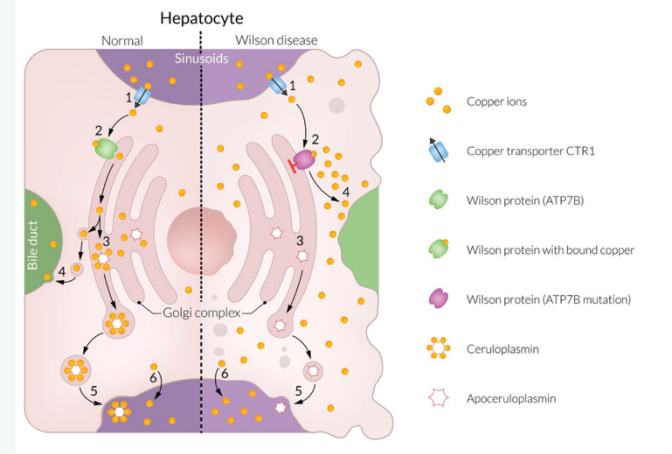


[Wilson disease]

➔**Definition**

- Autosomal Recessive disorder of Cu metabolism mutation **in ATP7B gene on chromosome 13,** which encodes an ATPase metal ion transporter in Golgi region
- > 80 mutations

➢ Gene frequency 1:200
➢ Incidence is 1:3000



Copper metabolism in normal hepatocyte and hepatocyte affected by Wilson disease

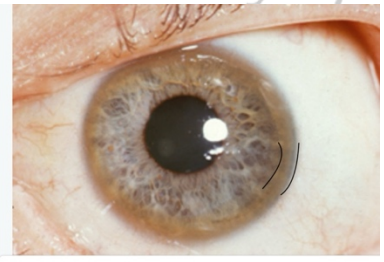
Left (physiologic):
(1) Copper ions are absorbed in the intestine and transported via the portal vein to the liver sinusoids, where they are taken up by the hepatocytes. (2) In the hepatocytes, copper ions enter the Golgi complex via the Wilson protein (ATP7B). (3) In the Golgi complex, the copper ions bind to apoceruloplasmin, thereby forming ceruloplasmin. (4) Excess copper is excreted into the bile via the Wilson protein. (5) Ceruloplasmin is secreted into plasma and spread throughout the body. (6) A small amount of unbound copper ions passes directly into the blood and is available as free serum copper.

Right (Wilson disease):
In Wilson disease, the Wilson protein is dysfunctional. Copper ions can neither be taken up by the Golgi complex (3) nor excreted into the bile (4). As a result, copper ions accumulate in the hepatocytes, which leads to hepatic damage. A large amount of excess, unbound copper ions passes directly into the bloodstream (6) raising the free serum copper concentration. This results in copper deposition in other organs.

➔ **Pathogenesis:**
Normally = Main source of Cu is from diet,
Absorption of ingested Cu (2-5 mg/d)
↓
Complex with albumin
↓
Hepatocellular uptake
↓
Incorporation with α-2-globulin to form Ceruloplasmin
↓
Secretion into plasma
(90 – 95% of plasma Cu)
↓
Hepatic uptake of ceruloplasmin
↓
Lysosomal degradation
↓
Secretion of free Cu into bile

➢ In Wilson disease absorbed Cu. Fails to enter the circulation in the form of ceruloplasmin & the biliary excretion of Cu. is ↓
➢ Defective function of ATP-7B →failure of Cu. excretion into bile & inhibits secretion of ceruloplasmin into the plasma →Cu. accumulation in liver
➢ ↑Cu. Accumulation in the liver results in:
1-Production of free radicals
2-Binding to sulfhydryl groups of cellular proteins
3-Displacement of other metals in hepatic Metalloenzymes
➢ By the age of 5yrs. Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands
➢ Urinary exc. Of cu. ↑

➔ **Morphology**:
➢ **Liver**:
1-Fatty change
2-Acute hepatitis
3-chronic hepatitis
4-cirrhosis
5-massive hepatic necrosis
➢ (rhodanine stain or orcein stain)
➢ **Brain**: Toxic injury to basal ganglia esp. the **putamen** causing atrophy & cavitation
➢ **Eye**:



Kayser-Fleischer ring

kayser- fleischer rings/ green – brown deposits of Cu. In descemet membrane in the limbus of the cornea (hepatolenticular degeneration)

➔ **Clinically:**

- Presentation > 6 yrs of age Most common presentation is acute on chronic hepatitis
- Neuropsychiatric presentation can occur

behavioral changes, Frank psychosis, Parkinson disease- like syndrome

➔ **Diagnosis:**

1- ↓ in serum ceruloplasmin level
2- ↑ in urinary exc. Of Cu.
3- ↑ hepatic content of copper
> 250 mg/gm dry wt

[α-1-Antitrypsin Deficiency]

➔**Overview**

- Autosomal recessive disorder
- Most common in North American White population
- Frequency: ~1 : 7000

➔**Normal Function**

- α-1 antitrypsin (A1AT) is a protease inhibitor
- It protects tissues from neutrophil enzymes such as:
  - Elastase
  - Cathepsin G
  - Proteinase 3
- These enzymes are released during inflammation and can damage tissues if not regulated

➔**Genetics**

- Gene: SERPINA1 (Pi gene system)
- Location: Chromosome 14
- 75 known genetic variants

➔**Common Genotypes**

- PiMM → normal genotype
  - Present in ~90% of individuals
  - Normal A1AT levels
- PiZZ → severe deficiency
  - Most clinically significant mutation
  - A1AT level: ~10–15% of normal
  - High risk of disease

➔**Clinical Significance (PiZZ)**

- Markedly reduced α-1 antitrypsin in blood → uncontrolled neutrophil elastase activity
- Leads to tissue damage (classically lungs and liver)

➔ **Pathogenesis:**

- The mutant polypeptide (PiZ) is abnormally

folded & polymerizes **causing its retention in the ER of hepatocytes**

- Although all individual with Pizz genotype

accumulate α-1-AT-Z protein only 10% of them develop clinical liver disease

- This is due to lags in ER protein degradation pathway
- The accumulated α-1-AT-Z is not toxic but

the autophagocytic response stimulated within the hepatocytes appear to be the cause of liver injury by autophagocytosis of the mitochondria

- 8-10% of patients develop significant liver

damage

➔ **Morphology:**

- Intracytoplasmic globular inclusions in hepatocytes, which are acidophilic in H&E. sections
- The inclusions are PAS-+ve & diastase resistant
- Neonatal hepatitis cholestasis & fibrosis
- Chronic hepatitis
- Cirrhosis
- Fatty change
- Mallory bodies

➔ **Clinical features:**

- Neonatal hepatitis with cholestatic
- jaundice appears in 10–20% of newborns with the disease
- Attacks of hepatitis in adolescence
- Chronic hepatitis & cirrhosis
- HCC in 2- 3 % of Pizz adults + cirrhosis

[Reye syndrome]

➔**Definition**

- Acute condition characterized by:
  - Hepatic dysfunction (fatty liver change)
  - Encephalopathy

➔**Epidemiology**

- Typically affects children < 4 years old

➔**Etiology / Association**

- Occurs 3–5 days after a viral illness (commonly influenza or varicella)
- Strongly associated with aspirin use in children

➔**Pathophysiology**

- Mitochondrial dysfunction → impaired fatty acid metabolism
- Leads to:
  - Microvesicular fatty infiltration of the liver
  - Hyperammonemia → cerebral edema → encephalopathy

➔**Clinical Features**

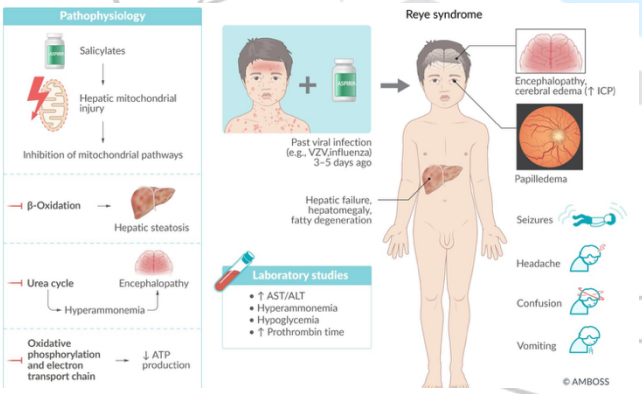
- Early:
  - Persistent vomiting
  - Lethargy
- Progressive:
  - Altered mental status
  - Irritability → confusion → coma
- Severe:
  - About 25% progress to coma

➔**Laboratory Findings**

- ↑ Liver enzymes (AST, ALT)
- Normal or mildly elevated bilirubin
- ↑ Ammonia
- Hypoglycemia

➔ **Pathogenesis:**

- Derangement of mitochondrial function along or in combination with viral infection & salicylate
- Micro vesicular steatosis
- Brain edema
- Absent inflammation
- Sk. Muscles, heart, kidneys – fatty change



[Budd-chiari syndrome]

➔**Definition**

- Thrombotic occlusion of hepatic veins → impaired hepatic venous outflow

➔**Clinical Features**

- Hepatomegaly
- Ascites
- Abdominal pain
- Weight gain (due to fluid retention**)**

Causes (Hypercoagulable States & Obstruction):

Hypercoagulable states

- Polycythemia vera (PCV)
- Pregnancy
- Postpartum state
- Oral contraceptive pills (OCPs)
- Paroxysmal nocturnal hemoglobinuria (PNH)

Other causes

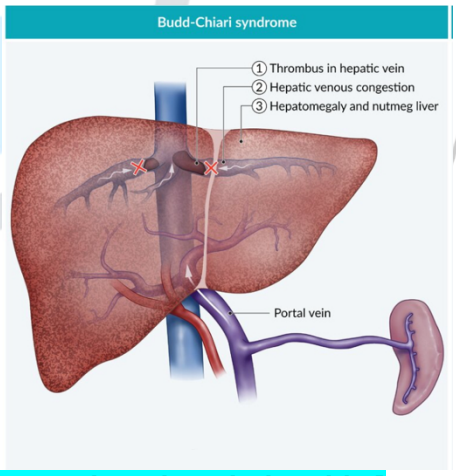
- Mechanical obstruction
- Tumors (e.g., hepatocellular carcinoma – HCC)
- Idiopathic (~30%)

➔**Morphology (Pathology)**

- Enlarged, swollen liver
- Red, congested appearance with tense capsule
- Centrilobular congestion & necrosis
- Fibrosis (chronic cases)
- Hepatic vein thrombosis

➔**Prognosis**

- High mortality if untreated



[primary sclerosing cholangitis]

➔**Definition**

- Chronic cholestatic liver disease characterized by:
  - Inflammation
  - Obliterative fibrosis
  - Segmental strictures with dilation (“beading”)
- Affects both:
  - Intrahepatic bile ducts
  - Extrahepatic bile ducts

➔**Epidemiology**

- Age: 3rd–5th decades
- Sex: Male > Female (2:1)

➔**Associations**

- Strong association with ulcerative colitis (UC):
  - ~70% of PSC patients have UC
  - ~4% of UC patients develop PSC

➔**Laboratory Findings**

- ↑ Alkaline phosphatase (ALP) (persistent, hallmark)
- Mild ↑ AST/ALT
- p-ANCA (atypical ANCA): positive in ~80%
- Anti-mitochondrial antibodies (AMA): usually negative (<10%)
  ➔ Helps distinguish from Primary Biliary Cholangitis (PBC)

➔**Clinical Features**

- Often asymptomatic early
- When symptomatic:
  - Fatigue
  - Pruritus (itching)
  - Jaundice
  - Weight loss

➔**Advanced Disease**

- Portal hypertension complications:
  - Ascites
  - Variceal bleeding
  - Hepatic encephalopathy

➔**Complications**

- Cholangiocarcinoma
- Cirrhosis → liver failure
- Fat-soluble vitamin deficiencies (A, D, E, K)

➔ **Morphology:**

- Concentric periductal onion-skin fibrosis & lymphocytic infiltrate
- Atrophy & obliteration of bile ducts
- Dilation of bile ducts in between areas of stricture
- Cholestasis & fibrosis
- Cirrhosis, cholangiocarcinoma (10 – 15%)

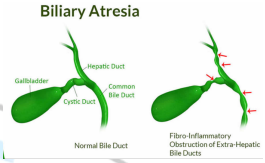
➔ **Pathogenesis:**

- Exposure to gut derived toxins
- Immune attack
- Ischemia of biliary tree

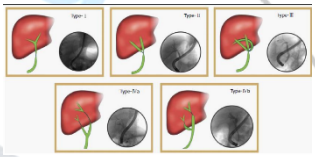
➔**Secondary biliary cirrhosis: Prolonged obstruction to extra hepatic biliary tree.**

Causes:

1. cholelithiasis
2. biliary atresia(Congenital absence or obliteration of extrahepatic bile ducts)



3. malignancies
4. Strictures(Acquired narrowing of bile ducts)



[primary biliary cirrhosis]

➔**Definition**

- Chronic, progressive cholestatic liver disease
- Autoimmune-mediated destruction of intrahepatic bile ducts
- Leads to fibrosis → cirrhosis → liver failure

➔**Pathophysiology**

- Non-suppurative granulomatous destruction of medium-sized intrahepatic bile ducts
- Portal tract inflammation → fibrosis → cirrhosis (over years–decades)

➔**Epidemiology**

- Age: 20–80 years (peak: 40–50 years)
- Sex: Female > Male

➔**Clinical Features**

- Insidious onset
- Early:
  - Pruritus (often first symptom)
  - Fatigue (very common, high-yield)
- Late:
  - Jaundice
  - Hepatomegaly
  - Signs of cirrhosis & portal hypertension

➔**Laboratory Findings**

- ↑ Alkaline phosphatase (ALP) (most important early marker)
- ↑ Cholesterol

- Mild ↑ AST/ALT
- Hyperbilirubinemia → indicates advanced disease / hepatic decompensation

➔Serology

- Anti-mitochondrial antibodies (AMA) → >90% sensitive (KEY diagnostic marker)

➔Associated Diseases (Autoimmune)

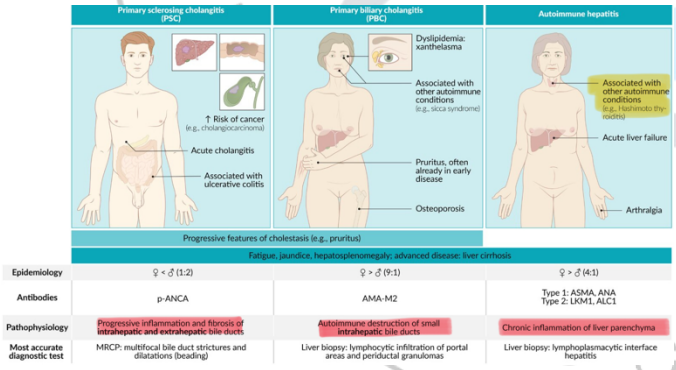
- Sjögren syndrome
- Systemic sclerosis
- Hashimoto thyroiditis
- Rheumatoid arthritis
- Raynaud phenomenon
- Membranous glomerulonephritis
- Celiac disease

➔Disease Course

- Slowly progressive
- Cirrhosis develops over ≥ 20 years

➔ Morphology:

- interlobular bile ducts are absent or severely destructed (florid duct lesion)
- intra epithelial inflammation
- Granulomatous inflammation
- Bile ductular proliferation
- Cholestasis
- Necrosis of parenchyma
- Cirrhosis



[Sinusoidal Obstruction Syndrome, Veno-occlusive disease]

➔Definition

- Hepatic condition caused by toxic injury to sinusoidal endothelial cells → obstruction of hepatic blood flow

➔Epidemiology / Risk Factors

- Classically described in Jamaican bush-tea drinkers (pyrrolizidine alkaloids)
- Most commonly occurs:
  - 20–30 days after bone marrow transplantation
- Causes:
  - Chemotherapy (e.g., cyclophosphamide)
  - Total body irradiation
- Incidence:
  - ~20% in allogeneic bone marrow transplant recipients

➔Clinical presentation:

- Mild – severe
- Death if does not resolve in 3 months

➔Mechanism:

Toxic injury to sinusoidal endothelium →emboli →blockage of bile Flow, Passage of blood into space of Disse →↑stellate cells → fibrosis

[peliosis hepatis]

➔Definition

- Rare condition characterized by blood-filled cystic spaces in the liver (sinusoidal dilation)

➔Etiology / Associations

- Anabolic steroids
- Oral contraceptives
- Danazol

➔Pathogenesis

- Unknown

➔Clinical Features

- Often asymptomatic
- Can present with:
  - Intra-abdominal hemorrhage (life-threatening),
  - Liver failure

[Liver tumor]

➔**General Concept**

- Metastatic tumors → Most common liver malignancy overall

➔**Benign Liver Tumors**

1) Cavernous Hemangioma

- Most common benign liver tumor
- Usually:
  - < 2 cm
  - Subcapsular
- Often asymptomatic and found incidentally

2) Hepatocellular Adenoma (Liver Cell Adenoma)

- Typical patient:
  - Young female
  - History of oral contraceptive use
- Key features:
  - Risk of rupture → intraperitoneal hemorrhage (↑ during pregnancy)
  - May mimic HCC on imaging
  - Rarely may contain or transform into HCC

➔**Liver Nodules**

1) Focal Nodular Hyperplasia (FNH)

- Pathology:
  - Well-demarcated hyperplastic hepatocytes
  - Central stellate scar
- Occurs in:
  - Non-cirrhotic liver
  - Females (reproductive age)
- Key concepts:
  - Not a true neoplasm → reactive hyperplasia
  - Caused by localized vascular abnormality
  - No malignant potential
  - ~20% associated with cavernous hemangioma

2) Macroregenerative Nodules

- Occur in:
  - Cirrhotic liver
- Features:
  - Larger than typical cirrhotic nodules
  - No atypia
  - Reticulin framework intact
- Clinical significance:
  - No malignant potential

3) Dysplastic Nodules

- Occur in:
  - Cirrhotic liver
- Size:
  - Typically > 1 mm
- Histology:
  - Cellular atypia
  - Pleomorphism & crowding
  - Increased proliferative activity
- Types:
  - Low-grade dysplasia
  - High-grade dysplasia
  - Subtypes:
    - Small-cell dysplastic nodules
    - Large-cell dysplastic nodules
- Key concept:
  - Premalignant (precursor to HCC)
  - Associated with monoclonality + genetic mutations

Hepatocellular carcinoma

➔**Epidemiology**

- Accounts for:
  - ~5.4% of all cancers
- Incidence:
  - Low (<5/100,000):
    - North & South America
    - Northern & Central Europe
    - Australia
  - Intermediate (~15/100,000):
    - Mediterranean regions
  - High (~36/100,000):
    - East Asia (Korea, Taiwan, China)
    - Africa (e.g., Mozambique)

➔**Demographics**

- More common in Black populations
- Male predominance

➔ **Predisposing factors:**

1) Hepatitis carrier state:
   - ➢ vertical transmission increases the risk 200X
   - ➢ cirrhosis may be absent
   - ➢ young age group (20-40yr)

2) >85% of cases of HCC occur in countries with high rates of chronic HBV infection

3) Cirrhosis

- In western countries cirrhosis is present in 85-90% of cases
- >60yr
- HCV & alcoholism

4) Aflatoxins
5) Hereditary tyrosinemia (in 40% of cases)
6) Hereditary hemochromatosis

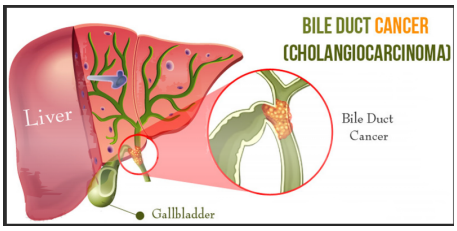
➔ Pathogenesis:

1) Repeated cycles of cell death & regeneration HBC, HCV, gene mutations, Genomic instability
2) Viral integration: HBV DNA integration which leads to clonal expansion
3) HBV DNA integration which leads to genomic instability not limited to integration site.
4) HBV, X-protein which leads to transactivation of viral & cellular promoters, Activation of oncogenes, Inhibition of apoptosis
5) Aflatoxins (fungus Aspergillus flavus), mutation of p53
6) Cirrhosis caused by: HCV, Alcohol, Hemochromatosis, Tyrosinemia (40% of pts. Develop HCC, despite adequate dietary control

➔ Morphology of primary liver cancer:

1) Hepatocellular carcinoma
   - Can be: Unofficial, Multifocal, diffusely infiltrative
   - Hepatocellular carcinoma can metastasize through vascular route to lungs, bones, adrenals, brain.

2) Cholangiocarcinoma
   - About 50% of patients with cholangiocarcinoma develop metastasis.
   - Cholangiocarcinoma is desmoplastic (refers to a fibrotic (scar-like) stromal reaction that occurs around a tumor.)



3) Mixed

4) Fibrolamellar carcinoma
   - It is considered a special subtype of Hepatocellular carcinoma
   - 20-40 yr
   - M=F
   - No relation to HBV or cirrhosis
   - better prognosis
   - single hard scirrhous tumor
   - Vascular invasion is common in all types.

➔Clinical presentation:

1) Abdominal pain
2) Malaise
3) Weigh loss
   - increase α-feto protein in 60 – 75% of pts.
   - α-feto protein increases also with: yolk sac tumor, cirrhosis, massive liver necrosis, chronic hepatitis, normal pregnancy, fetal distress or death, fetal neural tube defect

➔Prognosis:

- Death within 7 -10 months
- Causes:
  1. Cachexia
  2. GI bleeding
  3. Liver failure
  4. Tumor rupture and hemorrhage

The University of Jordan Gastroenterology Interest Group (UJ-GIG) Booklet

Pathology

Gallbladder Disorders

Written by: Mohammad Talal Harahsheh

Edited by: Momen alfawadleh

Reviewed by: Ahmad Al-Laham

Disorders of the Gallbladder:

1) **Cholelithiasis**
2) **Cholecystitis**
3) **Tumors**

[Cholelithiasis]

➔ **Definition:** formation of stones in the gallbladder (thus called gallstones)

- 80% are asymptomatic, so mostly they are silent, because stones don't cause problems unless they obstruct something.

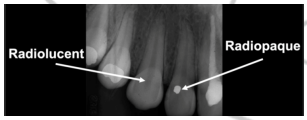
- **Pain comes from:** gallbladder ductal obstruction ➔ Increased pressure ➔ Inflammation (If none of these happen → patient feels completely normal)

[Types of Gallstones and Their pathogenesis]

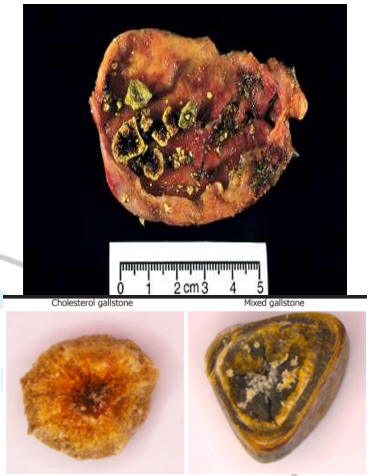
➔ **Two main types of gallstones:**

1. Cholesterol Stones

- Account for ~80% of gallstones in Western countries
- **How do they form:**
  - When bile becomes supersaturated with cholesterol, often due to:
    - ➢ Increased cholesterol secretion
    - ➢ Decreased bile salts
    - ➢ Impaired gallbladder motility
- **Their appearance:**
  - **Location:** Found almost exclusively in the gallbladder
  - **Number:** May be single or multiple
  - **Shape:** Often multi-faceted (They press against each other over time This pressure flattens their sides, creating edges and flat faces)



- **Radiology:**
  - Usually radiolucent (not visible on X-ray)
  - Up to 20% may appear radio-opaque(visible on X-ray) due to calcium content
- **Color & composition:**
  - Pure stones: pale yellow (mostly cholesterol)
  - Mixed stones: gray-white to black
    - ➢ Contain calcium carbonate, phosphates, and bilirubin



2. Pigment Stones

- Composed mainly of insoluble calcium bilirubinate
- **How do they form:**
  - due to excess unconjugated bilirubin in bile
- **Color & composition:**
  - Black pigment stones → associated with:
    - ➢ Chronic hemolysis (e.g., sickle cell disease)

  - Brown pigment stones → associated with:
    - ➢ Biliary infection and stasis
    - ➢ Contain calcium salts of unconjugated bilirubin (calcium bilirubinate), mucin glycoproteins & cholesterol.
- **Their Appearance:**
  - **Location**: Anywhere in biliary tree (Gallbladder, intrahepatic or extrahepatic bile ducts)

Risk Factors of Cholelithiasis

- **General Overview**
  - Very common condition in adults
  - Prevalence increases with age
  - In many patients, no clearly identifiable modifiable risk factor

- **Most Important Non-Modifiable Risk Factors**
  - Age
  - Female sex
    - ➢ related to hormonal effects on bile composition and gallbladder motility

Risk Factors for Cholesterol Stones:

1. **Age: elderly > young adults**
   → Cholesterol secretion increases and gallbladder motility decreases with age.
2. **Gender: females (2:1)**
   → Estrogen increases cholesterol in bile and progesterone slows gallbladder emptying.
3. **Oral contraceptives (OCPs), pregnancy**
   → Estrogen ↑ cholesterol secretion; progesterone ↓ gallbladder contraction → stasis.
4. **Demography: Western world**
   → High-fat diet leads to cholesterol-rich bile.
5. **Gallbladder stasis**
   → Poor emptying allows cholesterol crystals to form and stay in gallbladder.
6. **Family history**
   → Genetic tendency for altered bile composition and cholesterol handling.
7. **Inborn disorders of bile acid metabolism**
   → ↓ bile acids → cholesterol becomes insoluble → stone formation.
8. Obesity
   → ↑ cholesterol production and secretion into bile.
9. **Hyperlipidemia**
   → Excess circulating lipids increase bile cholesterol saturation.
10. **Rapid weight loss**
    → Fat breakdown releases large amounts of cholesterol into bile.
11. **Treatment with hypocholesterolemic drugs**
    → Some drugs (e.g., fibrates) increase cholesterol saturation in bile.

Risk Factors for Pigment Stones:

➔Demography:

- Asians, rural areas
  → Higher rates of biliary infections and parasitic exposure → ↑ pigment stone formation.

➔Chronic hemolytic syndromes

- → ↑ breakdown of RBCs → ↑ unconjugated bilirubin → calcium bilirubinate stones.

➔Biliary infection

- → Bacteria produce enzymes that deconjugate bilirubin → stone formation.

➔Gastrointestinal disorders (general)

- Disrupted bile salt circulation → altered bile composition → stone formation.

➔Specific GI conditions:

- Ileal disease (e.g., Crohn's disease)
  - ↓ bile acid reabsorption → less bile salts → more insoluble bilirubin precipitates.
- Ileal resection or bypass
  - Same mechanism: loss of bile acid recycling → altered bile composition.
- Cystic fibrosis with pancreatic insufficiency
  - Thick secretions + infection risk → biliary stasis and altered bile → pigment stones.

Clinical Features of Cholelithiasis

Clinical Presentation

➔70–80% are asymptomatic

- Because as we said before as long as there is no obstruction there will be no symptoms

➔**Biliary pain (biliary colic)**

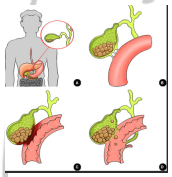
- Occurs when a stone temporarily obstructs the cystic duct or biliary tree
  - Pain is usually constant or colicky
  - Location: right upper quadrant or epigastrium
  - May radiate to back or right shoulder

➔**May be associated with inflammation of the gallbladder**

- Persistent obstruction can lead to cholecystitis

Complications:

1) **Empyema:**
   Pus-filled gallbladder due to infection
2) **Perforation**
3) **Fistulae**(abnormal connection (fistula) between structures usually with the bowel)



4) **Inflammation of biliary tree (cholangitis)**
5) **Obstructive cholestasis (jaundice**) ((Bile cannot drain → bilirubin builds up in blood → jaundice))
6) **Pancreatitis**
7) **Intestinal obstruction ("gallstone ileus")** (Large stone erodes into bowel and causes mechanical blockage)

[Cholecystitis]

➔ **Definition:**
→ Inflammation of the gallbladder
It can be:

- Acute
- Chronic
- Acute inflammation occurring on top of chronic disease

➔ **Pathophysiology** (Why it happens):

- Caused mainly by gallbladder obstruction, leading to:
  - Bile stasis
  - Chemical irritation from trapped bile
  - Ischemia (reduced blood flow due to distension)

➔**Association:**

- Most cases are associated with gallstones (calculous cholecystitis)
- Rarely occurs without stones (acalculous cholecystitis)
  → usually in critically ill patients

➔**Clinical importance:**

- One of the most common causes of acute abdomen(A sudden onset of severe abdominal pain that may indicate a serious, potentially life-threatening intra-abdominal condition and often requires urgent evaluation or surgery.)
- One of the most common indications for emergency abdominal surgery
  → especially acute calculous cholecystitis

➔**Epidemiology:**

- Follows the same pattern as gallstones
  → more common where Cholelithiasis is prevalent

Classification

1. Acute calculous cholecystitis
   → Stone blocks cystic duct → acute inflammation (most common)
2. Acute acalculous cholecystitis
   → No stone; occurs in severely ill patients (e.g., ICU, trauma, sepsis)
3. Chronic cholecystitis
   → Long-term inflammation from repeated irritation → fibrosis and thickened wall
4. Acute on chronic cholecystitis
   → Acute flare occurring in a chronically inflamed gallbladder

Pathology of acute cholecystitis

➔ Gross appearance of gallbladder
→ Gallbladder is:
- Enlarged (2–3× normal) and tense
- Wall shows hyperemia and edema
- May appear bright red or violaceous
  → due to vascular congestion and subserosal hemorrhage

➔Wall changes
- Thickened, edematous, hyperemic wall
  → reflects acute inflammation + increased vascular permeability

➔Exudate on serosa
- Fibrinous or suppurative exudate on outer surface
  → indicates severe inflammatory response (serositis)

➔Lumen contents
- Turbid bile ± fibrin, blood, or pus
  → represents progression from:
  - sterile inflammation → infection

➔ Gallstones (most cases)
- ~90% have obstruction of cystic duct or gallbladder neck
  → primary initiating event in calculous disease

➔Severe complications (advanced disease)
- Empyema
  → gallbladder filled with pus (suppurative infection)
- Gangrenous cholecystitis
  → black, necrotic gallbladder due to ischemia and tissue death

➔Histology

- Edema
- WBC infiltration
- Congestion
- Abscess formation
- Hemorrhage
- Necrosis

1) Acute Calculous Cholecystitis

➔Definition
- Acute inflammation of the gallbladder caused by stone obstruction of the cystic duct or gallbladder neck
- Accounts for ~90% of acute cholecystitis cases

➔Pathogenesis
- Step 1: Obstruction
  - → Gallstone blocks cystic duct/GB neck
    → Leads to bile trapping (stasis)
    → Rapid onset of symptoms
- Step 2: Chemical injury
  - Stagnant bile causes mucosal damage:
  - Phospholipases convert lecithin → lysolecithin (toxic)
  - Loss of protective mucous layer
    → bile salts directly injure epithelium
- Step 3: Increased pressure → ischemia
  - → Gallbladder distension increases intraluminal pressure
    → ↓ mucosal blood flow
    → ischemia + inflammation

➔Clinical behavior
- Pain can be:
  - mild
  - sudden
  - severe
- Some cases resolve spontaneously
- Others progress quickly to complications

➔Infection status
- Initially sterile inflammation (non-infectious)
  → Bacterial infection may occur later (secondary superinfection)

➔Clinical importance
- Most common indication for emergency cholecystectomy
  → Because of risk of:
  - Perforation
  - Sepsis
  - Peritonitis

2)Acute Acalculous Cholecystitis

➔**Definition:**

- Acute inflammation of the gallbladder without gallstones

➔**Epidemiology**

- Accounts for ~5–12% of acute cholecystitis cases
- Occurs mainly in critically ill or hospitalized patients

➔**Clinical Settings**

- Common in conditions of severe physiological stress:
  - Post-operative state
  - Severe trauma
  - Sepsis
  - Major burns
  - Postpartum period(after giving birth period)

➔**Pathophysiology:**

- Triggered by gallbladder dysfunction + ischemia rather than stones

➔**Risk Factors / Mechanisms:**

1. Dehydration
   → concentrates bile → sludge formation
2. Gallbladder stasis (↓ motility)
   → bile retention → inflammation
3. Vascular compromise
   → reduced blood flow → ischemia → wall injury
4. Secondary bacterial infection
   → may occur later and worsen inflammation

3)Chronic cholecystitis

➔**Definition**:

- Long-standing inflammation of the gallbladder
  → May occur after repeated acute attacks OR without prior acute episodes

➔**Etiology / Pathogenesis**

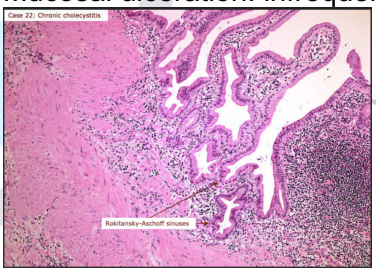
- Gallstones are present in most cases
- However, the main driver is:
  - chronic bile supersaturation and chemical irritation, not just obstruction

➔**Morphologic Appearance (Gross)**

- Most common pattern: CONTRACTED gallbladder
  - Small, fibrotic gallbladder Due to long-term inflammation and scarring
- Wall thickening
  - Due to fibrosis + chronic inflammatory remodeling
- Mucosal changes
  - Mucosal ulceration (less common) Irregular, damaged mucosa from chronic irritation
- Enlargement (less common)
  - Occurs if there is distension or fluid accumulation

➔**Histology (MICROSCOPY)**

- Chronic inflammatory infiltrate (mainly lymphocytes)
  - sometimes the only sign of disease
- Fibrosis of submucosa and subserosa
  - explains wall thickening and contraction
- Rokitansky–Aschoff sinuses
  → mucosal outpouchings extending into the wall (classic feature)
- Mucosal ulceration: infrequent



4)Acute on top of Chronic

➔**Definition**

- Acute on chronic cholecystitis is an acute inflammatory exacerbation occurring on a background of chronic gallbladder inflammation, usually due to gallstones, leading to sudden worsening of symptoms.

➔**Clinical Features**

- Pain pattern
  - Range: mild discomfort → severe RUQ pain
  - May resemble biliary colic
  - Pain typically lasts > 6 hours in acute exacerbations

- Severe RUQ pain may radiate to:
  - Right shoulder
  - Back
- Associated with tenderness and guarding

- Systemic symptoms
  - Fever
  - Nausea / vomiting
  - Leukocytosis
    → indicates systemic inflammatory response

- Possible laboratory finding
  - Conjugated hyperbilirubinemia
    → suggests possible common bile duct obstruction

➔Diagnosis

- Ultrasonography (first-line investigation)
  Findings:
  - Gallstones
  - Gallbladder wall thickening
  - Pericholecystic fluid

➔Complications

- Biliary / infectious complications
  - Cholangitis
  - Sepsis

- Gallbladder complications
  - Gallbladder perforation
  - Abscess formation
  - Rupture
  - Enteric fistula

- Intestinal complication
  - Gallstone ileus
    → intestinal obstruction due to migrated gallstone

- Severe systemic complications
  - Diffuse peritonitis
  - Multi-organ decompensation:
    - Cardiac
    - Pulmonary
    - Renal
    - Hepatic
      (especially in elderly or critically ill patients)

[Tumors of the Gallbladder]

➔Definition & Importance

- Most common malignant tumor of the extrahepatic biliary tract
  - Often discovered incidentally during gallbladder surgery for stones

➔Epidemiology

- More common in females
- Peak incidence: 7th decade (elderly)
- Incidence increases with age

➔Major Risk Factors

→ Strongly linked to chronic irritation:

- Gallstones (~95% of cases)
  → most important risk factor
- Chronic inflammation → epithelial damage → dysplasia → carcinoma
- Possible contribution of bile acid metabolites (carcinogenic effects)
- Primary sclerosing cholangitis (PSC) also increases risk

➔Pathogenesis

- Repeated injury from:
  - Stones
  - Chronic inflammation
- leads to:
  - Mucosal dysplasia
  - Malignant transformation

➔Morphology

Growth patterns:

- Infiltrative type (most common)
  → diffuse wall thickening + deep invasion into surrounding tissues
- Fungating (exophytic) type
  → mass grows into lumen (cauliflower-like) + invades wall

➔Histology

- Most are adenocarcinomas (from glandular epithelium)
- Rare variants:
  - Squamous carcinoma
  - Adenosquamous carcinoma

➔Clinical Presentation

→ Often nonspecific and similar to gallstone disease:

- RUQ pain
- Nausea, vomiting
- Anorexia
- Fat intolerance

→ Jaundice appears if bile duct obstruction occurs

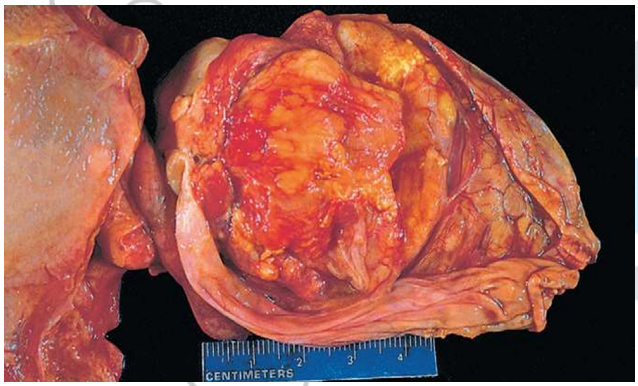
This leads to delayed diagnosis

➔Diagnosis & Timing

- If obstruction occurs early → may be detected earlier via imaging
- However:
    - <20% diagnosed preoperatively
    - ~10% are resectable at diagnosis(resectable means that surgery would lead to resolution of the disease why 10% , because the tumor will already have been metastasized so surgery won't lead to resolution of the disease)

➔Prognosis

- Very poor overall
- 5-year survival: ~5–12%
  → due to late presentation, invasion, and metastasis



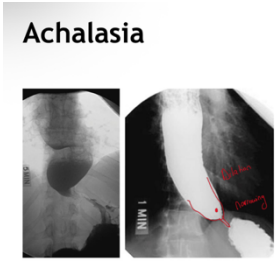
The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pathology

Pathology LAB

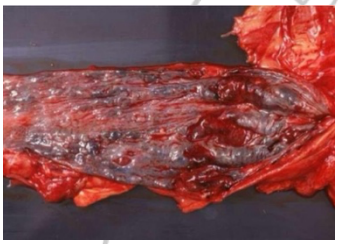
Written by: Mohammad Talal Harahsheh

Achalasia



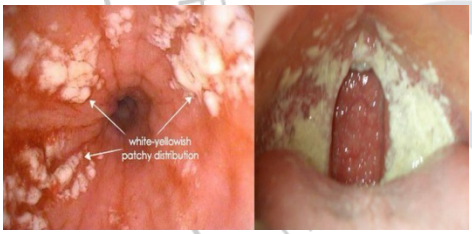
Barium Swallows Test ➔ The esophagus appears dilated at the top and constricted at the LES, so it appears as Bird beak منقار الطائر

Esophageal varices



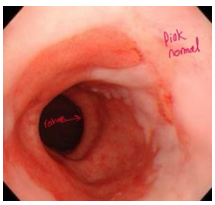
Tortuous Dilated submucosal veins (blackish vessels) engorged with blood in the distal esophagus

Esophageal candidiasis

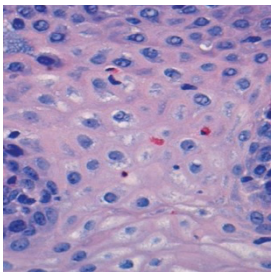


Fungal Infectious Esophagitis
o Adherent
o Gray-white pseudo membranes
o Composed of matted fungal hyphae and inflammatory cells

Reflux esophagitis – GERD

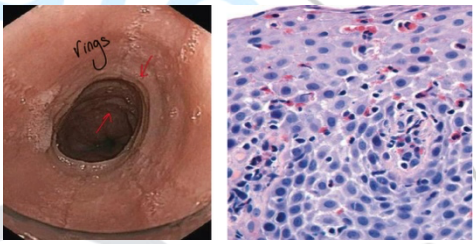


Erythema of the lower esophagus (Normally its pink)



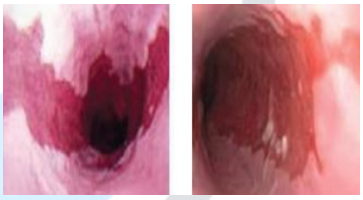
Eosinophils infiltration of the squamous epithelium (Earliest Manifestation)

Eosinophilic Esophagitis - eosinophilic Rings



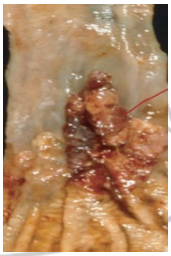
o Rings in the upper and middle esophagus.
o Numerous eosinophils in the epithelium (more than GERD)
o Far from the GEJ

Tongues in Barrett esophagus (precancerous)

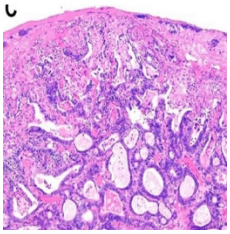


Red tongues extending upward from the GEJ

Esophageal adenocarcinoma

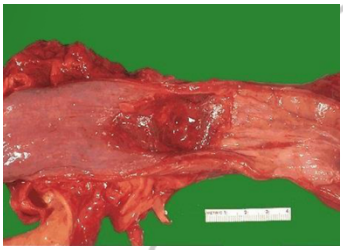


occur in the distal third of the esophagus (GEJ)
Early: flat or raised patches•
Later: exophytic infiltrative masses



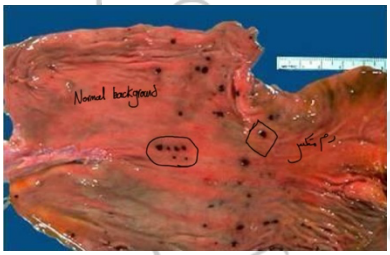
o formation of glandular structures
o production of mucin

Esophageal Squamous Cell Carcinoma Mid esophagus



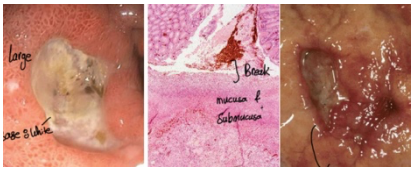
o arises in the middle third of the esophagus
o Polypoid, ulcerated
o Infiltrative wall thickening & luminal narrowing
o Invade surrounding structures
(bronchi, mediastinum, pericardium, aorta)

Stress gastric ulcers



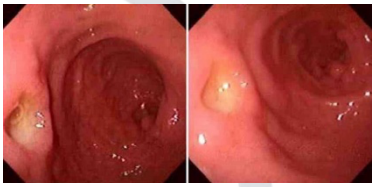
- Spectrum (Shallow to deep).
- Acute ulcers are :
o Rounded < 1 cm
o base brown to black
o Multiple, anywhere in stomach
o Normal adjacent mucosa
o No scarring,acute not chronic
o Healing with complete epithelial action occurs days or weeks after removal of injurious factors

Chronic gastric ulcers– Peptic Ulcer



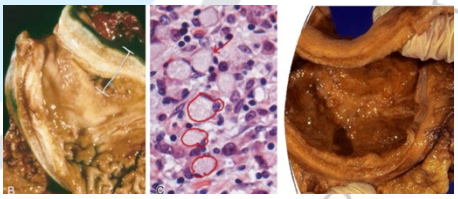
- usually in the antrum
o Single = Solitary = isolated alone
o large ulcer
o Round to Oval
o Sharply punched-out
o well demarcated
o Base of ulcer : smooth & clean
o Background whitish or pinkish (healing by granulation)
o Hyperemia & Redness in the surrounding stomach

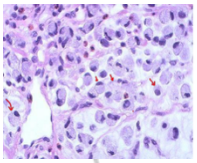
Duodenal ulcer, in the Anterior wall



o Area of ulceration is prominent

Gastric adenocarcinoma - Diffuse type (linitis plastica)

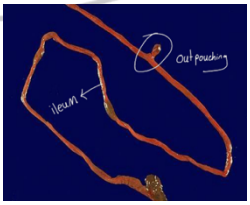




Diffuse type signet Ring cells

large mucin vacuoles that expand the cytoplasm & push the nucleus to the periphery

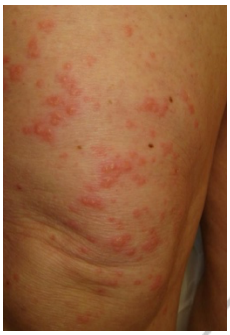
Meckel's diverticulum



True diverticulum from incomplete vitelline duct (omphalomesenteric) closure– includes all layers."

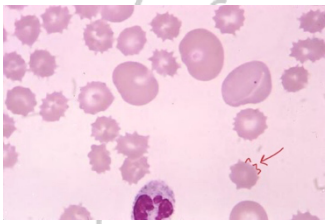
o 2% of people
o 2 inches long
o 2 feet distance from ileocecal valve
o 2 heterotrophic tissue (Gastric, Pancreatic)
o Most common cause of lower GI bleeding before age 2

Dermatitis herpetiformis with Celiac disease



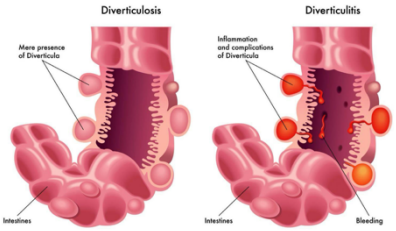
Vesicular lesions

Abetalipoproteinemia

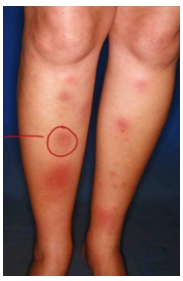


o Spur cells in peripheral blood

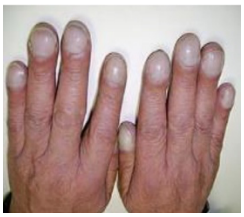
Diverticulosis



CIBD - Crohn disease & Ulcerative colitis Extra intestinal Manifestation

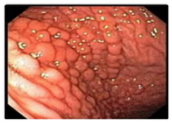


Erythema nodosum

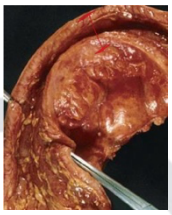


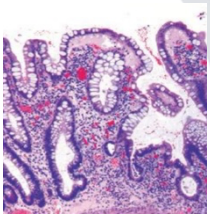
Clubbing

CIBD - Crohn disease

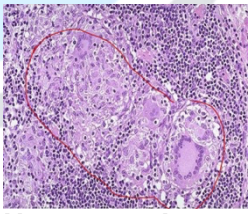


Cobblestone appearance



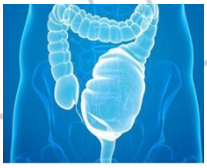


Haphazardly arranged crypts

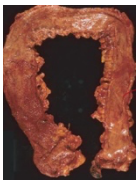


Non-caseating granuloma

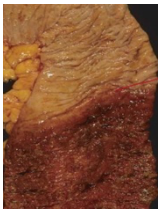
CIBD - Ulcerative colitis - Toxic megacolon



Thin wall maybe rupture & dilates because of infection and cause toxic megacolon
(massive distention of the transverse colon)

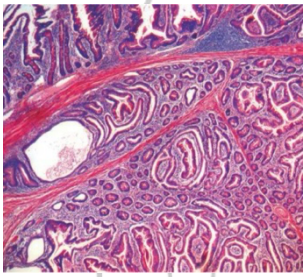


Pancolitis

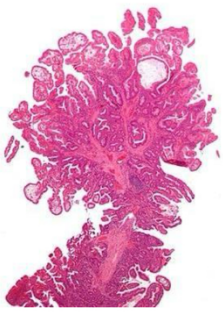


Abrupt transition b/w normal and disease segment

Non-neoplastic - Hamartomatous polyp
Peutz Jeghers polyp

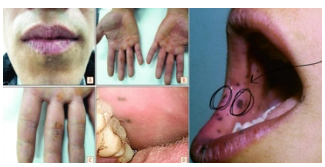


- Large, pedunculated, lobulated.
- Arborizing network of CT, smooth muscle, lamina propria, glands.
- Normal appearing intestinal epithelium



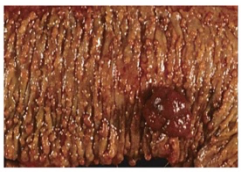
Christmas tree pattern

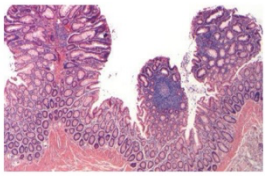
Non-neoplastic - Hamartomatous polyp
Peutz Jeghers polyp



Mucocutaneous Pigmentation

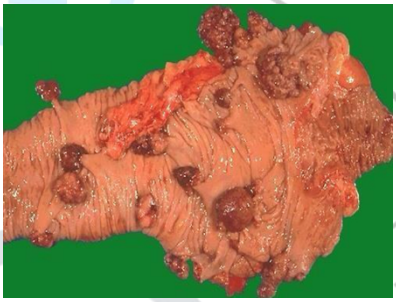
Familial adenomatous polyposis FAP





o At least 100 polyps are necessary for a diagnosis of classic FAP

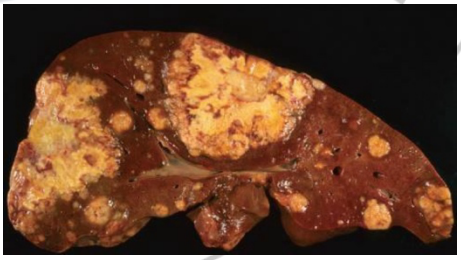
Hereditary Nonpolyposis Colorectal Cancer = HNPCC = Lynch syndrome



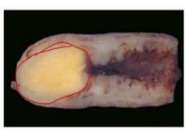
Cecal polyps in HNPCC

Exophytic adenocarcinoma, colon

Liver metastasis from colon cancer

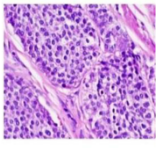


Carcinoid / neuroendocrine tumor



Gross

- Distal tip of the appendix



Microscopic

- Nest pattern Salt and pepper nuclei