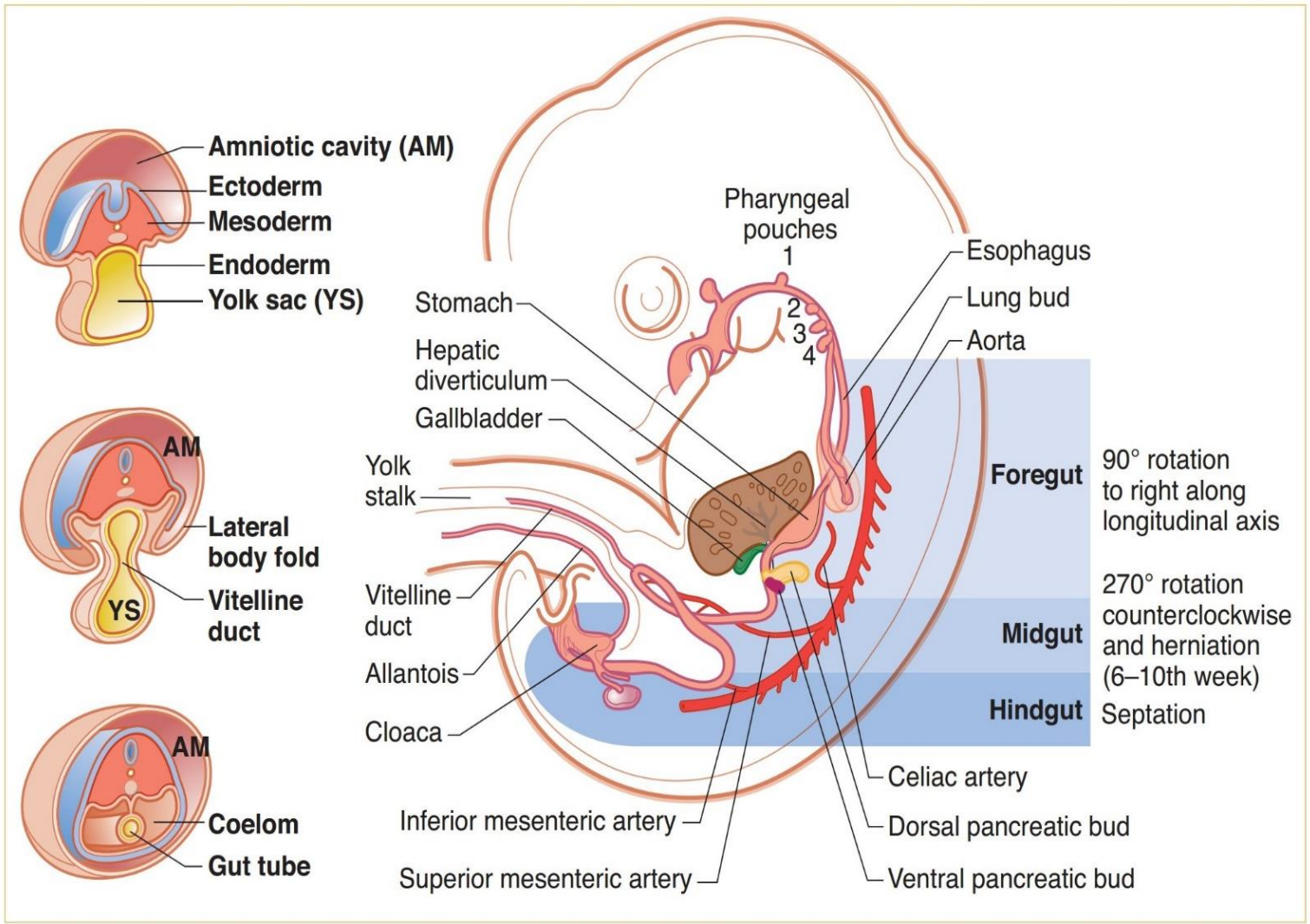
CHAPTER 1

Embryology

Primitive Gut Tube

- The primitive gut tube is divided into the foregut, midgut, and hindgut, each supplied by a specific artery and autonomic nerves:

- Foregut: pharynx to duodenum.
- Midgut: duodenum to proximal 2/3 of transverse colon.
- Hindgut: distal 1/3 of transverse colon to anal canal above pectinate line.



Development of Gastrointestinal Tract

Development and Rotation of Midgut

- Lateral and cephalic flexion of an embryo results in formation of the primitive gut tube, a precursor of the GI tract.

- It divides into foregut, midgut, and hindgut.

- The blood supply of the adult intestine reflects its embryologic source:

A. The foregut gives rise to the esophagus, stomach, liver, gallbladder, pancreas, and upper duodenum. These organs are supplied by the celiac trunk.

B. The midgut give rise to lower duodenum, small intestine, ascending colon, and proximal 2/3 of the transverse colon. These organs are supplied by the superior mesenteric artery (SMA).

C. The hindgut give rise to the distal third of the transverse colon, descending, and sigmoid colon. These organs are supplied by the inferior mesenteric artery (IMA).

- The midgut herniates through the umbilical ring at the 6th week of embryonic development to allow the rapid growth of the intestine and liver despite the slower growth of the abdominal cavity.

- The midgut returns to the abdominal cavity at the 10 week of fetal life, simultaneously completing a 270 degree turn counterclockwise around the axis of the superior mesenteric artery.

- This rotation allows for the proper placement and fixation of the intestine in the abdominal cavity on a wide-based mesentery.

- This rotation results in the jejunum being on the left, and the ileum and cecum being on the right. It also causes the colon to assume the shape of an inverted "U".

- If this process is abnormal, intestinal malrotation occurs:

- The cecum will rest in the right upper quadrant instead of the right lower quadrant (RLQ).

- Additionally, Ladd's (fibrous) bands connect the retroperitoneum to the right colon/cecum by passing over the second part of the duodenum, causing intestinal obstruction in the process. Obstruction manifests as bilious emesis during the first days of life.

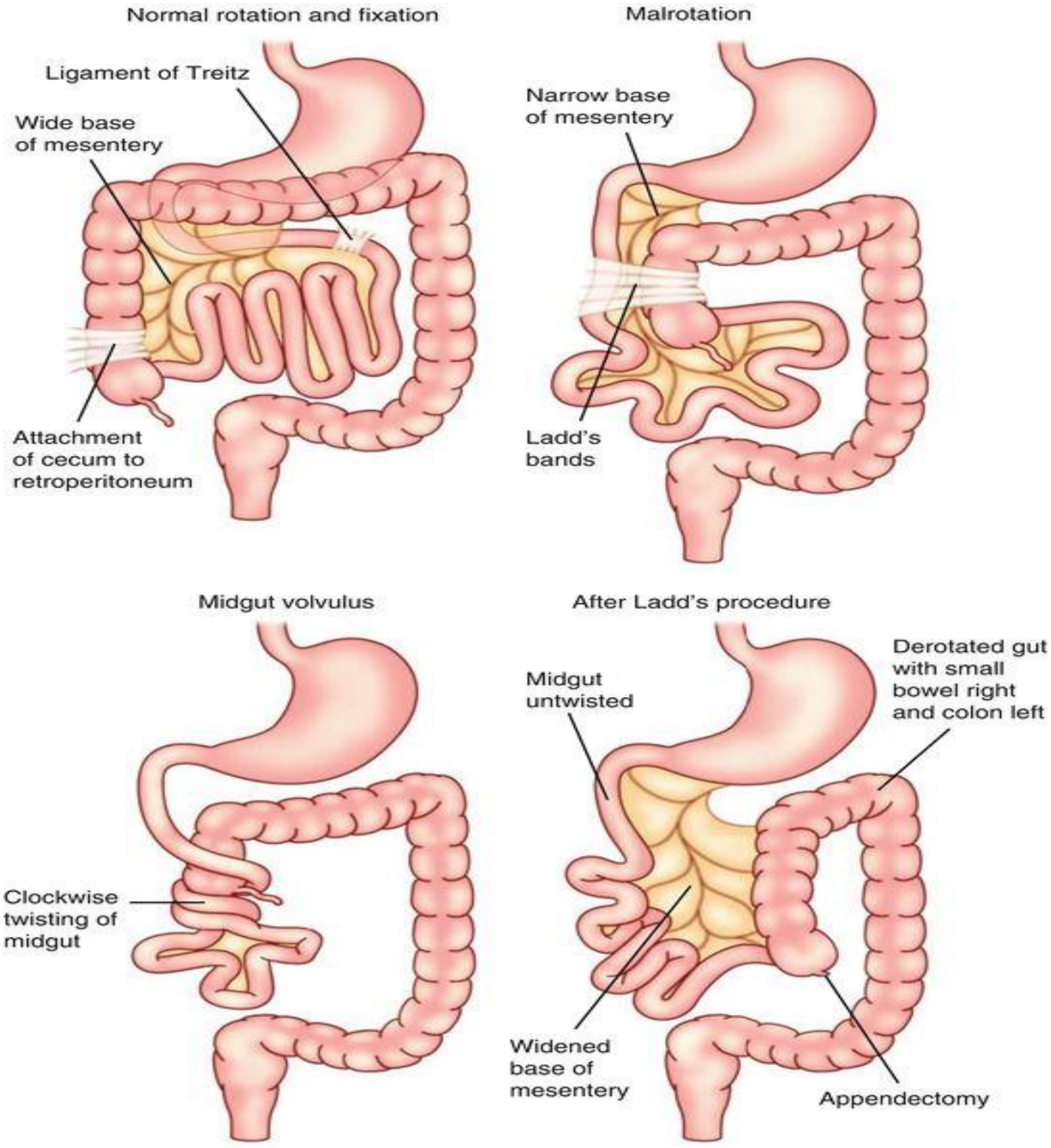
- Ladd's band is a growth of abnormal fibrous tissue that classically attaches the cecum to peritoneum and liver, crossing the duodenum in its course. Associated with intestinal obstruction and malrotation.

- In addition, because the mesenteric base is abnormally narrowed, the mesentery is vulnerable to twisting around the superior mesenteric artery. The twisting, referred to as midgut volvulus, compromises intestinal perfusion and may lead to life-threatening bowel necrosis.

❖ <u>In a nutshell:</u>

- Abnormal rotation and fixation of the midgut early during fetal life results in intestinal malrotation.

- Two main manifestations of this condition are intestinal obstruction (due to compression by the adhesive bands) and midgut volvulus (intestinal ischemia due to twisting around the blood vessels).



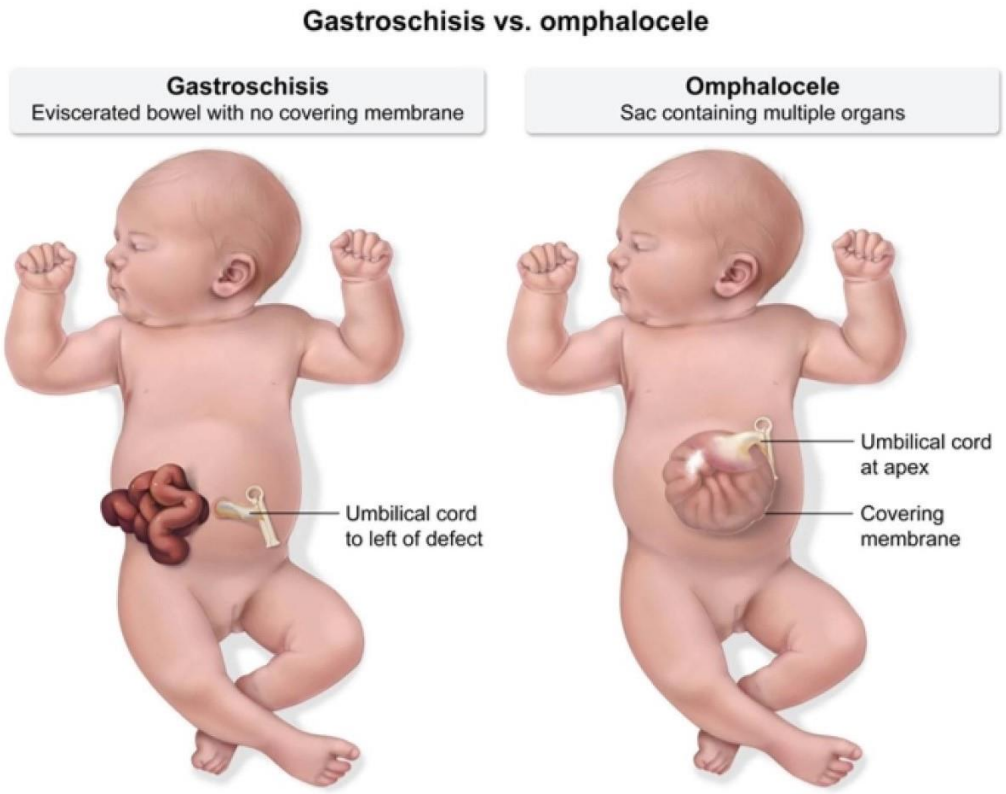
Ventral wall defects

- Developmental defects due to failure of:

- Rostral fold closure: sternal defects.

- Lateral fold closure: omphalocele, gastroschisis.

- Caudal fold closure: bladder exstrophy.



Gastroschisis

- Etiology:

- Gastroschisis is a congenital abdominal wall defect resulting in bowel herniation with no sac covering (typically right of umbilicus).

- Coverage:

- Not covered by peritoneum or amnion; "the abdominal contents are coming out of the G".

- Gastroschisis results in the bowel being exposed to amniotic fluid which causes inflammation and edema of the bowel wall. This inflammation increases the risk of complications.

- Associations:

- Not associated with chromosome abnormalities.

Omphalocele

- Etiology:
- An omphalocele is a defect in which intestines and organs form beyond the abdominal wall with a sac covering. It results from failure of the GI sac to retract at 10-12 weeks gestation.

- Coverage:
- Surrounded by peritoneum (light gray shiny sac); "abdominal contents are sealed in the O"

- Associations:
- Associated with congenital anomalies (trisomies 13 and 18, Beckwith-Wiedemann syndrome) and other structural abnormalities (cardiac, GU, neural tube).

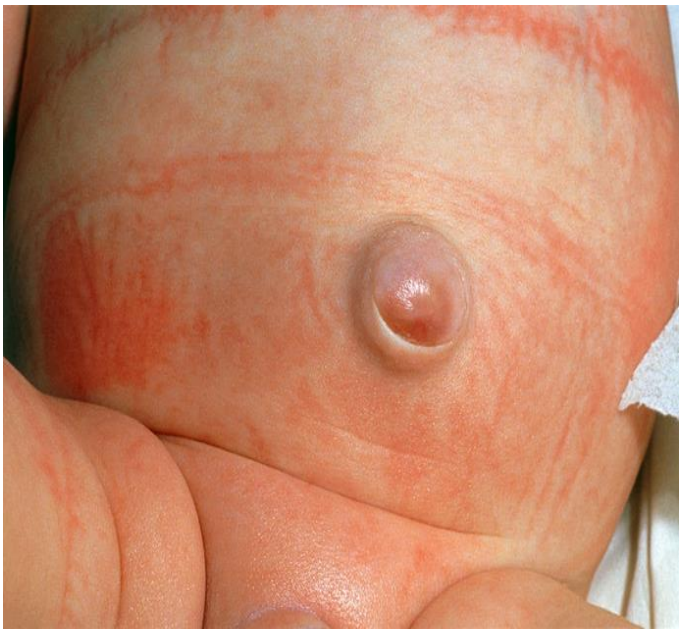
Congenital umbilical hernia

- An umbilical hernia is due to incomplete closure of the abdominal muscles around the umbilical ring at birth.

- It is most commonly associated with African-American race, premature birth, Ehlers-Danlos syndrome, Down syndrome and hypothyroidism.

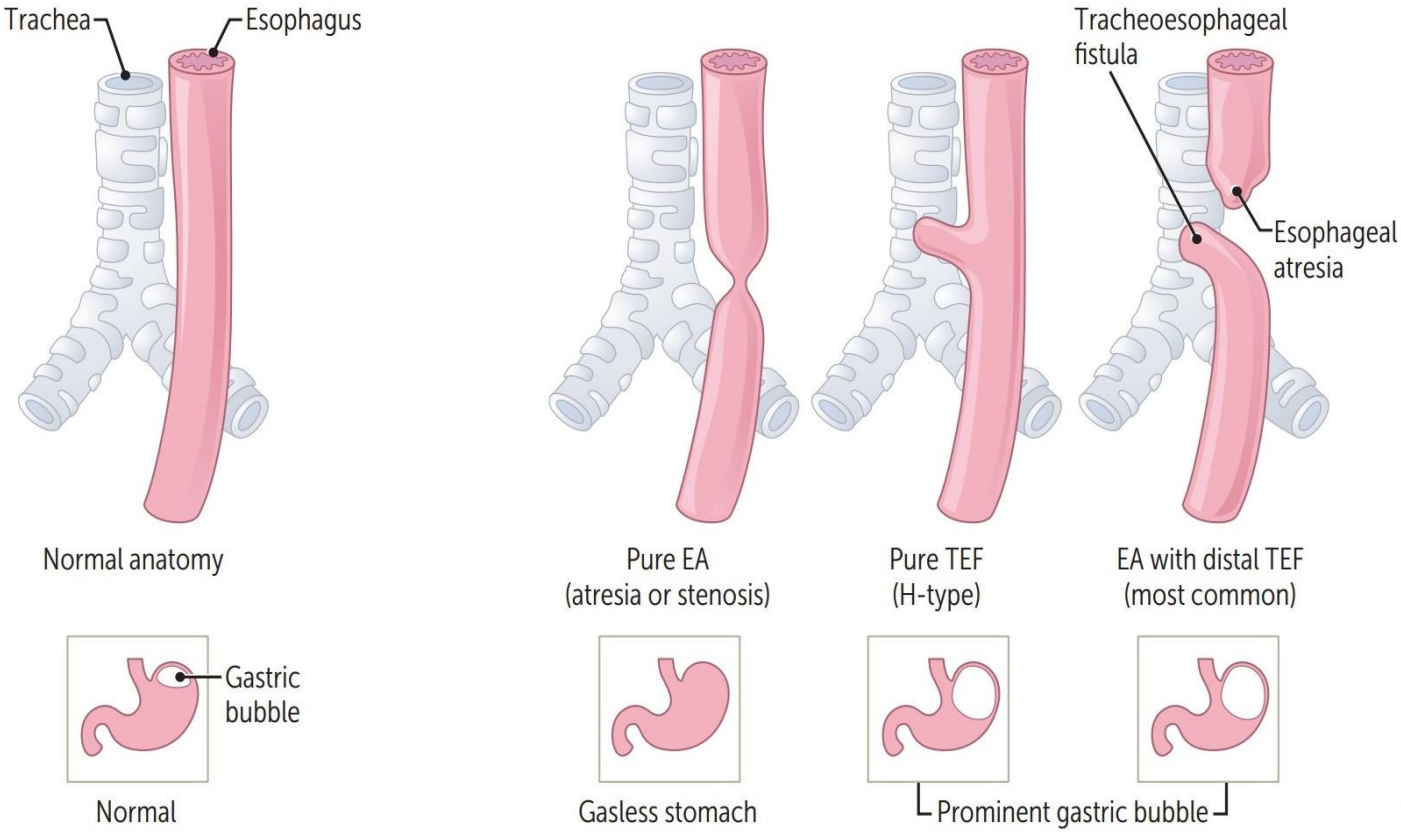
- Physical examination shows a soft, non-tender bulge covered by skin that protrudes during crying, coughing, or straining.

- Small umbilical hernias typically close spontaneously by concentric fibrosis and scar tissue formation.



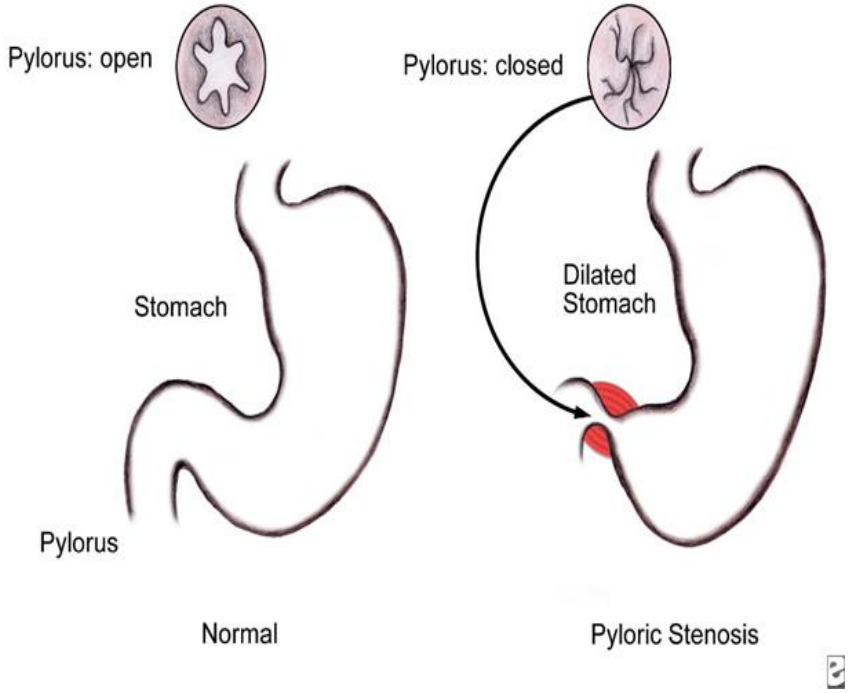
Tracheoesophageal Anomalies

- Tracheoesophageal fistula with esophageal atresia results from failure of the primitive foregut to appropriately divide into separate trachea and esophageal structures.
- Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%).
- The child will typically exhibit "vomiting with first feeding" or choking/coughing and cyanosis due to the TEF.
- There will be a history of possible polyhydramnios.
- TEF allows air to enter stomach (visible on CXR). In pure EA the CXR shows gasless abdomen.
- Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration).
- Recurrent aspiration pneumonia is due to secretions traveling into lungs via the TEF.
- Clinical test: Coiling of the NG tube seen on CXR and an inability to pass it into the stomach are diagnostic.
- In H-type, the fistula resembles the letter H.



Hypertrophic pyloric stenosis

- Congenital pyloric stenosis is a relatively common disorder that is encountered primarily in first born male infants (3:1 ratio) and characterized by a multifactorial pattern of inheritance.
- Most common cause of gastric outlet obstruction in infants.
- Associated with exposure to macrolides (Erythromycin) and formula feeding.
- Hypertrophy of the pylorus is not commonly found at birth but rather becomes most pronounced by the first month of life. It can present as late as 6 months after birth.
- Nonbilious (obstruction is proximal to the bile duct) projectile vomiting is the hallmark feature followed by hunger ("hungry vomiter").
- Olive sign, which delineates a palpable mass the size of an olive felt in the epigastric region, is highly associated with this condition. The mass is thought to develop secondary to hypertrophy of the pyloric muscularis mucosae.
- Auscultation will reveal a succussion splash, which is the sound of stomach contents slapping into the pylorus like waves on a beach.
- Metabolic imbalance demonstrates a hypochloremic, hypokalemic metabolic alkalosis due to the vast loss of hydrogen ions in the vomitus. The potassium loss also worsens from aldosterone release in response to hypovolemia.
- Treatment is surgical incision (pyloromyotomy).

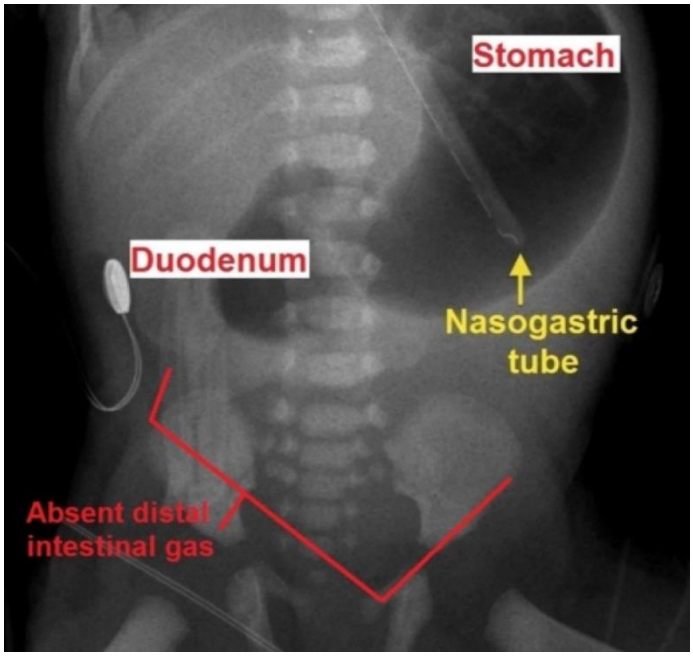


Intestinal atresia

- Intestinal atresia can occur anywhere along the gastrointestinal tract.
- Presents with bilious vomiting and abdominal distension within first 1-2 days of life.

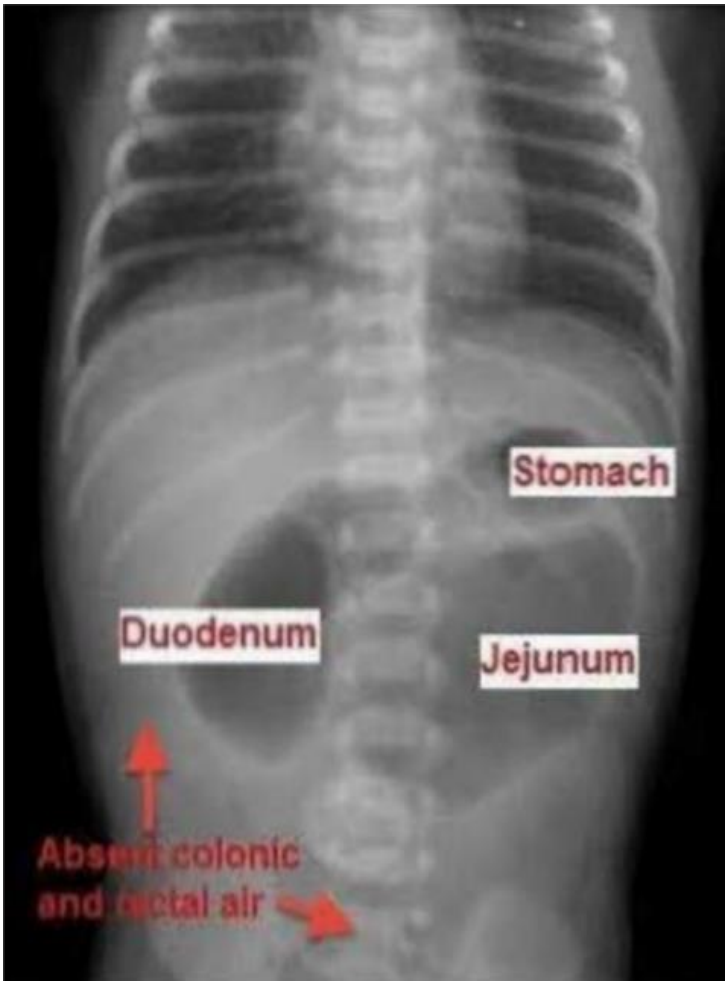
A. Duodenal atresia:

- Lack or absence of apoptosis (programmed cell death) that leads to improper canalization of the lumen of the duodenum → dilation of stomach and proximal duodenum ("double bubble" on x-ray) and no distal intestinal gas.
- Prenatal ultrasound will show polyhydramnios due to inability to swallow and remove amniotic fluid.
- Associated with Down syndrome.



B. Jejunal and ileal atresia:

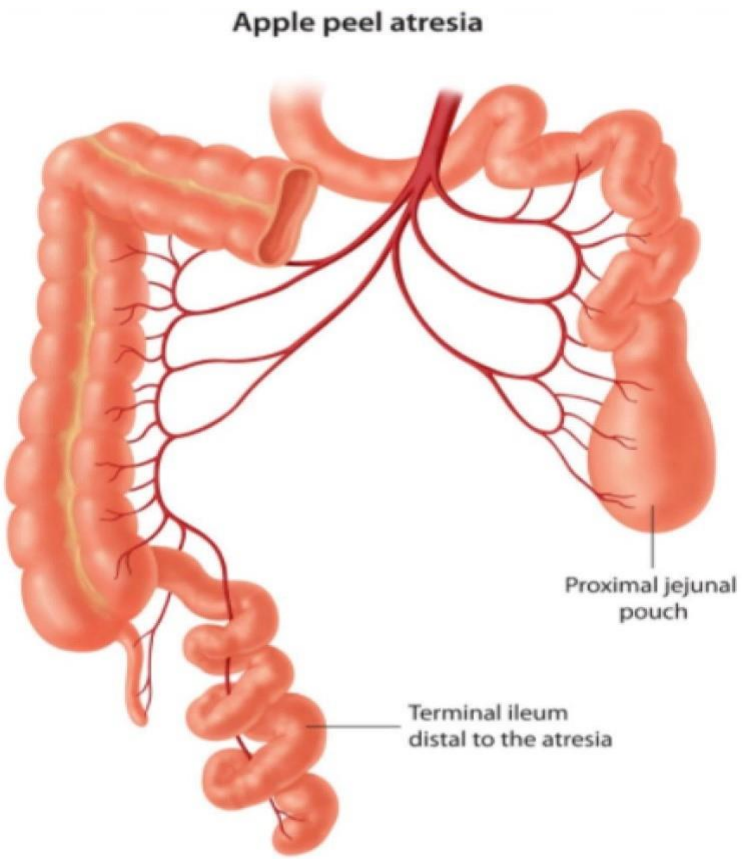
- Atresia of the jejunum or ileum is thought to occur due to a vascular accident in utero that causes necrosis and resorption of the fetal intestine, sealing off and leaving behind blind proximal and distal ends of intestine (bowel discontinuity or "apple peel").
- Risk factors include poor fetal gut perfusion from maternal use of vasoconstrictive medications or drugs such as cocaine and tobacco.
- In contrast to duodenal atresia, jejunal and ileal atresia are not associated with chromosomal abnormalities.
- The presence of the "triple bubble" sign and gasless colon on abdominal x-ray reflects gas trapping in the stomach, duodenum, and jejunum.



Intestinal atresias			
	Duodenal	**Jejunum/Ileum**	**Colonic**
Pathophysiology	• Failure of recanalization at 8-10 weeks gestation	• Vascular injury	• Unknown
Clinical findings	• Bilious or nonbilious emesis • **Double-bubble** sign on x-ray	• **Bilious** emesis • Abdominal distension	• Constipation • Abdominal distension
Associations	• **Down syndrome**	• Gastroschisis	• Hirschsprung disease

"apple-peel" atresia

- Bilious vomiting after the first 24 hours of life is a sign of intestinal obstruction below the second part of duodenum.
- Common causes of this condition are intestinal stenosis and atresia.
- Jejunal, ileal, and colonic atresia are not caused by abnormal fetal development (meaning that they are not congenital malformations).
- They are results of vascular accidents in utero. Diminished intestinal perfusion leads to ischemia of a segment of bowel, with subsequent narrowing or obliteration of the lumen. The ileum is affected most often.
- If a major vessel is occluded, (such as the superior mesenteric artery), the area of intestinal wall necrosis is large. This causes the formation of a blind-ending proximal jejunum with dissolution of a long length of small bowel and absence of the associated dorsal mesentery.
- The terminal ileum distal to the atresia assumes a spiral configuration around an ileocolic vessel. This specific appearance is known as an "apple-peel" or "Christmas tree" deformity.



Pancreas and spleen embryology

- Pancreas (derived from foregut):

A. Ventral pancreatic buds contribute to uncinate process and main pancreatic duct.

B. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct.

C. Both the ventral and dorsal buds contribute to pancreatic head.

- Spleen: Arises in the dorsal mesentery of stomach (hence is mesodermal) but has foregut supply (celiac trunk → splenic artery).

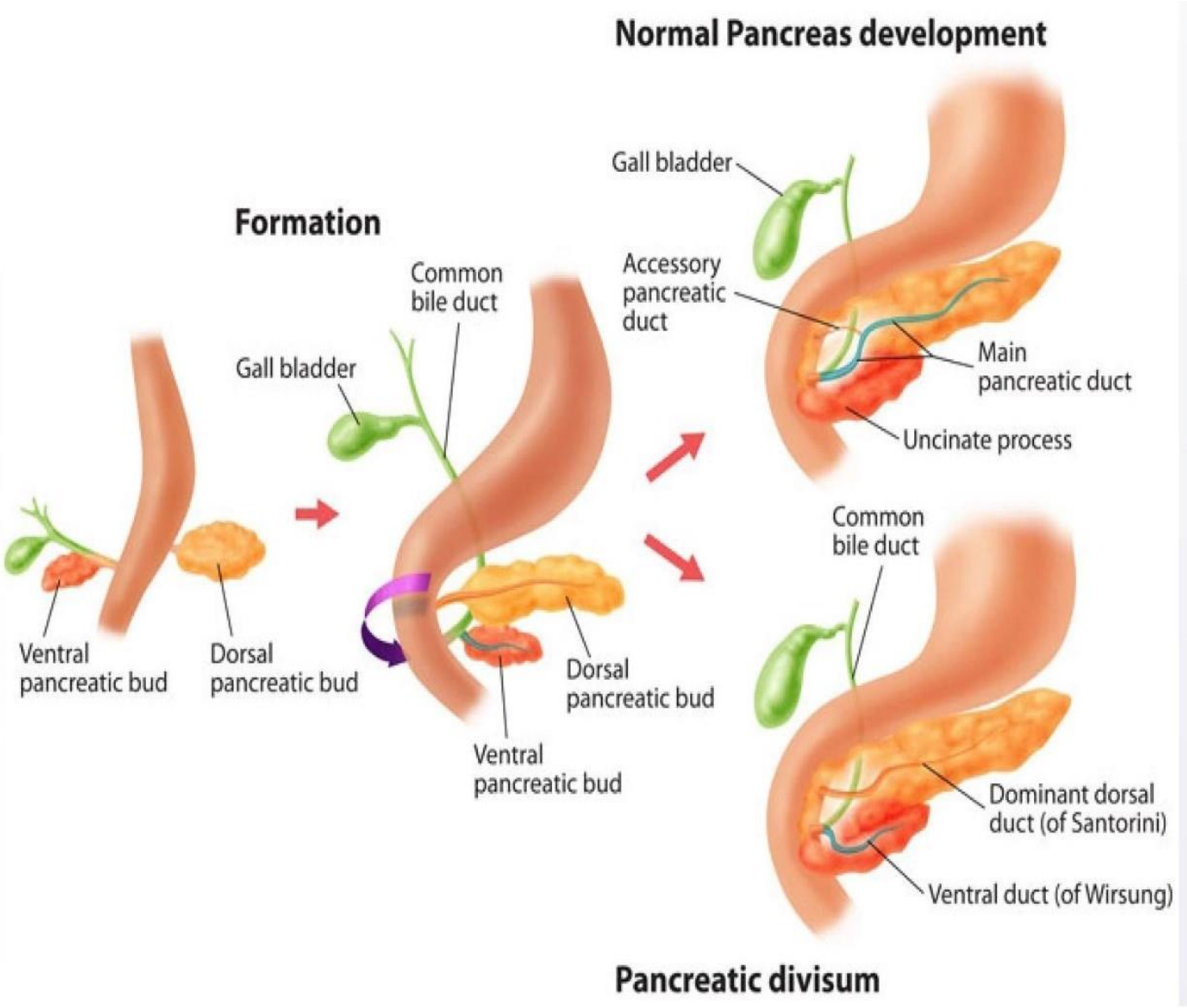
Pancreas divisum

- Common anomaly. Pancreas divisum is found in 5% of the population and is usually clinically silent.
- It is commonly detected as an incidental finding on imaging studies or at autopsy.
- Ventral and dorsal parts fail to fuse at 8th week of fetal life.
- Early in fetal life, the duodenal portion of the foregut gives rise to the dorsal and ventral pancreatic buds:

- The smaller ventral bud gives rise to the uncinate process, a portion of the pancreatic head, and the proximal portion of the main pancreatic duct.
- The dorsal pancreatic bud forms the pancreatic tail, body, most of the head, and the small accessory pancreatic duct.
- The dorsal and ventral pancreatic buds then fuse during the eighth week of fetal life. The remainder of the accessory duct fuses with the ventral duct to form the main pancreatic duct (of Wirsung).

- Pancreas divisum occurs when the ventral and dorsal pancreatic buds fail to fuse; the pancreatic secretions are instead drained via two separate duct systems:

- The dorsal duct opens into the duodenum via the minor papilla, and is responsible for draining the majority of the pancreas.
- The ventral duct opens into the major papilla, and functions to drain the inferior/posterior portion of the head and uncinate process.
- Mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.


Normal Pancreas development
Formation
Gall bladder
Common bile duct
Accessory pancreatic duct
Main pancreatic duct
Uncinate process
Ventral pancreatic bud
Dorsal pancreatic bud
Gall bladder
Common bile duct
Dorsal pancreatic bud
Ventral pancreatic bud
Dominant dorsal duct (of Santorini)
Ventral duct (of Wirsung)
Pancreatic divisum

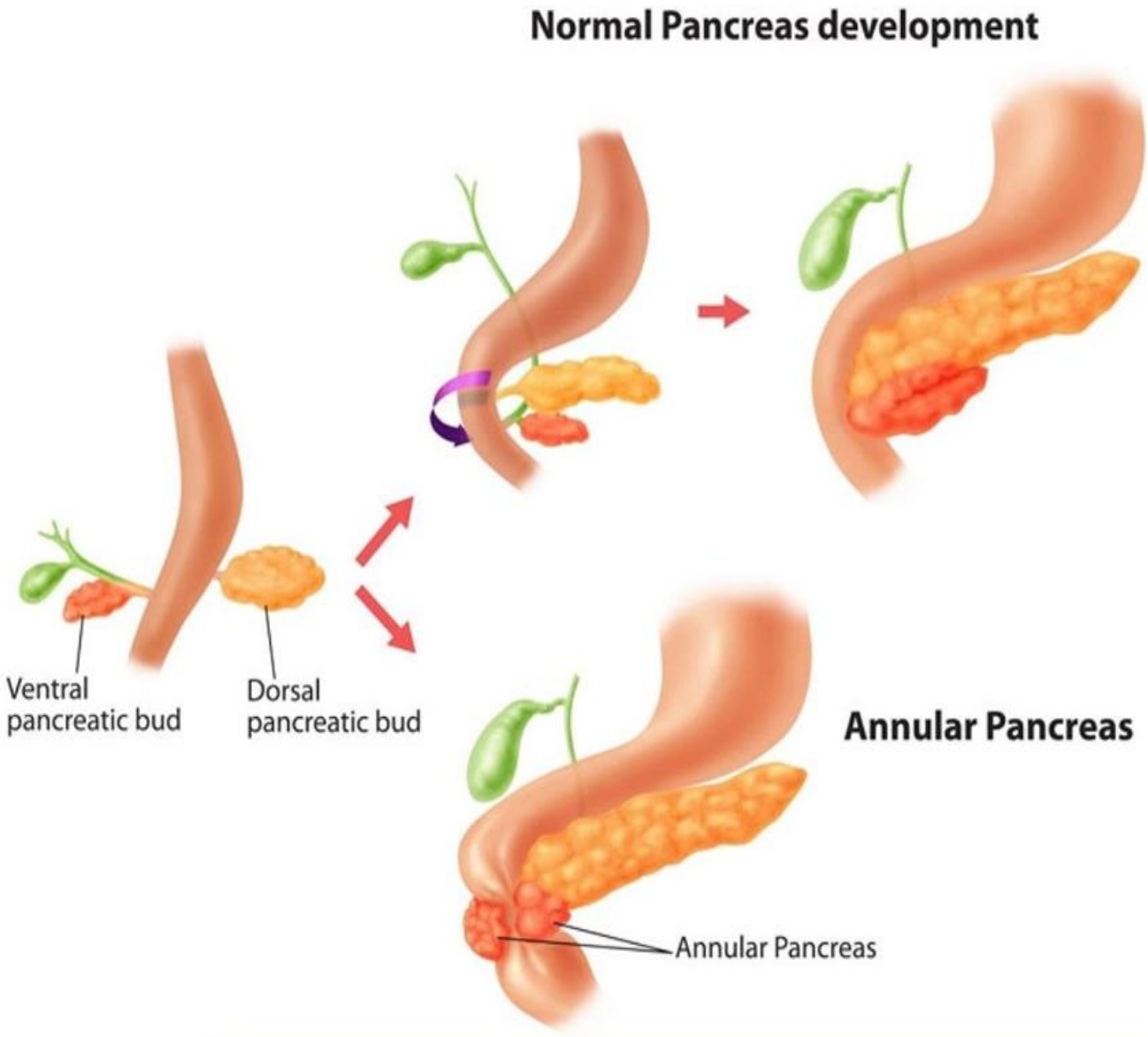
Annular pancreas

- Sometimes, the ventral pancreatic bud cleaves into two parts which subsequently form a ring around the descending portion of the duodenum and fuse with the dorsal bud from two sides → abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing.

- This abnormal migration of the ventral pancreatic bud leads to an annular pancreas, a rare congenital anomaly.

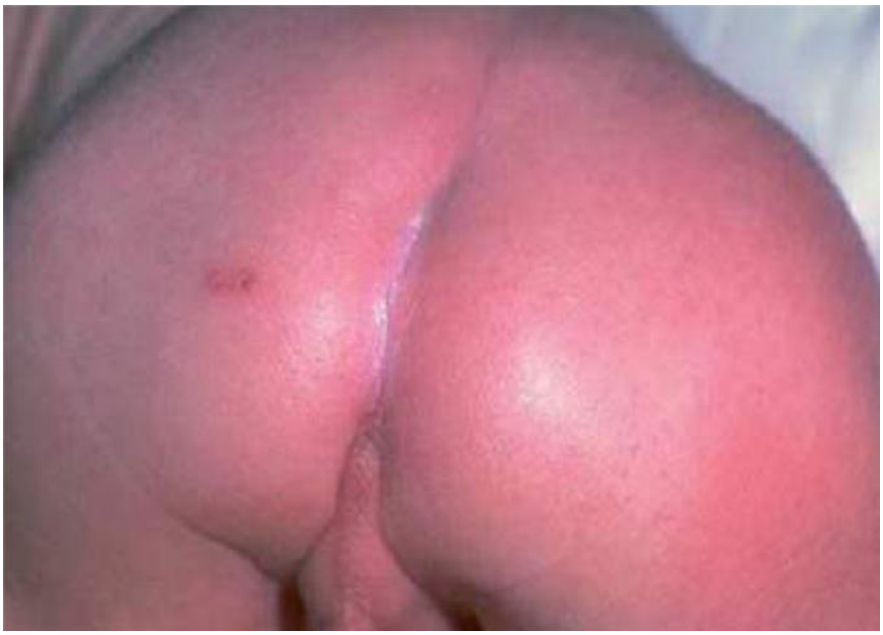
- Annular pancreas can compress the duodenal lumen, causing duodenal stenosis or result in obstructed pancreatic drainage (acute or chronic pancreatitis).

- Infants may present with symptoms of upper intestinal obstruction (recurrent bilious vomiting) soon after birth. In others, the annular pancreas remains asymptomatic.



Imperforate anus

- The term "imperforate anus" covers a spectrum of disorders associated with abnormal development of anorectal structures.
- It manifests during the first days of life by inability to pass meconium.
- Alternatively, meconium may discharge from the urethra or vagina if a fistula is present.
- Patients with an imperforate anus often have other congenital malformations, with urogenital tract anomalies being the most common. These malformations include renal agenesis, hypospadias, epispadias, and bladder extrophy. Such abnormalities are reported in up to 50% of patients with imperforate anus.



Vitelline duct

- The omphalomesenteric (vitelline) duct connects the midgut lumen with the yolk sac cavity early in embryonic life.

- It normally obliterates during the 7th week of embryonic development. If its obliteration is incomplete or abnormal, a number of abnormalities can result:

1. A persistent vitelline duct, or vitelline fistula:

- Occurs due to complete failure of the vitelline duct to close.

- A small connection between the intestinal lumen and the outside of the body exists at the umbilicus.

- Meconium discharge from the umbilicus is seen soon after birth if such a fistula is present.

2. Meckel diverticulum:

- It is the most common vitelline duct anomaly.

- It results from a partial closure of the vitelline duct, with the patent portion attached to the ileum.

- A fibrous band may connect the tip of the Meckel diverticulum with the umbilicus.

3. Vitelline sinus: It results from a partial closure of the vitelline duct, with the patent portion open at the umbilicus.

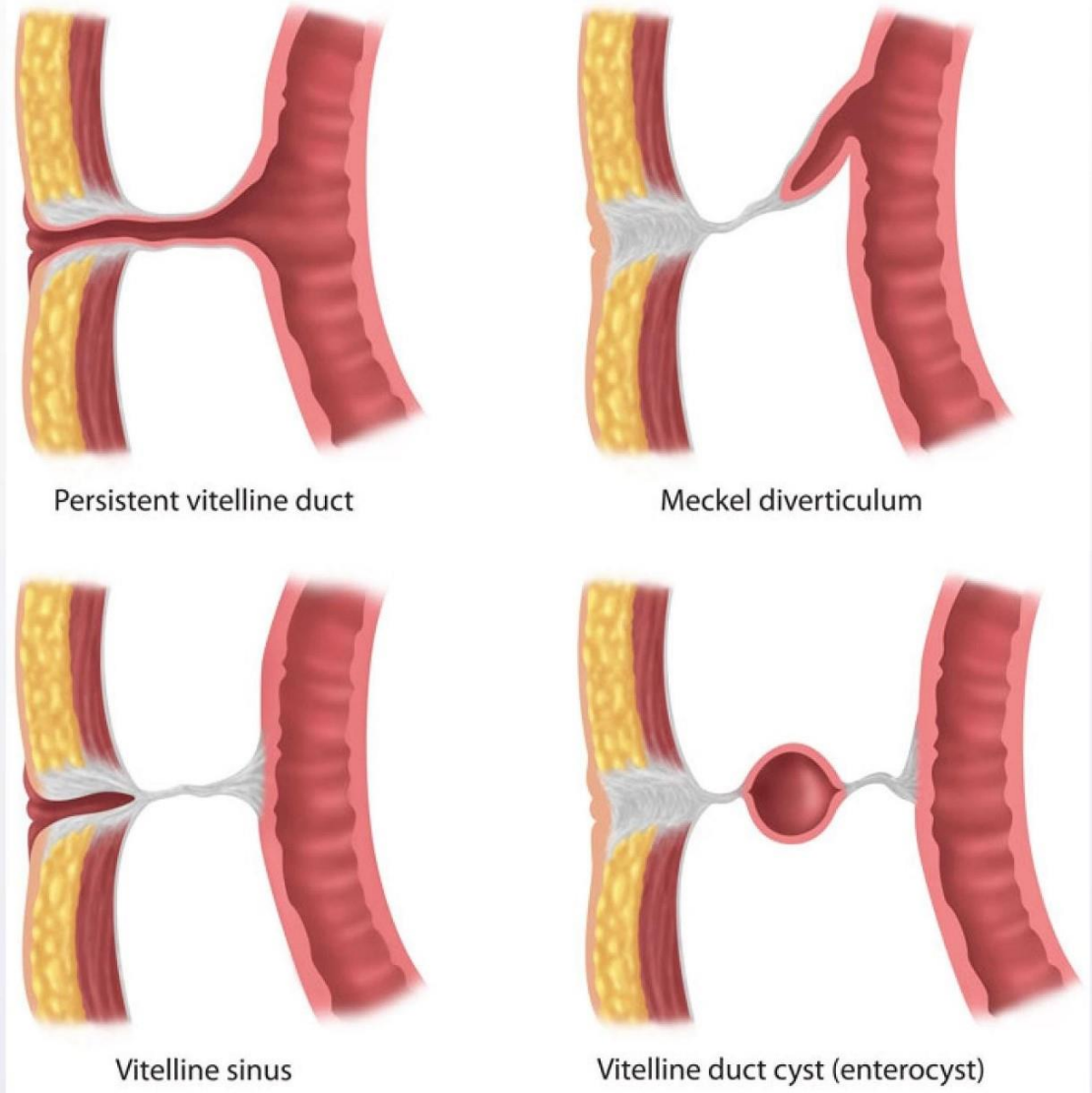
4. Vitelline duct cyst (enterocyst):

- It forms if peripheral portions of the vitelline duct (connected to the ileum and umbilicus) obliterate, but the central part remains.

- This cyst is connected with the ileum and abdominal wall by fibrous bands.

- Most vitelline duct abnormalities are asymptomatic and often discovered incidentally.

- However, Meckel diverticulum may present with rectal bleeding or intestinal obstruction.

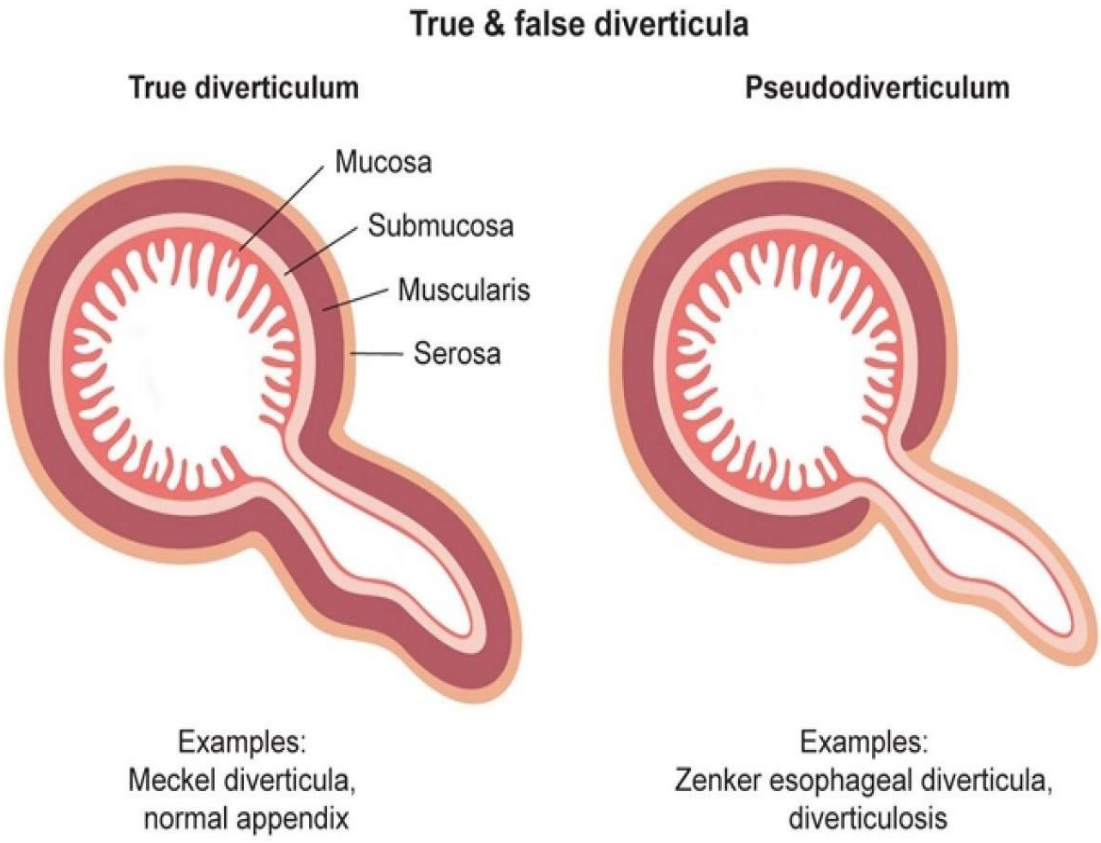

Persistent vitelline duct
Meckel diverticulum
Vitelline sinus
Vitelline duct cyst (enterocyst)

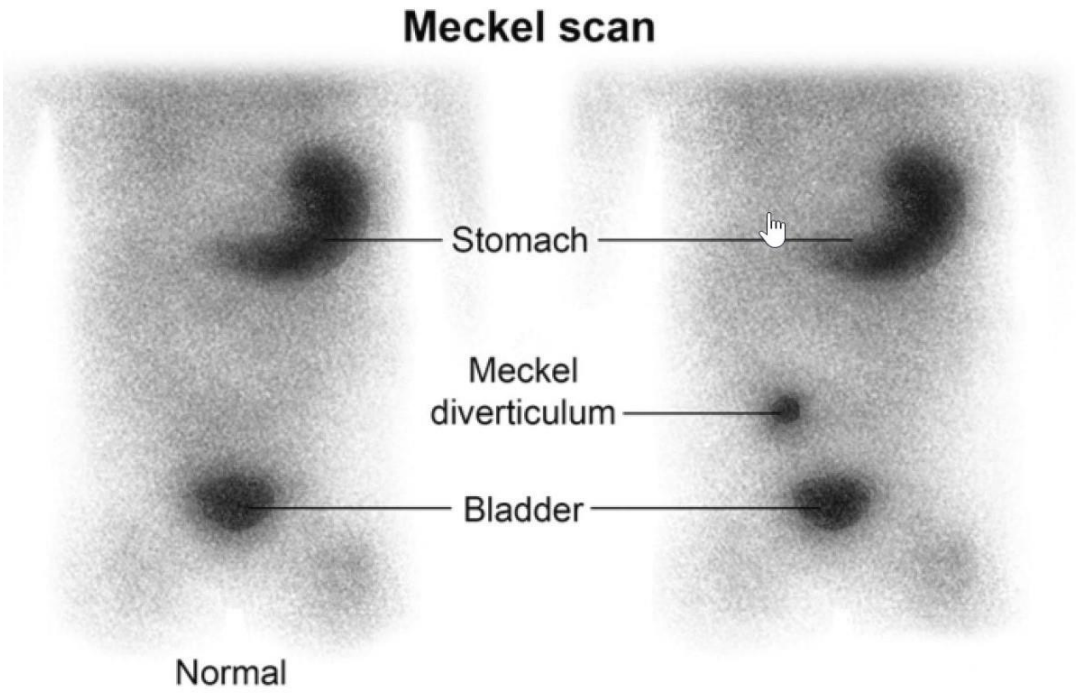
Meckel's diverticulum

- Meckel diverticulum is the most common congenital anomaly of the small intestine, being present in 2% of the population.
- It forms due to incomplete obliteration of the omphalomesenteric duct that connects the midgut lumen and yolk sac cavity early in fetal life.
- Meckel's diverticulum may present with rectal bleeding or intestinal obstruction; however, most cases are asymptomatic.
- Remember the rule of 2's with Meckel's diverticulum: 2% of the population, 2 feet from the ileocecal valve, 2 inches in length, 2% are symptomatic, and males are 2 times more likely to be affected.
- In contrast to false diverticula, which contain mucosa and submucosa only, Meckel's diverticulum is a true diverticulum, consisting of all three parts of the intestinal wall: mucosa, submucosa, and muscularis.
- Meckel diverticulum may present with rectal bleeding or intestinal obstruction:

- A variety of tissues have been found in Meckel diverticulum, including gastric, pancreatic, colonic, jejunal, duodenal and endometrial.
- This is example of ectopy (also called heterotopy).
- "Ectopy" is a term that identifies microscopically and functionally normal cells/tissues found in an abnormal location due to embryonic maldevelopment.
- The most common of these is gastric tissue, which is significant because gastric epithelium produces acid that can cause ulceration of adjacent mucosa and lower GI bleeding (melena/hematochezia).
- Meckel diverticulum most often presents with painless melena.
- The diverticulum may also become inflamed and simulate the clinical presentation of acute appendicitis.
- The diverticulum itself may also predispose the intestine to intussusception, which manifests as a colicky abdominal pain and "currant jelly" stools (If you've never seen currant jelly, it looks a lot like strawberry jam).

- 99mmTc-pertechnetate scan detects the presence of gastric mucosa. Accumulation of pertechnetate in the right lower abdominal quadrant is diagnostic of a Meckel diverticulum that contains ectopic gastric mucosa.


True & false diverticula
True diverticulum
Pseudodiverticulum
Mucosa
Submucosa
Muscularis
Serosa
Examples:
Meckel diverticula,
normal appendix
Examples:
Zenker esophageal diverticula,
diverticulosis


Meckel scan
Stomach
Meckel
diverticulum
Bladder
Normal

Hirschsprung disease

- Hirschsprung disease (congenital aganglionic megacolon) is a congenital lack of innervation of the distal bowel by the Auerbach plexus; most commonly involves the rectosigmoid. The affected colonic segment cannot relax and therefore is chronically contracted.

- Neural crest cells start migrating to the intestinal wall very early during embryonic development.

- They give rise to ganglion cells of the submucosal (Meissner) and myenteric (Auerbach) plexi of the bowel wall.

- These parasympathetic ganglia are responsible for intestinal peristalsis. Neural crest cells move caudally along the vagal nerve fibers. They are present in the wall of proximal colon at 8th week of gestation and in the rectum by 12th week.

- The arrest of migration of neural crest cells causes Hirschsprung disease, in which a segment of colon is deprived of ganglion cells.

- Since neural crest cells migrate caudally, the rectum is always involved in Hirschsprung disease.

- The absence of ganglion cells in the colonic wall causes the affected segment to be narrowed because it cannot relax. The passage of intestinal contents through this area is difficult, and compensatory dilatation of proximal areas of the colon occurs.

- Severity depends on the extent of colonic involvement:

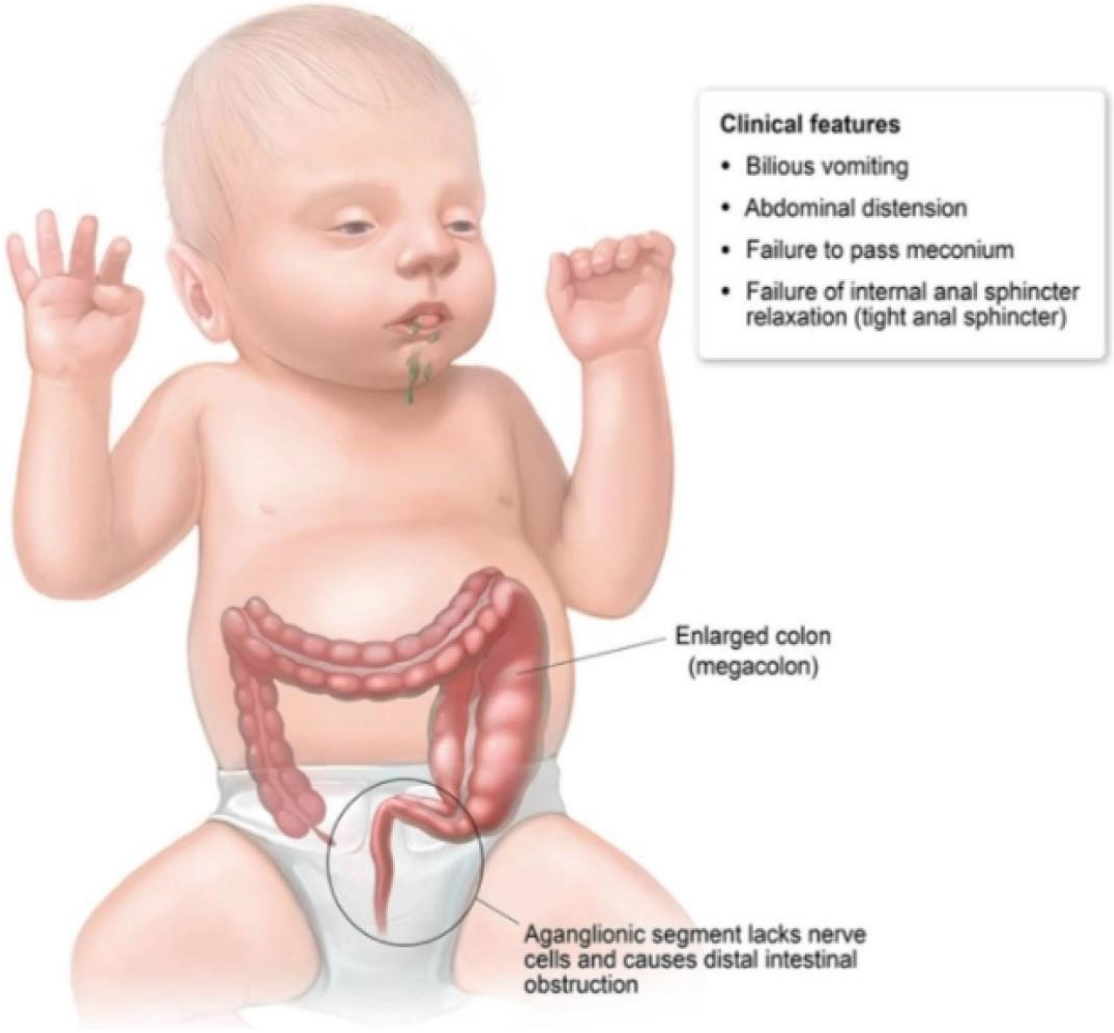
- If a large area of the bowel is involved, the disease will manifest during the first few days of life with obstructive symptoms (failure to pass meconium, bilious vomiting, and abdominal distention).

- If only a short area is affected, the disease may go undetected for months or years.

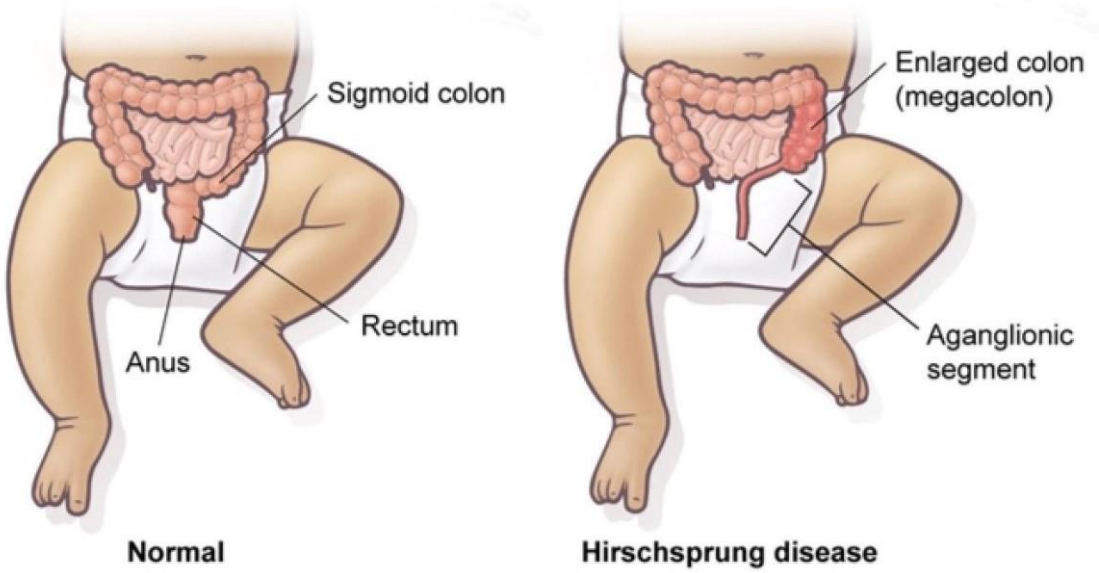
- Newborns with Hirschsprung disease fail to pass meconium within 48 hours of birth. They also demonstrate other symptoms of intestinal obstruction, such as bilious vomiting and abdominal distention.

- The bowel is filled with stool, but the rectum is empty; the tone of the anal sphincter is usually increased.

- Rectal biopsy is necessary for the diagnosis of Hirschsprung disease. The submucosa of rectum (the narrowed segment) should be biopsied to demonstrate the absence of ganglionic cells. The submucosa of the narrowed area is the most superficial layer where the absence of ganglion cells can be seen.



Hirschsprung disease

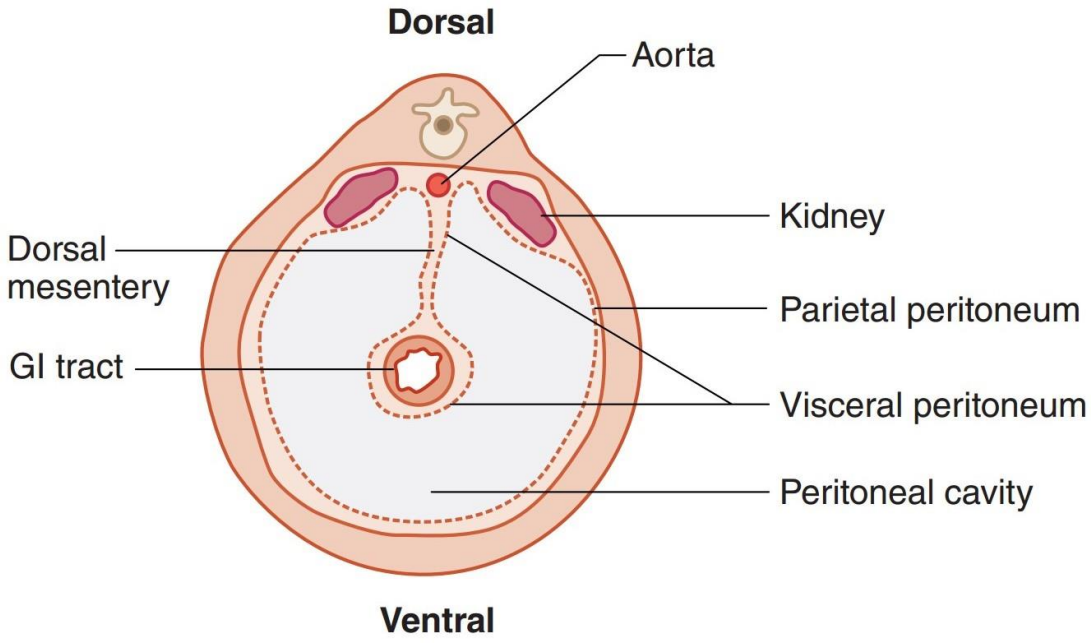


CHAPTER 2

Anatomy

Peritoneum

- The peritoneum is the serous membrane related to the viscera of the abdominal cavity. It is divided into 2 layers: parietal and visceral.



- <u>The parietal layer (Pain sensitive):</u>

- It lines the body wall and covers the retroperitoneal organs on one surface.

- Parietal peritoneum is very sensitive to somatic pain and is innervated by the lower intercostal nerves and the ilioinguinal and the iliohypogastric nerves of the lumbar plexus.

- <u>The visceral layer:</u>

- It encloses the surfaces of the intraperitoneal organs.

- The visceral peritoneum usually forms double-layered peritoneal membranes (mesenteries) that suspend parts of the GI tract from the body wall.

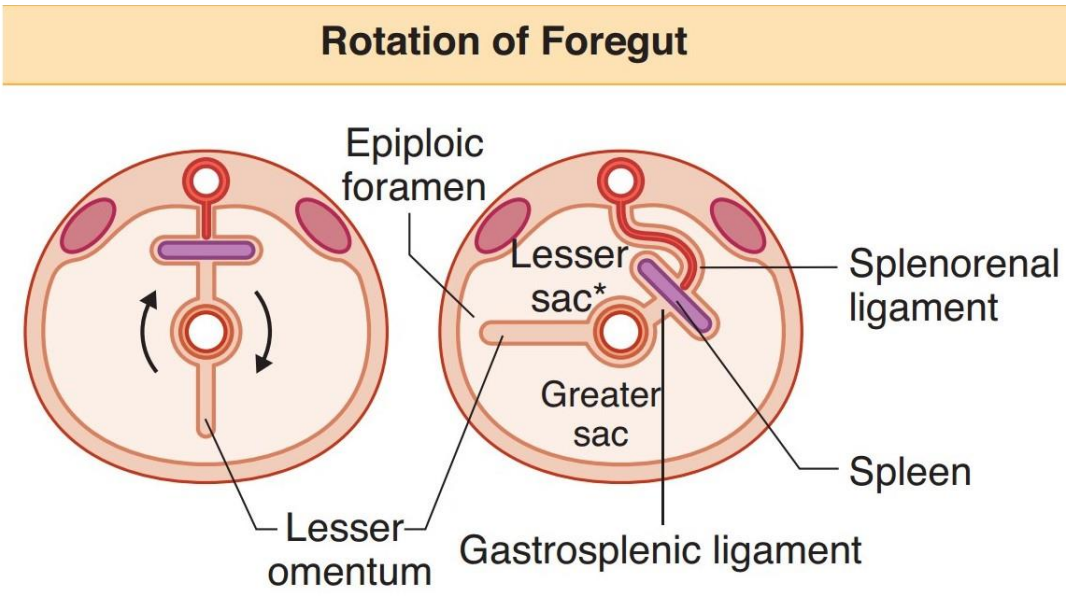
- The mesenteries allow for the passage of vessels, nerves, and lymphatics to reach the GI tract.

- <u>Peritoneal Cavity:</u>

- The peritoneal cavity is the potential space located between the parietal and visceral peritoneal layers. The 90° rotation and the shift of the embryonic mesenteries divide the peritoneal cavity into 2 sacs:

A. The lesser sac: is formed posterior to the stomach and the lesser omentum.
B. The greater sac: is formed by the larger area of the remaining peritoneal cavity.

- The only communication between the lesser sac and the greater sac is the epiploic foramen (of Winslow).

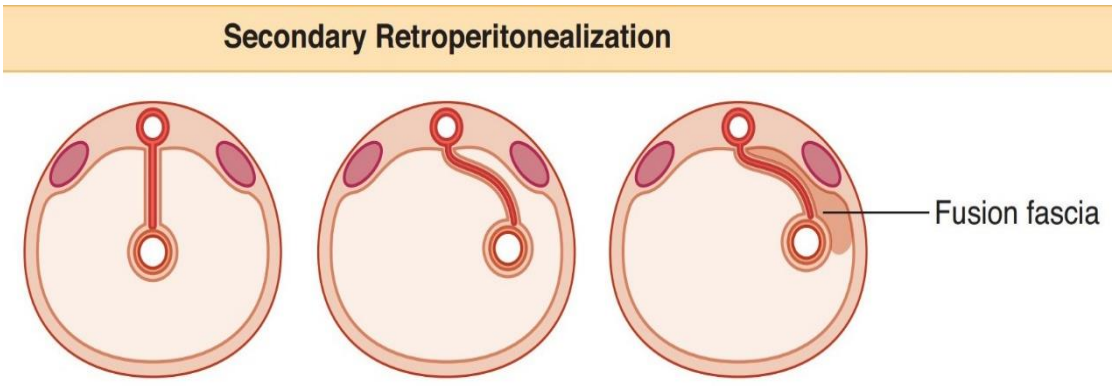


- Intraperitoneal versus Retroperitoneal Organs:

- The abdominal viscera are classified according to their relationship to the peritoneum:

1. Intraperitoneal organs: They are suspended by a mesentery and are almost completely enclosed in visceral peritoneum. They are mobile.

2. Retroperitoneal organs:
   - They are partially covered on one side with parietal peritoneum.
   - They are immobile or fixed.
   - Many retroperitoneal organs are originally suspended by a mesentery and become secondarily retroperitoneal.
   - In secondary retroperitonealization, parts of the gut tube (most of the duodenum, pancreas, ascending colon, descending colon, part of rectum) fuse with the body wall by way of fusion of visceral peritoneum with parietal peritoneum.
   - This causes the organs to become secondarily retroperitoneal (and the visceral peritoneum covering the organ is renamed as the parietal peritoneum). The vessels within the mesentery of these gut structures become secondarily retroperitoneal.



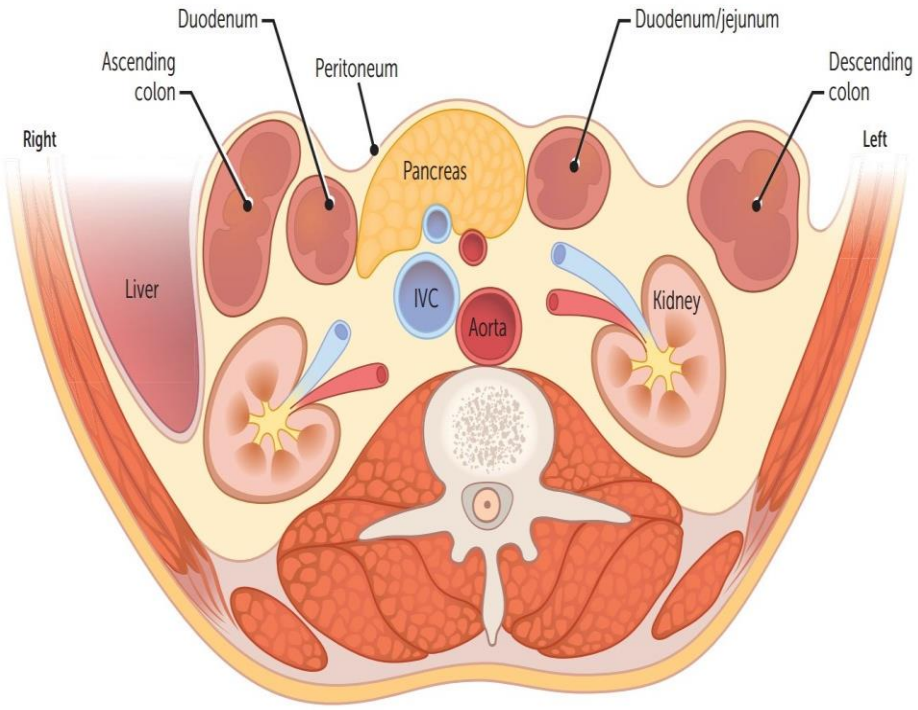
Intraperitoneal and Retroperitoneal Organs

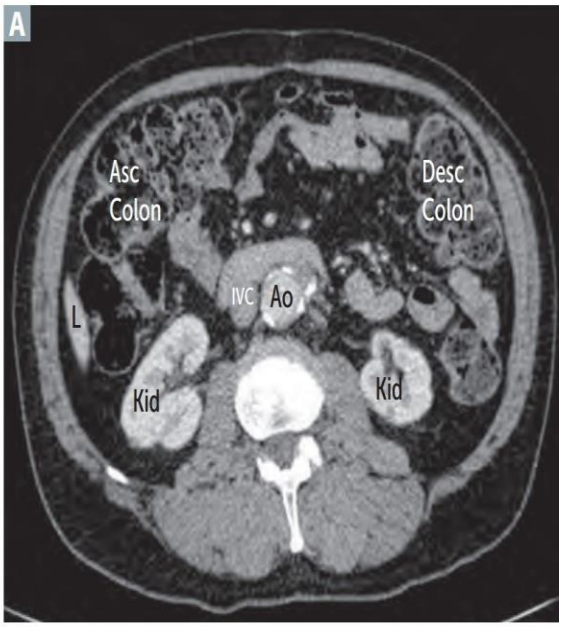
Major Intraperitoneal Organs (suspended by a mesentery)	**Major Secondary Retroperitoneal Organs** (lost a mesentery during development)	**Major Primary Retroperitoneal Organs** (never had a mesentery)
Stomach Liver and gallbladder Spleen Duodenum, 1st part Tail of pancreas Jejunum Ileum Appendix Transverse colon Sigmoid colon	Duodenum, 2nd and 3rd parts Head, neck, and body of pancreas Ascending colon Descending colon Upper rectum	Kidneys Adrenal glands Ureters Aorta Inferior vena cava Lower rectum Anal canal

Retroperitoneal structures

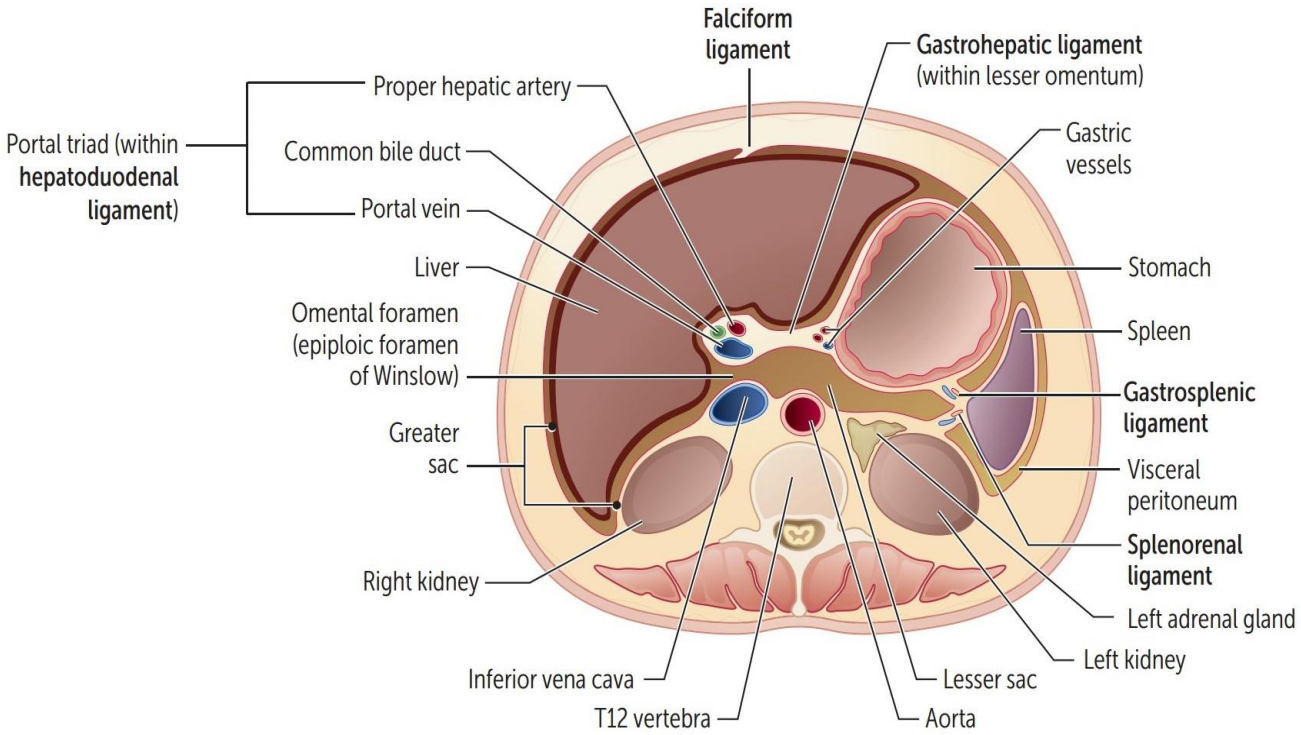
- Retroperitoneal structures include GI structures that lack a mesentery and non-GI structures.
- Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.
- SAD PUCKER:

- Suprarenal (adrenal) glands [not shown].
- Aorta and IVC.
- Duodenum (2nd through 4th parts).
- Pancreas (except tail).
- Ureters [not shown].
- Colon (descending and ascending).
- Kidneys.
- Esophagus (thoracic portion) [not shown].
- Rectum (partially) [not shown].





Important gastrointestinal ligaments



Ligament	Connects	Structures Contained	Notes
Falciform	Liver to anterior abdominal Wall	Ligamentum teres hepatis (derivative of fetal umbilical vein)	Derivative of ventral mesentery
Hepatoduodenal	Liver to duodenum	Portal triad: proper hepatic artery, portal vein, common bile duct	▪ Pringle maneuver: ligament may be compressed between thumb and index finger placed in omental foramen to control bleeding. ▪ Borders the omental foramen, which connects the greater and lesser sacs.
Gastrohepatic	Liver to lesser curvature of Stomach	Gastric arteries	▪ Separates greater and lesser sacs on the right. ▪ May be cut during surgery to access lesser sac. ▪ Part of lesser omentum
Gastrocolic (not shown)	Greater curvature and transverse colon	Gastroepiploic arteries	▪ Part of greater omentum
Gastrosplenic	Greater curvature and spleen	Short gastrics, left gastroepiploic vessels	▪ Separates greater and lesser sacs on the left ▪ Part of greater omentum
Splenorenal	Spleen to posterior abdominal Wall	Splenic artery and vein, tail of Pancreas	

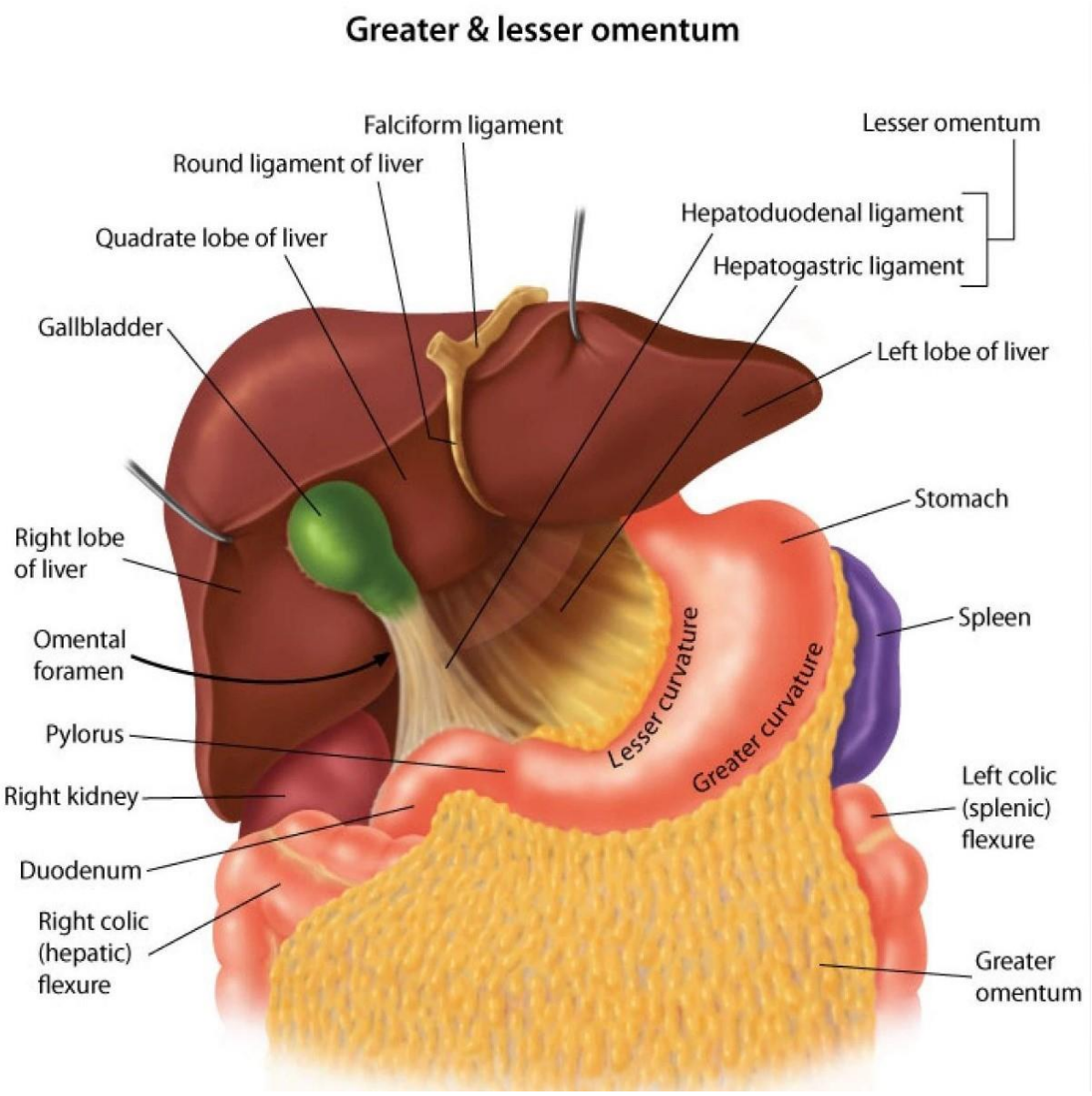
- The lesser omentum is a double layer of peritoneum that extends from the liver to the lesser curvature of the stomach and the beginning of the duodenum.

- Anatomically, the lesser omentum is divided into 2 ligaments:

- Hepatogastric ligament: the portion connecting to the lesser curvature of the stomach.

- Hepatoduodenal ligament: the portion connecting to the duodenum.

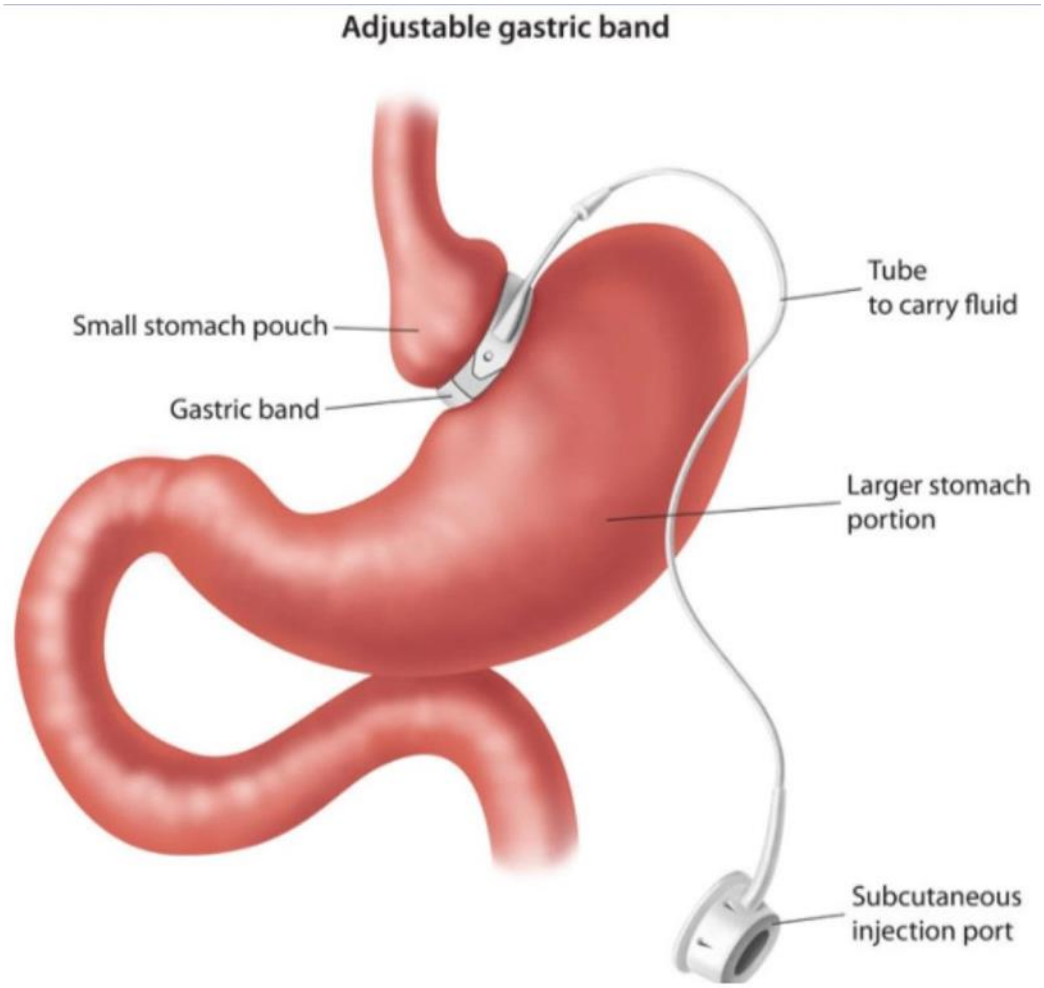
- The greater omentum is a large fold of visceral peritoneum that extends from the greater curvature of the stomach, travels interiorly over the small intestine, and then reflects on itself and ascends to encompass the transverse colon before reaching the posterior abdominal wall. The gastrocolic ligament is the section that stretches from the greater curvature of the stomach to the transverse colon. It forms part of the anterior wall of the lesser sac and is often divided during surgery to provide access to the anterior pancreas and posterior wall of the stomach.



❖ N.B:

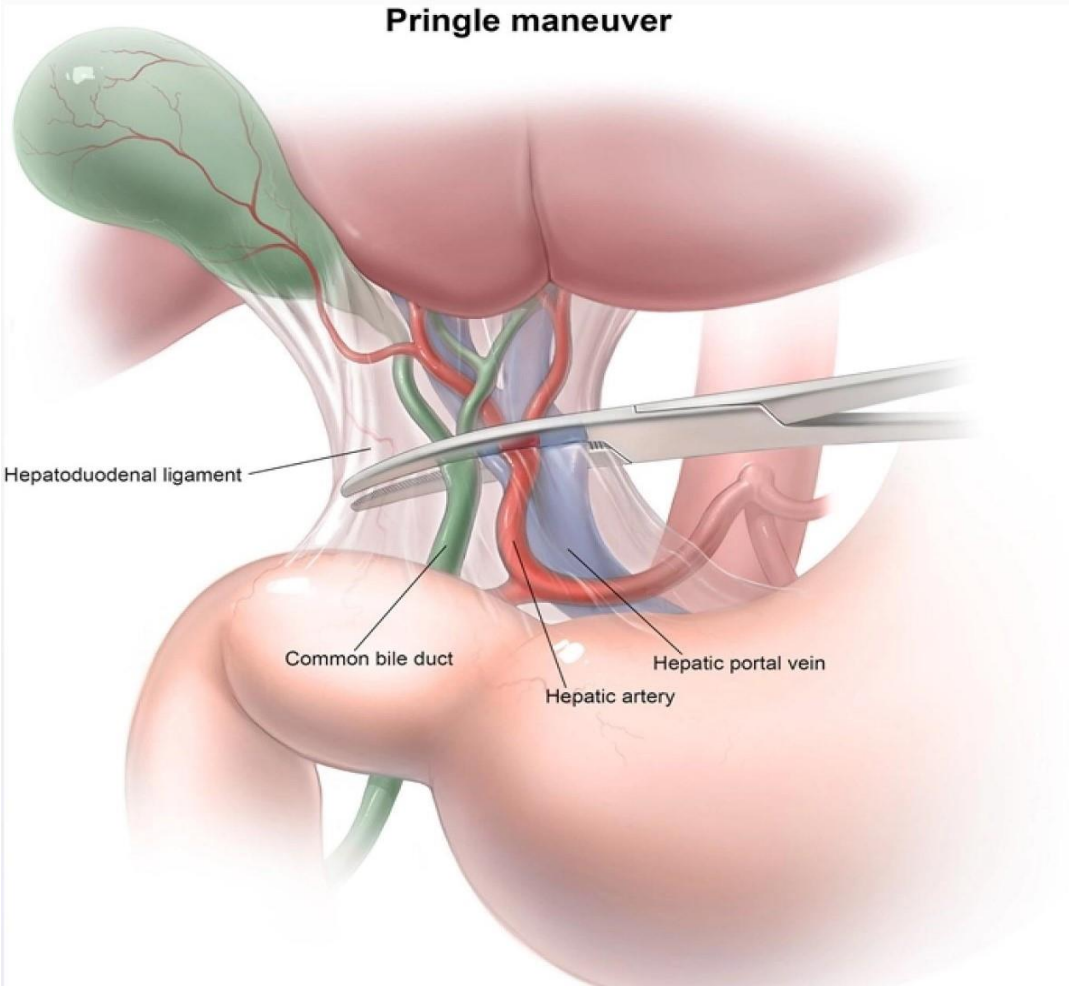
1. Adjustable gastric banding is a type of restrictive bariatric surgery designed for obese patients.

- The adjustable gastric band is an inflatable silicone device placed around the gastric cardia. It is intended to slow the passage of food, increasing satiety and limiting the amount of food consumed.
- To encircle the upper stomach, the gastric band must pass through the lesser omentum.



2. Occlusion of the portal triad (Pringle maneuver) is a surgical technique used to distinguish the source of right upper quadrant bleeding. If hepatic bleeding persists after occlusion of the portal triad, the inferior vena cava or hepatic veins are likely to be injured.

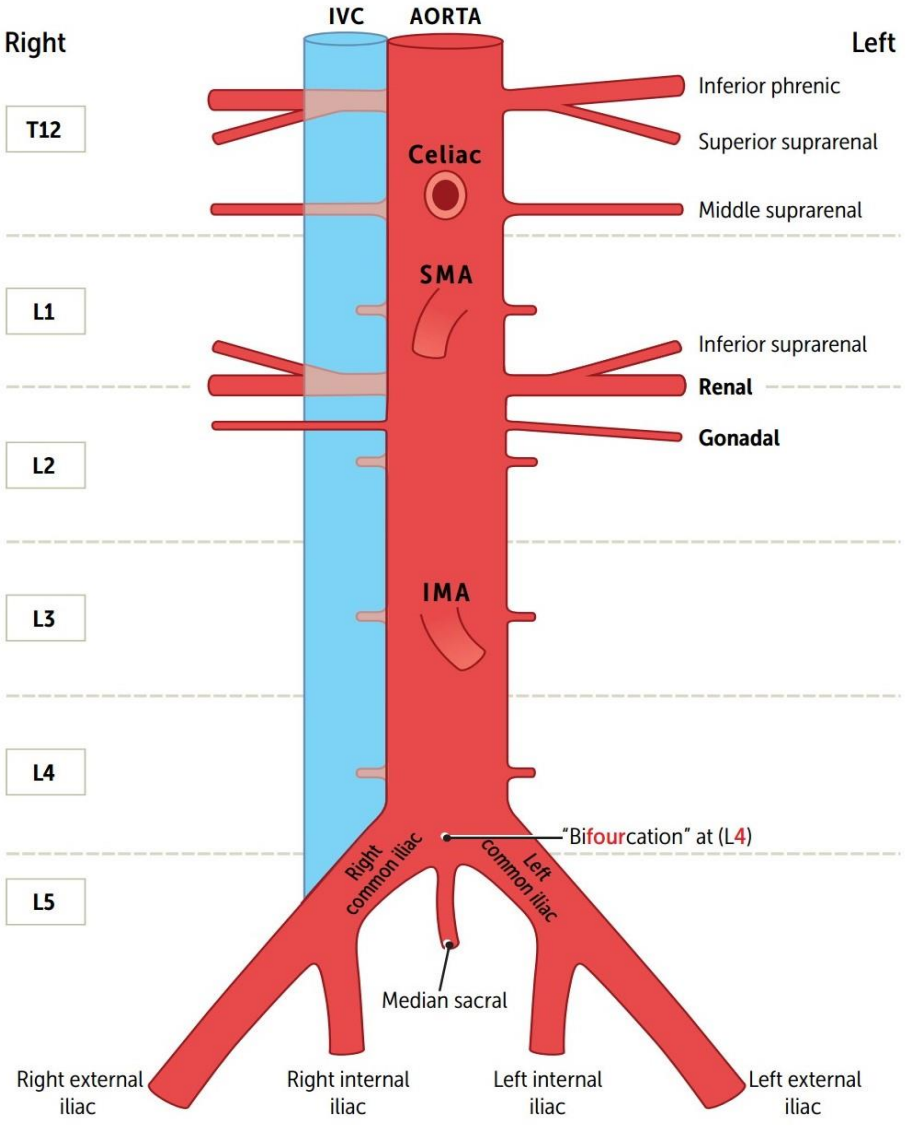
- The portal triad runs through the hepatoduodenal ligament and is composed of the hepatic artery, portal vein, and common bile duct.
- In the setting of traumatic liver injury with persistent bleeding, occlusion of the hepatoduodenal ligament can be performed to identify the vascular source (the Pringle maneuver).
- If liver bleeding does not cease when the portal triad is occluded, it is likely that there has been injury to the inferior vena cava or hepatic veins.


Pringle maneuver
Hepatoduodenal ligament
Common bile duct
Hepatic portal vein
Hepatic artery

Abdominal aorta and branches

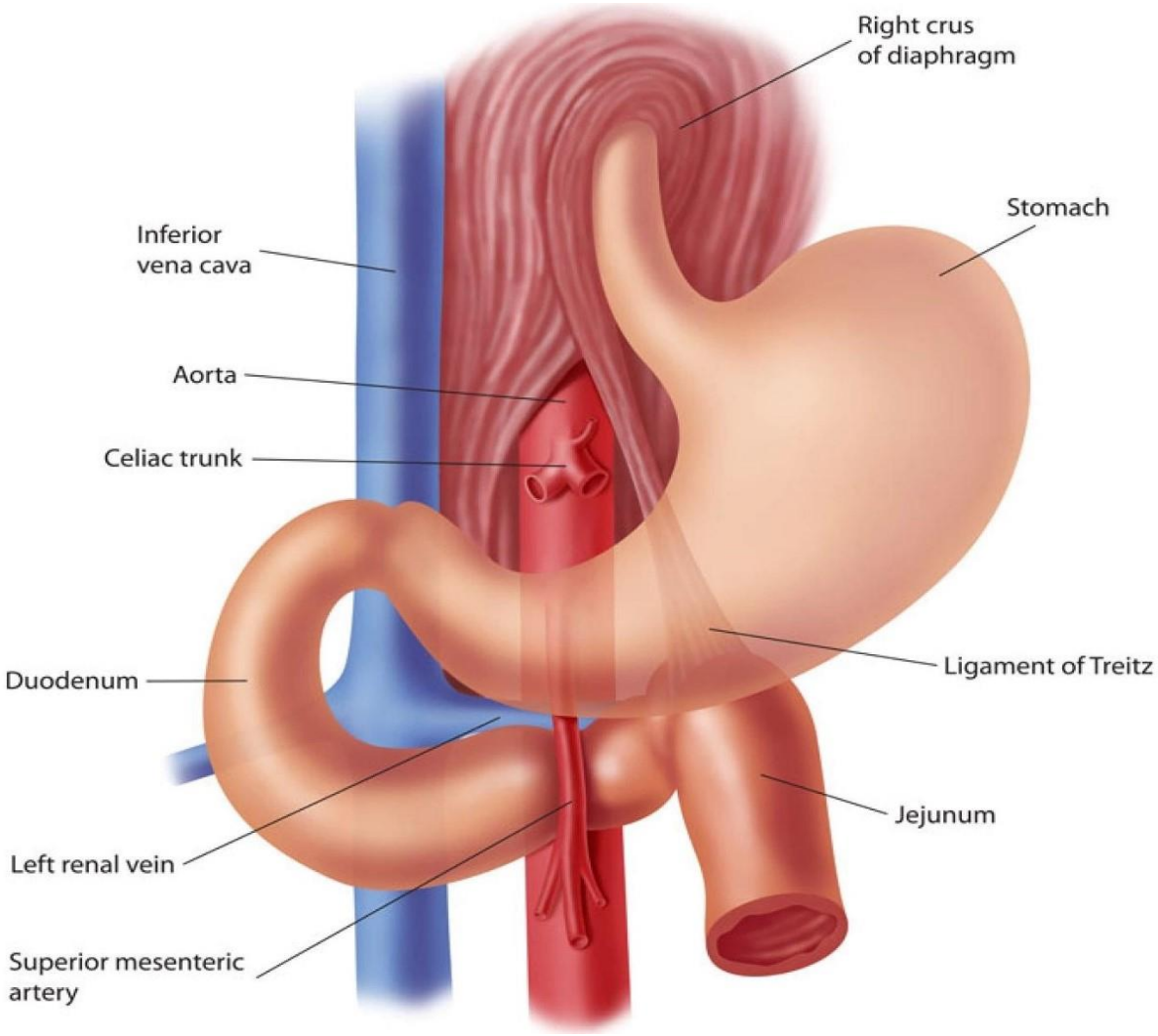
- Arteries supplying GI structures branch anteriorly.
- Arteries supplying non-GI structures branch laterally and posteriorly.
- Gastrointestinal blood supply and innervation:

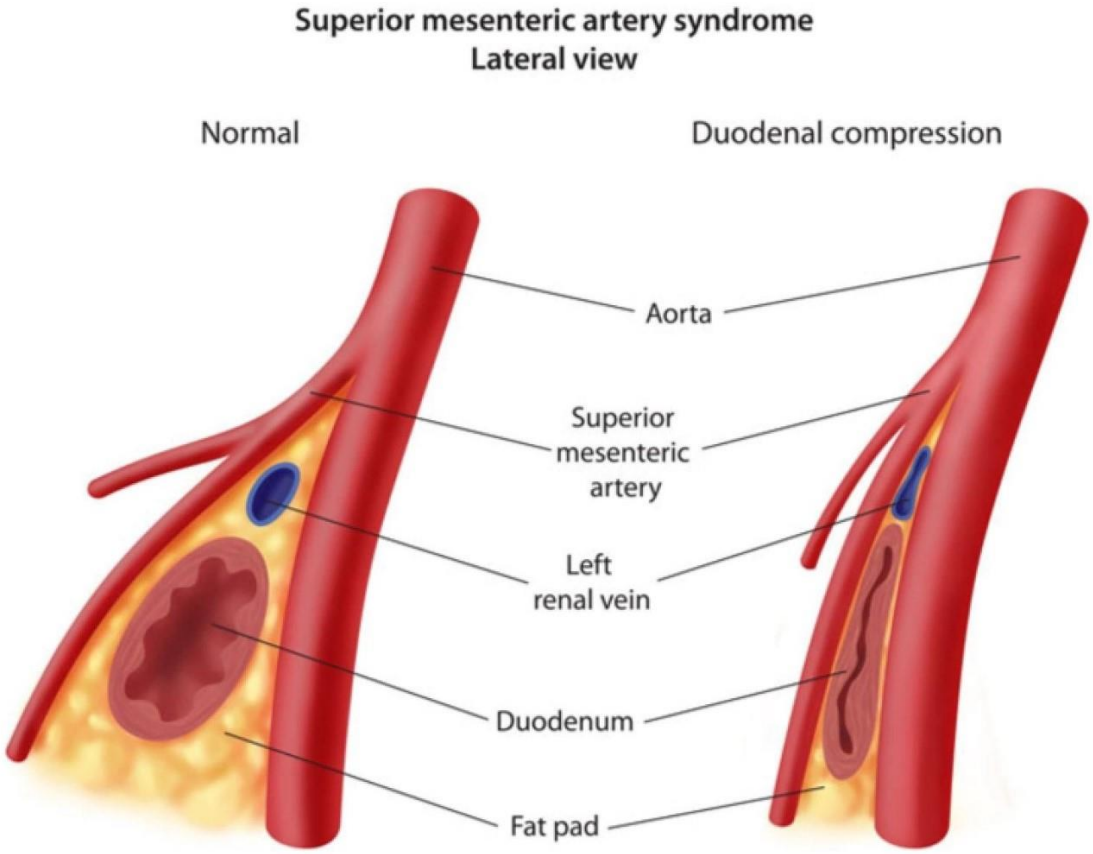
Embryonic Gut region	Artery	Parasympathetic Innervation	Vertebral Level	Structures supplied
Foregut	Celiac	Vagus	T12/L1	Pharynx and esophagus to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm).
Midgut	SMA	Vagus	L1	Distal duodenum to proximal 2/3 of transverse Colon.
Hindgut	IMA	Pelvic	L3	Distal 1/3 of transverse colon to upper portion of Rectum.



Superior mesenteric artery syndrome

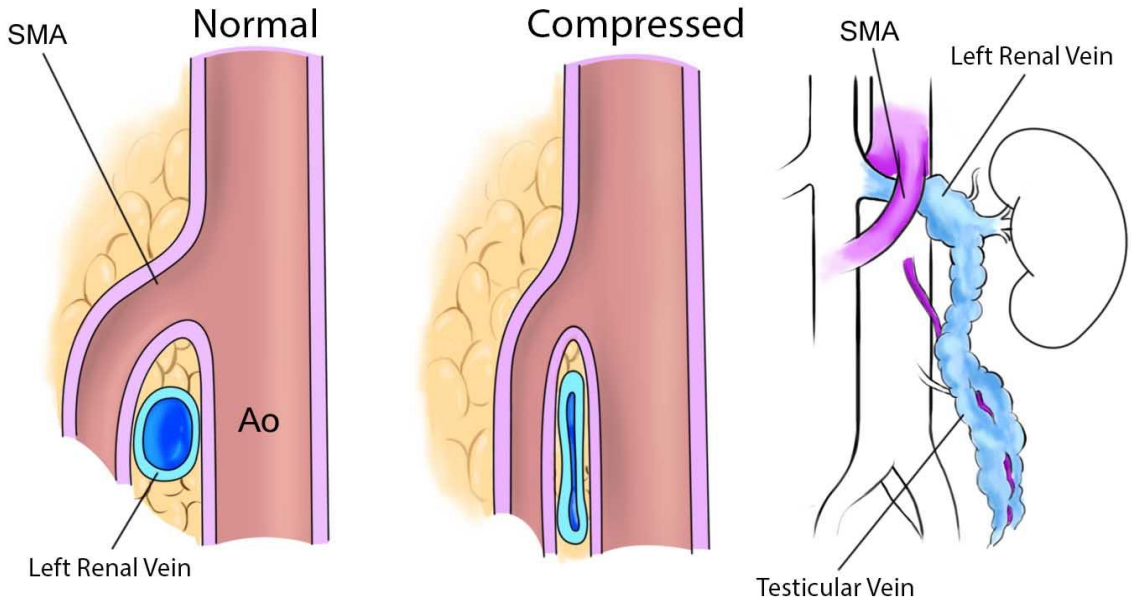
- Superior mesenteric artery syndrome occurs when the transverse portion of the duodenum is entrapped between the SMA and aorta, causing symptoms of partial intestinal obstruction.
- Narrowing of the aortomesenteric angle can occur with any condition that causes diminished mesenteric fat, including low body weight, recent weight loss, severe burns or other inducers of catabolism, and prolonged bed rest.
- It can also occur with pronounced lordosis or after surgical correction of scoliosis, as this procedure lengthens the spine resulting in decreased mobility of the SMA.
- Characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when transverse (third) portion of duodenum is compressed between SMA and aorta.





Nutcracker syndrome

- Compression of left renal vein between superior mesenteric artery and aorta.
- Characterized by abdominal (flank) pain and gross hematuria (from rupture of thin-walled renal varicosities).

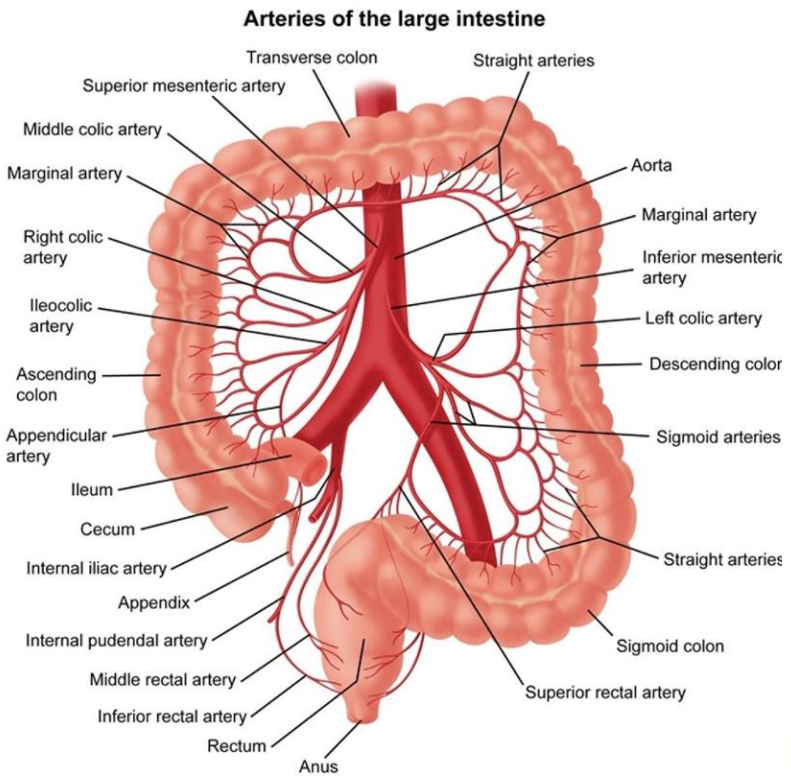


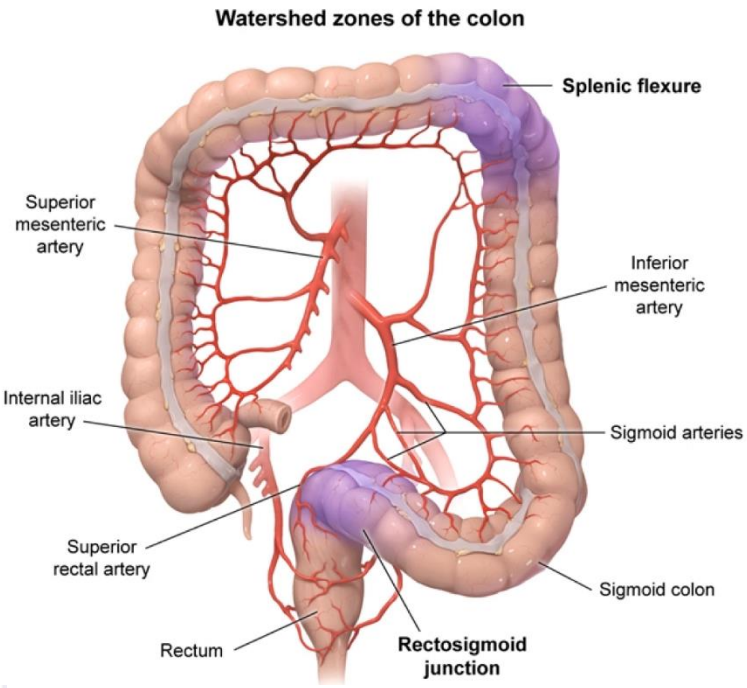
❖ N.B:

1. Two areas of the colon have dual blood supply from distal arterial branches ("watershed regions") → susceptible in colonic ischemia:

- Splenic flexure: SMA and IMA.
- Rectosigmoid junction: the last sigmoid arterial branch from the IMA and superior rectal artery.

▪ It typically follows an episode of hypotension (Ischemic colitis is a common complication of vascular surgery).





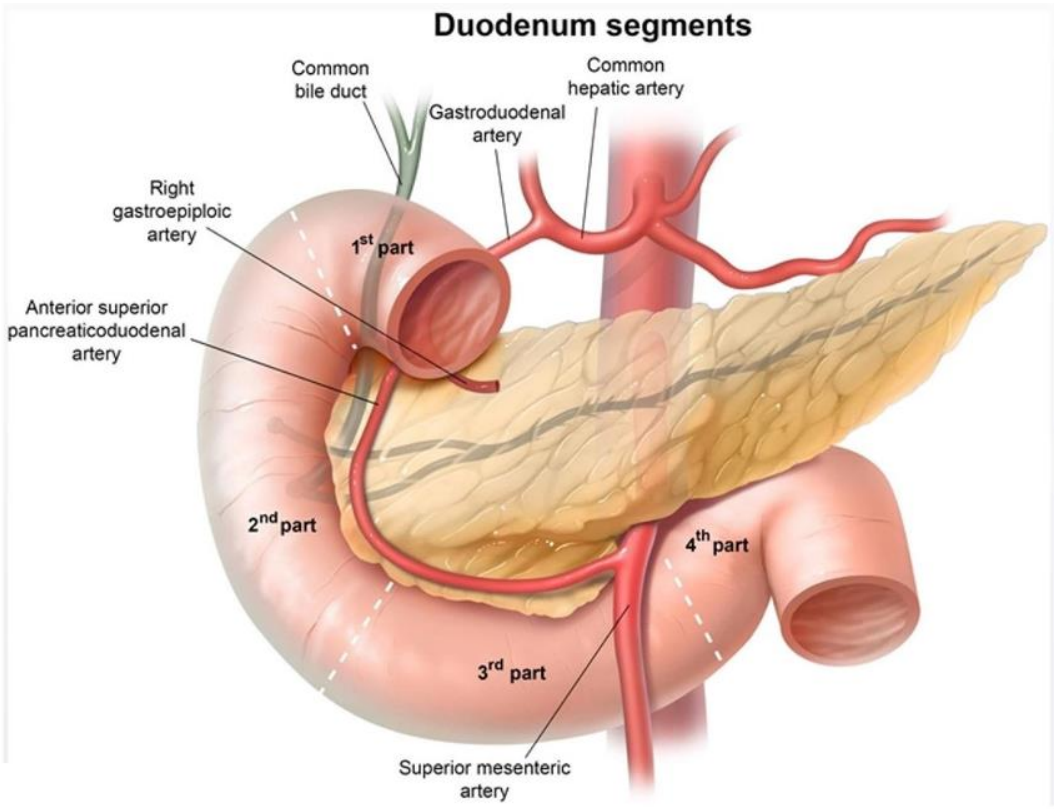
2. The first part of the duodenum emerges from the pylorus of the stomach and is horizontally oriented over the first lumbar vertebra. It is the only part of the duodenum that is not retroperitoneal.

▪ The second part of the duodenum courses interiorly from the level of L1 to L3. This part of the duodenum is in close relation to the head of the pancreas and contains the ampulla of Vater, the site where pancreatic and common bile duct secretions are released.

▪ The third part of the duodenum courses horizontally over L3, the abdominal aorta, and the inferior vena cava. It is in close association with the uncinate process of the pancreas and the superior mesenteric artery and vein.

▪ Small bowel malignancies are rare; if they occur in the third part of the duodenum, anterior tumor invasion could compromise the superior mesenteric vessels.

▪ The fourth part of the duodenum courses superiorly and to the left of the L2 and L3 vertebrae and becomes the jejunum past the ligament of Treitz.


Duodenum segments
Common bile duct
Common hepatic artery
Gastroduodenal artery
Right gastroepiploic artery
1st part
Anterior superior pancreaticoduodenal artery
2nd part
4th part
3rd part
Superior mesenteric artery

Celiac trunk

- The vascular supply to the upper abdomen mainly comes from the celiac trunk (celiac artery), which is the first anterior branch of the abdominal aorta.

- The celiac trunk branches into the left gastric, common hepatic, and splenic arteries:

A. The left gastric artery further divides into the esophageal and stomach branches, which supply blood to the abdominal esophagus and upper stomach.

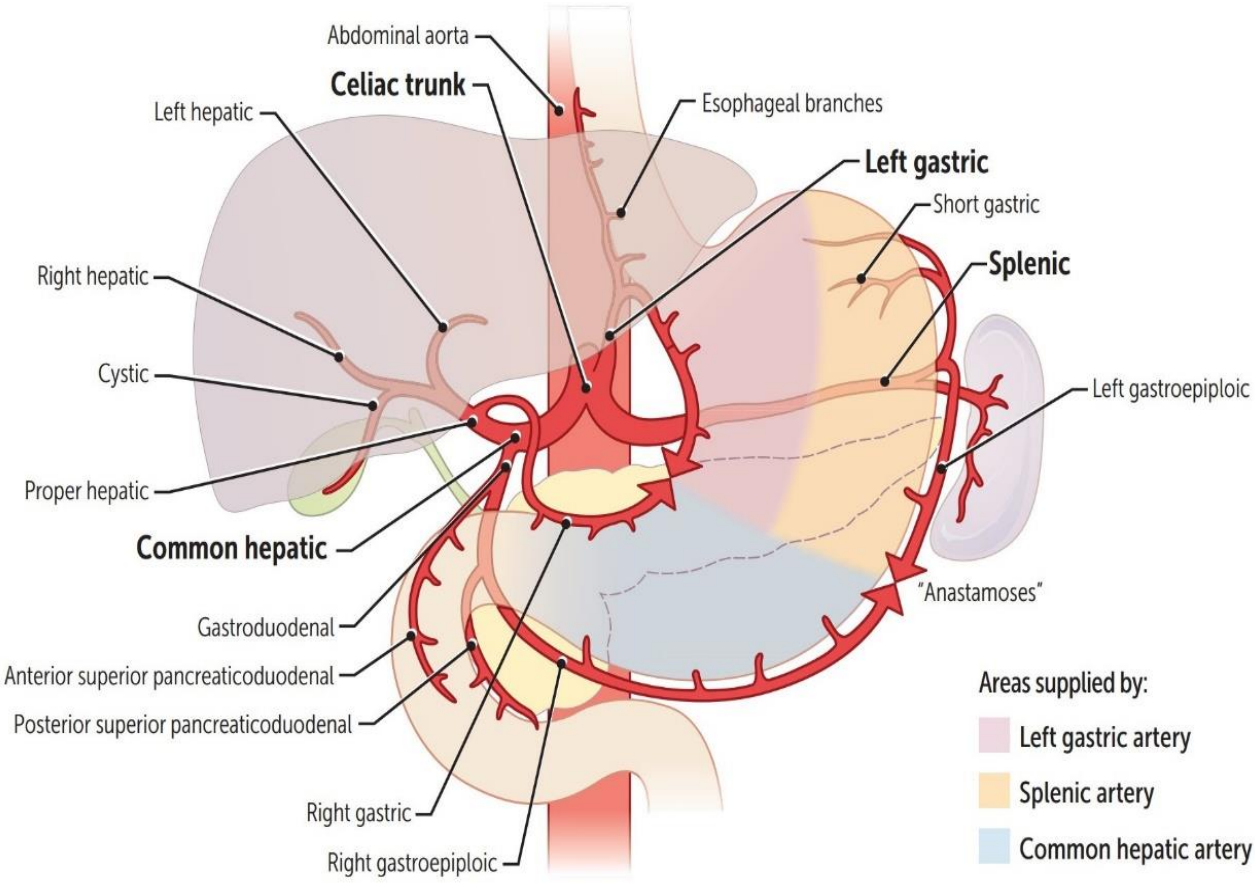
B. The splenic artery and its branches (dorsal pancreatic, short gastric, left gastroepiploic, and greater pancreatic arteries) provide blood to the spleen, pancreas, and gastric fundus.

C. The common hepatic artery further divides into the gastroduodenal, right gastric, and proper hepatic arteries:

- The gastroduodenal artery supplies blood to the pylorus, proximal duodenum, and pancreatic head.

- The right gastric artery supplies blood to the gastric fundus along the lesser curvature before combining with the left gastric artery.

- The proper hepatic artery runs with the portal vein and common bile duct to form the portal triad in the liver.



- Strong anastomoses exist between:

- Left and right gastroepiploics.

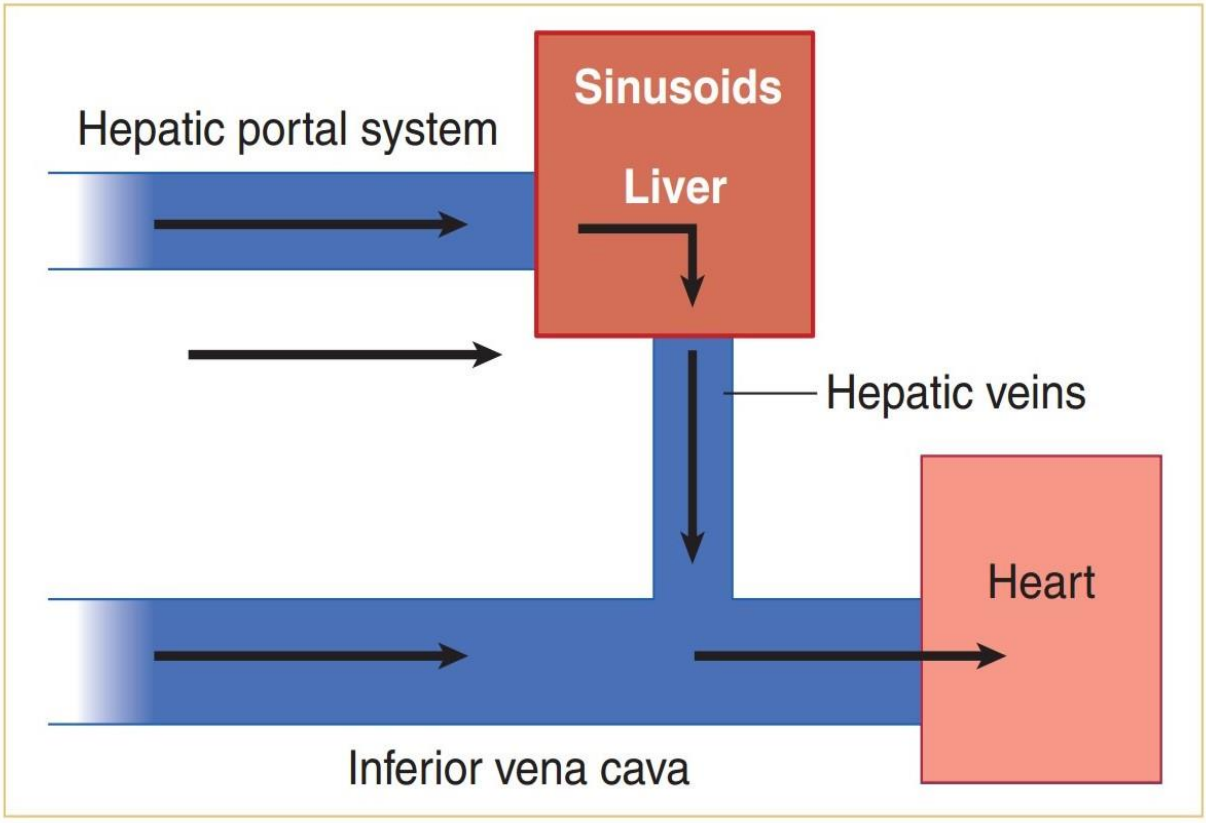
- Left and right gastrics

❖ N.B:

- The splenic artery originates from the celiac artery and gives off several branches to the stomach and pancreas (pancreatic, short gastric, and left gastroepiploic arteries) before finally reaching the spleen.
- The short gastric arteries and the left gastroepiploic artery arise from the splenic artery immediately after it passes the greater curvature of the stomach.
- The short gastric arteries have very poor anastomoses, and the tissue supplied by them is vulnerable to ischemic injury following splenic artery blockage.
- In contrast, tissues supplied by the left gastroepiploic artery can be alternatively supplemented by its strong anastomotic connection with the right gastroepiploic artery

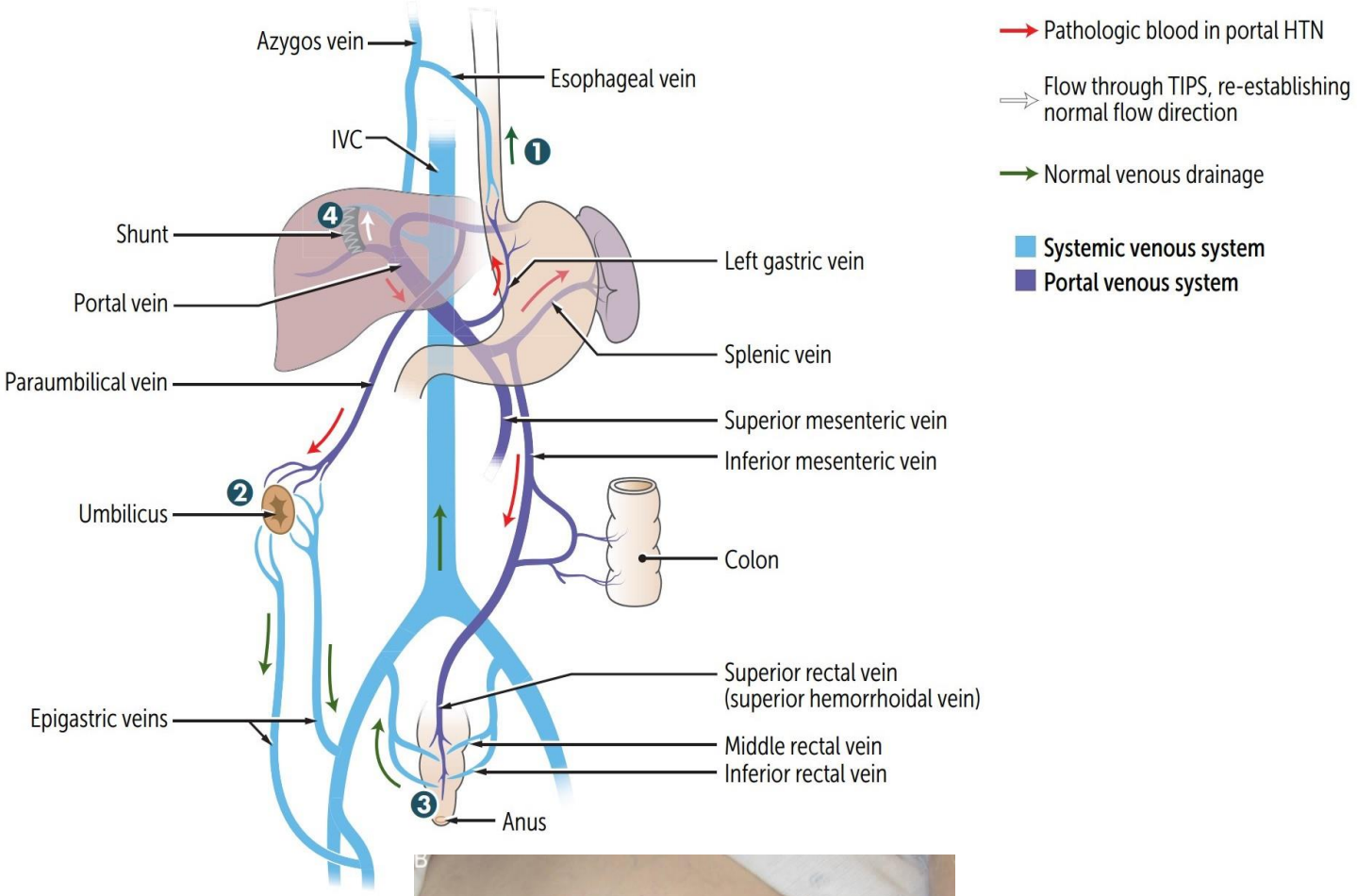
Portosystemic anastomoses

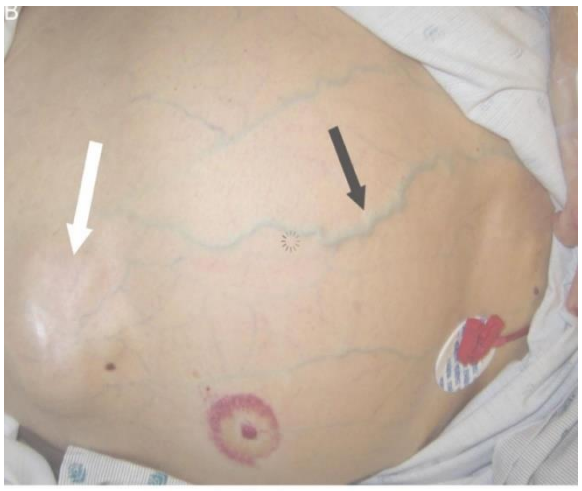
- An important cause of cirrhosis-related morbidity and mortality is the development of variceal hemorrhaging as a direct consequence of portal hypertension.
- Cirrhosis (of any type) represents the End-stage of progressive hepatic fibrosis. It is characterized by distortion of the hepatic architecture and formation of regenerative nodules.
- Cirrhosis is the most common cause of portal hypertension, which arises from increased resistance to portal flow at the hepatic sinusoids.
- Chronic portal hypertension leads to dilation of small, pre-existing vascular channels between the portal and systemic circulations.
- These dilated collateral vessels (portosystemic anastomoses) commonly form in the anterior abdomen (caput medusae), lower rectum (anorectal varices), and inferior end of the esophagus (esophageal varices).
- Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. Can precipitate hepatic encephalopathy.



Site of anastomosis	Clinical sign	Portal ↔ Systemic
Esophagus	Esophageal varices	Left gastric ↔ azygos
Umbilicus	Caput medusae	Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.
Rectum	Anorectal varices	Superior rectal ↔ middle and inferior rectal

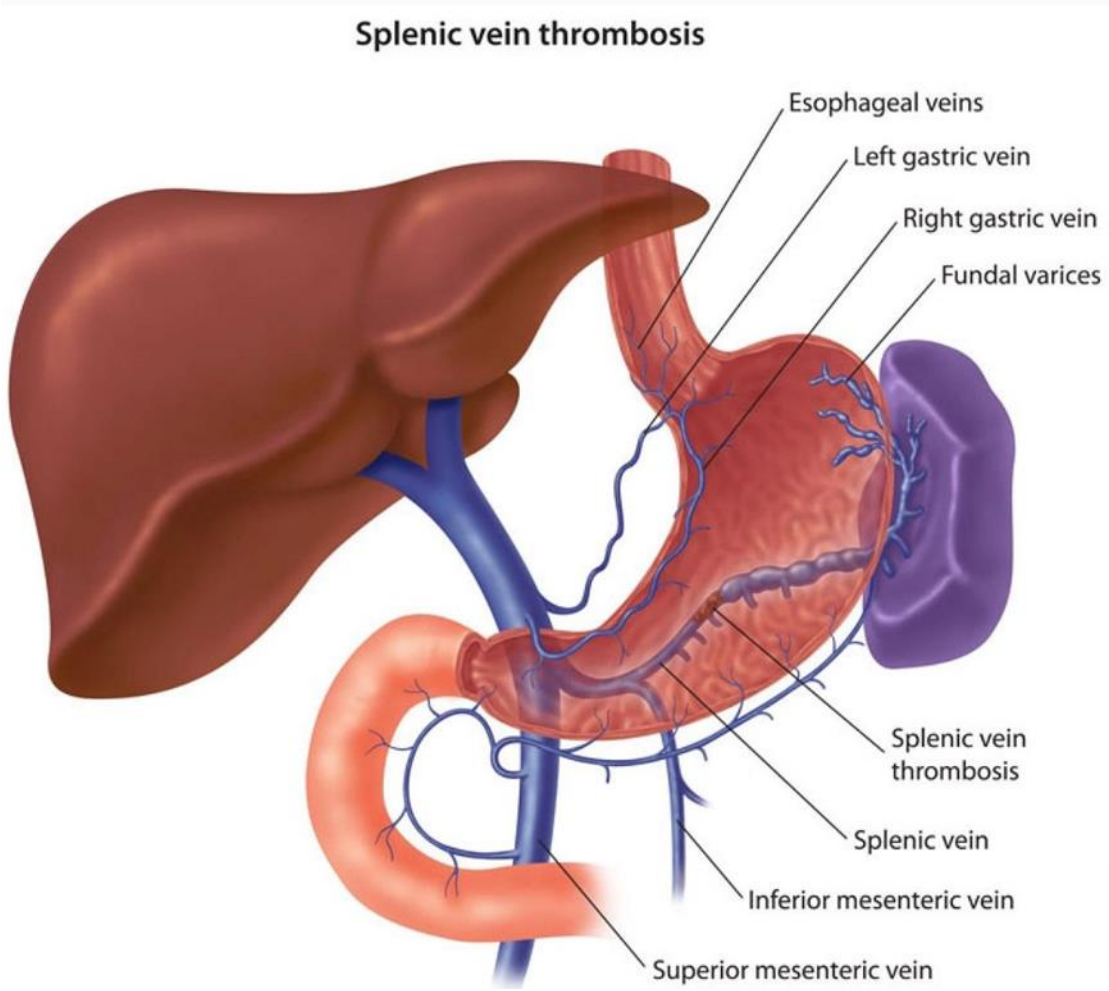
- Varices of gut, butt, and caput (medusae) are commonly seen with portal hypertension.





❖ N.B:

- Gastric varices are dilated submucosal veins that can cause life-threatening bleeding in the upper gastrointestinal tract.
- The varices are commonly due to portal hypertension, which can be a complication of cirrhosis. Gastric varices can also be seen with splenic vein thrombosis due to chronic pancreatitis, pancreatic cancer, and abdominal tumors.
- Pancreatic inflammation (pancreatitis, pancreatic cancer) can cause a blood clot within the splenic vein.
- The splenic vein runs along the posterior surface of the pancreas and can develop a blood clot from pancreatic inflammation. The short gastric veins drain the fundus of the stomach into the splenic vein. Splenic vein thrombosis can increase pressure in the short gastric veins and cause gastric varices only in the fundus. The rest of the stomach and esophagus are usually not affected (isolated gastric varices).



Pectinate (dentate) line

- Also called dentate line. Formed where endoderm (hindgut) meets ectoderm.

- Above pectinate line:

- Internal hemorrhoids, adenocarcinoma.

- Internal hemorrhoids receive visceral innervation and are therefore not painful.

- Below pectinate line:

- External hemorrhoids, anal fissures, squamous cell carcinoma.

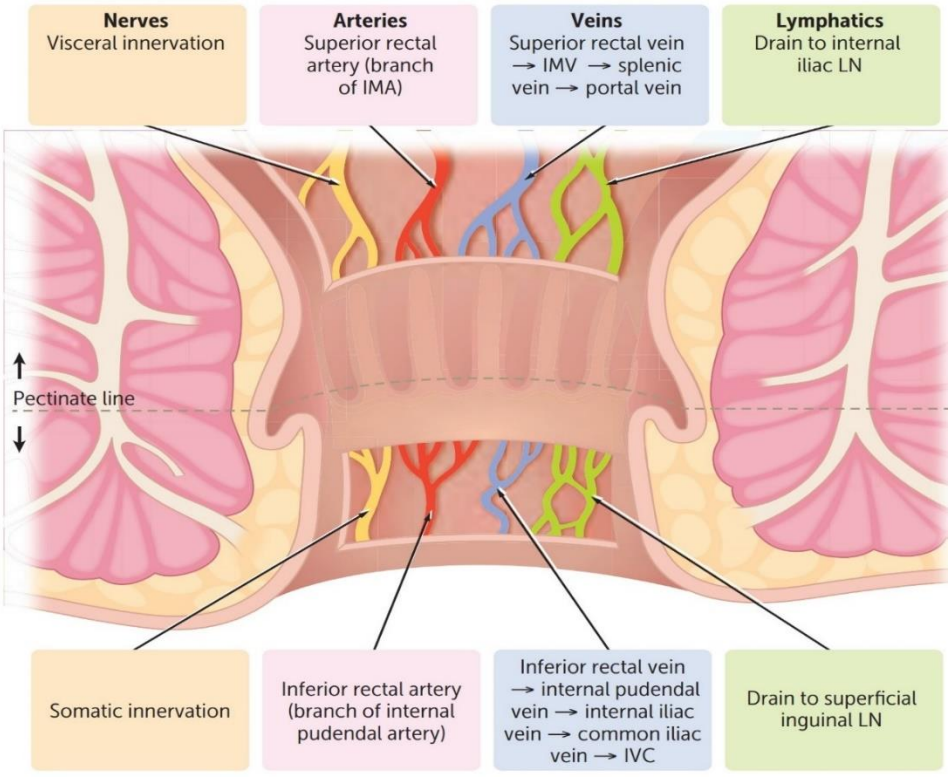
- External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore painful if thrombosed.

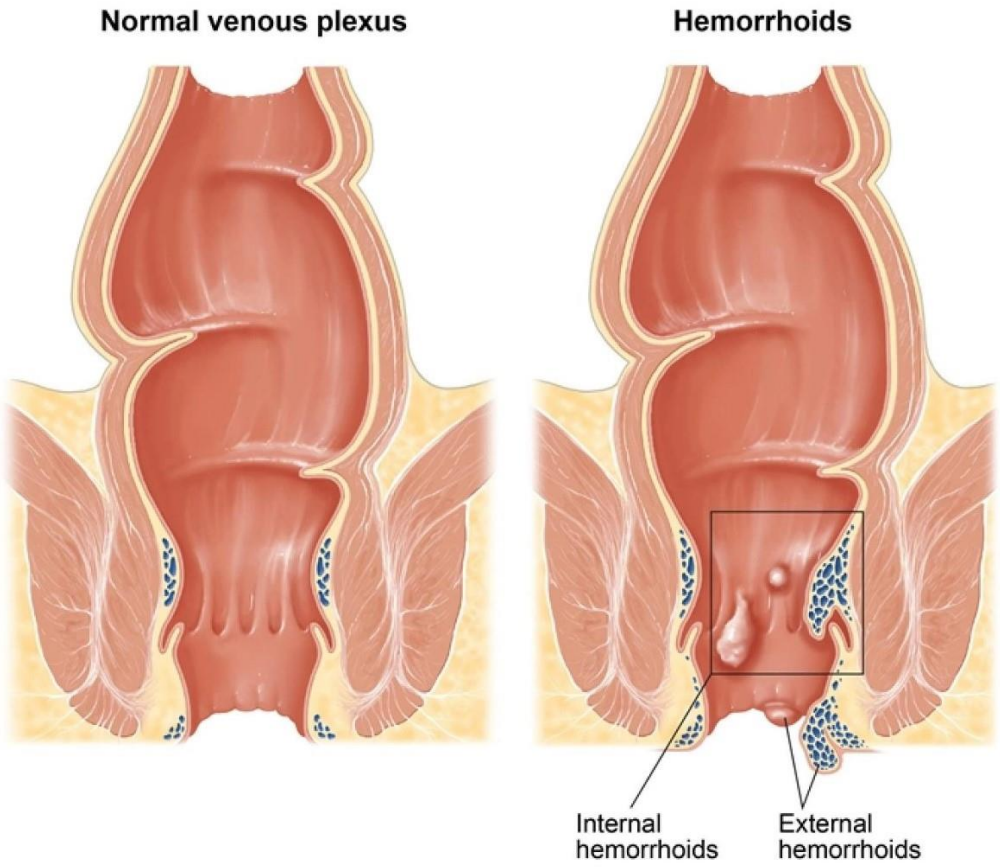
- Internal hemorrhoids

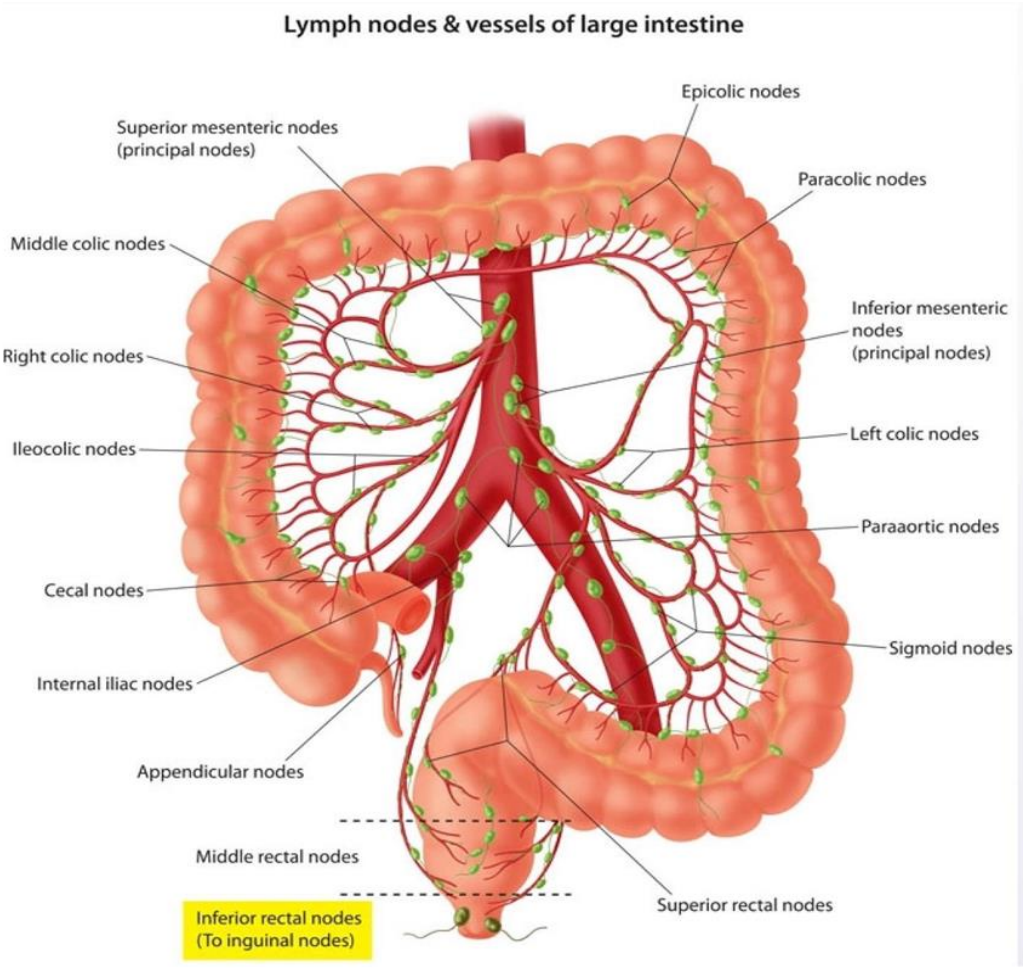
- Originate above the dentate line and are covered by columnar epithelium. They have autonomic innervation from the inferior hypogastric plexus, which is only sensitive to stretch and not pain, temperature, or touch.

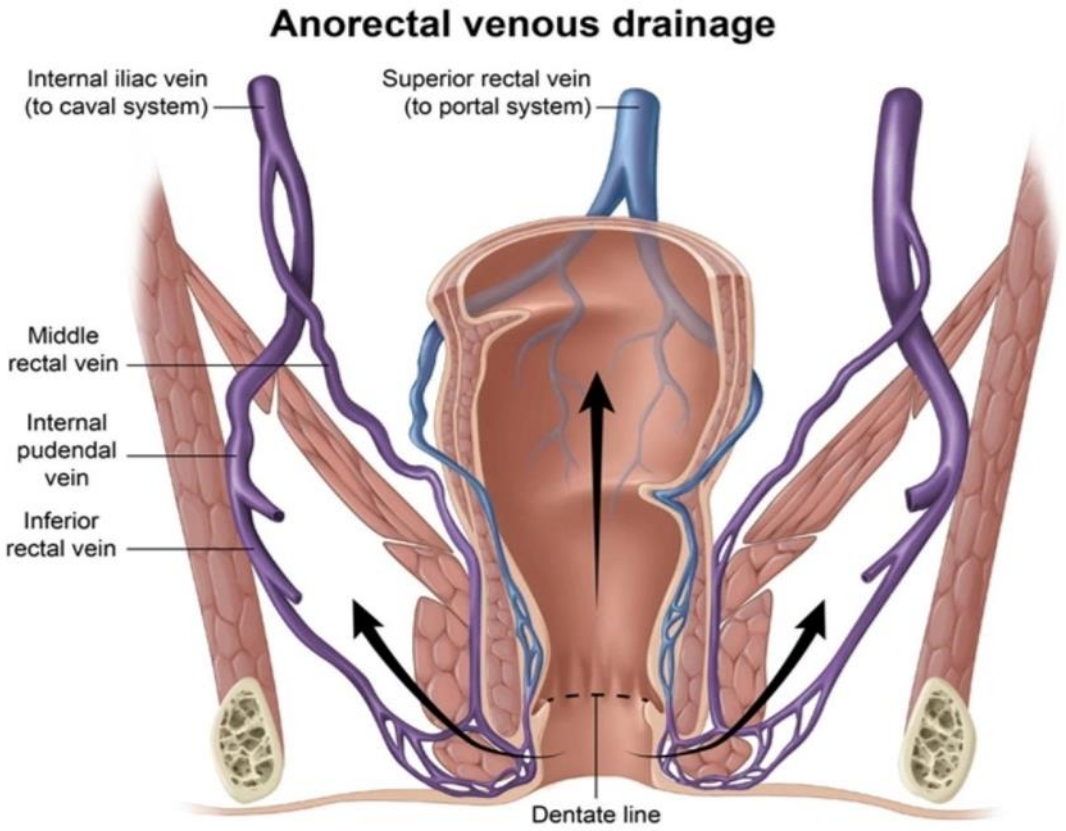
- External hemorrhoids:

- Originate below the dentate line, are covered by modified squamous epithelium and have cutaneous (somatic) nervous innervation from the inferior rectal nerve, a branch of the pudendal nerve. Branches of the pudendal nerve supply the perineum and external genitalia in males and females and are very sensitive to touch, temperature, and pain. External hemorrhoids are generally asymptomatic but can become exquisitely painful if they thrombose.




Normal venous plexus
Hemorrhoids
Internal hemorrhoids
External hemorrhoids


Lymph nodes & vessels of large intestine
Epicolic nodes
Superior mesenteric nodes (principal nodes)
Paracolic nodes
Middle colic nodes
Inferior mesenteric nodes (principal nodes)
Right colic nodes
Left colic nodes
Ileocolic nodes
Paraaortic nodes
Cecal nodes
Sigmoid nodes
Internal iliac nodes
Appendicular nodes
Middle rectal nodes
Superior rectal nodes
Inferior rectal nodes (To inguinal nodes)


Anorectal venous drainage
Internal iliac vein
(to caval system)
Superior rectal vein
(to portal system)
Middle
rectal vein
Internal
pudendal
vein
Inferior
rectal vein
Dentate line

Digestive tract anatomy

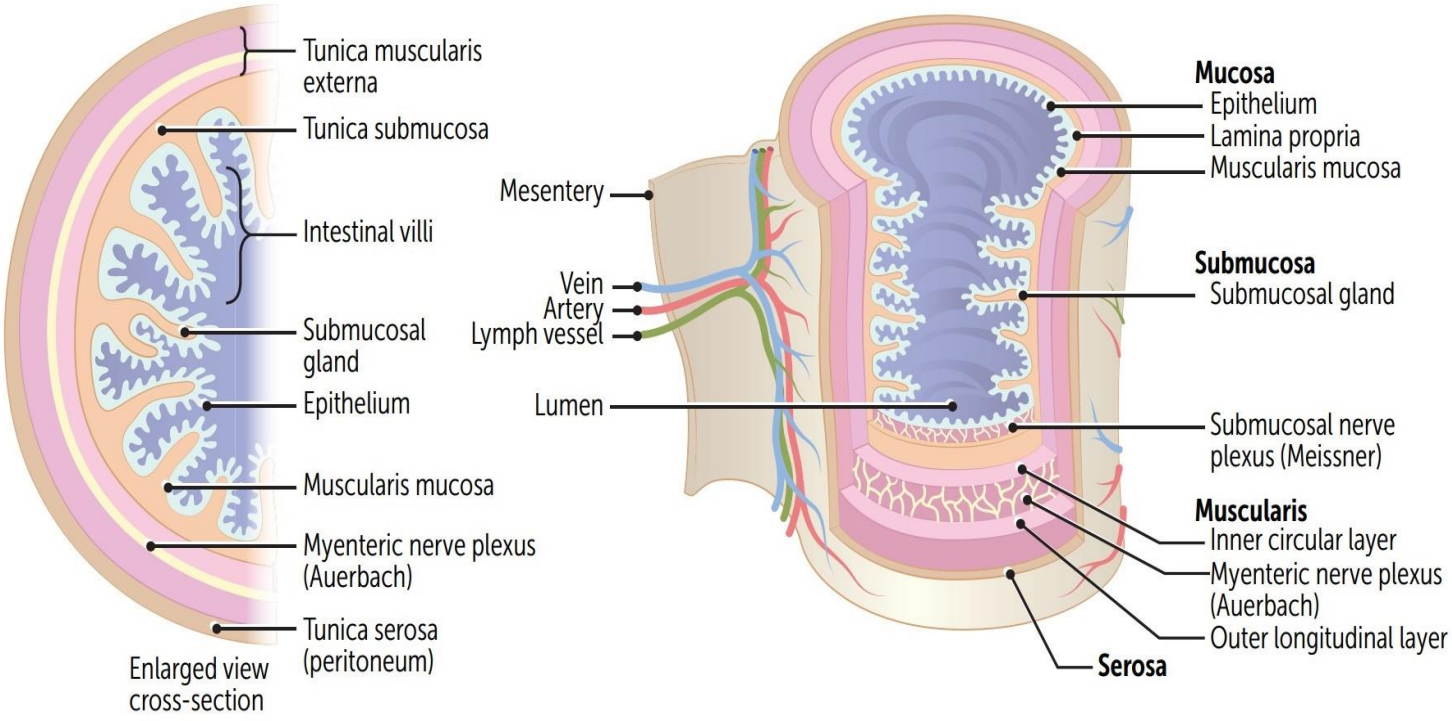
- Layers of gut wall (inside to outside - MSMS):

- Mucosa: The mucosa is the innermost layer and has 3 components: epithelium, lamina propria, muscularis mucosa.

- Submucosa:
  - A layer of loose areolar connective tissue that attaches the mucosa to the muscularis externa and houses the larger blood vessels and mucous-secreting glands.
  - Includes Submucosal nerve plexus (Meissner), Secretes fluid.

- Muscularis externa:
  - The muscularis externa is usually comprised of 2 layers of muscle: an inner circular and an outer longitudinal. The muscularis externa controls the lumen size and is responsible for peristalsis.
  - Includes Myenteric nerve plexus (Auerbach), Motility.

- Serosa (when intraperitoneal), adventitia (when retroperitoneal).



- Frequencies of basal electric rhythm (slow waves):

- Stomach: 3 waves/min.

- Duodenum: 12 waves/min.

- Ileum: 8-9 waves/min.

Digestive tract histology

- Esophagus:

- Nonkeratinized stratified squamous epithelium.

- The muscularis externa of the esophagus consists of striated muscle in the upper third, smooth muscle in the distal third, and a combination of both in the middle third.

- Stomach:

- The mucosa of the stomach is thrown into folds (rugae) when empty, but disappears when the stomach is full. The surface is lined by a simple columnar epithelium.

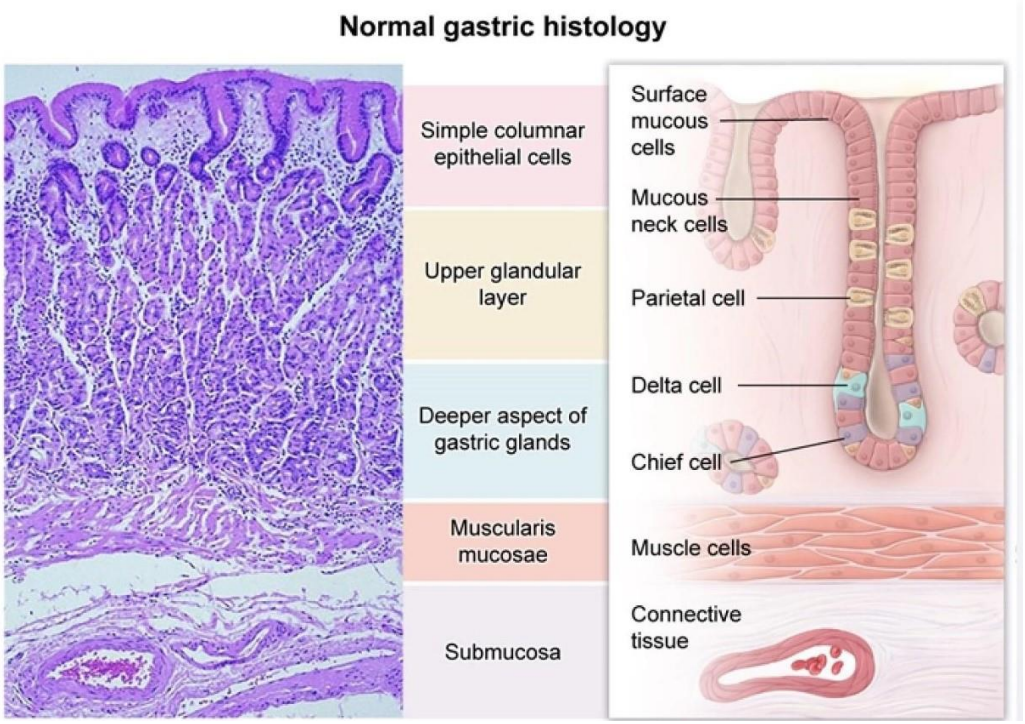
- Gastric pits form numerous deep tubular invaginations that line the inner surface of the stomach. The gastric pits are closely spaced; they penetrate into the thickness of the mucosa and extend into gastric glands.

- Gastric glands (A): deliver gastric juice (containing HCl and enzymes) to each pit, and from there to the stomach lumen. There are about 5 million glands in the stomach, secreting some 2 liters of fluid per day.

- Mucous-secreting cells: produce a thick layer of mucous which covers and protects the stomach.

- Oxyntic or parietal cells secrete HCl into the stomach lumen in response to histamine, gastrin, and acetylcholine. These cells also secrete intrinsic factor (a glycoprotein necessary for absorption of vitamin B12).

- Chief or peptic cells secrete pepsinogen, an enzyme precursor that is stored in secretory (zymogen) granules before its induced secretion. Low pH, in the stomach lumen, converts pepsinogen to pepsin.



- Duodenum:

- Villi and microvilli which are finger-like outpouchings that project into the lumen ↑ absorptive surface (B).

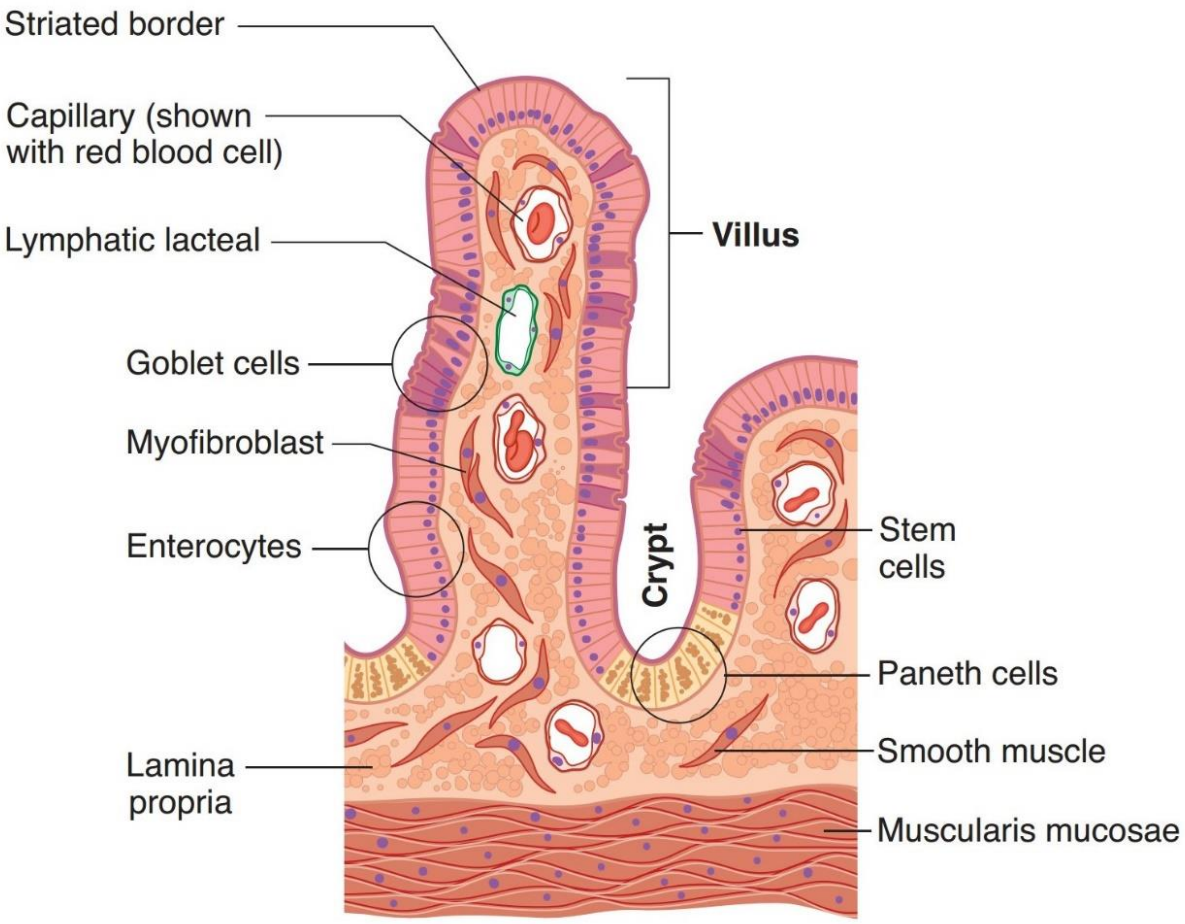
- Brunner glands (alkaline mucus secreting cells of submucosa) and crypts of Lieberkühn (contain stem cells that replace enterocytes/goblet cells and Paneth cells that secrete defensins, lysozyme, and TNF).

- Mucous production occurs in surface epithelial cells throughout the GI tract, by Brunner glands in the duodenum and goblet cells in the mucosa throughout the intestine.

- Mucous functions include lubrication of the GI tract, binding bacteria, and trapping immunoglobulins where they have access to pathogens.

- The luminal surface of the small intestine is perforated by the openings of numerous tubular invaginations (the crypts of Lieberkühn). The crypts penetrate through the lamina propria and reach the muscularis mucosae.

- Unique to the duodenum, the compound tubular Brunner's glands of the submucosa secrete alkaline mucus into ducts that empty into the crypts of Lieberkühn.



Small Intestine Mucosal Histology

- Jejunum:

- Villi, crypts of Lieberkühn, and plicae circulares (also present in distal duodenum) C.

- Plicae circulares (circular folds) are foldings of the inner surface that involve both mucosa and submucosa. Plicae circulares increase the surface area.

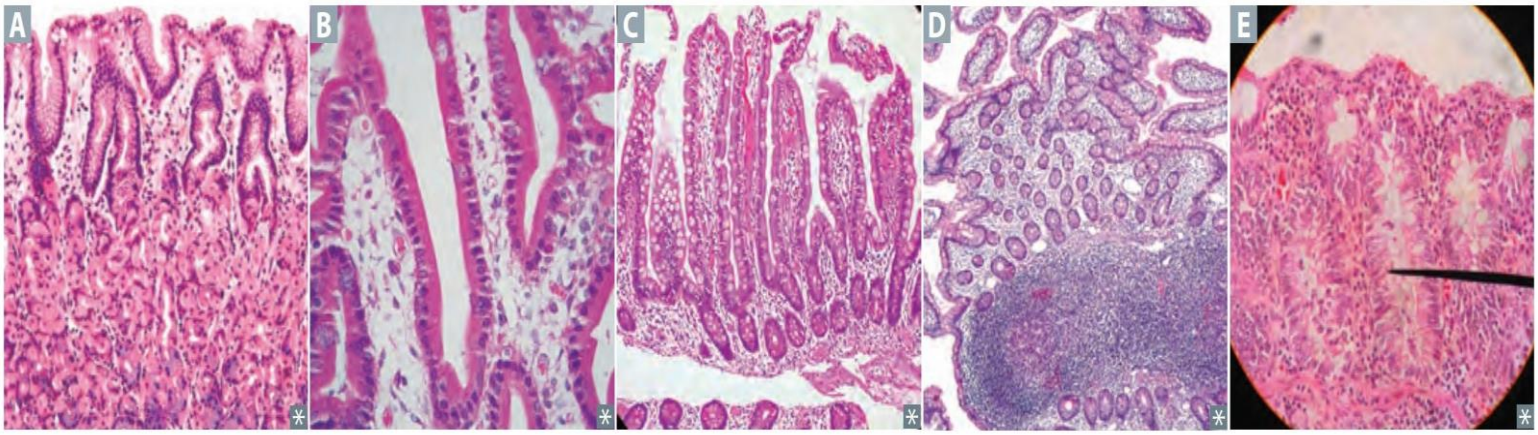
- Ileum:

- Peyer patches D (lymphoid aggregates specific to the ileum in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn.

- Largest number of goblet cells in the small intestine.

- Colon:

- Crypts of Lieberkühn with abundant goblet cells, but no villi (E).



❖ N.B:

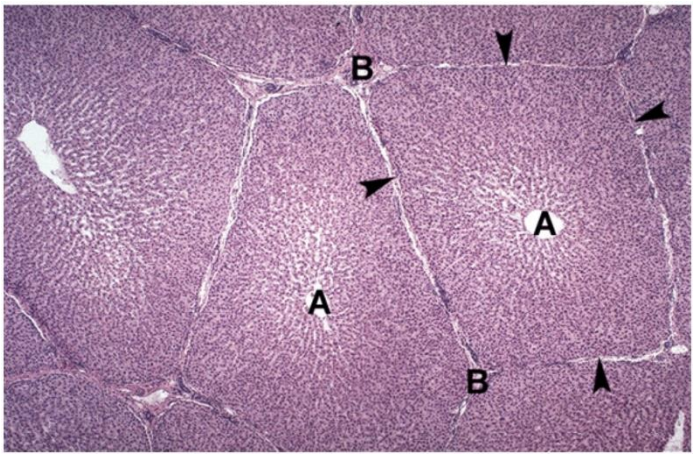
- The integrity of the small intestinal mucosa depends on the complete and rapid neutralization of hydrochloric acid in gastric contents. This is accomplished by alkaline secretions from 2 primary sources:

1. Submucosal (Brunner) glands secrete copious amounts of alkaline mucus into the duodenum. The ducts of these glands pass through the muscularis mucosa and terminate in the mucosal crypts (crypts of Lieberkuhn).
2. The epithelial cells of the pancreatic ductules and ducts produce watery secretions containing high concentrations of bicarbonate ions. The strongly alkaline pancreatic secretions are then emptied into the duodenum at the ampulla.

- Tactile stimulation of the duodenal mucosa and increased parasympathetic activity following meals induce bicarbonate secretion from the submucosal glands.
- In addition, the presence of acid in the duodenum and jejunum causes release of secretin from the mucosa, stimulating secretion of bicarbonate from the submucosal glands and pancreas.
- Excess gastric acid secretion, such as seen in Helicobacter pylori infection, can cause increased production of secretin that, over time, can lead to hyperplasia of the submucosal glands.

Liver tissue architecture

- The functional unit of the liver is made up of hexagonally arranged lobules surrounding the central vein with portal triads on the edges (consisting of a portal vein, hepatic artery, bile ducts, as well lymphatics)



- Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.
- Kupffer cells, which are specialized macrophages, form the lining of these sinusoids.
- Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated). When stimulated during liver injury, Ito cells may release type I collagen and other matrix components into the space of Disse, contributing to scarring of the liver in some diseases (cirrhosis due to ethanol).
- Blood flow is from the triads into the central vein and bile flow is opposite, from the central vein to the triads.
- The hepatocytes receiving the first blood flow (and the most oxygen and nutrients) are designated zone 1, while those receiving the last blood flow (and least oxygen and nutrients) are near the central veins and designated zone 3. Zone 2 hepatocytes are in between zones 1 and 3.
- <u>The metabolic activity of hepatocytes varies within the zones of the acinus:</u>

- Zone 1 hepatocytes are most involved in glycogen synthesis and plasma protein synthesis (albumin, coagulation factors and complement components).
- Zone 3 cells are most concerned with lipid, drug, and alcohol metabolism and detoxification.

- <u>Zone I (periportal zone):</u>

- Affected 1st by viral hepatitis.
- Ingested toxins (cocaine).

- <u>Zone II (intermediate zone):</u> Yellow fever.

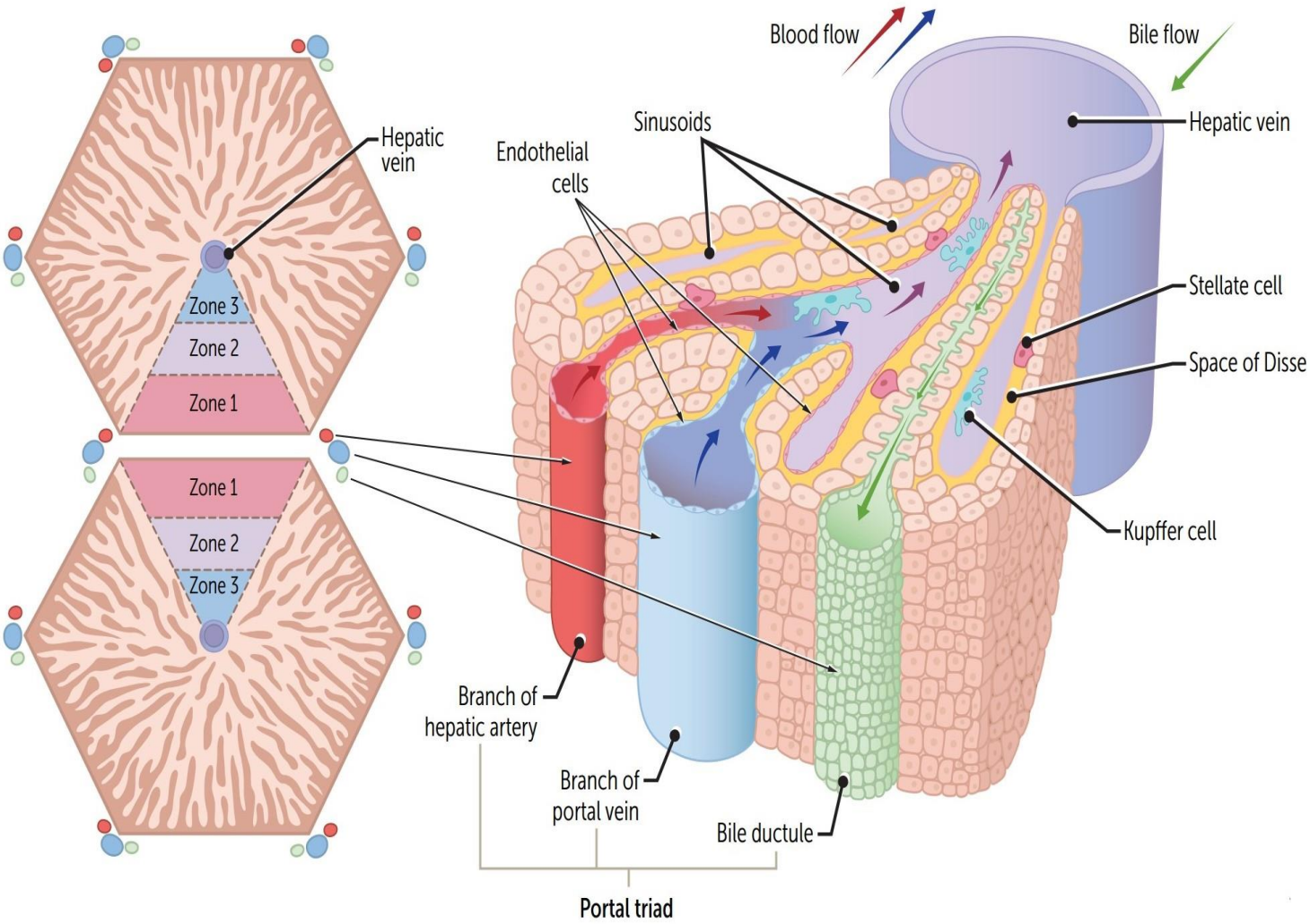
- Zone III: pericentral vein (centrilobular) zone:

- Affected 1st by ischemia.

- Contains cytochrome P-450 system.

- Most sensitive to metabolic toxins (ethanol, CCl4, halothane, rifampin, acetaminophen).

- Site of alcoholic hepatitis.



❖ N.B:

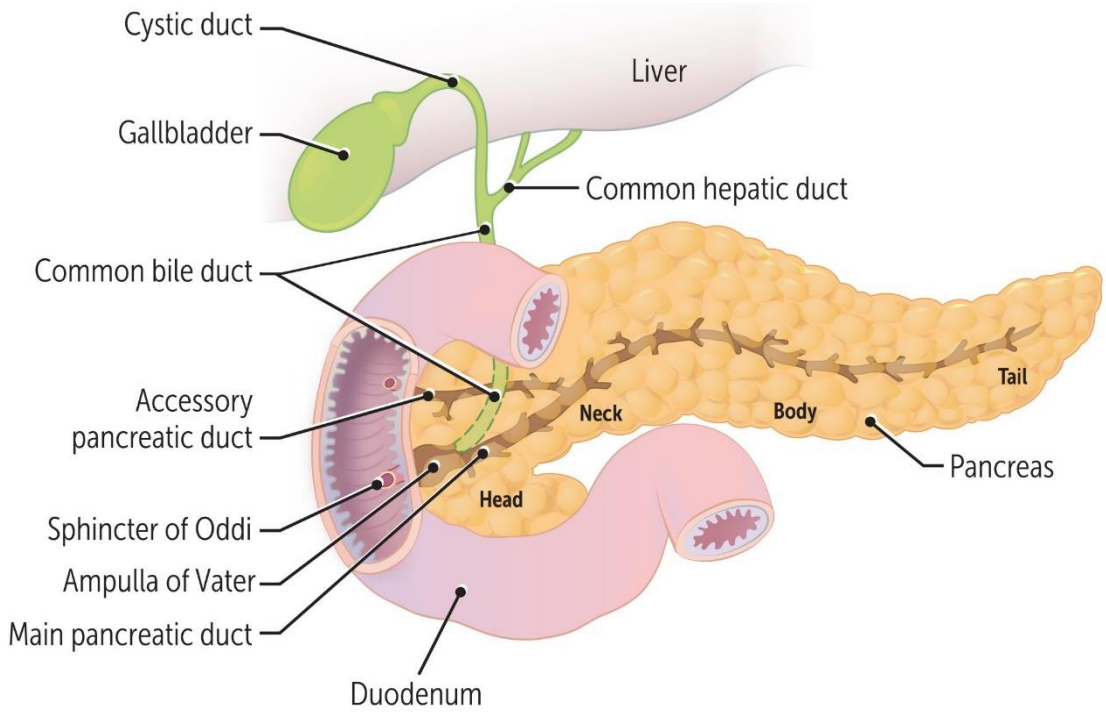
- Organ susceptibility to infarction after occlusion of a feeding artery is ranked from greatest to least as follows: central nervous system, myocardium, kidney, spleen, and liver.
- The presence of a dual and/or collateral blood supply (as seen in the liver, which is supplied by the hepatic artery and portal vein) enables an organ to tolerate arterial occlusion better than those with end-arterial circulations.
- The notable exception is when a transplanted liver undergoes hepatic artery thrombosis. In this case, the liver can develop biliary tree infarction and organ failure because the collateral blood supply is severed during transplantation.

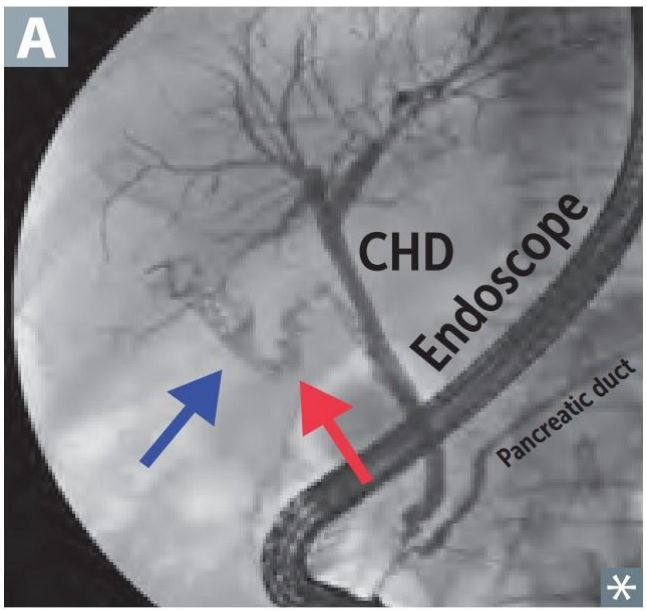
Biliary structures

- Gallstones (filling defects, red arrows in A) that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

- Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).

- Cholangiography shows filling defects in gallbladder (blue arrow) and cystic duct (red arrow).





Femoral region

- Organization:

- Lateral to medial: Nerve-Artery-Vein-Lymphatics.

- You go from lateral to medial to find your NAVeL.

- Femoral triangle:

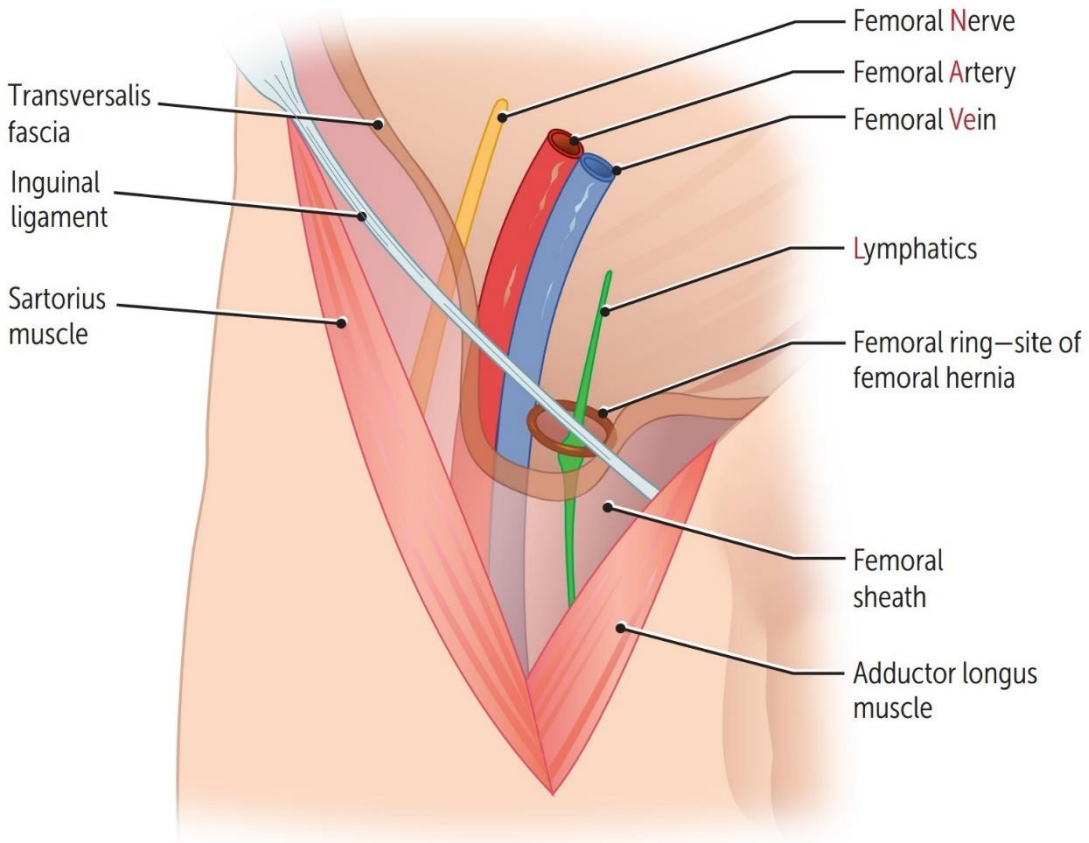
- Contains femoral nerve, artery, vein.

- Venous near the penis.

- Femoral sheath:

- Fascial tube 3-4 cm below inguinal ligament.

- Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.



Inguinal canal

- Anterior Abdominal Wall Layers:

A. Skin.

B. Superficial fascia:

- Camper (fatty) fascia is the outer.
- Scarpa (fibrous) fascia is the deeper layer of superficial fascia devoid of fat.

C. External oblique layer (Muscle, Aponeurosis, Fascia).

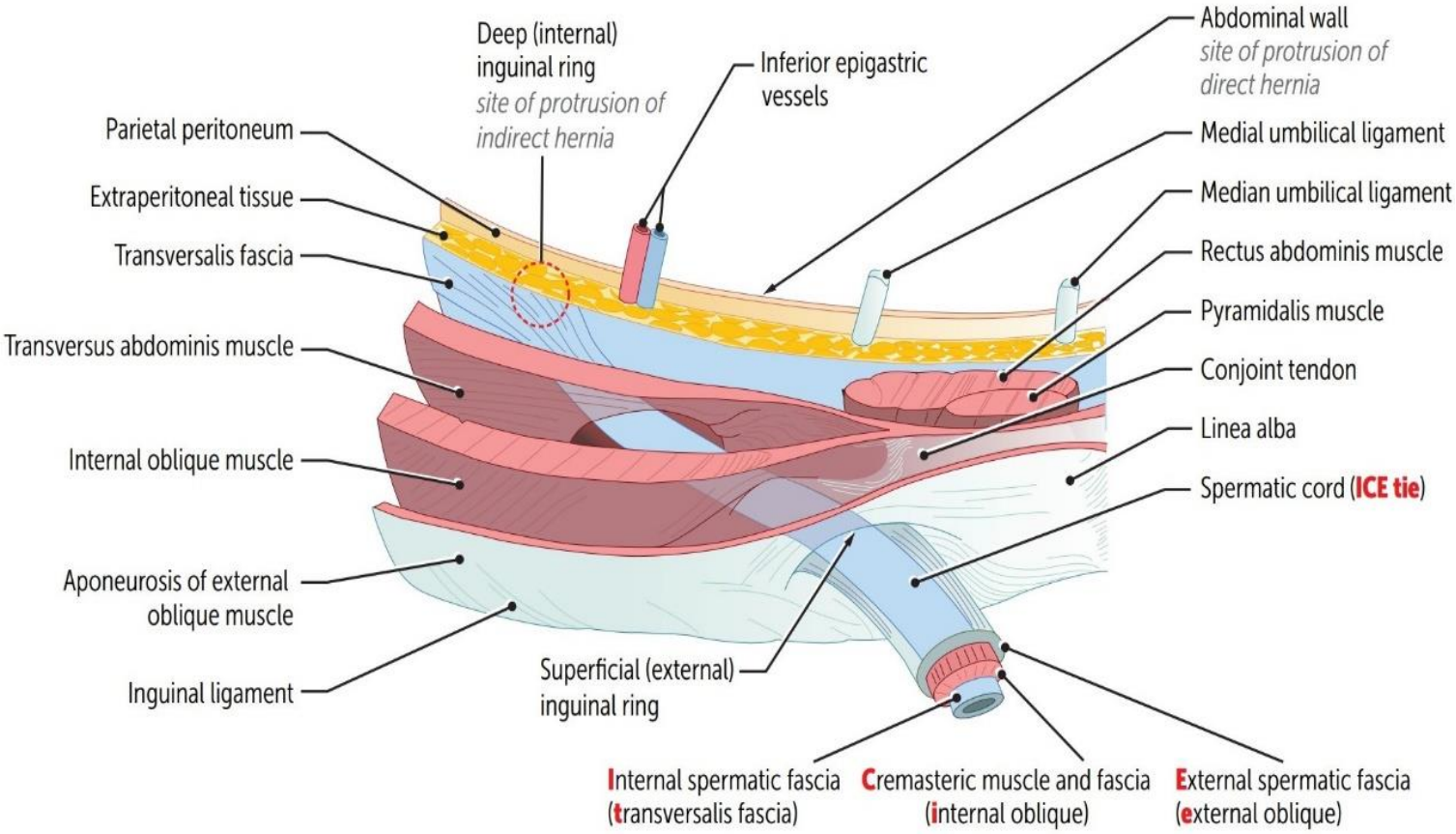
D. Internal oblique layer (Muscle, Aponeurosis, Fascia).

E. Transversus abdominis layer (Muscle, Aponeurosis, Fascia).

F. Transversalis fascia.

G. Extraperitoneal connective tissue.

H. Parietal peritoneum.



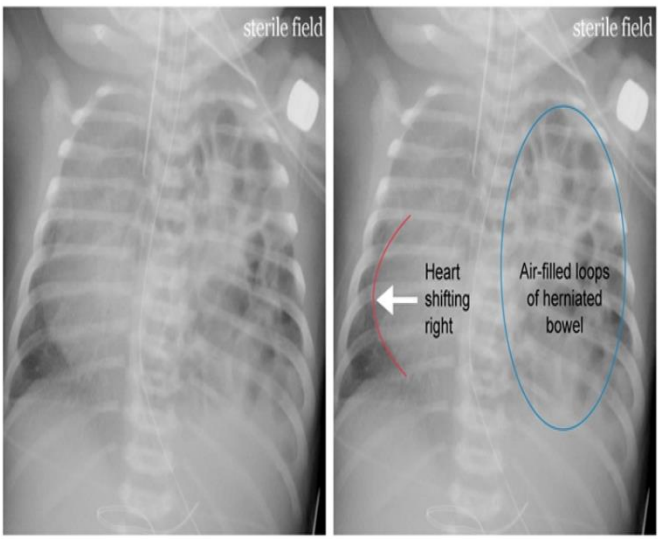
Hernias

- Protrusion of peritoneum through an opening, usually at a site of weakness.
- Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis).
- Complicated hernias can present with tenderness, erythema, fever.

Diaphragmatic hernia

- Congenital diaphragmatic hernia (CDH) is a defect in the diaphragm that results from incomplete fusion of the pleuroperitoneal folds during fetal development.
- Protrusion of abdominal contents through this defect (most commonly left-sided due to relative protection of right hemidiaphragm by liver) into the thoracic cavity compromises lung development, leading to pulmonary hypoplasia.
- In utero remodeling of pulmonary vasculature also leads to arterial muscular hyperplasia and persistent pulmonary hypertension.
- Shortly after birth, patients develop respiratory distress (tachypnea, cyanosis, retractions), often accompanied by absent breath sounds on the side of the hernia. A barrel-shaped chest and scaphoid abdomen (due to displaced abdominal contents) are characteristic findings.
- Bowel sounds may be heard in chest.
- Chest x-ray is diagnostic for CDH that is not detected prenatally (lack of prenatal care). Imaging shows intrathoracic bowel loops and a displaced cardiac silhouette.

Left congenital diaphragmatic hernia



Hiatal Hernia

- Stomach herniates upward through the esophageal hiatus of the diaphragm.

A. Sliding hiatal hernia:

- Gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; "hourglass stomach".

- The distal esophagus is normally attached circumferentially to the diaphragm by the phrenoesophageal membrane at the gastroesophageal (GE) junction; disruptions in membrane integrity can result in hernia formation which typically results from repetitive stress on the membrane (coughing, vomiting).

- This allows the GE junction and proximal stomach to slide upward into the thoracic cavity and predisposes patients to reflux symptoms (heartburn, regurgitation, epigastric/chest pain) due to incompetence of the lower esophageal sphincter.

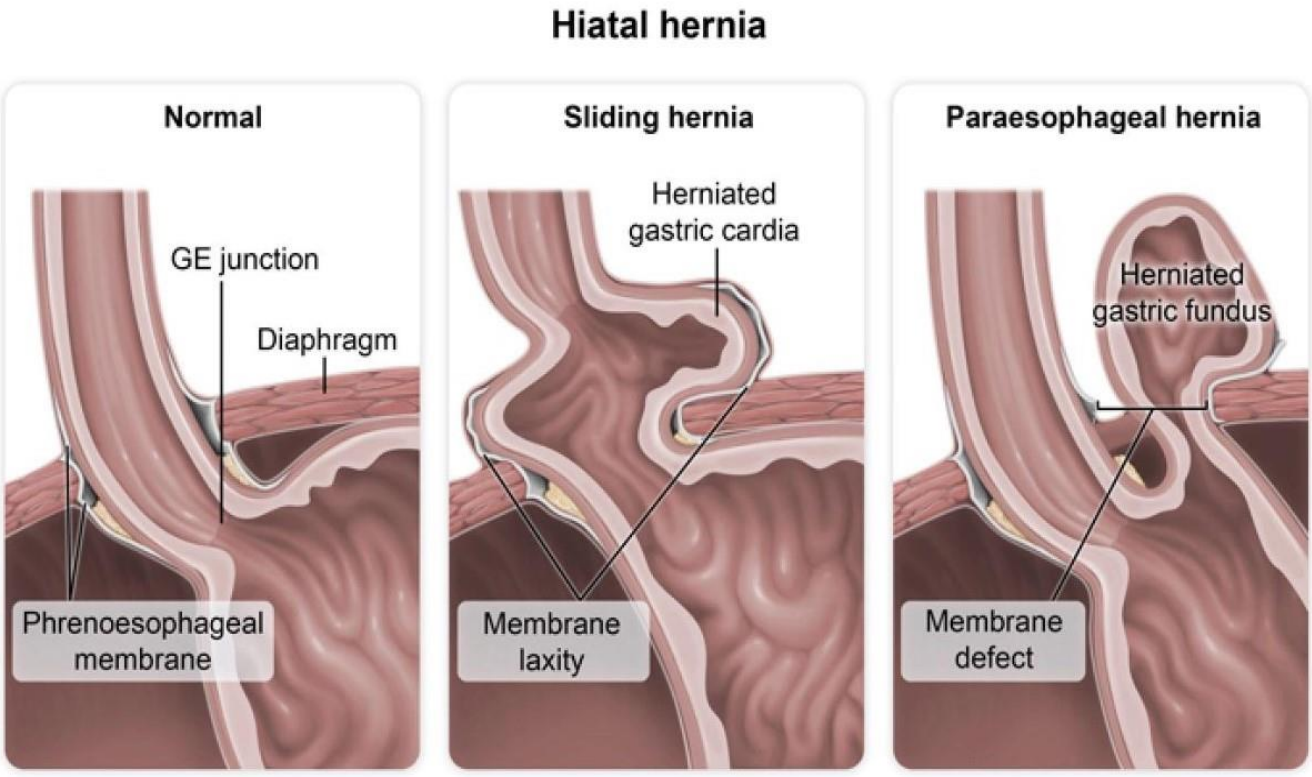
- Most common type.

B. Paraesophageal hiatal hernia:

- Paraesophageal hernias are rarer and occur due to a defect (hole) in the phrenoesophageal membrane.

- Laxity of the gastrocolic and gastrosplenic ligaments (which anchor the stomach in the abdomen) allows the gastric fundus to migrate into the thoracic cavity.

- Gastroesophageal junction is usually normal but gastric fundus protrudes into the thorax.



GE = gastroesophageal.

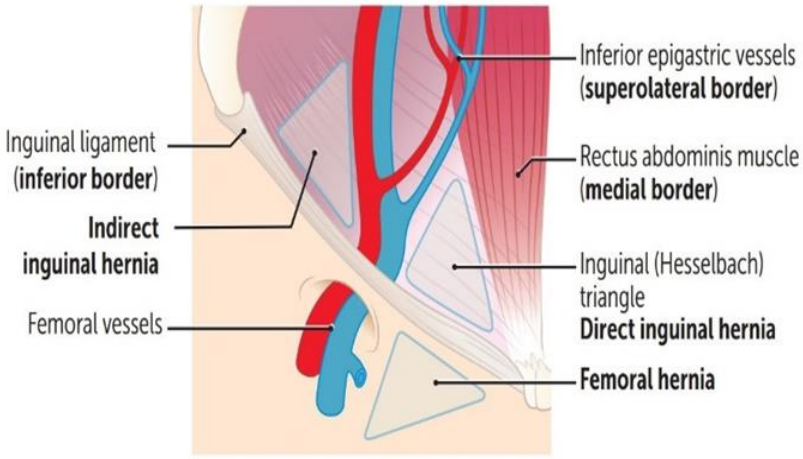
Indirect inguinal hernia

- In early fetal life, the testes are located in the peritoneal cavity and descend into the scrotum before birth.
- During the descent, they are accompanied by an invagination of the peritoneum called the processus vaginalis.
- This structure follows the testes into the scrotum and obliterates after testicular descent is complete.
- Remnants of the processus vaginalis form the tunica vaginalis of the testes.
- Failure of obliteration of the processus vaginalis leads to a persistent connection between the scrotum and the peritoneal cavity through the inguinal canal.
- If the opening is small and allows for fluid leakage only, hydrocele occurs. Diagnosis is by transillumination of the scrotum and scrotal ultrasound, which reveal fluid (only) in the tunica vaginalis sac.
- If the communication between the peritoneal cavity and the scrotum allows for the passage of abdominal organs, an indirect inguinal hernia develops.
- A bulge on the groin that increases during straining is the typical manifestation.
- Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the scrotum. Enters internal inguinal ring lateral to inferior epigastric vessels. Occurs in infants owing to failure of processus vaginalis to close (can form hydrocele). Much more common in males.
- An indirect inguinal hernia follows the path of descent of the testes. Covered by all 3 layers of spermatic fascia.

Direct inguinal hernia

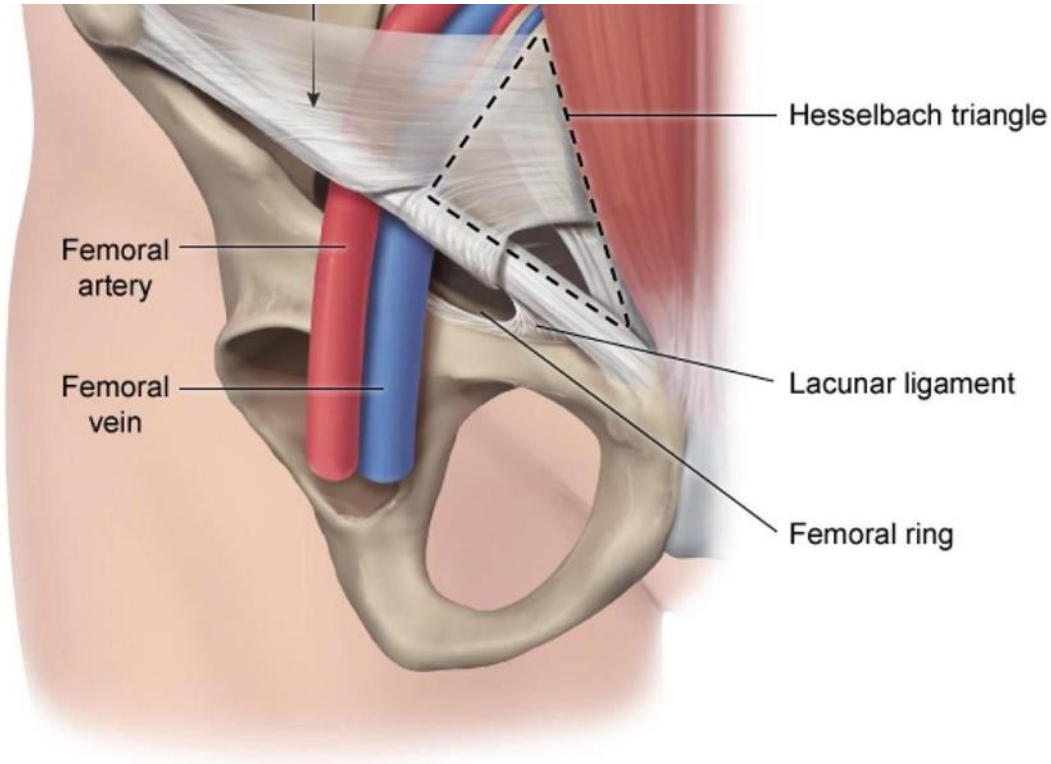
- Protrudes through the inguinal (Hesselbach) triangle. Bulges directly through abdominal wall medial to inferior epigastric vessels.
- Goes through the external (superficial) inguinal ring only.
- Covered by external spermatic fascia.
- Usually in older men due to an acquired weakness in the transversalis fascia.
- MDs don't LIe:

- Medial to inferior epigastric vessels = Direct hernia.
- Lateral to inferior epigastric vessels = Indirect hernia.



Inguinal (Hesselbach) triangle:

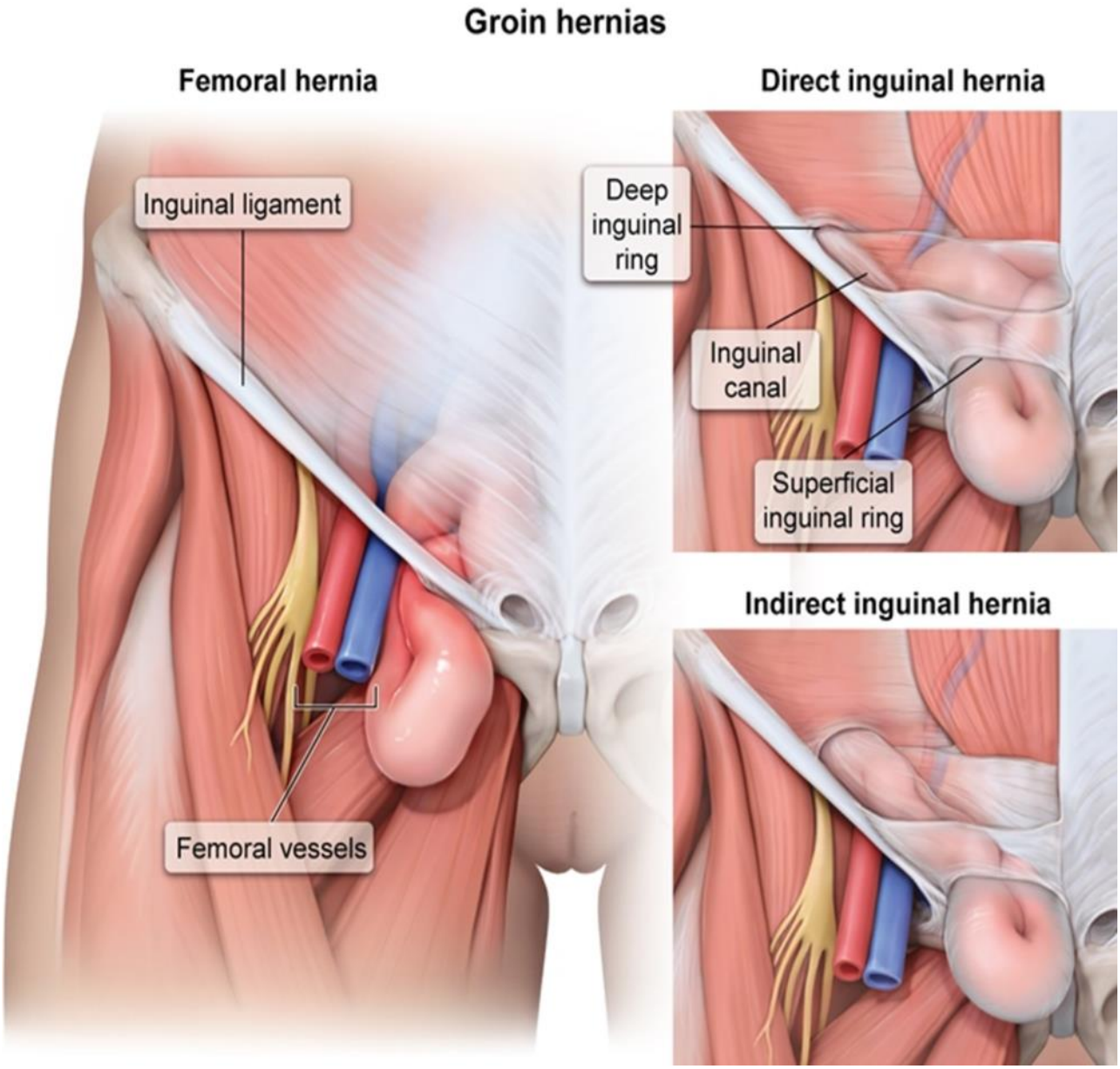
- Inferior epigastric vessels
- Lateral border of rectus abdominis
- Inguinal ligament



Type of hernia	Site of protrusion	Lower border	Medial border	Lateral border
Direct inguinal	Hesselbach triangle	Inguinal ligament	Rectus abdominis muscle	Inferior epigastric vessels
Indirect inguinal	Deep inguinal ring	Inguinal ligament	Inferior epigastric vessels	

Femoral hernia

- Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle.
- More common in females.
- Because femoral hernias pass through a narrow orifice, they are associated with a substantial risk of incarceration (trapping of abdominal/pelvic contents within the hernia) and strangulation (constriction of blood flow with subsequent ischemia/necrosis).
- In contrast, inguinal hernias (hernia above the inguinal ligament) are associated with a lower risk for incarceration and strangulation because hernia contents pass through a wider orifice. Therefore, most asymptomatic inguinal hernias can be managed with reassurance and watchful waiting.



Groin hernias			
Type	**Classic presentation**	**Pathophysiology**	**Anatomy**
Indirect inguinal	Male infants	Patent processus vaginalis	• Content protrudes through deep inguinal ring • Travels lateral to inferior epigastric vessels
Direct inguinal	Older men	Weakness of transversalis fascia	• Content protrudes through Hesselbach triangle • Travels medial to inferior epigastric vessels
Femoral	Women	Weakness of proximal femoral canal	• Content protrudes through femoral ring • Travels inferior to inguinal ligament

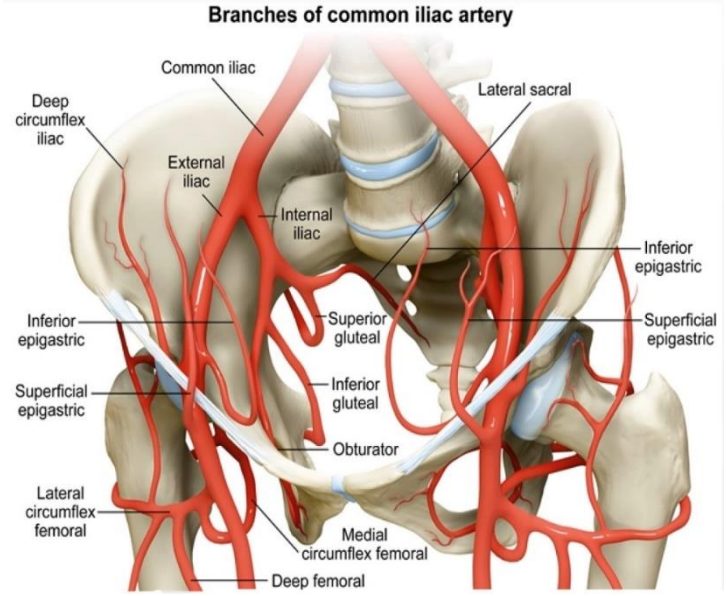
❖ N.B:

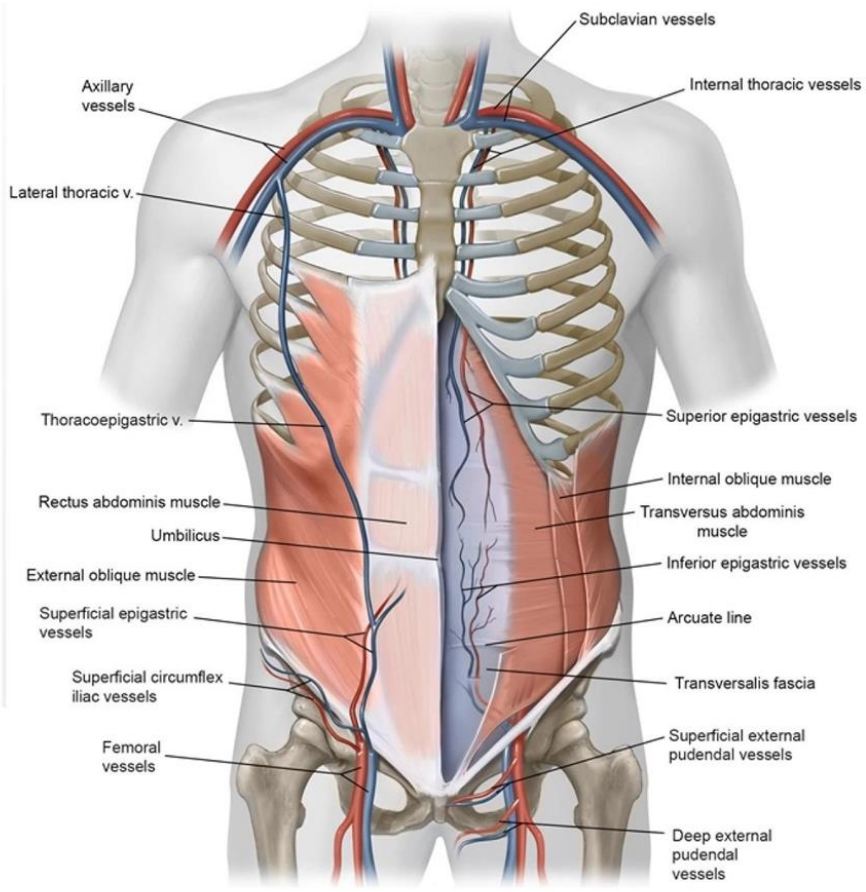
1. The phrenic nerves originate from C3-C5 and pass between the lung and heart to provide motor function to the diaphragm.
- The phrenic nerves also provide sensory fibers to the pericardium, mediastinal pleura, and diaphragmatic peritoneum.
- The supraclavicular nerves originate from C3-C4 and their branches innervate the sternoclavicular joint, local muscles (sternocleidomastoid), and the skin of the upper and posterior shoulder.
- Any abdominal process (ruptured spleen, peritonitis, hemoperitoneum) irritating the sensory fibers around the diaphragm can cause referred shoulder pain via the phrenic nerve to the C3-C5 shoulder region (Kehr sign).
- Phrenic nerve irritation can also cause hiccups due to spasmodic diaphragmatic contraction pulling air against a closed larynx.

2. As the aorta courses through the lower abdomen, it divides into the common iliac arteries, which subsequently branch into the internal and external iliac arteries.
- The inferior epigastric artery is 1 of 2 branches of the external iliac artery and takes off immediately proximal to the inguinal ligament (the external iliac artery becomes the common femoral artery once it passes the inguinal ligament).
- As the inferior epigastric artery runs superiorly and medially up the abdomen, it provides blood supply to the lower anterior abdominal wall.
- The other main branch off the external iliac artery is the deep circumflex iliac artery, which branches more laterally but also supplies blood to the lower abdominal wall.

3. Regardless of the direction of skin incision, a cesarean delivery typically involves midline vertical separation of the rectus abdominis muscle.

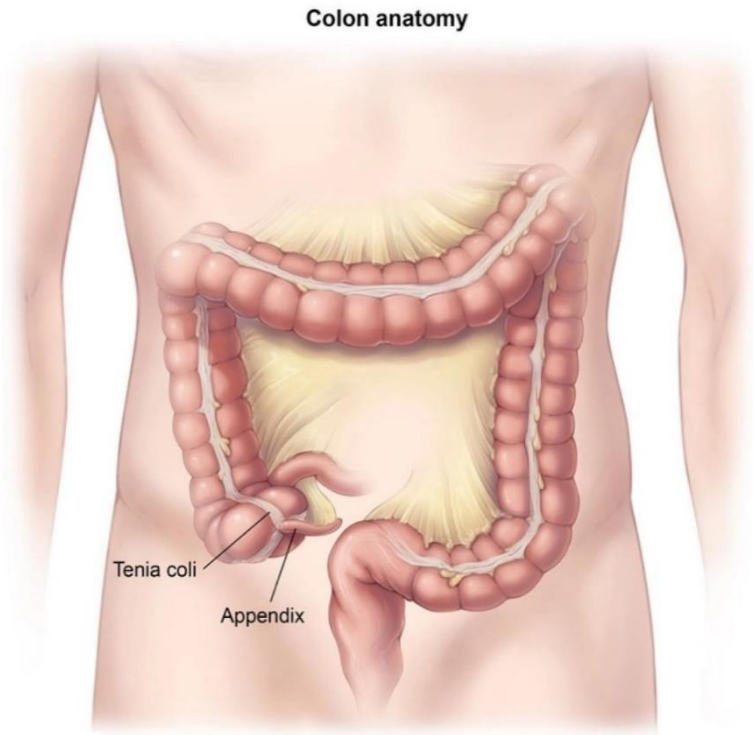
- Horizontal transection of the rectus abdominis muscle may be considered when additional space is necessary (due to fetal weight or position).
- If the rectus abdominis is transected horizontally, the inferior epigastric arteries must be identified and ligated bilaterally to prevent bleeding complications (hematoma). The inferior epigastric arteries below the arcuate line are susceptible to injury (hematoma) due to lack of a supporting posterior rectus sheath.





4. During appendectomy, the teniae coli can be used as a surgical landmark.

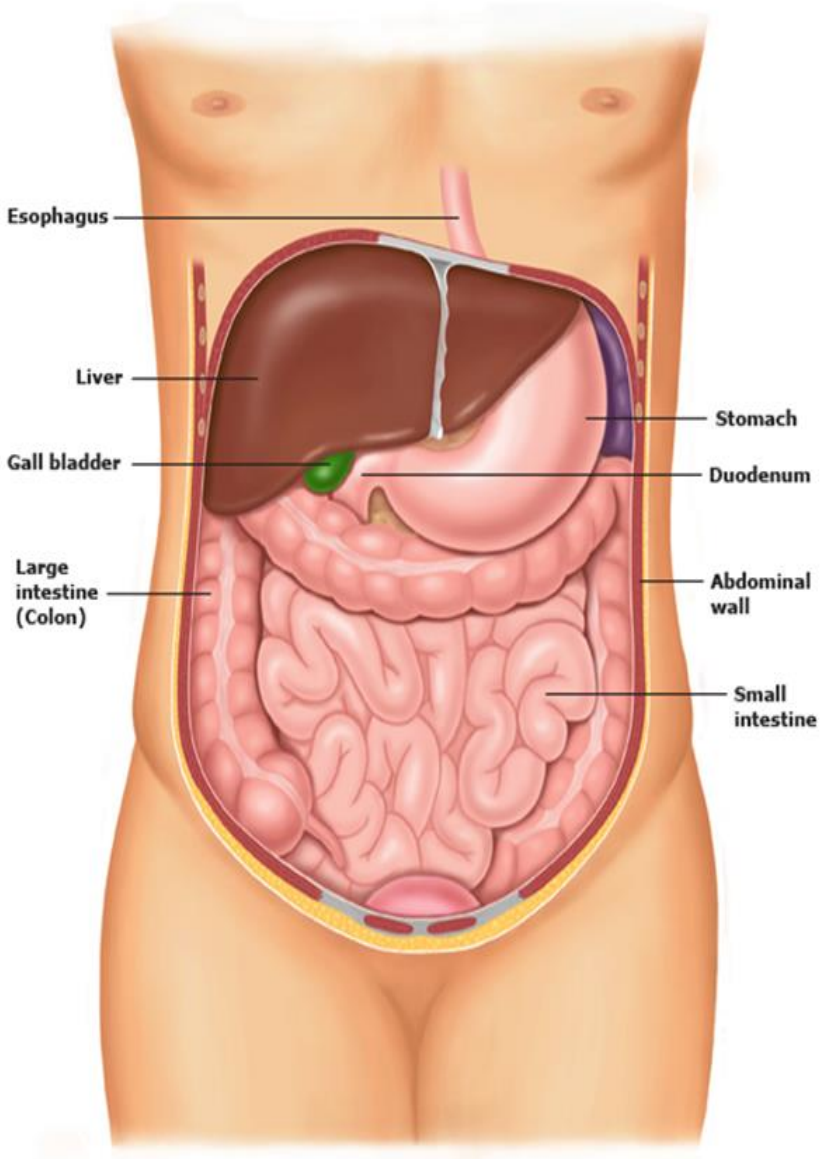
- The teniae coli begin as a continuous layer of longitudinal muscle that surrounds the rectum just below the serosa.
- At the rectosigmoid junction, this layer condenses to form 3 distinct longitudinal bands that travel on the outside of the entire colon before converging at the root of the vermiform appendix.
- If the appendix cannot be identified by palpation during an appendectomy, it can be located by following the teniae coli to its origin at the cecal base.



Radiology of the abdomen

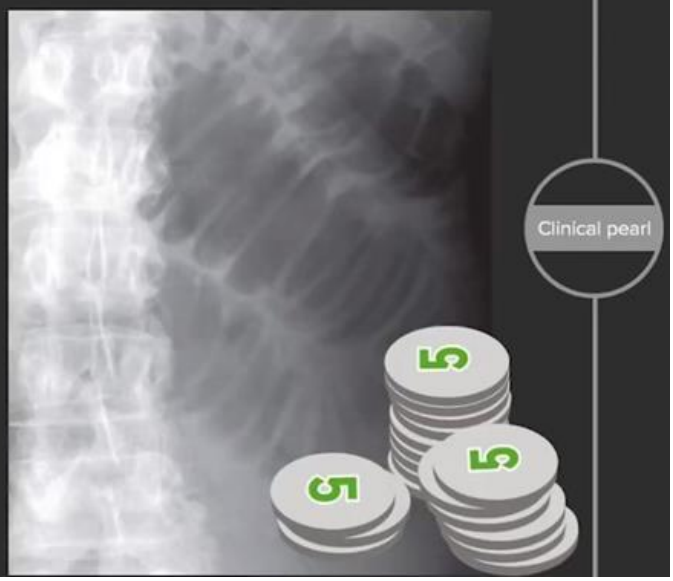
Abdominal X-ray

- Abdominal x-ray has very few indications.
- The best indication for an abdominal film is ileus or small bowel obstruction.
- However, abdominal x- ray is not accurate for stones of the kidney and will miss at least 20% of cases. Abdominal x-ray does not reliably find air under the diaphragm because it does not always visualize the top of the diaphragm, especially in a tall person.
- For perforation of the bowel, get an upright chest x-ray, not an abdominal x-ray.



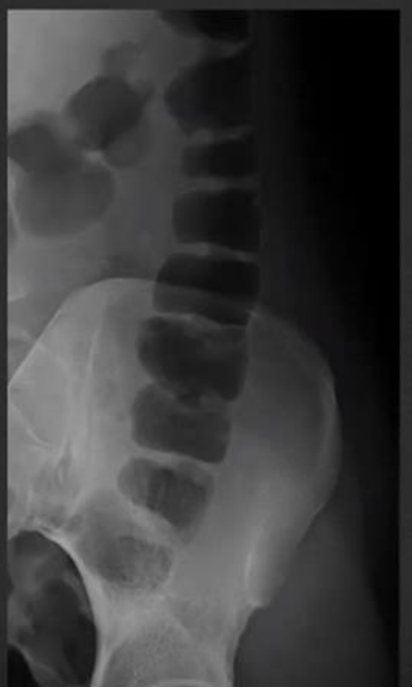
Small bowel

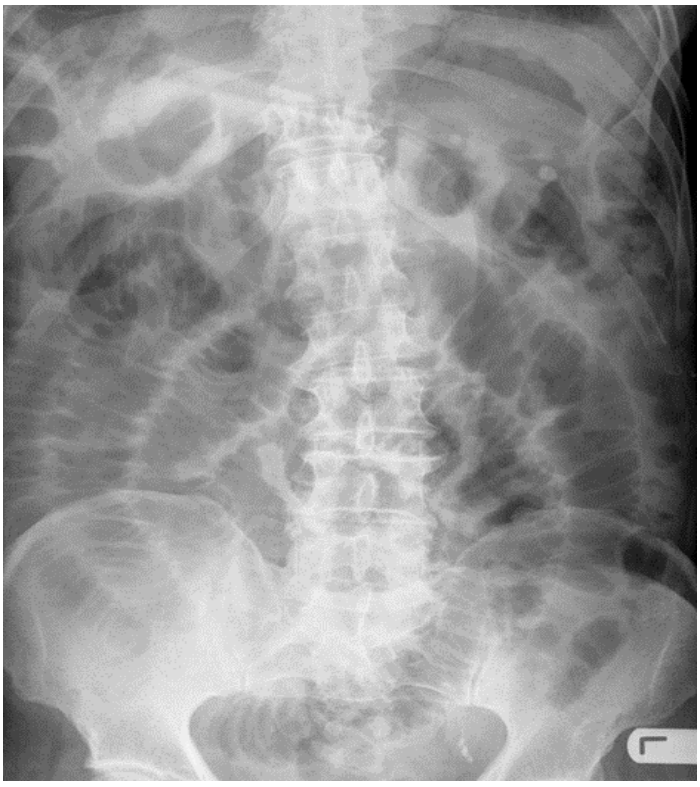
- Located centrally
- Valvular markings, called valvulae conniventes, cross the entire width of the bowel and spaced close together
- "Stacked coin" appearance

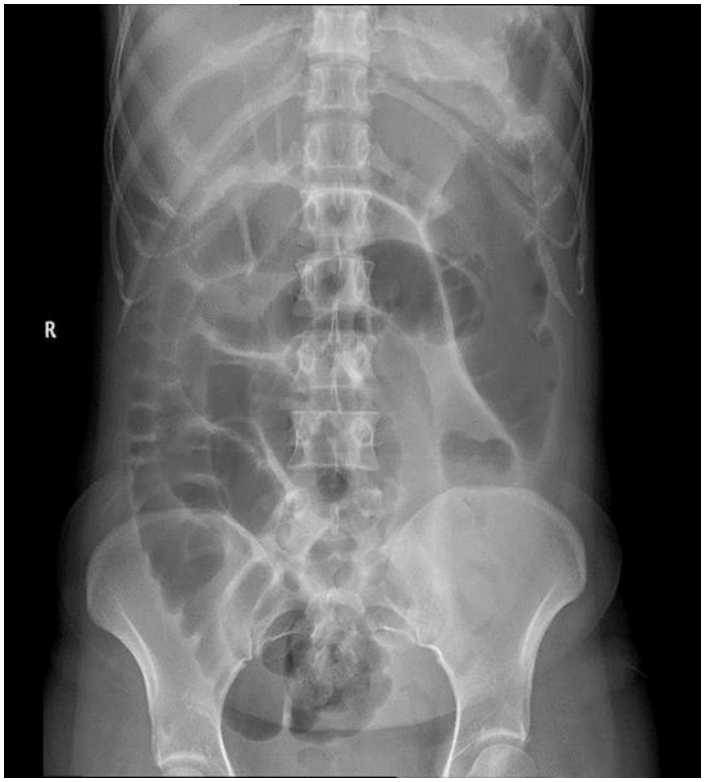


Large Bowel

- Located peripherally
- Contains haustra which either...
  - ...do not connect from one wall to the other OR...
  - ...are spaced wider apart than the valvulae conniventes of the small bowel



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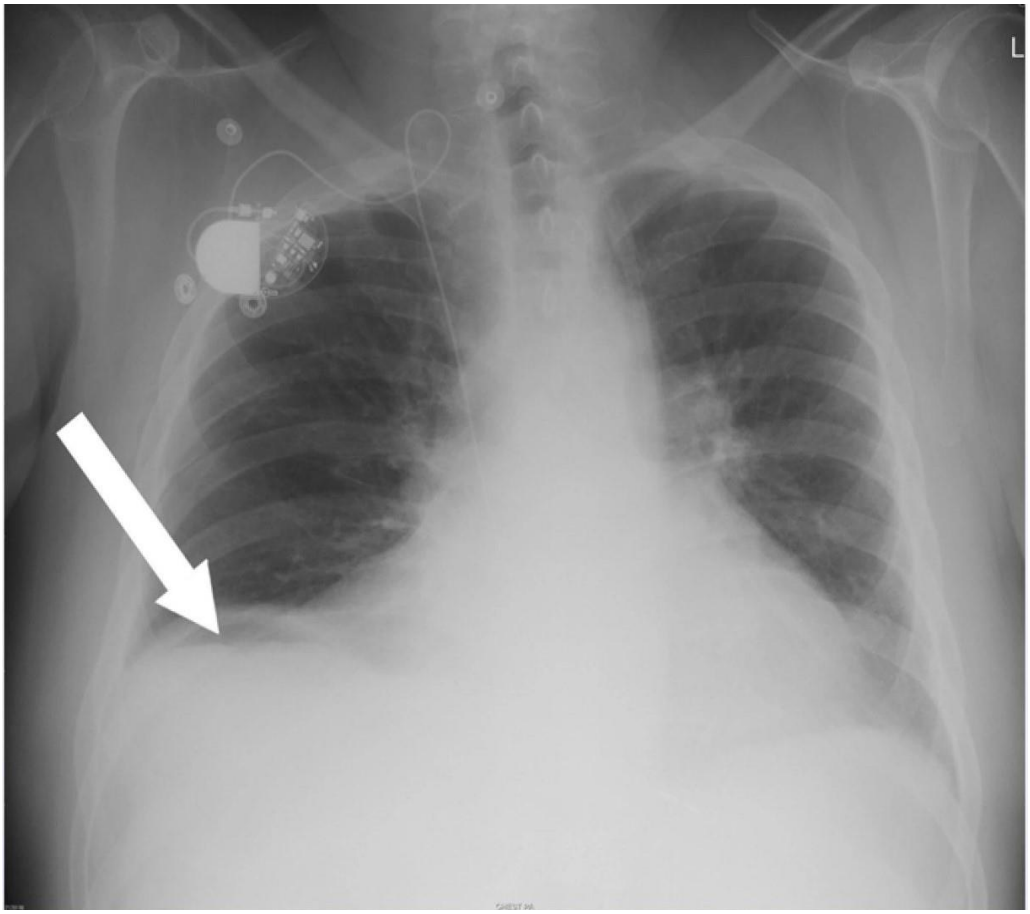

L

❖ N.B:

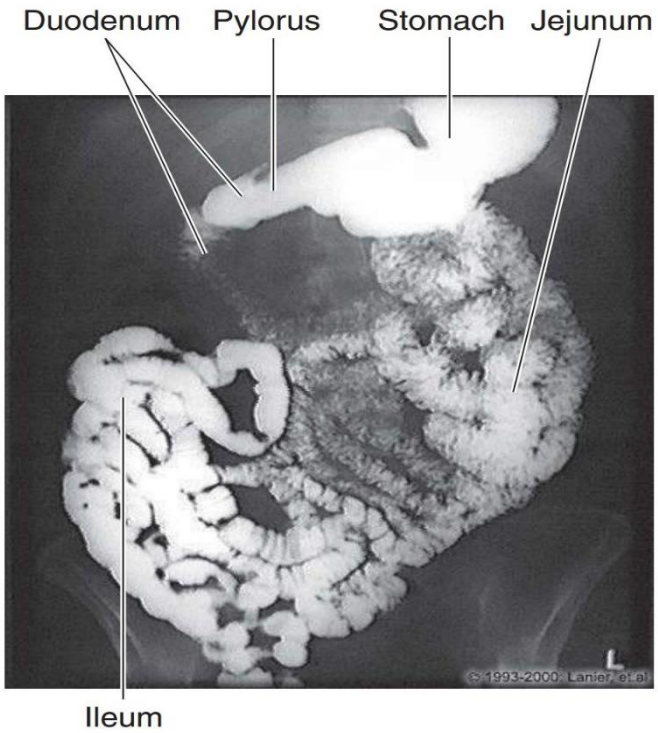
- Pneumoperitoneum is air or gas in the peritoneal cavity; it can be seen as free air under the diaphragm in an upright chest x-ray.
- The most common cause is a perforated duodenal ulcer, but perforation can occur anywhere along the gastrointestinal (or female reproductive) tract.
- Contamination of the sterile peritoneal cavity with bowel contents leads to chemical (acid or chyme-related) or bacterial peritonitis, which, if left untreated, can progress to sepsis and death. Diffuse irritation of the parietal peritoneum results in severe abdominal pain with rigidity and rebound tenderness with referred shoulder pain due to diaphragmatic irritation.

Abdominal CT

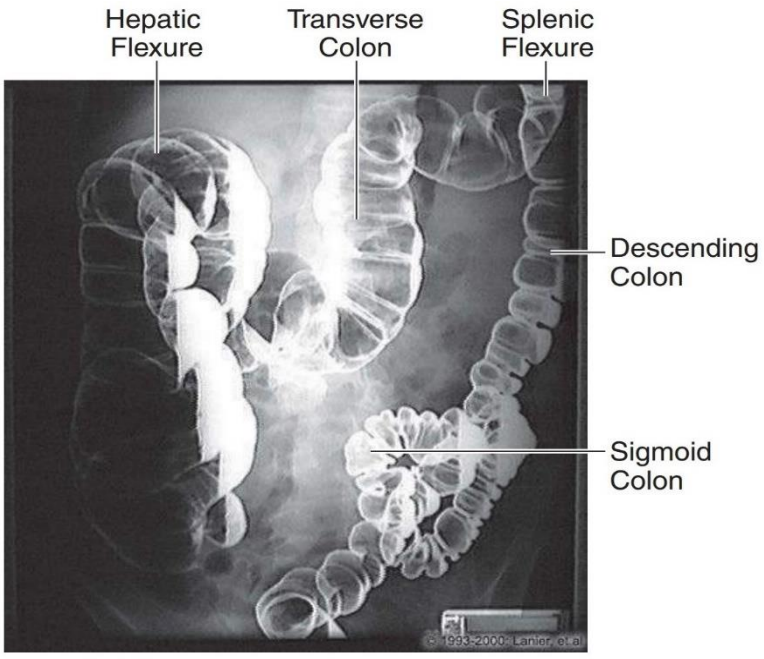
- This study should be performed with both intravenous and oral contrast.
- Oral contrast is indispensable in outlining abdominal structures that are pressed against each other and would otherwise be difficult to visualize.
- CT images are always visualized as though standing at the patient's feet and looking through the patient's body toward the head; therefore, the left side of the image corresponds to the patient's right side.
- Abdominal CT is also good for:

- Retroperitoneal structures: Organs such as the pancreas are difficult to visualize with sonography. In sonography, the transducer is placed against the anterior abdominal wall. This makes it difficult to visualize structures that are further away from the anterior abdominal wall.
- Appendicitis and other intraabdominal infections.
- Most accurate test for nephrolithiasis; this is a case in which contrast is not needed.
- Masses within abdominal organs such as the liver and spleen.

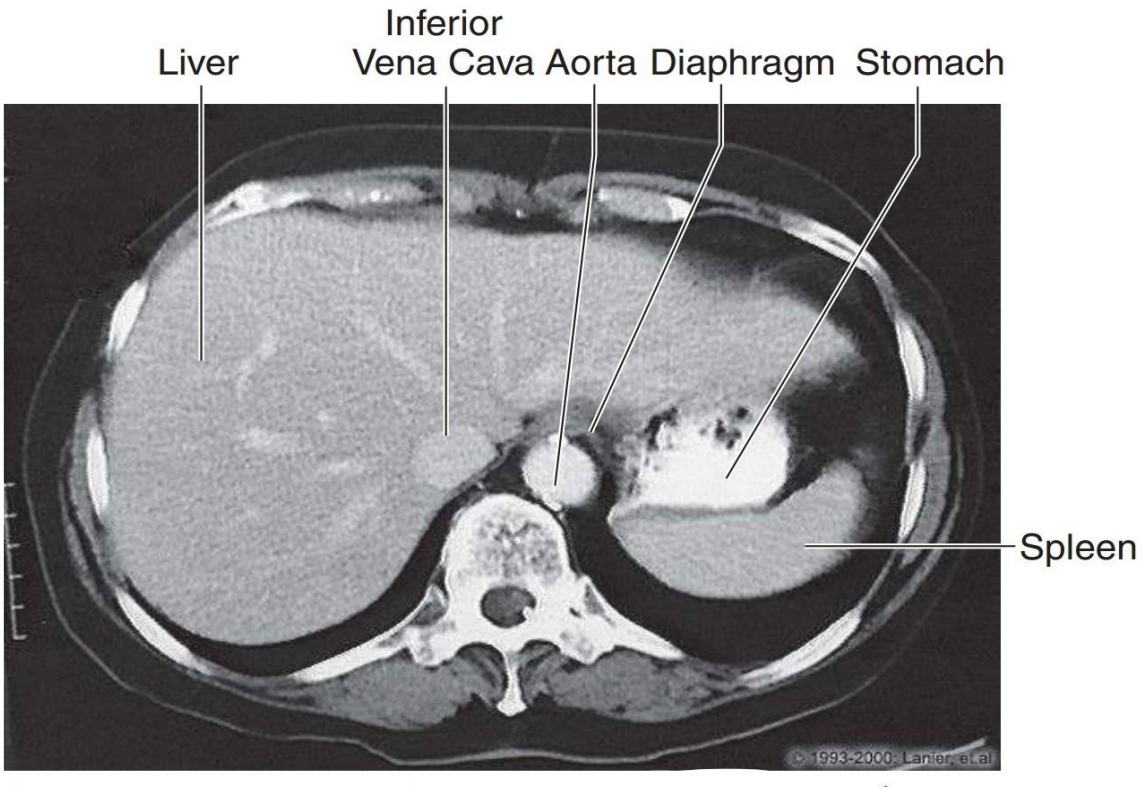
- CT is the “most accurate test” for diverticulitis.
- Choose abdominal CT to visualize the pancreas.
- CT is the “most accurate test” for kidney stones



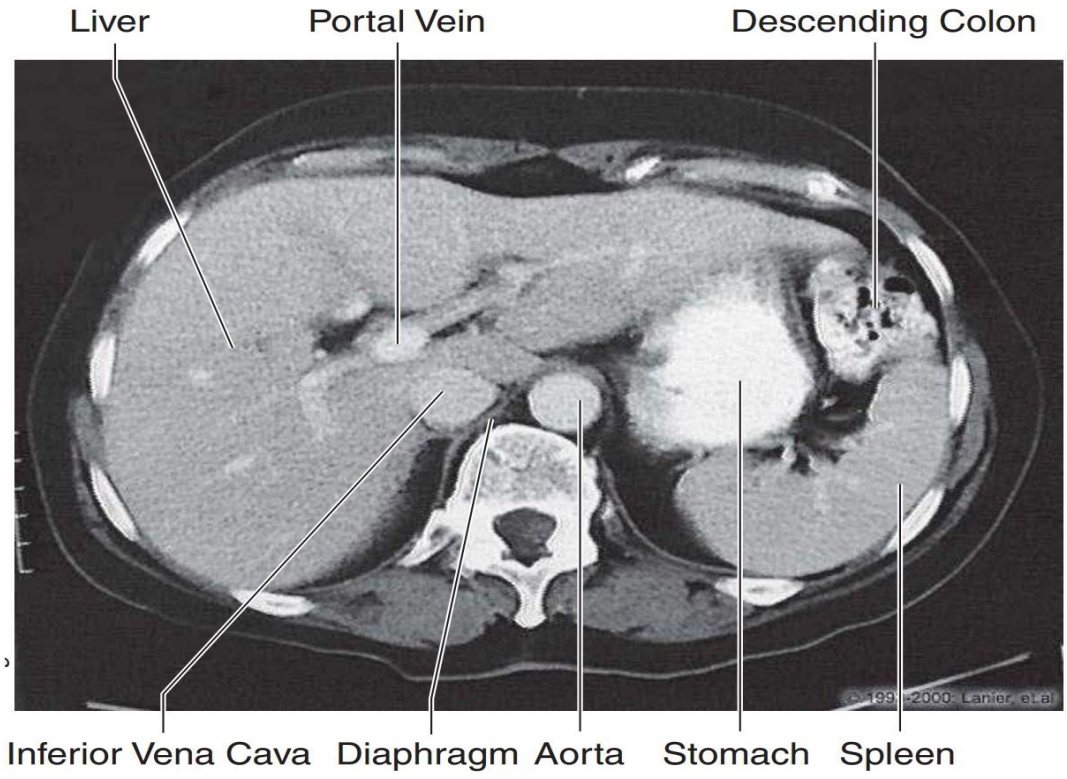
Abdomen: Upper GI, Small Bowel



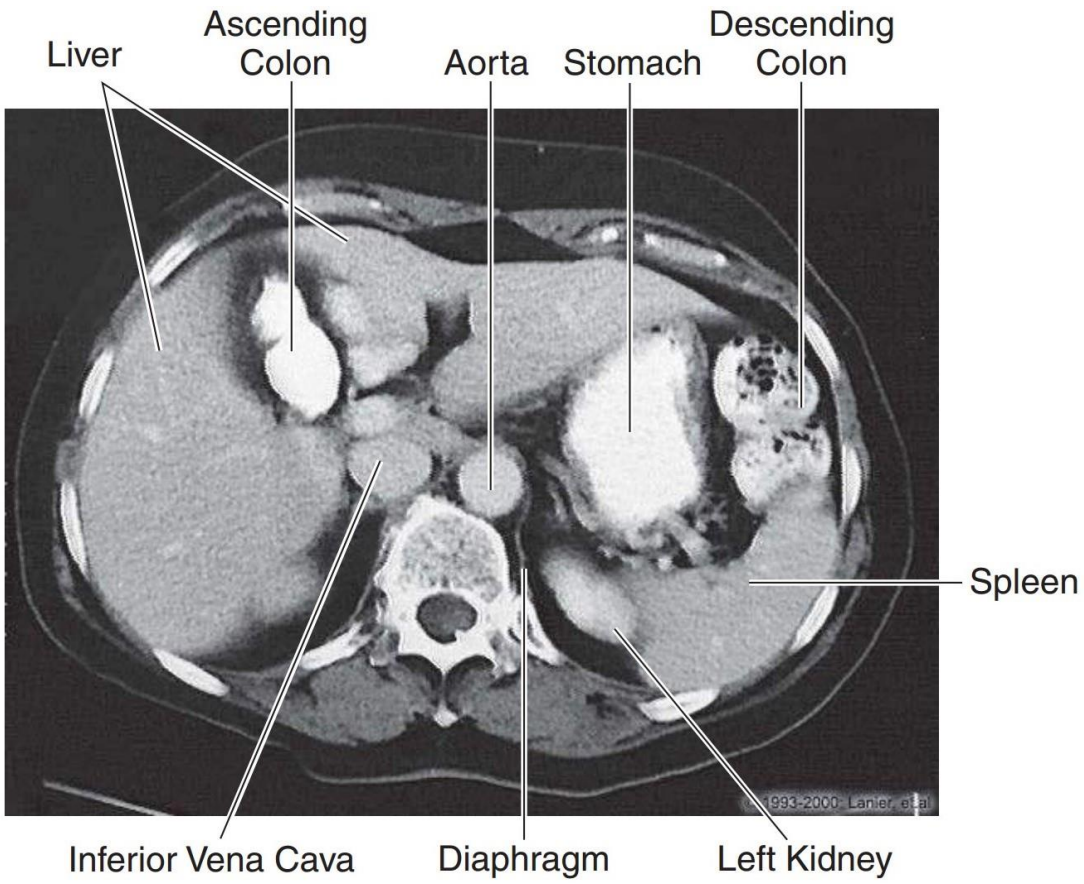
Abdomen: Barium Enema



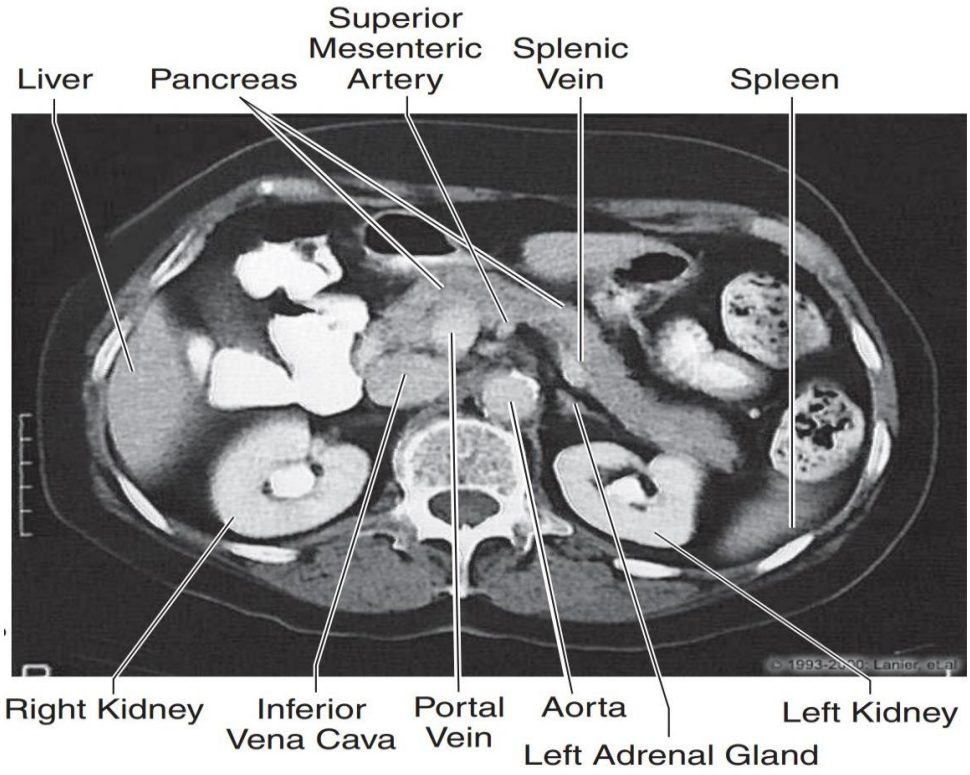
Abdomen: CT, T11



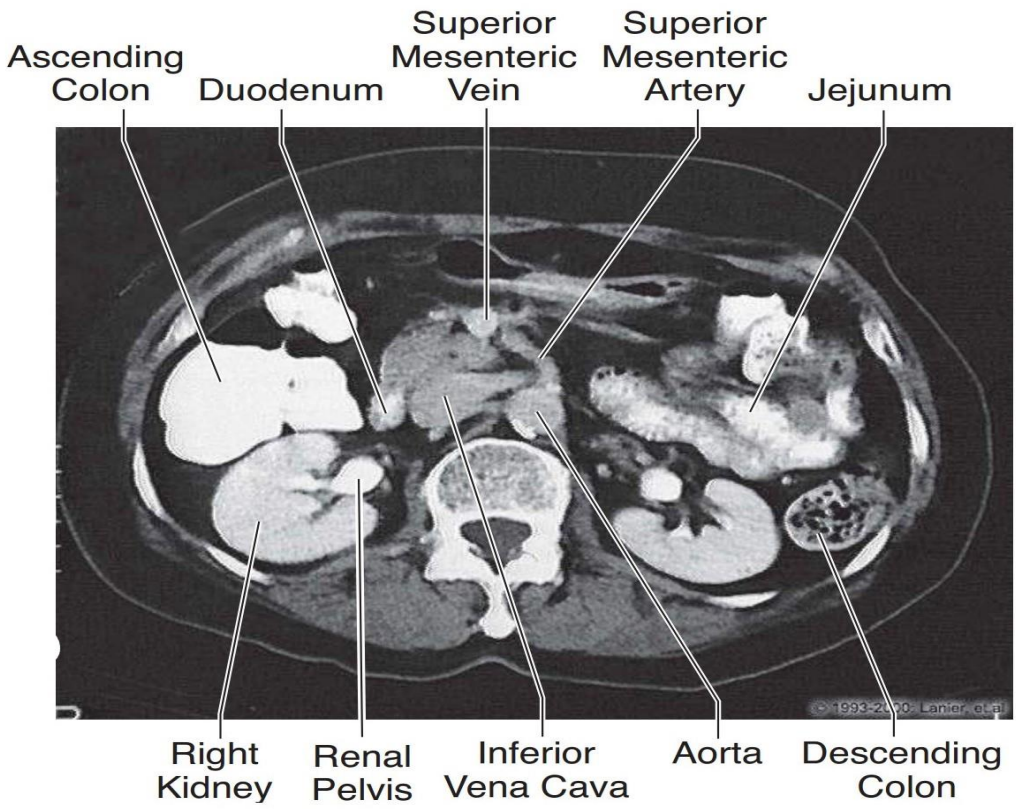
Abdomen: CT, T12



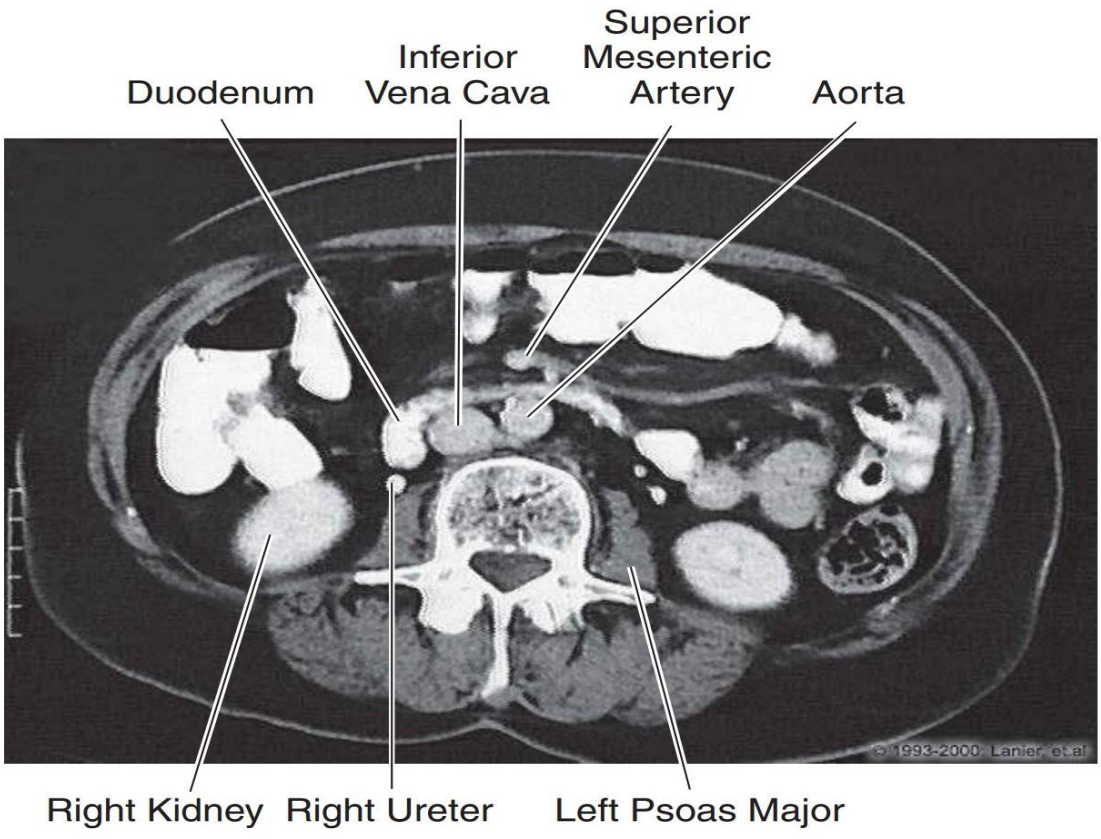
Abdomen: CT, T12



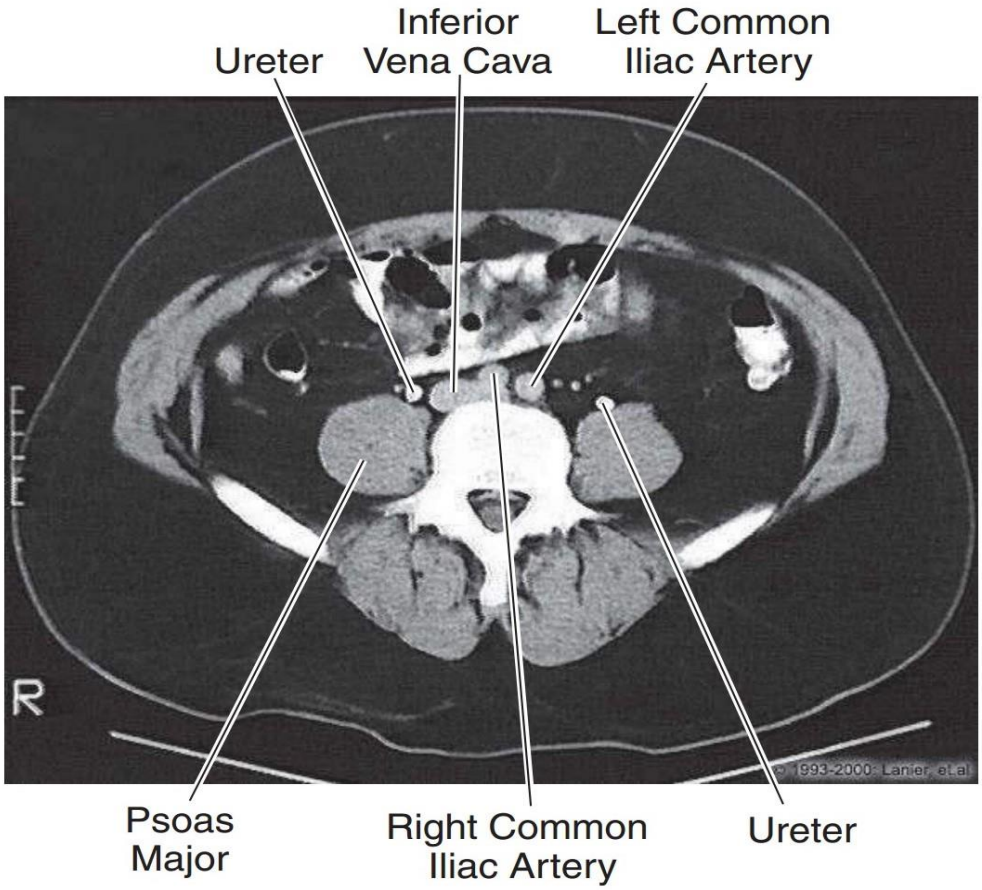
Abdomen: CT, L1



Abdomen: CT, L2



Abdomen: CT, L3

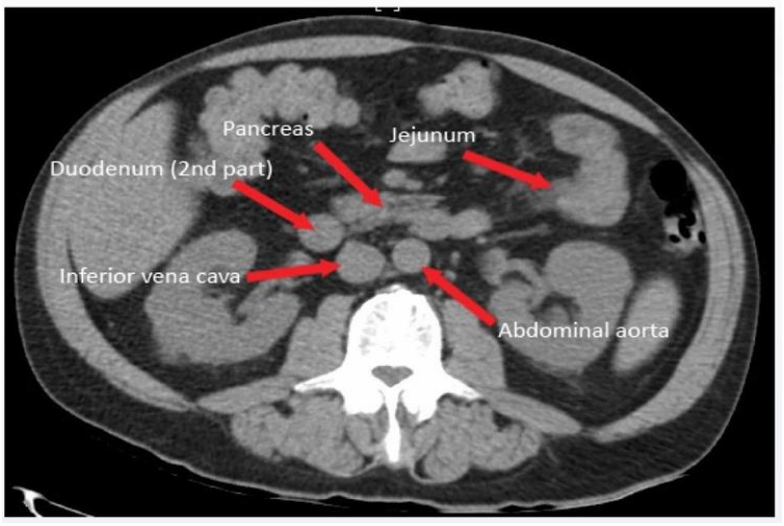


Abdomen: CT, L4

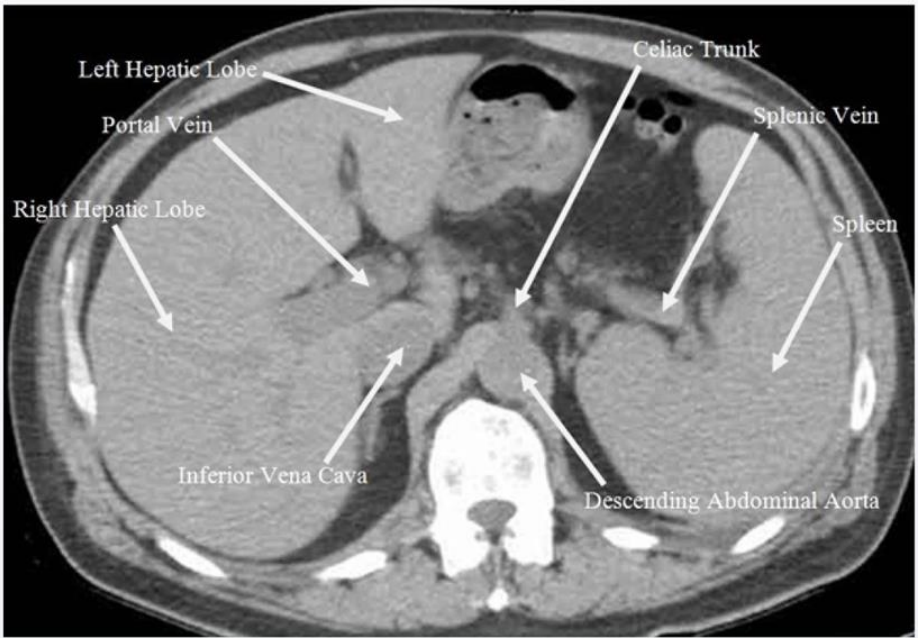
❖ N.B:

1. Chronic pancreatitis often presents with epigastric pain and pancreatic exocrine insufficiency resulting in fat malabsorption/steatorrhea.

- On abdominal CT scan, the pancreas can be identified by its head in close association with the second part of the duodenum; its body overlying the aorta, left kidney, and renal vessels; and its tail lying within the splenorenal ligament.

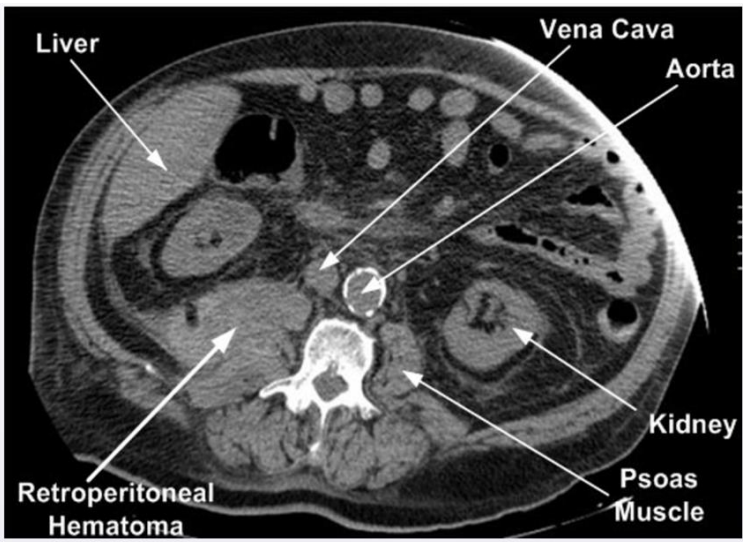


2. The portal vein can be identified on cross-sectional scans lying medial to (or just within) the right lobe of the liver and anterior to the inferior vena cava. The pressure in the portal system is elevated in liver cirrhosis.



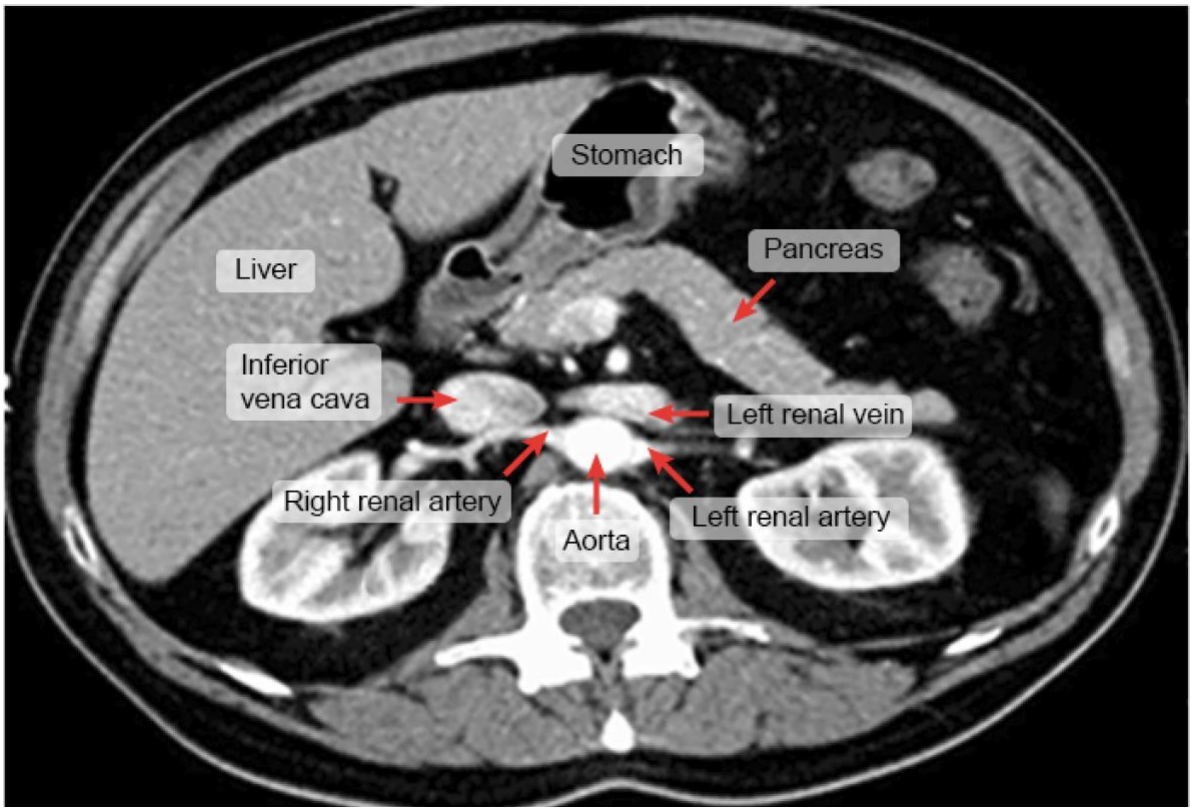
3. The retroperitoneum is the space located behind the peritoneal cavity. It includes the following structures.

- Retroperitoneal hematomas are commonly associated with abdominal and pelvic trauma; they develop in up to half of patients with blunt abdominal trauma.
- Pancreatic injury with formation of a retroperitoneal hematoma can occur due to severe blunt or penetrating abdominal trauma.
- It can frequently be caused by direct abdominal blows from malpositioned seat belts or by steering wheels during automobile collisions.
- Pancreatic injury can cause mild symptoms or be asymptomatic.
- An abdominal CT scan should be performed in stable patients with blunt abdominal trauma to exclude the possibility of retroperitoneal hematoma.

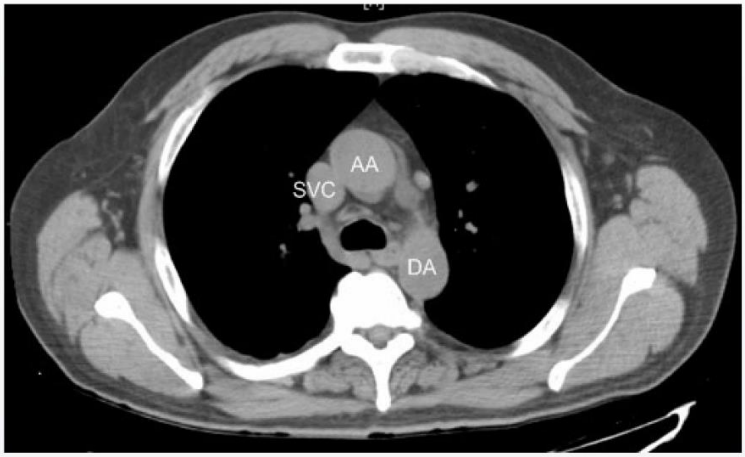


4. IVC filters are designed to prevent the embolization of DVT from the legs to the lung vasculature (pulmonary embolism), and are used in patients who have contraindications to anticoagulation.

- The inferior vena cava is formed by the union of the right and left common iliac veins at the level of L4-L5.



5. The esophagus is located between the trachea and the vertebral bodies in the superior thorax. It is typically collapsed with no visible lumen on CT images of the chest.



AA- Ascending aorta DA- Descending aorta SVC- Superior vena cava

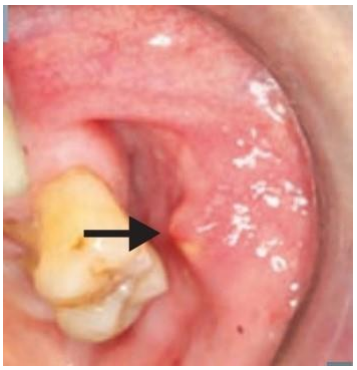
CHAPTER 3

Pathophysiology

Salivary gland

- Salivary glands are exocrine glands that secrete saliva.
- Divided into major (parotid, submandibular, and sublingual glands), and minor glands (hundreds of microscopic glands distributed throughout the oral mucosa).

Sialolithiasis



- Stone(s) in salivary gland duct.
- Can occur in 3 major salivary glands (parotid, submandibular, sublingual).
- Single stone more common in submandibular gland (Wharton duct).
- Caused by dehydration or trauma.
- Presents as recurrent pre-/periprandial pain and swelling in affected gland.
- Treat conservatively with NSAIDs, gland massage, warm compresses, sour candies (to promote salivary flow).

Sialadenitis

- Inflammation of the salivary gland due to obstruction, infection, or immune-mediated mechanisms (Sjogren syndrome).
- Most commonly due to an obstructing stone (sialolithiasis) leading to Staphylococcus aureus infection; usually unilateral.

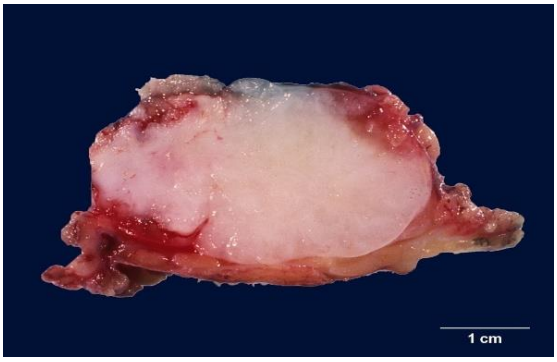
Salivary gland tumors

- Most are benign and commonly affect parotid gland (80-85%).
- Nearly half of all submandibular gland neoplasms and most sublingual and minor salivary gland tumors are malignant.
- Typically present as painless mass/swelling.

- CN VII signs (facial paralysis or pain) suggest malignant involvement.

A. **Pleomorphic adenoma:**

- Benign mixed tumor composed of stromal (cartilage) and epithelial tissue.
- Most common tumor of the salivary gland.
- Usually arises in parotid; presents as a mobile, painless, circumscribed mass at the angle of the jaw.
- High rate of recurrence; extension of small islands of tumor through tumor capsule often leads to incomplete resection.
- Rarely may transform into carcinoma, which presents with signs of facial nerve damage (facial nerve runs through parotid gland).

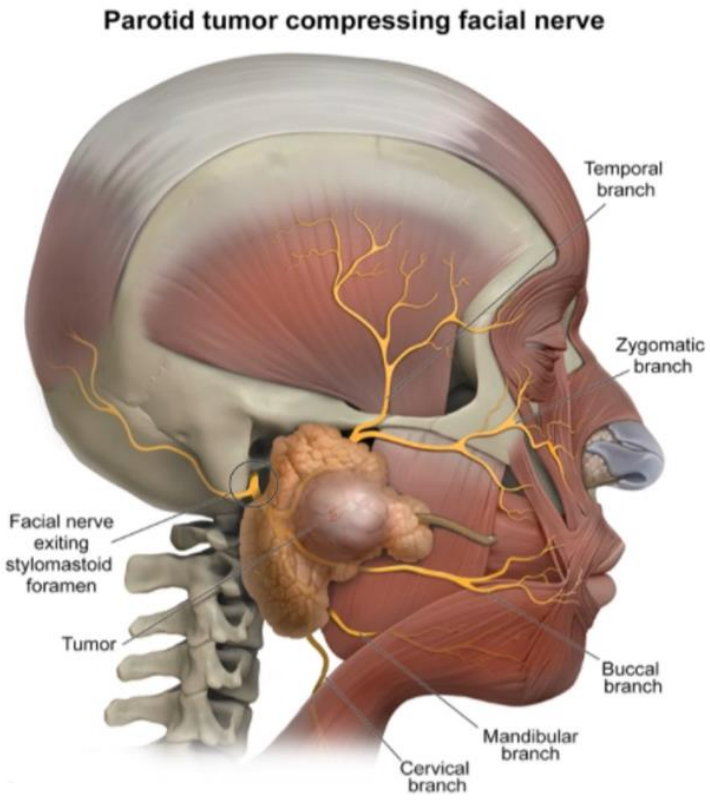


B. **Warthin tumor (papillary cystadenoma lymphomatosum):**

- Benign cystic tumor with abundant lymphocytes and germinal centers (lymph node-like stroma).
- 2nd most common tumor of the salivary gland.
- Almost always arises in the parotid.
- Typically found in smokers.
- Bilateral in 10%; multifocal in 10%.
- "Warriors from Germany love smoking."

C. **Mucoepidermoid carcinoma:**

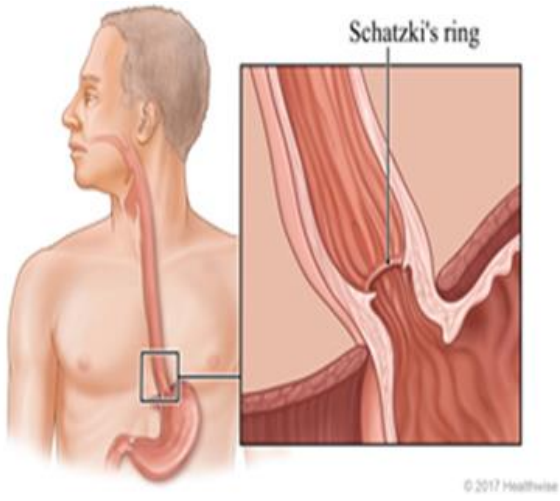
- Malignant tumor composed of mucinous and squamous cells.
- Most common malignant tumor of the salivary gland.
- Usually arises in the parotid; commonly involves the facial nerve.

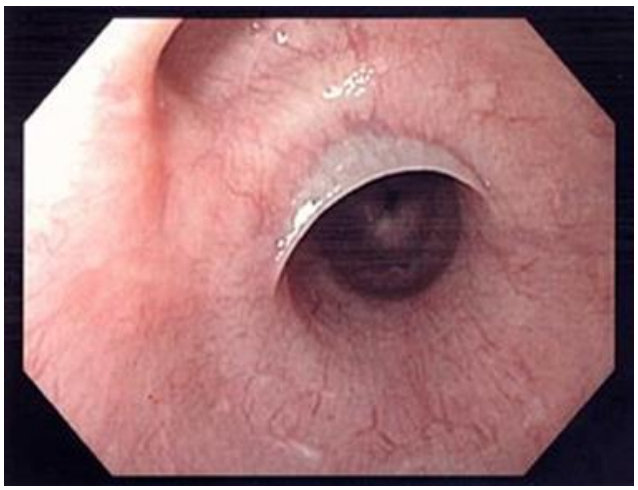


Esophagus

Esophageal Rings and Webs

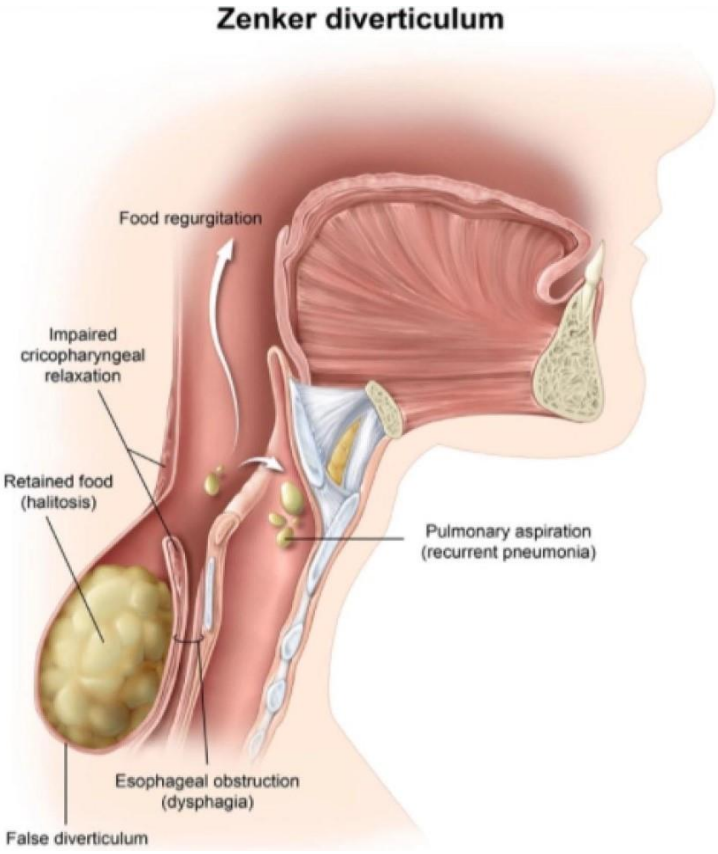
- Esophageal web is thin protrusion of esophageal mucosa, most often in the upper esophagus.
- Presents with dysphagia for poorly chewed food.
- Increased risk for esophageal squamous cell carcinoma.
- Plummer-Vinson syndrome is characterized by severe iron deficiency anemia, esophageal web, and beefy-red tongue due to atrophic glossitis. Increased risk of esophageal squamous cell carcinoma.
- Schatzki rings: Rings formed at gastroesophageal junction, typically due to chronic acid reflux. Can present with dysphagia.

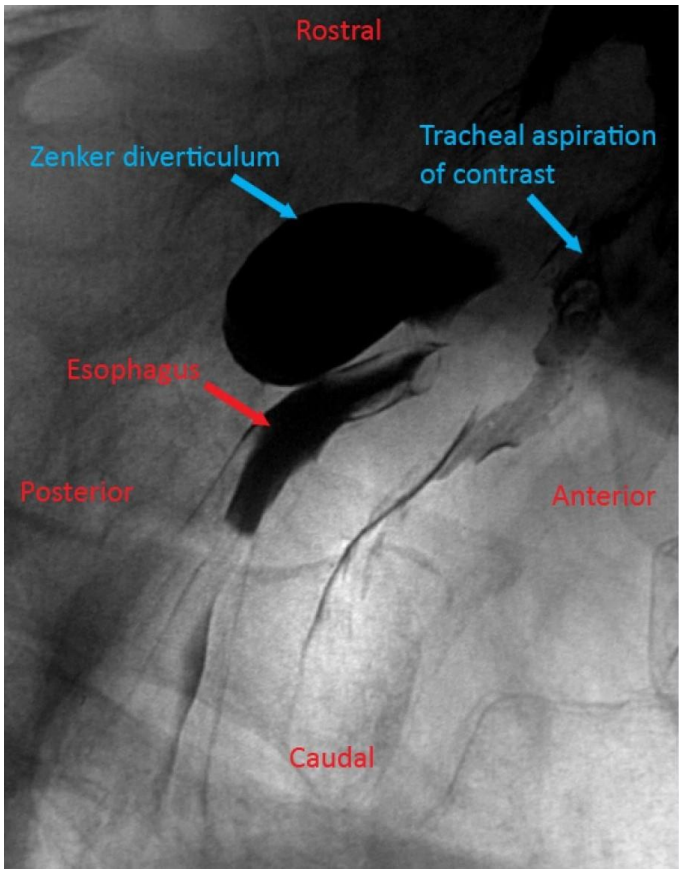




Zenker diverticulum

- Outpouching of pharyngeal mucosa through an acquired defect in the posterior pharyngeal constrictor muscles (false diverticulum).
- Arises above the upper esophageal sphincter at the junction of the esophagus and pharynx.
- Presents with dysphagia, halitosis, and regurgitation of food particles. Some patients suffer from aspiration pneumonia when the contents of the diverticulum end up in the lung.
- They often have foul-smelling breath (halitosis) secondary to pooling of material in the diverticulum.





❖ N.B:

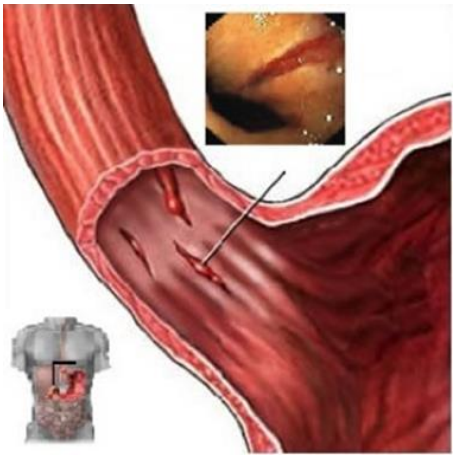
- Deglutition (swallowing) is a complex process that includes three phases:

A. The oral phase is voluntary: The food bolus is collected at the back of the mouth and lifted upwards to the posterior wall of the pharynx.
B. This initiates the pharyngeal phase, which consists of involuntary pharyngeal muscle contractions that propel the food bolus to the esophagus.
C. During the esophageal phase, food enters the esophagus and stretches the walls. Peristalsis begins just above the site of distention and moves the food downward. Relaxation of the lower esophageal sphincter (LES) follows, allowing the food bolus to enter the stomach.

- Cricopharyngeal muscle dysfunction occurs due to diminished relaxation of pharyngeal muscles during swallowing. More force is subsequently required to move the food bolus downward. More intense contractions of the pharyngeal muscles increase the oropharyngeal intraluminal pressure.
- With time, the pharyngeal mucosa will herniate through muscle fibers in the zone of weakness (posterior hypopharynx), forming a Zenker diverticulum.
- Remember that when a diverticulum consists only of mucosa, it is a false, or pulsion, diverticulum. A traction diverticulum, alternatively, consists of all layers of the organ wall.

Mallory-Weiss syndrome

- Longitudinal laceration of mucosa at the gastroesophageal (GE) junction → bleeding due to injury to the submucosal arteries or veins.
- Mallory-Weiss tears are caused by high intragastric pressure being transmitted to the esophagus through a tight lower esophageal sphincter.
- They are most commonly caused by repetitive retching and vomiting usually due to alcoholism or bulimia. Other precipitating factors include coughing, hiccupping, other repeated abdominal straining, and abdominal trauma.
- Mallory-Weiss tears can be asymptomatic or can lead to gastrointestinal hemorrhage that manifests as hematemesis. About 10% of all upper gastrointestinal bleeds are from Mallory-Weiss syndrome. The intensity of hemorrhage and amount of blood loss varies widely according to the length and depth of the tears, but is almost never life-threatening.
- Repetitive vomiting leads to metabolic alkalosis due to net loss of acidic gastric secretions.
- Additionally, hiatal hernias are found in about half of patients with Mallory-Weiss syndrome and are considered a strong predisposing factor.
- Risk of Boerhaave syndrome: rupture of esophagus (transmural tear) leading to air in the mediastinum and subcutaneous emphysema (crepitus in the neck region or chest wall).



Characteristics of gastroesophageal mural injury

	Mallory-Weiss syndrome	Boerhaave syndrome
Etiology	• Forceful retching • **Mucosal** tear • Submucosal venous or arterial plexus bleeding	• Forceful retching • **Transmural** tear • Spillage of esophageal air/fluid into surrounding tissues
Clinical presentation	• Epigastric/back pain • **Hematemesis** (bright red or coffee-ground) • Possible hypovolemia	• Chest/back/epigastric pain • **Crepitus, crunching sound** (Hamman sign) • Odynophagia, dyspnea, fever, sepsis
Studies	• **Upper GI endoscopy** confirms diagnosis (& can treat persistent bleeding)	• Chest x-ray: pneumothorax, pneumomediastinum, pleural effusion • **Esophagography or CT scan with water-soluble contrast** confirms diagnosis
Management	• Acid suppression • **Most heal spontaneously**	• Acid suppression, antibiotics, NPO • **Emergency surgical consultation**

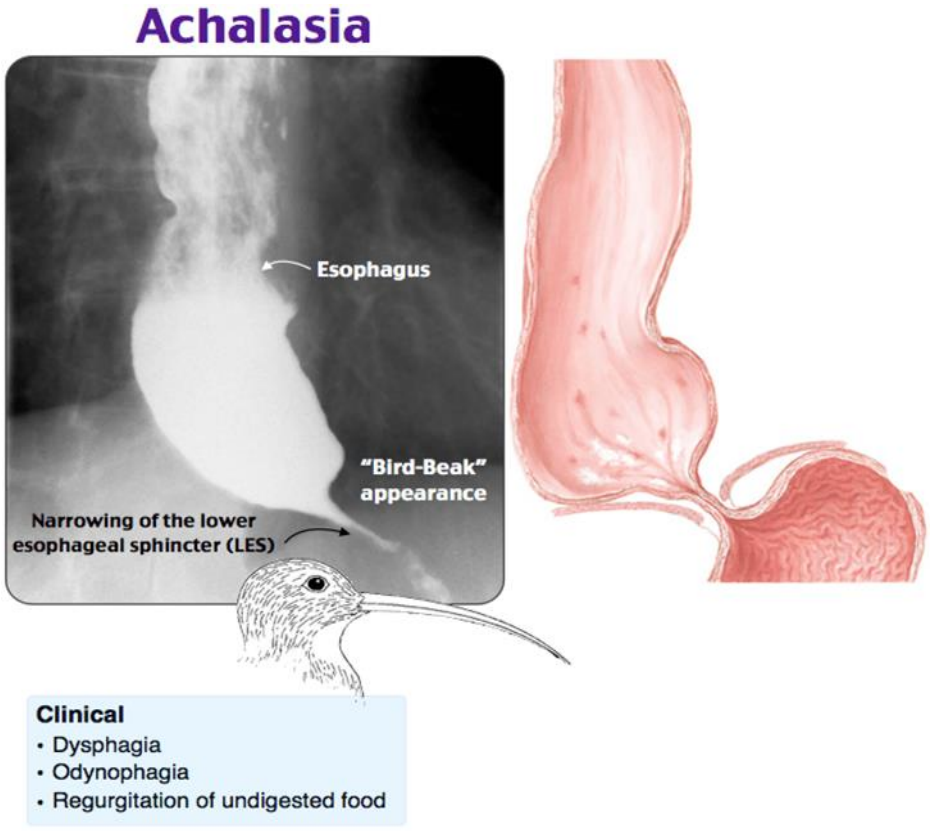
GI = gastrointestinal.

Achalasia

- A-chalasia = absence of relaxation.
- Disordered esophageal motility + inability to relax the lower esophageal sphincter (LES).
- Due to damaged postganglionic inhibitory neurons in the myenteric plexus (which contain NO and VIP). Ganglion cells of myenteric plexus are located between the inner circular and outer longitudinal layers of the muscularis propria and are important for regulating bowel motility and relaxing the LES.
- 2° achalasia (pseudoachalasia) may arise from Chagas disease (T. Cruzi infection) or extraesophageal malignancies (mass effect or paraneoplastic).
- Clinical features:

- Dysphagia to both solids and liquids at the same time.
- Food regurgitation and aspiration.
- Putrid breath.
- Manometry findings include uncoordinated or absent peristalsis with high LES resting pressure.
- Bird-beak' sign on barium swallow study.

- Increased risk for esophageal squamous cell carcinoma.



Gastroesophageal reflux disease (GERD)

- Gastroesophageal reflux disease (GERD) is a very common condition.
- Gastroesophageal junction incompetence is the primary pathophysiologic mechanism responsible for GERD.
- Acidic gastric contents reflux back into the esophagus and irritate the esophageal mucosa, leading to an inflammatory reaction and epithelial repair.
- Risk factors include alcohol, tobacco, obesity, fat-rich diet, caffeine, and hiatal hernia.
- Clinical features:

- GERD usually manifests with heartburn and regurgitation. However, patients can have "silent GERD" which means they may have symptoms like dysphagia, nocturnal cough, and sore throat even though they don't feel heartburn.
- Asthma (adult-onset) and cough.
- Damage to enamel of teeth.
- GERD usually does not cause esophageal mucosal injury, but frequent exposure to highly acidic secretions can overwhelm esophageal mucosal defense mechanisms and result in epithelial damage and complications, such as:

A. Erosive esophagitis with esophageal ulcers: often marked by a worsening of baseline GERD symptoms and the development of odynophagia (painful swallowing). GERD is the most common cause of esophagitis.

B. Barrett esophagus: metaplastic columnar epithelium replaces the normal stratified squamous epithelium in the distal esophagus. Most cases are asymptomatic with no change in baseline GERD manifestations. However, Barrett esophagus is a premalignant condition for esophageal adenocarcinoma, which typically presents with dysphagia and weight loss.

C. Esophageal stricture: typically develops in the setting of a healing esophageal ulcer when collagen fibers contract and cause narrowing of the esophageal lumen. Patients usually present with dysphagia and a sensation of food getting stuck in the esophagus.

❖ N.B:

- Reflux occurs in most pregnant women and is common in all trimesters.
- The major underlying cause is elevated estrogen and progesterone levels, which relax the smooth muscle of the LES leading to decreased LES tone and reduced sensitivity to contractile stimuli (high-protein meal).
- Later in pregnancy, reflux can also occur when the gravid uterus compresses the stomach and results in an altered LES angle or increased gastric pressure.

Gastroesophageal reflux disease	
Pathophysiology	• Decreased tone or excessive transient relaxation of LES • Anatomic disruption to gastroesophageal junction (eg, hiatal hernia) • ↑ Risk with obesity, pregnancy, smoking, alcohol intake
Manifestations	• Regurgitation of acidic material in mouth • **Heartburn** • Odynophagia (often indicates reflux esophagitis) • Extraesophageal symptoms (eg, cough, laryngitis, wheezing)
Complications	• Erosive esophagitis • Strictures • Barrett esophagus → adenocarcinoma
Initial treatment	• Lifestyle (eg, weight loss) & dietary changes • H2R blocker or proton pump inhibitor

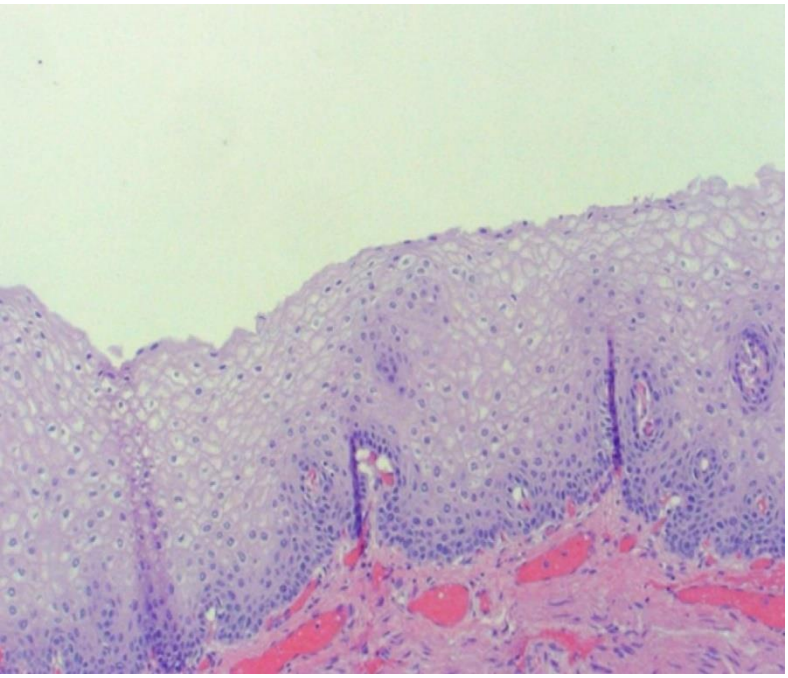
H2R = histamine 2 receptor; **LES** = lower esophageal sphincter.

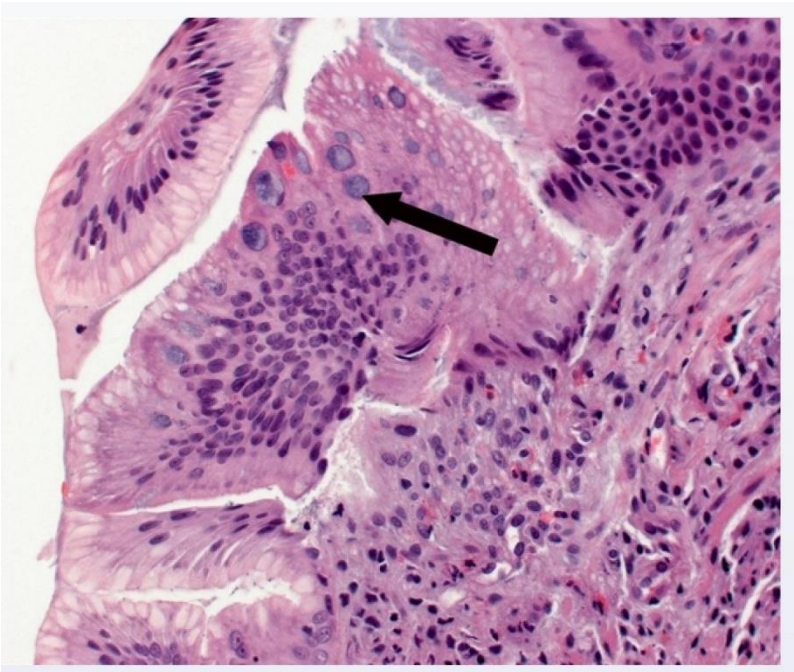
Barret Esophagus

- People with a history of severe and long-standing reflux disease are most prone to Barrett esophagus.
- When acidic gastric contents enter the esophagus, they irritate the mucosa, causing inflammation and subsequent epithelial necrosis.
- Sustained epithelial damage promotes the replacement of normal, stratified squamous epithelium with intestinal-type columnar cells.
- This metaplasia is hypothesized to be adaptive at first, as intestinal-type epithelium is more resistant to acidic environment; however, it is also a major risk factor for esophageal adenocarcinoma.
- Barrett esophagus is a pre-malignant condition that increases the risk of adenocarcinoma of the esophagus by 30-40 times. Adenocarcinomas develop through the progression from intestinal metaplastic epithelium → dysplasia → malignancy.
- This malignant cancer typically develops from the metaplastic intestinal epithelium in the distal part of esophagus; it is clinically silent until it obstructs the esophageal lumen. At this point, the cancer is usually large; thus, it is very important to diagnose Barrett esophagus early. Regular biopsies of the area should be performed to monitor for cellular dysplasia.

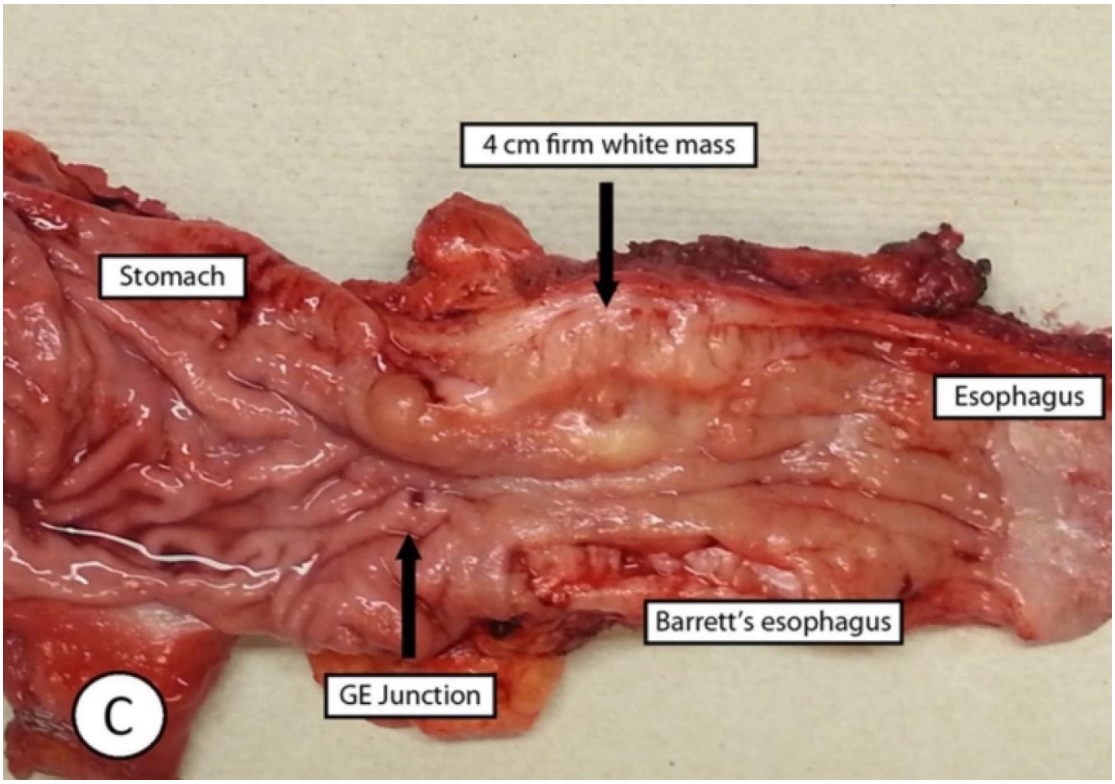
❖ N.B:

- The slide below shows intestinal columnar epithelium with goblet cells (arrow).
- This type of epithelium should not be present in the esophagus (Normally, the esophagus is lined by stratified squamous epithelium).
- The presence of intestinal-type epithelium in the esophagus is diagnostic of Barrett esophagus.





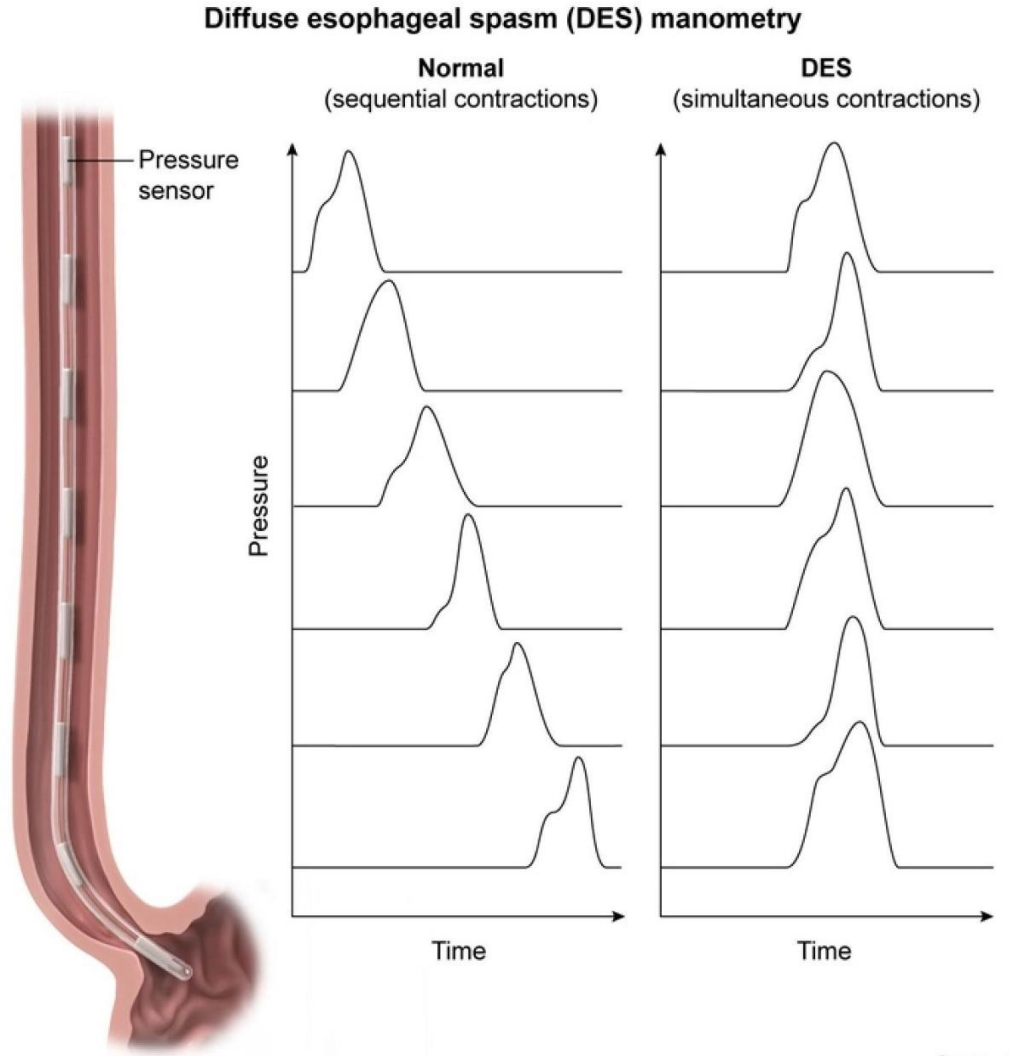
Normal Esophagus



Diffuse esophageal spasm

- Diffuse esophageal spasm (DES) occurs due to uncoordinated contractions of the esophagus.
- The pathogenesis of DES likely involves impaired inhibitory neurotransmission within the esophageal myenteric plexus.
- These contractions are both inefficient in propelling food into the stomach and may cause symptoms of dysphagia and chest pain. This chest pain may mimic unstable angina; thus, complete cardiac work-up should be considered in every patient suspected of having DES, so that a cardiac cause may be ruled out.
- Normally, esophageal muscle contractions are coordinated. Contractions are normally stimulated by esophageal distention by a food bolus; the contractions originate above the site of distention and propel the bolus downwards.
- In DES, several segments of the esophagus contract at the same time, which prevents the propagation of the food bolus towards the stomach.
- Additionally, these involuntary muscle contractions can be painful.
- Esophageal manometry studies show disorganized non-peristaltic contractions of the body of esophagus.
- Simultaneous contractions cause a so-called "corkscrew" esophagus, as seen on barium esophagogram.
- Treatment includes nitrates and CCBs.

Diffuse esophageal spasm	
Pathophysiology	• Uncoordinated, simultaneous contractions of esophageal body
Symptoms	• Intermittent **chest pain** • **Dysphagia** for solids & liquids
Diagnosis	• Esophagram: "**Corkscrew**" pattern • Manometry: Intermittent peristalsis, multiple **simultaneous contractions**
Treatment	• Calcium channel blockers • Alternate: Nitrates, tricyclics



Infectious esophagitis

- Infectious esophagitis is common in HIV-positive patients or transplant on immunosuppressant drugs.
- The most common cause is Candida albicans, although CMV and HSV-1 are also frequently implicated.
- Over 90% of esophageal infections in patients with AIDS are caused by Candida. Empiric therapy with fluconazole is the best course of action. If fluconazole does not improve symptoms, then endoscopy is performed.
- Diagnosis relies on endoscopic and microscopic findings.
- Clinically, it is not possible to distinguish which of the three is present as all cause dysphagia (difficulty swallowing) and/or odynophagia (pain on swallowing).
- Accurate diagnosis, however, is essential for treatment of these patients.
- Endoscopic and microscopic criteria are given in the table below.

Pathogen	Endoscopic findings	Microscopic findings
Candida albicans	Patches of adherent, grey/ white pseudomembranes on erythematous mucosa	Yeast cells and pseudohyphae that invade mucosal cells
HSV-1	Small vesicles that evolve into typical "punched out" ulcers	Eosinophilic intranuclear inclusions (Cowdry type A) in multinuclear squamous cells at the margins of the ulcers
CMV	Linear ulceration	Both intranuclear and cytoplasmic inclusions

❖ N.B:

- Pill esophagitis is due to a direct effect of certain medications on esophageal mucosa. Tetracyclines, potassium chloride, bisphosphonates. and nonsteroidal anti-inflammatory drugs are common causes.
- Patients experience sudden-onset odynophagia and retrosternal pain that can sometimes cause difficulty swallowing.

Eosinophilic Esophagitis

- Patients with eosinophilic esophagitis have swallowing difficulty and food impaction.
- Look for a history of asthma and allergic diseases.
- The most accurate diagnostic test is a biopsy finding eosinophils.
- The best initial therapy is PPIs and eliminating allergenic foods.

Sclerodermal esophageal dysmotility

- Systemic sclerosis may result in esophageal dysmotility and incompetence of the lower esophageal sphincter due to atrophy and fibrous replacement of the esophageal muscularis.
- The esophageal body and the lower esophageal sphincter become atonic and dilated, resulting in symptoms of gastroesophageal reflux (heartburn, regurgitation, dysphagia).
- This increases the risk of Barrett's esophagus and fibrous stricture formation.

Esophageal Carcinoma

- Subclassified as adenocarcinoma or squamous cell carcinoma:

A. Esophageal Adenocarcinoma:

- It is a malignant proliferation of glands; most common type of esophageal carcinoma in America.
- Arises from preexisting Barrett esophagus; usually involves the lower one-third of the esophagus.

B. Esophageal Squamous cell carcinoma:

- It is a malignant proliferation of squamous cells; most common esophageal cancer worldwide.

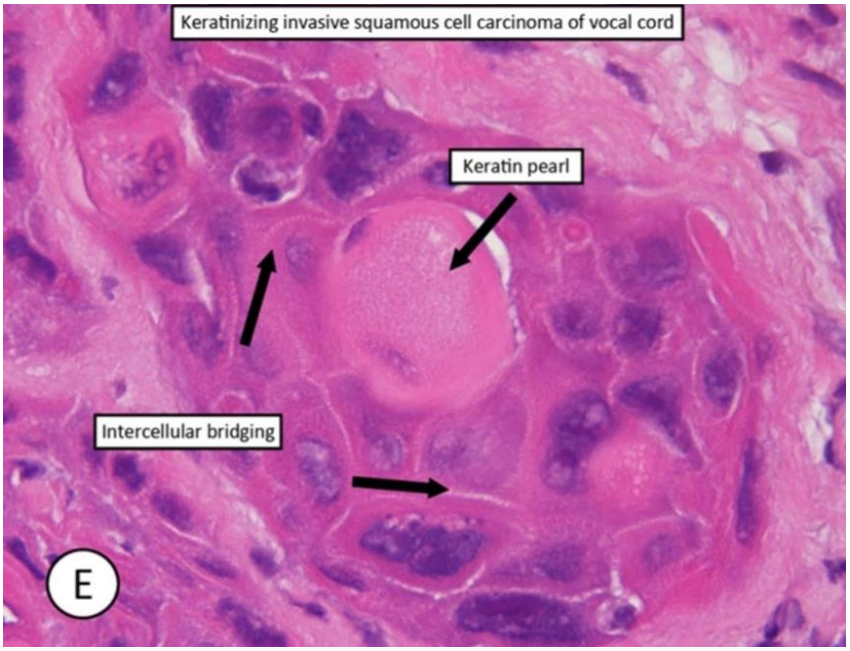
- The incidence of esophageal SCC is decreasing in the United States, with middle-aged and older individuals of African or Asian heritage at greatest risk for developing the disease.

- The most significant risk factors for the development of SCC in the United States include cigarette smoking and alcohol intake.

- In Asia, the chewing of betel nuts and consumption of foods containing N-nitroso compounds (often found in preserved or pickled vegetables) are commonly associated with SCC. Other risk factors include preexisting esophageal disease (achalasia, caustic injury) and ingestion of high-temperature liquids (very hot tea).

- Histologically, squamous cell carcinoma (SCC) demonstrates flattened polyhedral or ovoid epithelial cells with eosinophilic cytoplasm, keratin nests or "pearls" within or between cells, and intercellular bridging. Large hyperchromatic cells with bizarre nuclei and atypical mitoses are commonly observed.

Squamous cell carcinoma of the esophagus	
Risk factors	• Alcohol, smoking, foods containing N-nitroso • Age >50
Location	• Proximal two-thirds of esophagus (most common in the middle third) • Associated mediastinal lymphadenopathy
Histopathology	• Sheets of eosinophilic squamous cells • Keratin pearls, intercellular bridges



- Esophageal carcinoma presents late. The prognosis for esophageal cancer is generally poor as many patients present with incurable locally advanced or metastatic disease.

- Chronic gastrointestinal blood loss is a frequent finding in this patient population and may result in iron deficiency anemia.

- Symptoms include progressive dysphagia (Patients typically present with solid food dysphagia as the tumor gradually obstructs the esophageal lumen, which can progress to liquid dysphagia), weight loss, pain, and hematemesis.

- Squamous cell carcinoma may additionally present with hoarse voice (recurrent laryngeal nerve involvement) and cough (tracheal involvement).

- location of lymph node spread depends on the level of the esophagus that is involved:

- Upper 1/3: cervical nodes.
- Middle 1/3: mediastinal or tracheobronchial nodes.
- Lower 1/3: celiac and gastric nodes.

❖ N.B:

1. Chronic gastroesophageal reflux disease (GERD) that progress to dysphagia with solid foods, weight loss, and a mass in his lower esophagus, raise strong suspicion for esophageal adenocarcinoma.

- Most cases of esophageal adenocarcinoma arise in the setting of Barrett esophagus, a metaplastic condition whereby the normal stratified squamous epithelium in the distal esophagus is replied with intestine-like columnar cells in response to chronic acidic damage.
- Although these metaplastic columnar cells are better suited to handle the presence of acid in the distal esophagus, they are also much more likely to become dysplastic and undergo malignant transformation into esophageal adenocarcinoma.
- Major risk factors for esophageal adenocarcinoma are similar to those that promote Barrett esophagus and include:

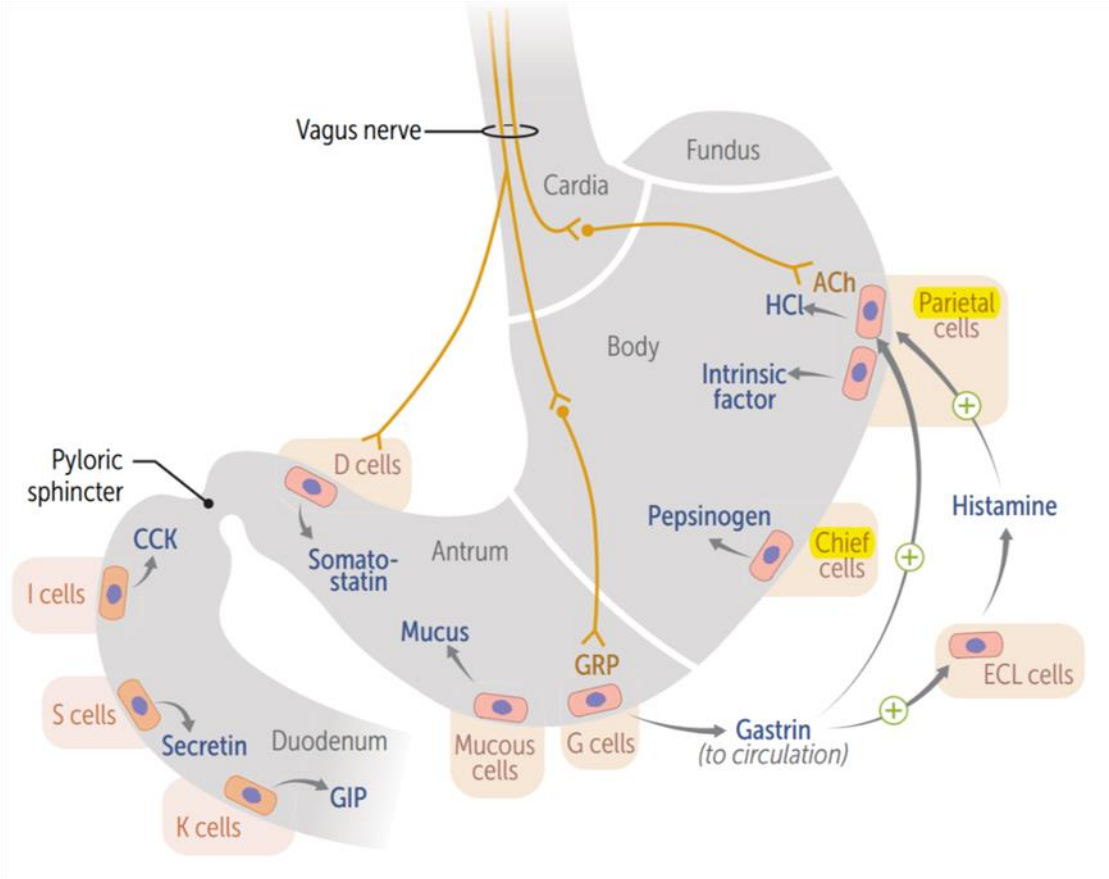
- Chronic GERD.
- Obesity: increases intragastric pressure, frequency of lower esophageal sphincter relaxation, and rates of hiatal hernia, which promote GERD.
- Smoking.
- Use of medications that lower esophageal sphincter pressure (nitroglycerin).

2. The esophagus can be subdivided (based on anatomy and embryonic formation) into thirds; malignancies occur at different frequencies within each segment:

A. Proximal and middle third: SCC is more common, and occurs at the highest frequency in the middle third. Lymphatics drain to mediastinal nodes; metastatic disease may present with mediastinal lymphadenopathy.

B. Distal third: Adenocarcinoma is more common. Lymphatics drain caudally to the gastric and celiac nodes; metastatic disease may present with abdominal lymphadenopathy.

Gastrointestinal regulatory substances



- Classically, the stimulation of acid secretion within the stomach is separated into three phases (cephalic, gastric, and intestinal):

A. The cephalic phase: mediated primarily by cholinergic and vagal mechanisms, and is triggered by the thought, sight, smell, and taste of food.

B. The gastric phase: mediated by the presence of gastrin (which stimulates histamine secretion and therefore, indirectly, acid secretion), and is triggered by the chemical stimulus of food and distension of the stomach.

C. The intestinal phase: initiated when protein- containing food enters the duodenum, but this phase plays only a minor role in stimulating gastric acid secretion.

- In fact, intestinal influences are effective in down-regulating gastric acid secretion after a meal. The ileum and colon release peptide YY, which binds to receptors on the endocrine, histamine-containing cells described as enterochromaffin-like (ECLs). Such binding counteracts the cephalic and gastric phases of acid secretion by inhibiting gastrin-stimulated histamine release from ECLs. Other factors that inhibit acid secretion include somatostatin and prostaglandins.

- The stomach performs a number of important functions:

1. Protein digestion:

- Gastric parietal cells and chief cells produce hydrochloric acid (HCl) and pepsinogen, respectively.

- HCl helps to denature dietary protein (improving proteolysis) and also converts pepsinogen to its active form, pepsin, which preferentially cleaves polypeptides at aromatic amino acid locations.

- Pancreatic and intestinal proteases further degrade dietary proteins into basic amino acids in the small intestine.

2. Intrinsic factor (IF) secretion:

- Parietal cells in the body and fundus of the stomach also secrete IF, a glycoprotein that normally binds to vitamin B_{12}.

- The B_{12}-IF complex is then absorbed by enterocytes in the terminal ileum. However, in patients who have undergone total gastrectomy, IF can no longer be produced and vitamin B_{12} cannot be effectively absorbed. Therefore, very high-dose oral or parenteral vitamin B_{12} becomes necessary.

3. Gastric reservoir:

- The stomach also serves as a reservoir for ingested food.

- This function is lost after total gastrectomy, and accelerated emptying of hyperosmolar food boluses into the small bowel results in dumping syndrome (characterized by colicky abdominal pain, nausea, and diarrhea). Avoidance of large meals and low dietary intake of simple sugars improves these symptoms.

❖ N.B:

- Diabetic gastroparesis results from the destruction of enteric neurons due to chronic hyperglycemia, leading to impaired relaxation and disordered and ineffective peristalsis.
- This causes delayed gastric emptying, which presents as postprandial fullness, regurgitation of undigested food, nausea, and vomiting.

Gastrin

- Source: G cells (antrum of stomach, duodenum).

- Action:

- ↑ gastric H secretion: Gastrin ↑ acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

- ↑ growth of gastric mucosa.

- ↑ gastric motility.

- Regulation:
- ↑ by stomach distention/alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP).
- ↓ by pH < 1.5.

- Notes:
- ↑ by chronic PPI use.
- ↑ in chronic atrophic gastritis (H. pylori).
- ↑↑ in Zollinger-Ellison syndrome (Gastrinoma).

Somatostatin

- Source: D cells (pancreatic islets, GI mucosa).

- Action:
- ↓ gastric acid and pepsinogen secretion.
- ↓ pancreatic and small intestine fluid secretion.
- ↓ gallbladder contraction.
- ↓ insulin and glucagon release.

- Regulation:
- ↑ by acid.
- ↓ by vagal stimulation.

- Notes:
- Inhibits secretion of various hormones (encourages somato-stasis).
- Octreotide is an analog used to treat acromegaly, carcinoid syndrome, and variceal bleeding.

Cholecystokinin

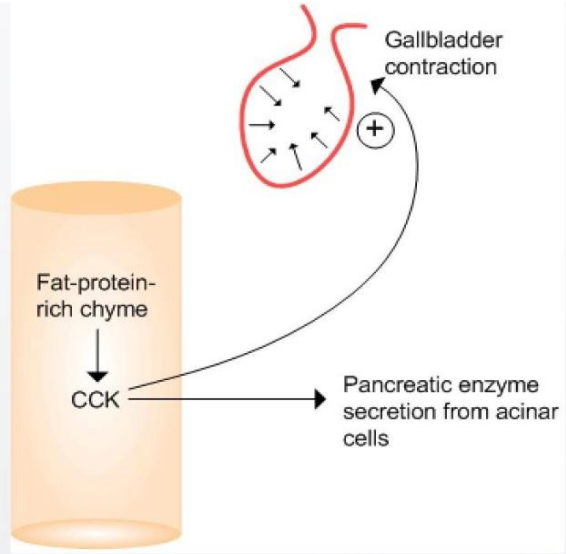
- Source: I cells (duodenum, jejunum).

- Action:
- ↑ gallbladder contraction.
- ↑ sphincter of Oddi relaxation.

- ↓ gastric emptying.
- ↑ pancreatic secretion.

▪ Regulation: ↑ by fatty acids, amino acids.

▪ Notes:
- In cholecystitis, fatty foods increase CCK production and pain occurs when an inflamed and/or obstructed gallbladder contracts.

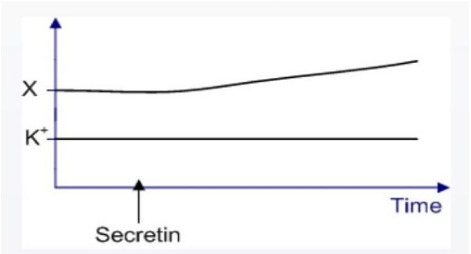


Secretin

▪ Source: Secretin is produced by S cells in the duodenal mucosa in response to stimulation by intraluminal acidity.

▪ Action:
- Secretin stimulates the release of bicarbonate-rich secretions from the exocrine pancreas, which is the major source of acid-neutralizing bicarbonate entering the duodenum, allowing pancreatic enzymes to function.
- ↓ gastric acid secretion.
- ↑ bile secretion.

▪ Regulation: ↑ by acid, fatty acids in lumen of duodenum.



▪ Notes:
- Remember that pancreatic juice is an isotonic secretion, which normally contains Na and K in the same concentrations as found in plasma, a higher HCO_3 concentration than in plasma and a lower Cl concentration than in plasma. As pancreatic juice flow rates and secretin stimulation increase, the concentration of HCO_3 increases and the concentration of Cl decreases.

Glucose dependent insulinotropic peptide

- Also known as gastric inhibitory peptide (GIP).
- Source: K cells (duodenum, jejunum).
- Action:
  - Exocrine: ↓ gastric H secretion.
  - Endocrine: ↑ insulin release.
- Regulation: ↑ by fatty acids, amino acids, oral glucose.
- Notes: Oral glucose load leads to ↑ insulin compared to IV equivalent due to GIP secretion.

Motilin

- Source: Small intestine.
- Action: Produces migrating motor complexes (MMCs).
- Regulation: ↑ in fasting state.
- Notes: Motilin receptor agonists (erythromycin) are used to stimulate intestinal peristalsis.

Vasoactive intestinal polypeptide

- Source: Parasympathetic ganglia in sphincters, gallbladder, small intestine.
- Action:
  - ↑ intestinal water and electrolyte secretion.
  - ↑ relaxation of intestinal smooth muscle and sphincters.
- Regulation:
  - ↑ by distention and vagal stimulation.
  - ↓ by adrenergic input.
- Notes:
  - VIPoma: non-α, non-β islet cell pancreatic tumor that secretes VIP. Watery Diarrhea, Hypokalemia, and Achlorhydria (WDHA Syndrome).

Nitric oxide

- Action: ↑ smooth muscle relaxation, including lower esophageal sphincter (LES).
- Notes: Loss of NO secretion is implicated in ↑ LES tone of achalasia.

Ghrelin

- Source: Stomach.
- Action: ↑ appetite.
- Regulation:
  - ↑ in fasting state.
  - ↓ by food.
- Notes:
  - ↑ in Prader-Willi syndrome → Polyphagia.
  - ↓ after gastric bypass surgery.

Intrinsic factor

- Source: Parietal cells (stomach).
- Action: Vitamin B_{12} binding protein (required for B_{12} uptake in terminal ileum).
- Notes: Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.

Gastric acid

- Source: Parietal cells (stomach).
- Action: ↓ stomach pH.
- Regulation:
  - ↑ by ACh, gastrin, histamine.
  - ↓ by somatostatin, GIP, prostaglandin, secretin.

Pepsin

- Source: Chief cells (stomach).
- Action: Protein digestion.
- Regulation: ↑ by vagal stimulation, local acid.
- Notes: Pepsinogen (inactive) is converted to pepsin (active) in the presence of H.

Bicarbonate

- Source: Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum).
- Action: Neutralizes acid.
- Regulation: ↑ by pancreatic and biliary secretion with secretin.
- Notes: Trapped in mucus that covers the gastric epithelium.

Important gastrointestinal hormones

Hormone	Actions	Secretion site
Gastrin	• ↑ Gastric H^+ secretion	G cells (gastric antrum, duodenum)
Somatostatin	• ↓ Secretion of most GI hormones	D cells (pancreatic islets, gut mucosa)
Cholecystokinin	• ↑ Pancreatic enzyme & HCO_3^- secretion	I cells (small intestine)
Secretin	• ↑ Pancreatic HCO_3^- secretion • ↓ Gastric H^+ secretion	S cells (small intestine)
GIP	• ↑ Insulin release • ↓ Gastric H^+ secretion	K cells (small intestine)
Motilin	• ↑ GI motility	M cells (small intestine)

GI = gastrointestinal; GIP = gastric inhibitory peptide; H^+ = hydrochloric acid; HCO_3^- = bicarbonate.

Stomach

Acute gastritis

- Acidic damage to the stomach mucosa.
- Due to imbalance between mucosal defenses and acidic environment.
- Defenses include mucin layer produced by foveolar cells, bicarbonate secretion by surface epithelium, and normal blood supply (provides nutrients and picks up leaked acid).
- Risk factors:

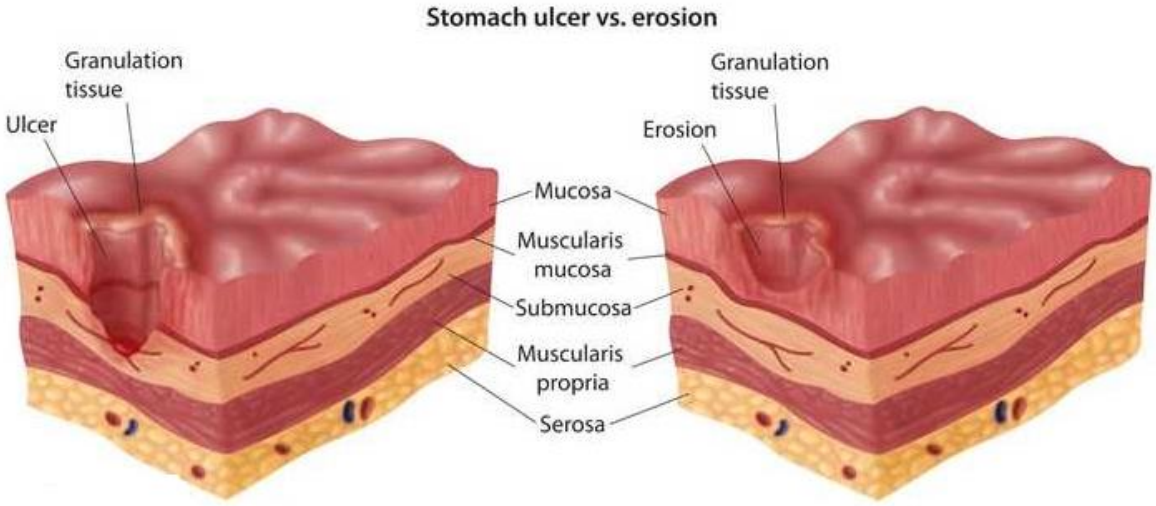
- NSAIDs: NSAIDs induce gastric injury by inhibiting prostaglandin synthesis. As a result, they decrease the stomach's protective abilities by reducing mucin and bicarbonate secretion, gastric epithelial cell proliferation, and gastric perfusion. NSAIDs also increase gastric acid secretion and can penetrate the cells of the gastric mucosa, causing direct cell damage.
- Heavy alcohol consumption.
- Severe burn (Curling ulcer): Hypovolemia leads to decreased blood supply.
- Increased intracranial pressure (Cushing ulcer): Cushing ulcers are likely induced by direct stimulation of the vagus nerve by increased intracranial pressure, thereby resulting in hypersecretion of gastric acid.
- Shock: Multiple (stress) ulcers may be seen in ICU patients.
- Chemotherapy.

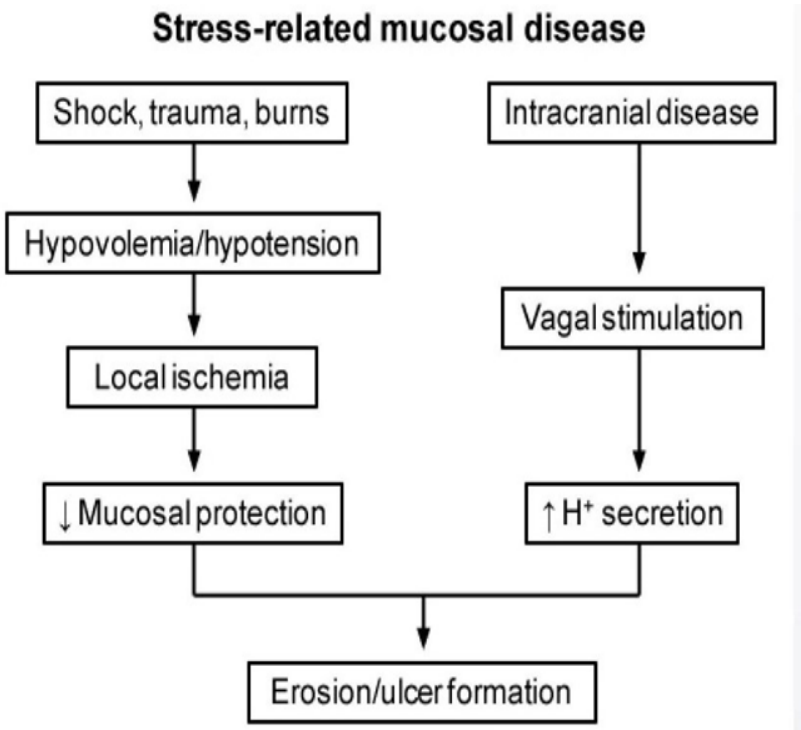
- Once the causative stressors are resolved, healing with full re-epithelization of the gastric mucosa occurs within days to weeks.
- Acid damage results in superficial inflammation, erosion (loss of superficial epithelium), or ulcer (loss of mucosal layer).

❖ N.B:

- Gastric erosions are defined as mucosal defects that do not fully extend through the muscularis mucosa (erosions are limited to the mucosal layer).
- Gastric ulcers, on the other hand, penetrate through the mucosal layer and extend into the submucosal layers.
- Erosions usually occur in the setting of acute erosive gastropathy, a condition that results from short-term, severe mucosal injury leading to inflammation and superficial mucosal destruction.
- A number of causative agents can cause acute erosive gastropathy. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), surgical stress, head trauma (Cushing ulcers), burns (Curling ulcers), smoking, and alcohol consumption are the most common causes.

- Clinical manifestations of acute erosive gastropathy vary widely; patients may be asymptomatic or present with life-threatening upper gastrointestinal bleeding.
- Epigastric discomfort or pain, nausea, and vomiting are the most common symptoms. These symptoms usually subside a few days after withdrawal of the offending medication.



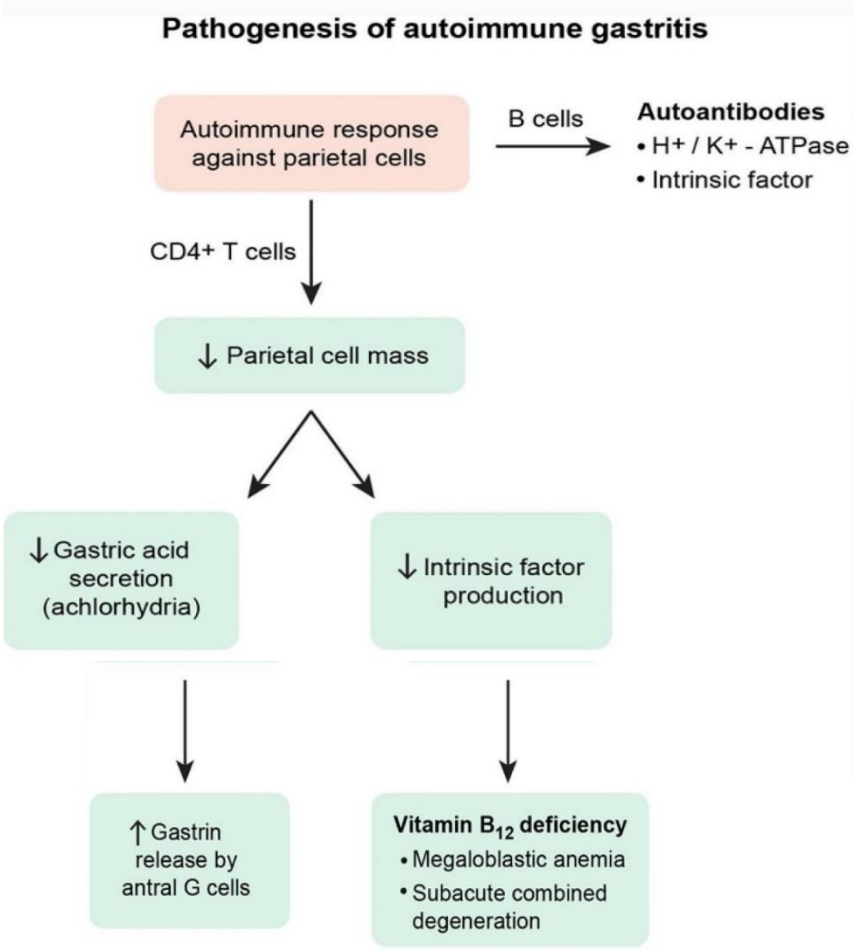


Chronic gastritis

- Chronic Inflammation of stomach mucosa.
- Divided into two types based on underlying etiology (chronic autoimmune gastritis and chronic H pylori gastritis).

A. Chronic autoimmune gastritis:

- It is due to autoimmune destruction of gastric parietal cells, which are located in the stomach body and fundus.
- Associated with antibodies against parietal cells and/or intrinsic factor; useful for diagnosis, but pathogenesis is mediated by T cells (type IV hypersensitivity).
- Clinical features:
  - Atrophy of mucosa with intestinal metaplasia (precancerous).
  - Achlorhydria with increased gastrin levels and antral G-cell hyperplasia.
  - Megaloblastic (pernicious) anemia due to lack of intrinsic factor.
  - Increased risk for gastric adenocarcinoma (intestinal type).



B. Chronic H pylori gastritis:

- It is due to H pylori-induced acute and chronic inflammation; most common form of gastritis (90%).

- Antrum is the most common site (Affects antrum first and spreads to body of Stomach).

- Chronic antral inflammation leads to a decrease in the number of somatostatin-producing cells (delta cells).

- Somatostatin is a hormone that inhibits gastrin release. In its absence, high gastrin levels act both directly and indirectly to increase hydrogen ion secretion by parietal cells. This results in gastric fluid with very low pH that is not adequately neutralized by duodenal bicarbonate production, leading to duodenal ulceration and duodenal gastric metaplasia.

- H. Pylori is susceptible to gastric acidity but is protected by the mucus layer and endogenous urease production. Urease converts urea to ammonia, alkalinizing the surrounding pH, which allows the bacteria to survive.

- Presents with epigastric abdominal pain; increased risk for ulceration (peptic ulcer disease), gastric adenocarcinoma (intestinal type) and MALT lymphoma (low-grade B-cell lymphoma).

- The composition of the inflammatory cell infiltrate helps to differentiate acute (neutrophil predominant) from chronic (lymphocyte and plasma cell predominant) gastritis.

- Treatment involves triple therapy. Eradication of the H. pylori infection causes symptom improvement, restoration of normal histology, and less risk of malignancy for these patients (reverses intestinal metaplasia).

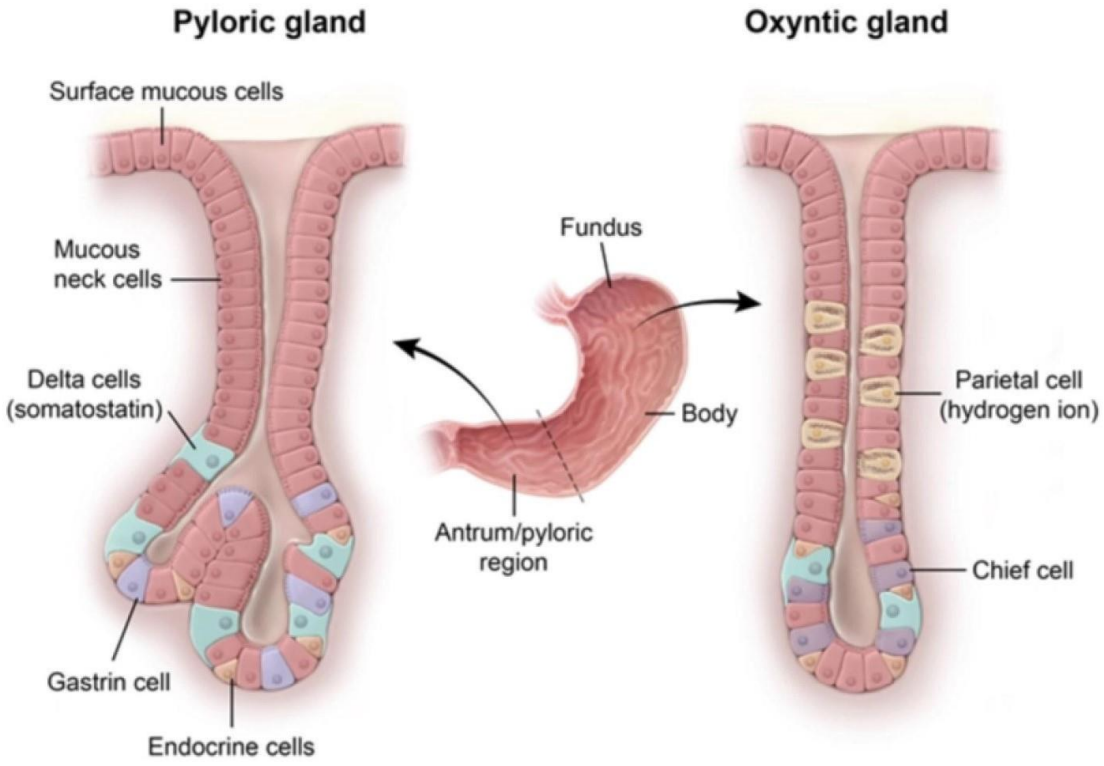
- Negative urea breath test and lack of stool antigen confirm eradication of H pylori.

❖ N.B:

- Pernicious anemia is a condition thought to arise from the immune-mediated destruction of gastric mucosa. Over time, this damage results in chronic atrophic gastritis, a condition characterized by:

1. Loss of the intrinsic factor-secreting parietal cells in the upper glandular layer.
2. Marked lymphocytic and plasma cell infiltration.
3. Megaloblastic changes in mucosal cells. Once the number of parietal cells has been sufficiently depleted and the stores of vitamin B_{12} are exhausted, pernicious anemia classically manifests with symptoms such as fatigue and paresthesias.

- The combination of lower extremity paresthesias, macrocytic red blood cells (RBCs), and gastric body and fundal atrophy is highly suggestive of pernicious anemia (PA).



Peptic ulcer disease

- Solitary mucosal ulcer involving proximal duodenum (90%) or distal stomache (10%).

A. Duodenal ulcer:

- It is almost always due to H pylori (> 95%); rarely, may be due to ZE syndrome.
- Presents with epigastric pain that improves with meals.
- Diagnostic endoscopic biopsy shows ulcer with hypertrophy of Brunner glands.
- The vast majority of duodenal ulcers occur within the first part of the duodenum (more than 95%). However, multiple or refractory ulcers beyond the duodenal bulb may be seen in patients with gastrinoma (Zollinger Ellison syndrome).

B. Gastric ulcer:

- It is usually due to H pylori (75%); other causes include NSAIDs and bile reflux.
- NSAID use is very common in the United States and is the second most common cause of gastric ulcers after Helicobacter pylori.
- Presents with epigastric pain that worsens with meals.
- Ulcer is usually located on the lesser curvature of the antrum.
- Rupture carries risk of bleeding from left gastric artery.

- Differential diagnosis of ulcers includes carcinoma:

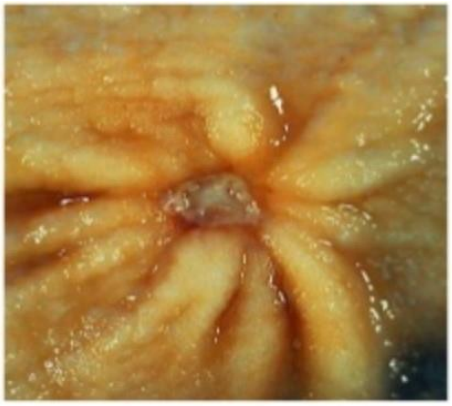
- Duodenal ulcers are almost never malignant (duodenal carcinoma is extremely rare).

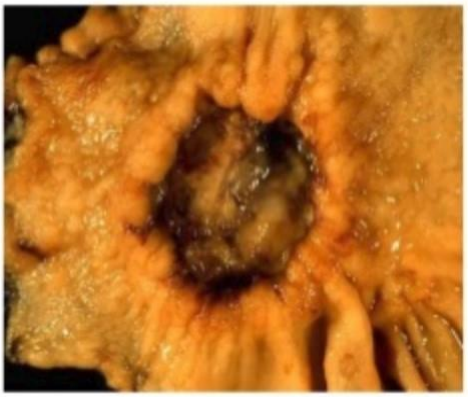
- Gastric ulcers can be caused by gastric carcinoma (intestinal subtype).

- Benign peptic ulcers are usually small (< 3 cm), sharply demarcated ("punched-out"), and surrounded by radiating folds of mucosa.

- Malignant ulcers are large and irregular with heaped up margins.

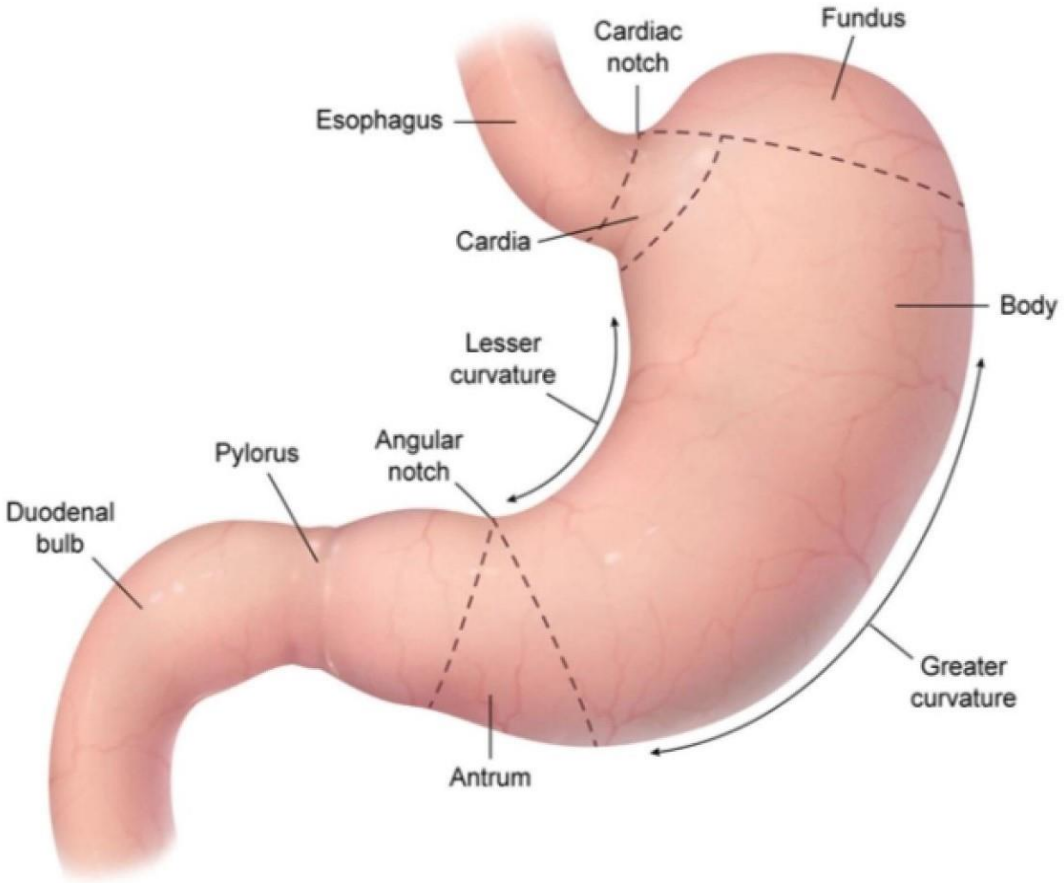
- Biopsy is required for definitive diagnosis.



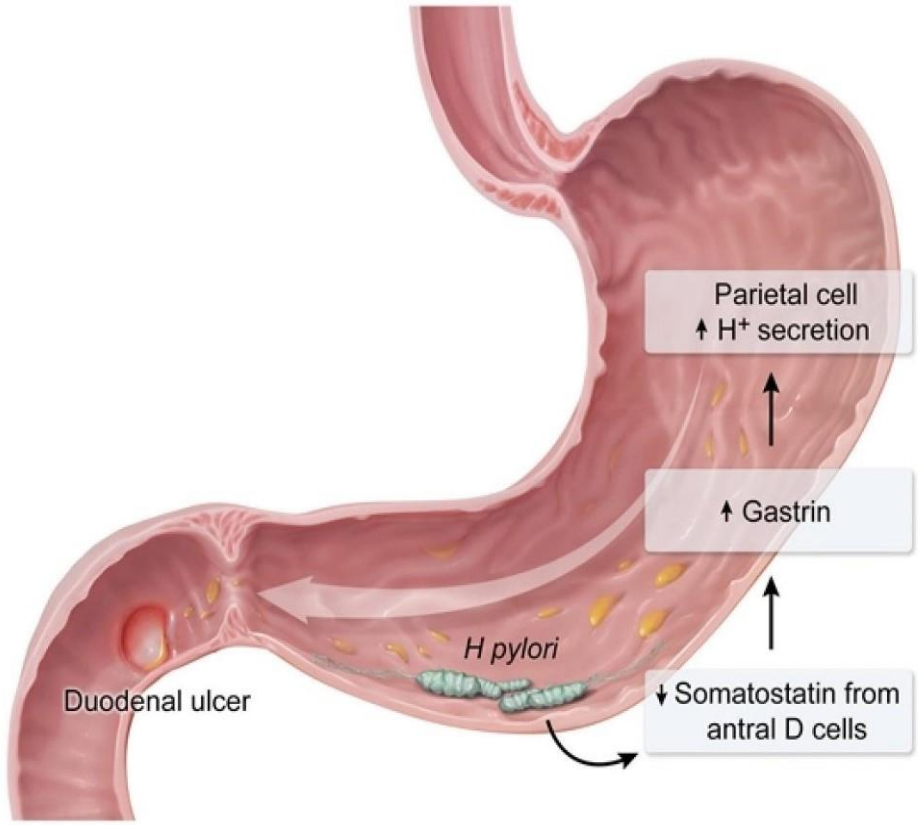


	Gastric ulcer	Duodenal ulcer
PAIN	Can be Greater with meals—weight loss	Decreases with meals—weight gain
H PYLORI INFECTION	~ 70%	~ 90%
MECHANISM	↓ mucosal protection against gastric acid	↓ mucosal protection or ↑ gastric acid secretion
OTHER CAUSES	NSAIDs	Zollinger-Ellison syndrome
RISK OF CARCINOMA	↑	Generally benign
OTHER	Biopsy margins to rule out malignancy	Hypertrophy of Brunner glands

Regions of the stomach



***Helicobacter pylori* and duodenal ulcers**



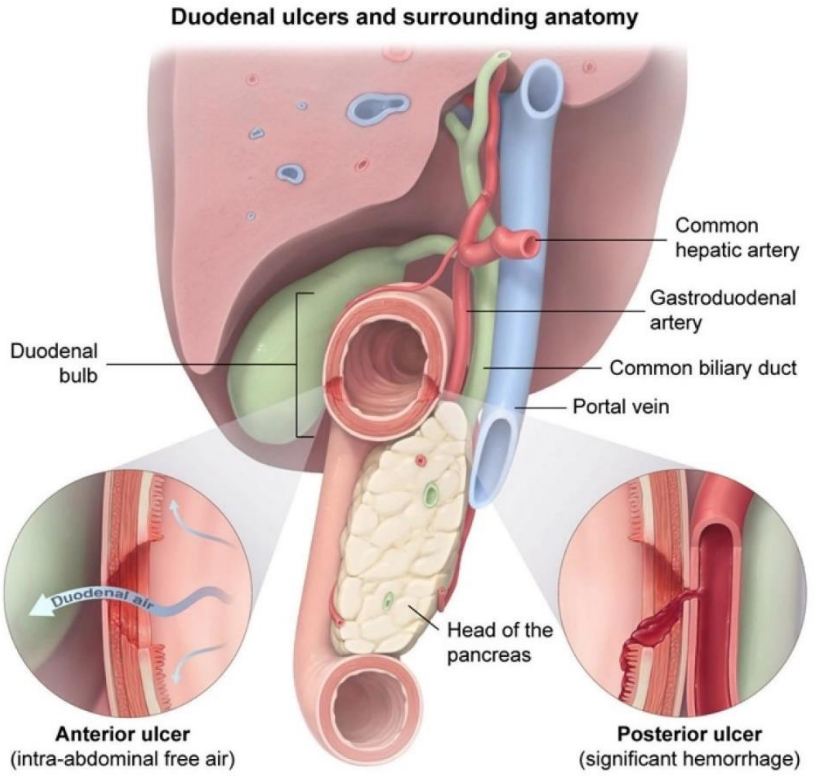
❖ N.B:

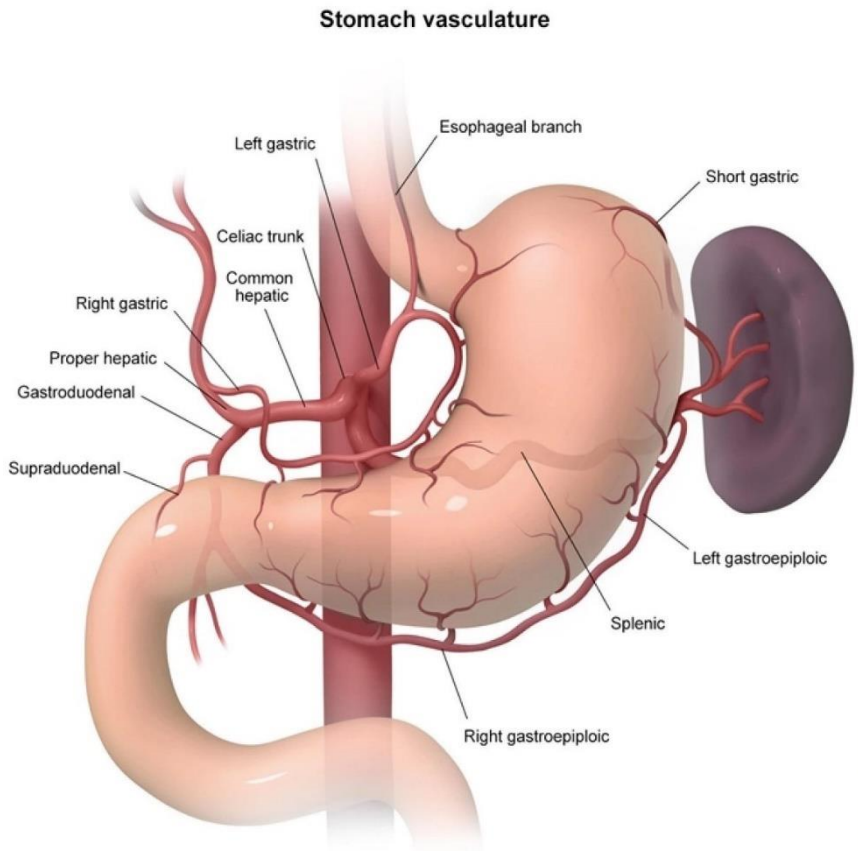
1. Gastric biopsy specimens are taken for direct tissue diagnosis of H. pylori infection.

- In contrast to the time-intensive task of culturing H. pylori organisms, the rapid urease test is able to make a relatively quick diagnosis from tissue samples.
- Helicobacter pylori is typically found in greatest concentration in the prepyloric area of the gastric antrum. As a result, biopsy of the prepyloric area would have the greatest yield of the organism.
- H. pylori produces large amounts of extracellular urease enzyme, hence the use of a urea solution in this test.
- Urease converts urea to carbon dioxide and ammonia, causing a pH increase and resultant color change of the phenol red pH indicator.
- An alkaline (pink) color persisting more than five minutes is considered a positive test for H. pylori.

2. Duodenal ulcers are more common than gastric ulcers and tend to occur anteriorly.

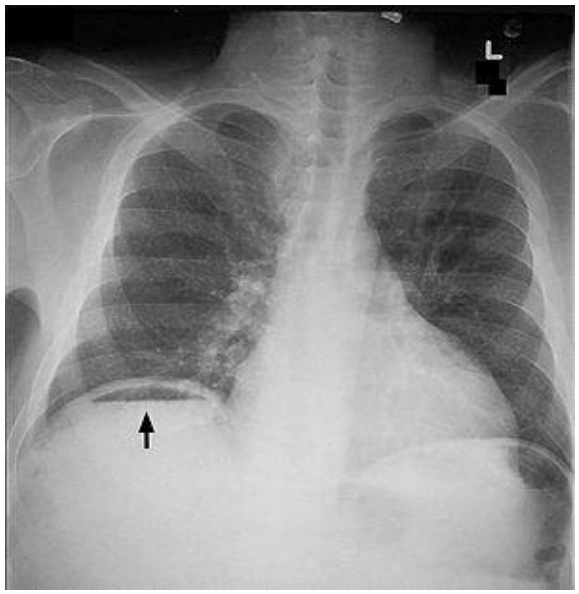
- Ulcers located on the anterior wall of the duodenal bulb are more prone to perforation; those on the posterior wall are more likely to cause hemorrhage.
- These complications are explained by the relationship of the duodenal bulb to adjacent organs. The duodenal bulb is approximately 5 cm long, beginning at the pylorus and ending at the neck of the gallbladder.
- The gallbladder and liver lie anterior to the duodenal bulb within the intraperitoneal space; the gastroduodenal artery, common biliary duct, and portal vein are posterior to the bulb; and the head of the pancreas is located interiorly.
- When an ulcer penetrates the posterior duodenal wall, it is likely to erode into the gastroduodenal artery, which perfuses both the pylorus and the proximal part of the duodenum. Damage to the gastroduodenal artery can cause significant upper gastrointestinal bleeding.
- Most gastric ulcers arise along the lesser curvature of the stomach, usually at the transitional zone between the gastric corpus (body) and antrum. The left and right gastric arteries run along the lesser curvature and are likely to be penetrated by ulcers, causing gastric bleeding.





3. Chronic epigastric pain that suddenly worsens and becomes diffuse with a pneumoperitoneum (upright chest x-ray shows free air under the right diaphragm which is best seen between the liver and the diaphragm) is concerning for likely perforated peptic ulcer disease (PUD).

- Gastric secretions/contents are released into the peritoneal cavity, resulting in peritonitis, with rebound tenderness and guarding.



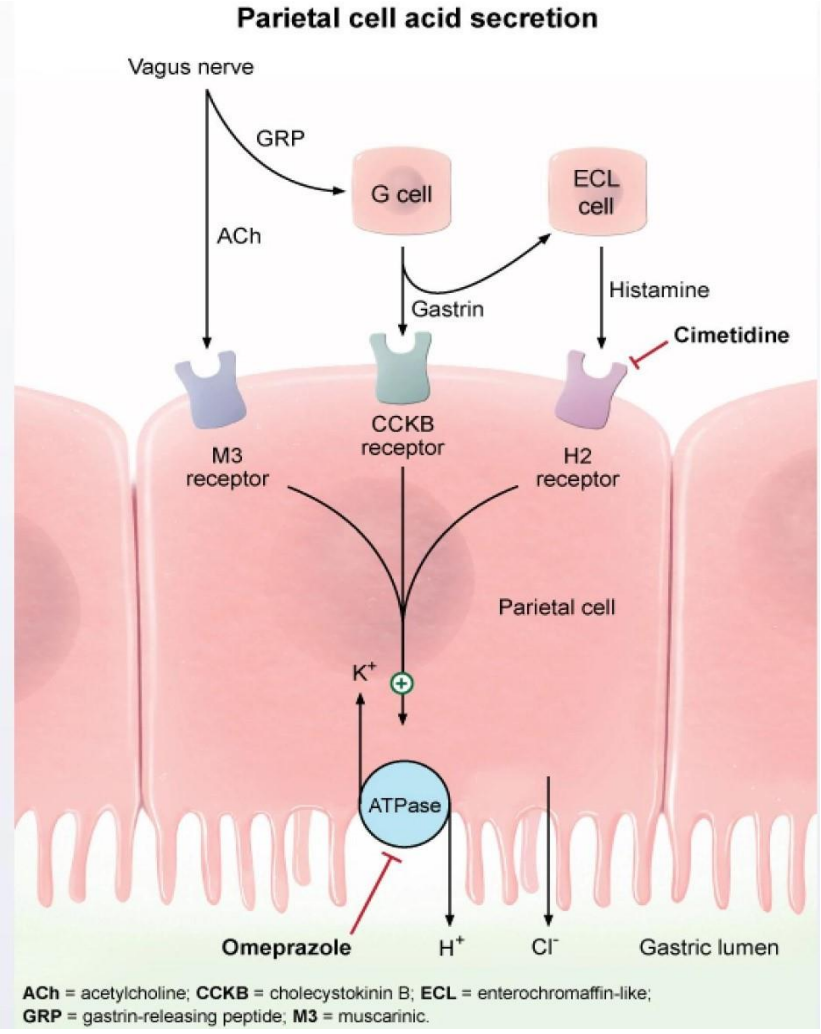
4. Helicobacter pylori is a common cause of peptic ulcers.

- Duodenal ulcers are associated with heavy colonization in the gastric antrum, whereas colonization in the gastric corpus is associated with gastric ulcers.

5. Systemic mastocytosis is characterized by the abnormal proliferation of mast cells and increased histamine secretion.

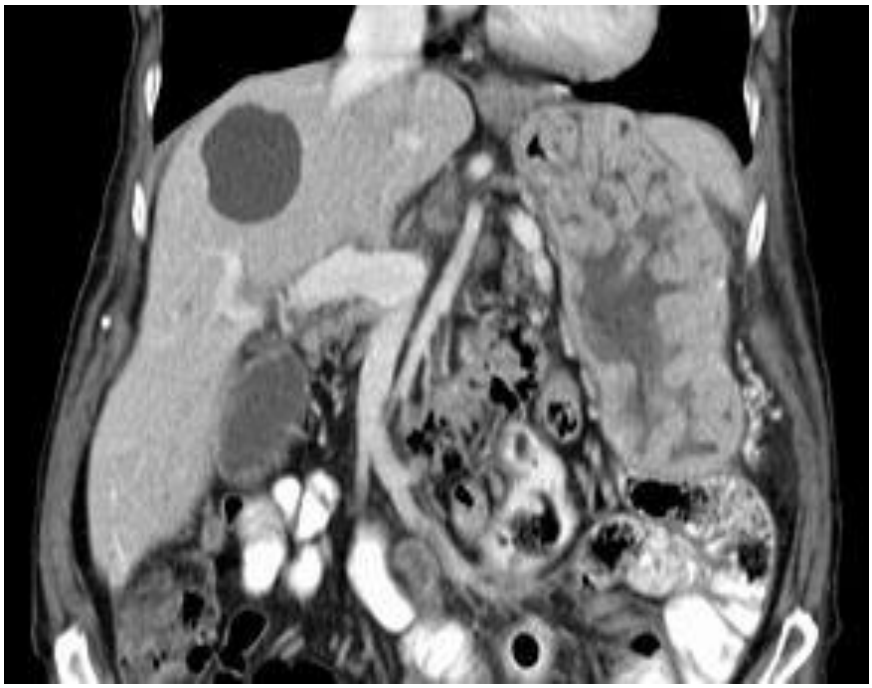
- Histamine increases the production of gastric acid by parietal cells. Gastric hypersecretion, therefore, is a common occurrence in systemic mastocytosis.
- In systemic mastocytosis, mast cell proliferation occurs in the bone marrow and in other organs.
- Increased histamine secretion ensues; as a result, many clinical symptoms of this disease are mediated by histamine:

- Gastric acid secretion increases, which inactivates pancreatic and intestinal enzymes, causing diarrhea. Other GI symptoms include nausea, vomiting, and abdominal cramps. Gastric ulcerations may occur.
- Other histamine-mediated symptoms of mastocytosis are syncope, flushing, hypotension, tachycardia, and bronchospasm.
- Skin manifestations, such as pruritus, urticaria, and dermatographism are typical.



Ménétrier disease

- Also known as hypoproteinemic hypertrophic gastropathy.
- Associated with H. pylori and CMV infections.
- Hypertrophic gastropathy secondary to hyperplasia of mucus-producing cells → hypertrophied rugae (look like brain gyri).
- Causes excess mucus production with resultant protein loss.
- Parietal cell atrophy with → ↓ acid production.
- Presents with Weight loss, Anorexia, Vomiting, Epigastric pain, Edema (due to protein loss) (WAVEE).
- Precancerous.



Gastric carcinoma

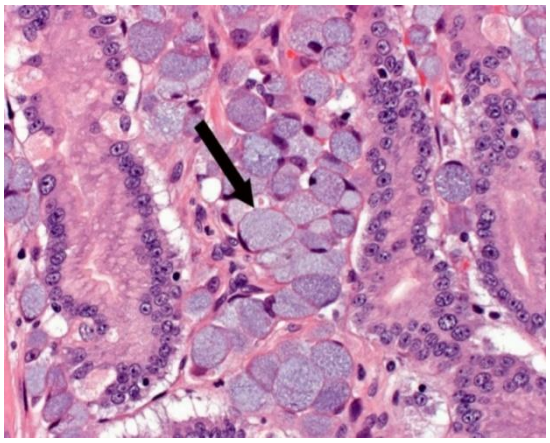
- Malignant proliferation of surface epithelial cells (adenocarcinoma).
- Subclassified into intestinal and diffuse types.

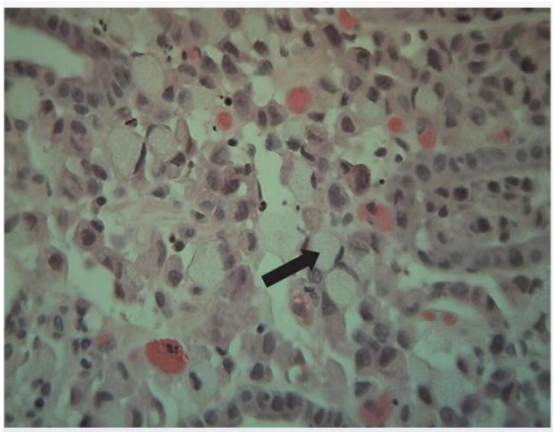
A. **Intestinal type (more common):**

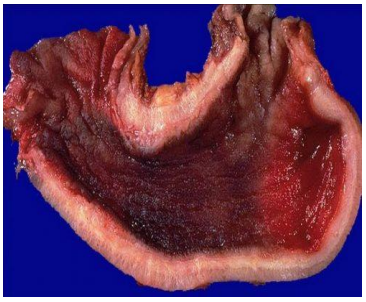
- Presents as a large, irregular ulcer with heaped up margins; most commonly involves the lesser curvature of the antrum (similar to gastric ulcer).
- Intestinal-type adenocarcinomas of the stomach closely resemble colon cancers. They tend to grow as nodular, polypoid, and well-demarcated masses. On light microscopy, well-formed glands that consist of columnar or cuboidal cells are seen.
- Risk factors include intestinal metaplasia (due to H pylori and autoimmune gastritis), nitrosamines in smoked foods (Japan), and blood type A.

B. **Diffuse type (Signet-ring carcinoma):**

- It is characterized by signet ring cells that diffusely infiltrate the gastric wall (due to loss of the cell adhesion protein E-cadherin); desmoplasia results in thickening of stomach wall causing a "leather-bottle stomach" (linitis plastica).
- Cells often contain abundant mucin droplets that push the nucleus to one side and lead to the characteristic appearance of a "signet ring" in profile.
- Not associated with H pylori, intestinal metaplasia, or nitrosamines.







- Presentation:

- The most important factors that influence survival rate are the depth of invasion through the gastric wall and whether regional lymph nodes are involved.

- Gastric carcinoma presents late with weight loss, abdominal pain, anemia, and early satiety; rarely presents as acanthosis nigricans or Leser-Trelat sign (the abrupt appearance of multiple seborrhoeic keratoses that rapidly increase in their size and number).

- Left undiagnosed or untreated, gastric carcinomas will eventually extend through the gastric wall to the serosa.

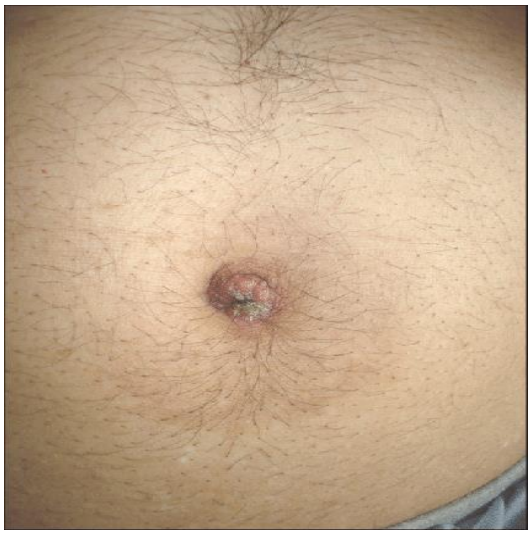
- Involvement of regional and distant lymph nodes is common, with metastasis to a left supraclavicular sentinel node (Virchow's node) frequently the first clinical manifestation of occult gastric cancer.

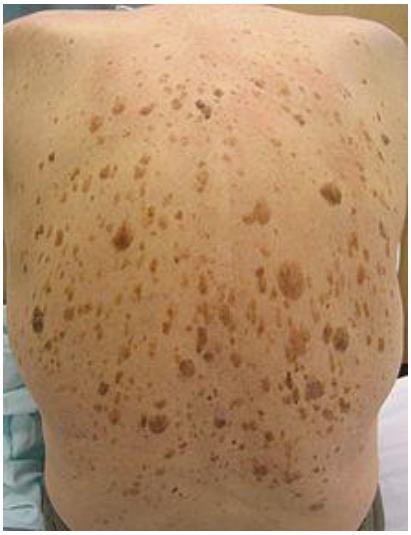
- Metastasis to the periumbilical region can result in the formation of a subcutaneous mass termed the Sister Mary Joseph nodule (after the nun who observed that this finding was an indicator of metastatic carcinoma).

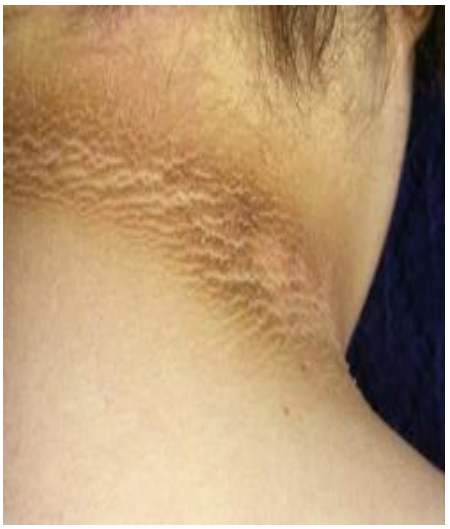
- In time, extensive peritoneal seeding and widespread metastasis to the liver and lungs occurs.

- In women, metastatic spread of adenocarcinoma to one or both ovaries may occur in association with primary cancers of the stomach, breast, pancreas, and gallbladder. This classic finding of mucin-producing, signet-ring neoplastic cells in the ovarian stroma (bilateral) is described as Krukenberg tumor and is one of the most common types of metastatic ovarian cancer.

- Blumer shelf: palpable mass on digital rectal exam suggesting metastasis to pouch of Douglas.



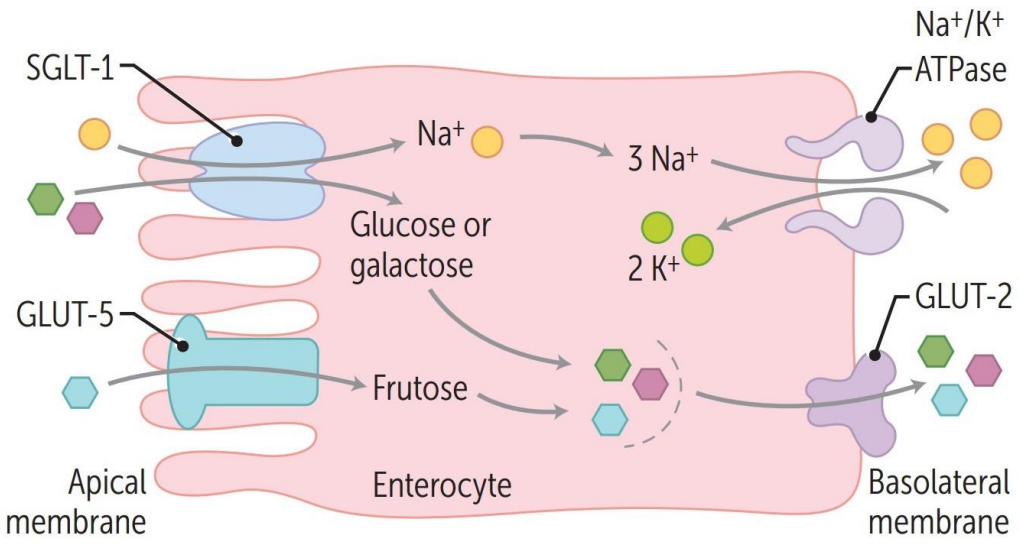




Small bowel

Carbohydrate absorption

- Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes.
- Glucose and galactose are taken up by SGLT1 (Na dependent).
- Fructose is taken up via Facilitated diffusion by GLUT5.
- All are transported to blood by $GLUT_2$.

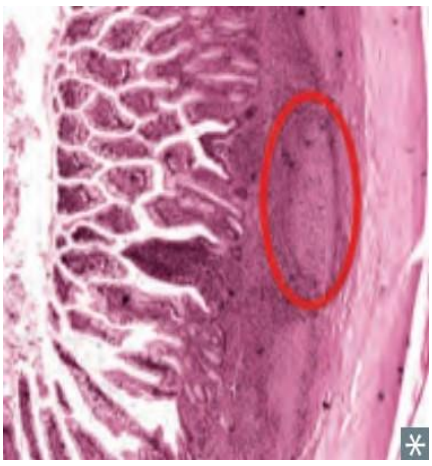


Vitamin/mineral absorption

- Iron is absorbed as Fe^2 in duodenum.
- Folate is absorbed in jejunum.
- B_{12} is absorbed in terminal ileum along with bile salts, requires intrinsic factor.
- Iron Fist, Bro.
- Clinically relevant in patients with small bowel disease or after resection.

Peyer patches

- Unencapsulated lymphoid tissue found in lamina propria and submucosa of ileum.
- Contain specialized M cells that sample and present antigens to iMmune cells.
- B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria.
- IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.
- Think of IgA, the Intra-gut Antibody. And always say "secretory IgA."



Malabsorption syndromes

- Malabsorption is a syndrome of impaired intestinal digestion and absorption.
- Disorders that cause malabsorption are divided into the following major groups:

A. Intestinal mucosal defects:

- Examples include celiac disease, tropical sprue, Whipple disease, Crohn's disease, and many others.
- Structural defect or injury to the intestinal epithelial cells hampers nutrient transport from the intestinal lumen and/or from intestinal cells to peripheral organs.

B. Pancreatic exocrine insufficiency:

- Chronic pancreatitis and cystic fibrosis belong to this group of disorders.
- Diminished production of digestive pancreatic enzymes leads to impaired hydrolysis of nutrients in the small intestine.

C. Bacterial proliferation:

- This occurs in the small bowel with surgically created blind loops, small bowel diverticulosis, and diabetic neuropathy.
- Bacteria compete for nutrients, causing relative nutrient deficiency.

- Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies.

- Fats are typically the most severely affected macronutrient in generalized malabsorption, and testing the stool for fat (with Sudan III stain) is the most sensitive strategy for screening for malabsorptive disorders (Stool should normally contain no measurable fat).

Lactose intolerance

- Decreased function of the lactase enzyme found in the brush border of enterocytes.

- Lactase deficiency by any means causes incomplete hydrolysis of the disaccharide lactose into the monosaccharides glucose and galactose. The undigested lactose then accumulates within the gastrointestinal lumen, leading to osmotic diarrhea.

- Deficiency may be congenital (rare autosomal recessive disorder) or acquired (common; often develops in late childhood); temporary deficiency is seen after small bowel infection (lactase is highly susceptible to injury of the gastrointestinal mucosa).

- Presents with abdominal distension and diarrhea with ↓ stool pH upon consumption of milk products.

- The fermentation of undigested lactose by gut bacteria leads to increased production of short- chain fatty acids that acidify the stool (decreased stool pH). During this process, hydrogen gas is also produced, leading to increased breath hydrogen content. In addition, the high amounts of undigested lactose in the bowel lead to elevated stool osmolality, which attracts excess water in the bowel lumen, causing osmotic diarrhea.

- Lactose hydrogen breath test: ⊕ for lactose malabsorption if post-lactose breath hydrogen value rises > 20 ppm compared with baseline.

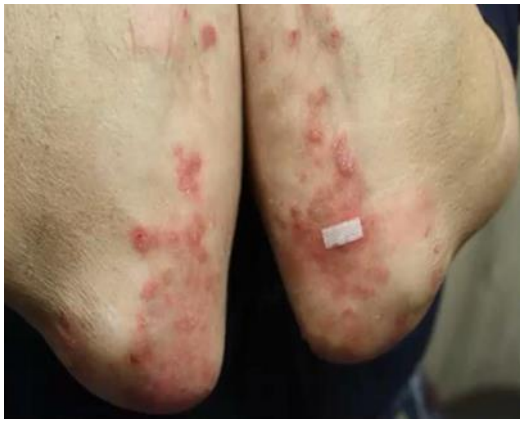
- Light and electron microscopic examination of the bowel mucosa in lactase-deficient patients has never demonstrated an identifiable abnormality, so normal intestinal mucosa would be the expected finding in this patient population.

- The lactose tolerance test entails the oral administration of 50 g of lactose, with blood levels measured at 0, 60, and 120 minutes. If the blood glucose increases < 20 mg/dl and the individual experiences symptoms (abdominal pain, bloating, flatulence, diarrhea, or vomiting), the diagnosis of lactose intolerance is confirmed.

Celiac disease

- Celiac disease is a chronic malabsorptive disorder caused by a hypersensitivity to gluten, a protein found in wheat. Gliadin, a breakdown product of gluten, triggers an immune-mediated reaction.
- Once absorbed, gliadin is deamidated by tissue transglutaminase (tTG).
- Deamidated gliadin is presented by antigen presenting cells via MHC class II.
- Helper T cells mediate tissue damage.
- Clinical presentation:

- Celiac sprue may manifest at an early age or later in life:
  - Children classically present with abdominal distension, diarrhea, and failure to thrive.
  - Adults classically present with chronic diarrhea and bloating.
- Small, herpes-like vesicles may arise on skin (dermatitis herpetiformis). The eruptions are symmetrically distributed and extremely pruritic (Dermatitis herpetiformis is NOT related to the herpes virus, except that the lesions look similar). Due to IgA deposition at the tips of dermal papillae; resolves with gluten-free diet.



- Laboratory findings:

- Diagnosis of celiac sprue most commonly begins with non-invasive serologic testing for IgA anti-endomysial, anti-deamidated gliadin peptide antibodies and anti-tissue transglutaminase antibodies before the use of more invasive methods such as endoscopic biopsy.
- IgG antibodies are also present and are useful for diagnosis in individuals with IgA deficiency (increased incidence of IgA deficiency is seen in celiac disease).
- Duodenal biopsy reveals flattening of the mucosa with loss of villi, hyperplasia of crypts, and chronic inflammatory infiltration of the lamina propria with lymphocytes. The most pronounced changes are seen in the duodenum and proximal jejunum because the concentration of gluten is higher there.

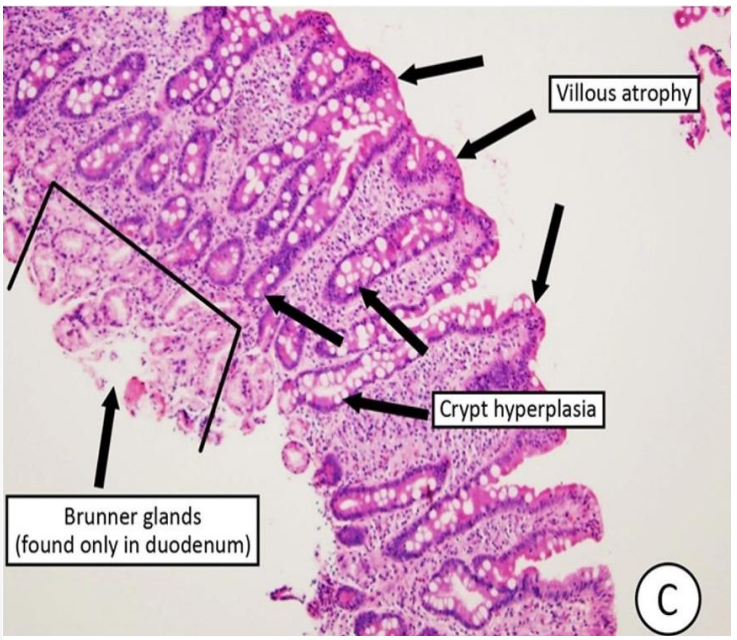
- The resulting villus atrophy and chronic inflammation of the lamina propria impairs nutrient absorption in the duodenum and proximal jejunum, where the concentration of gluten is the highest.

- Common symptoms are those of malabsorption: diarrhea, steatorrhea, flatulence, and symptoms of nutrient deficiencies. Other manifestations can include delayed puberty and growth failure in children and difficulty gaining weight and anemia in adults.

- With strict adherence to a gluten-free diet, symptom resolution occurs within weeks and is followed by normalization of histology and antibody levels.

- Small bowel carcinoma and T-cell lymphoma are late complications that present as refractory disease despite good dietary control.

Celiac disease	
Symptoms	• Gastrointestinal: ○ Abdominal pain ○ Nausea &/or vomiting ○ Diarrhea (rarely, constipation) ○ Flatulence & bloating • Extraintestinal: ○ Short stature & weight loss ○ Iron deficiency anemia ○ Dermatitis herpetiformis
Diagnosis	• ↑ Tissue transglutaminase IgA • ↑ Antiendomysial antibodies • Duodenal biopsy showing ↑ intraepithelial lymphocytes & flattened villi



Tropical sprue

- Damage to small bowel villi due to an unknown organism resulting in malabsorption.

- <u>Similar to celiac disease except:</u>

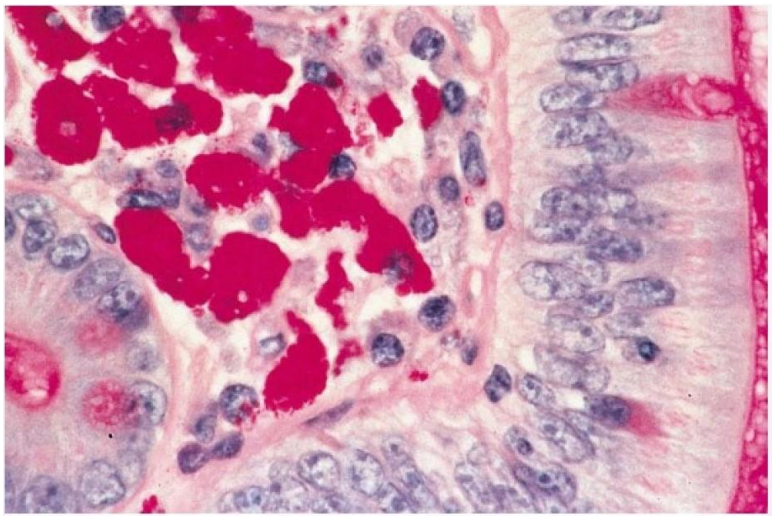
- Occurs in tropical regions (Caribbean).

- Arises after infectious diarrhea and responds to antibiotics.

- ↓ mucosal absorption affecting duodenum and jejunum but can involve ileum with time. Associated with megaloblastic anemia due to folate deficiency and, later, B12 deficiency.

Whipple disease

- Whipple disease is a rare systemic illness caused by the gram-positive actinomycete Tropheryma whippelii that involves the small intestine, joints, and central nervous system.
- The actinomycete proliferates only within the macrophages of these tissues, provoking no inflammatory response as a consequence.
- Classic site of involvement is the small bowel lamina propria. Macrophages compress lacteals → Chylomicrons cannot be transferred from enterocytes to lymphatics → Results in fat malabsorption and steatorrhea.
- Arthropathy, polyarthritis, and psychiatric and cardiac abnormalities may also be observed.
- Antibiotic therapy is usually successful in quickly resolving the illness.
- Classic histologic findings include small intestine mucosa containing enlarged, foamy macrophages packed with both rod-shaped bacilli and PAS-positive, diastase-resistant granules (which consist of lysosomes and partially digested bacteria).
- The glycoprotein present in the cell walls of the gram-positive actinomycete Tropheryma whippelii appears magenta with PAS and is diastase-resistant, which makes this stain an excellent choice when microscopically evaluating small bowel mucosa for Whipple disease.



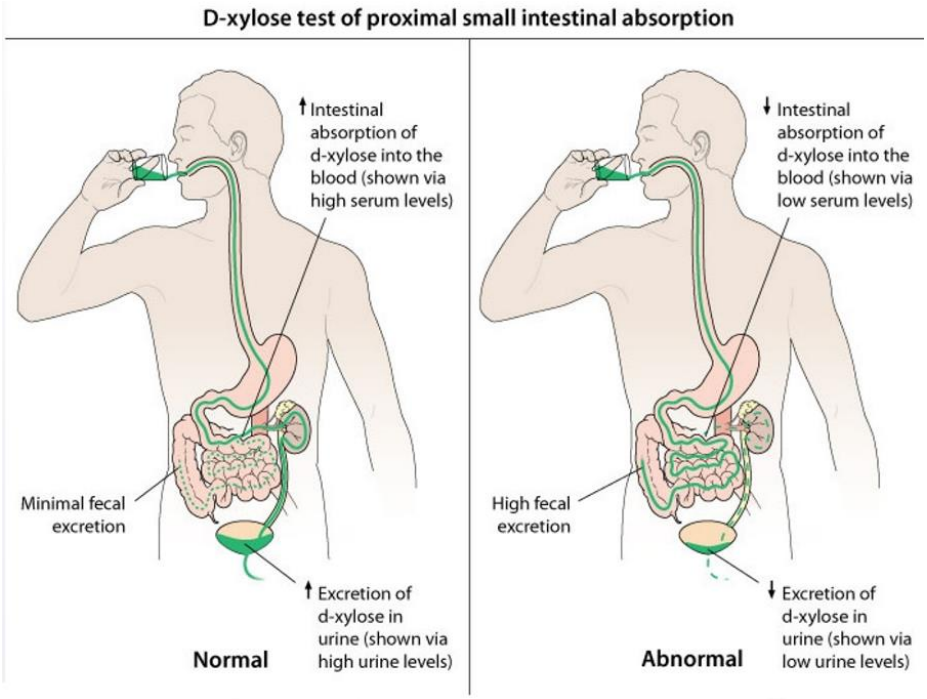
Pancreatic insufficiency

- Due to chronic pancreatitis, cystic fibrosis, obstructing cancer.
- Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin B_{12}.
- ↓ duodenal bicarbonate (and pH) and fecal elastase.

❖ N.B:

1. D-xylose, like glucose and galactose, is a monosaccharide that can be absorbed directly without the action of pancreatic enzymes.

- D-xylose is sometimes used to test for brush border absorptive function independent of pancreatic function in cases where it is necessary to determine if malabsorption is due to pancreatic or intestinal pathology.



2. Short bowel syndrome typically occurs in patients with massive small bowel resection and/or Crohn disease due to loss of intestinal absorptive surface area and a decrease in intestinal transit time.

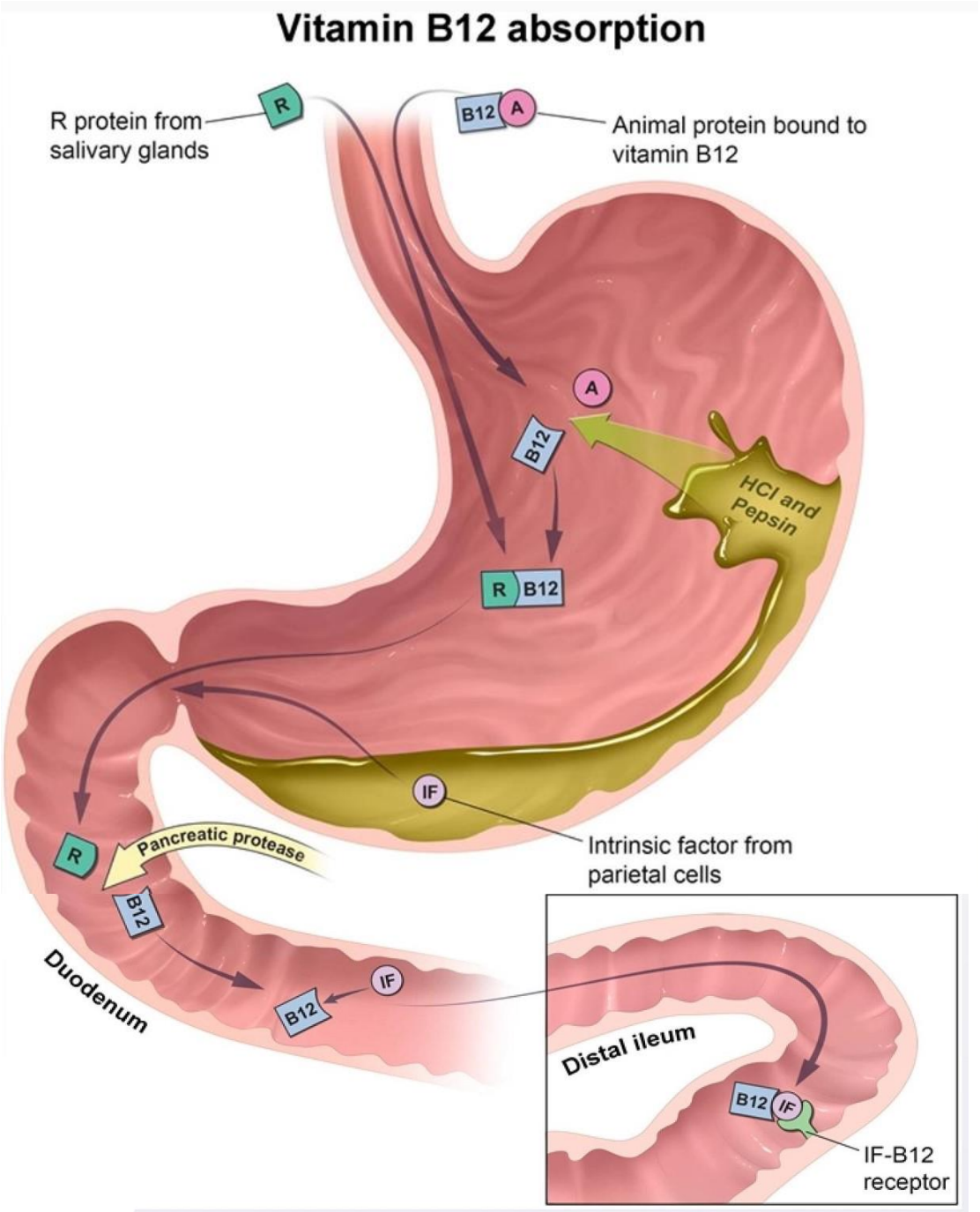
- Patients usually present with postprandial voluminous diarrhea and weight loss due to malabsorption.
- Loss of functional distal ileum may specifically result in vitamin B12 deficiency with macrocytic anemia, peripheral neuropathy, and subacute combined degeneration of the spinal cord (impaired vibration and position sense).

3. Vitamin B12 deficiency may occur due to:

- Low dietary intake of this vitamin.
- The presence of antibodies against intrinsic factor (pernicious anemia).
- Malabsorption.

- The Schilling test helps differentiate between these causes.
- In the first step of the test an oral dose of radiolabeled vitamin B_{12} is given concomitantly with an intramuscular injection of non-radiolabeled vitamin B_{12}.
- Urine is collected for the next 24 to 48 hours, and the excretion of radioactive vitamin B_{12} is measured.
- High urinary excretion of radioactive cobalamin during this step is evidence of normal absorption of this vitamin and is diagnostic of dietary B_{12} deficiency.
- The purpose of concomitant parenteral administration of vitamin B_{12} is to ensure excretion of the radiolabeled form by creating a state of excess circulating vitamin B_{12}.
- If the parenteral dose were not administered, all of the orally administered radioactive B12 would be taken up by the tissues in the case of dietary vitamin deficiency and little would be excreted in the urine.

- Low urinary excretion of radioactive cobalamin rules out dietary deficiency and is suggestive of poor absorption of this vitamin.
- Poor absorption can result from lack of intrinsic factor (pernicious anemia) or from a malabsorption syndrome.
- Phase II of the Schilling test helps to differentiate between these two causes.
- During phase II, radiolabeled is administered concomitantly with intrinsic factor, and its urinary excretion is measured If the cause of impaired absorption of cobalamin is lack of intrinsic factor, it will be corrected during this stage of testing and urinary excretion of radiolabeled vitamin B12 would increase.
- Low excretion of radiolabeled cobalamin after administration of intrinsic factor suggests another cause of poor cobalamin absorption. Causes of intestinal malabsorption of B12 include pancreatic insufficiency, intestinal bacterial overgrowth or ileal disease.



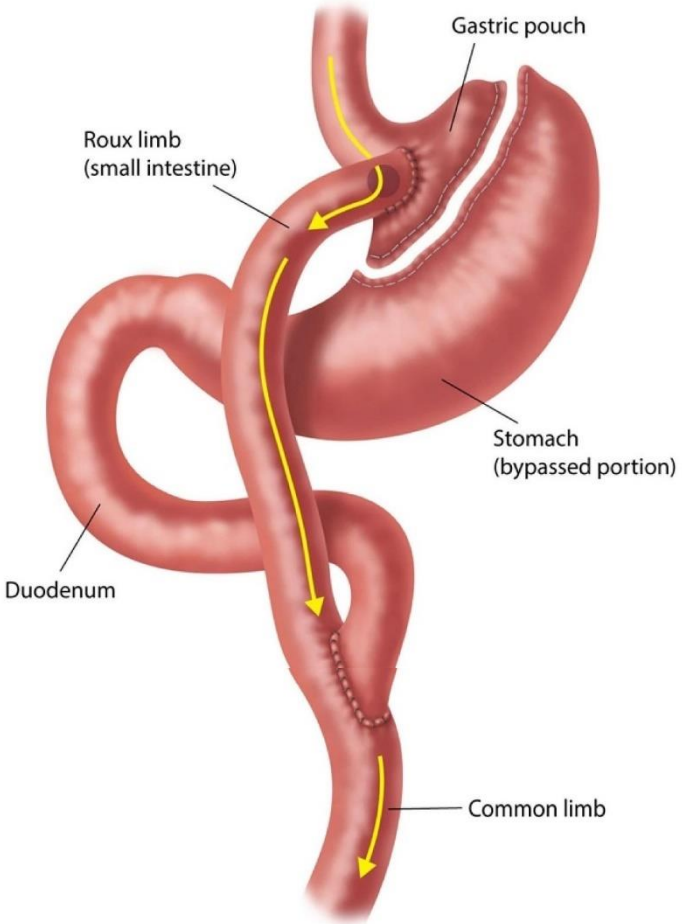
4. Vitamin B_{12} needs an intact bowel wall and pancreatic enzymes to be absorbed.

- If vitamin B_{12} is ingested in its free (or nonprotein bound form), it will bind to a carrier protein known as R-binders that is secreted by the salivary glands.
- If the vitamin B_{12} is ingested in its protein bound form, it must first undergo a proteolytic cleavage in the stomach or duodenum where it will bind to an R-binder and enter into the duodenum for further cleavage.
- Upon entry into the second segment of the duodenum, the pancreas will secrete additional protease which will then degrade the R-binders holding onto the vitamin B_{12}.
- It is at this point that vitamin B_{12} will bind to or complex with intrinsic factor for the remainder of its journey to the ileum of the small intestine for absorption.

5. The normal small intestine is colonized with facultative anaerobes, lactobacilli, enterococci, and gram-positive aerobes.

- Enteric bacteria can produce vitamins (vitamin K, folate), inhibit proliferation of surrounding pathogenic bacteria, and digest unabsorbed dietary sugars and convert them to fatty acids.
- A Roux-en-Y gastric bypass surgery typically creates a small gastric pouch, which is removed from the remainder of the stomach and attached to the jejunum via a gastrojejunal anastomosis.
- The larger bypassed portion of the stomach and duodenum are reattached to the jejunum distally. This results in a closed-ended gastroduodenal limb, in which bacteria can proliferate and ferment any food that may be diverted into this segment.
- Small intestinal bacterial overgrowth (SIBO) is characterized by overproduction of vitamin K and folate, associated with nausea, bloating, abdominal discomfort, and malabsorption.

Roux-en-Y gastric bypass



Inflammatory bowel disease

- Crohn's disease and ulcerative colitis are often collectively referred to as inflammatory bowel disease (IBD).

- They may have similar clinical manifestations and similar extra-intestinal complications.

Crohn's disease

- Crohn's disease is a chronic inflammatory condition of the gut that can involve any part of the GI tract from the mouth to the anus.

- It is most classically a disease of the small bowel, with the terminal ileum is one of the most common locations. However, involvement of the remainder of the GI tract is common.

- Etiology:

- The cause of Crohn's disease is unknown, although genetic predisposition and immune hyperreactivity to an unknown antigen are thought to play an important role.

- The increased activity of Th_1 helper cells in Crohn's disease serves as evidence of the immunologic hypothesis. Th_1 cells mediate delayed hypersensitivity reactions and granuloma formation.

- They also produce IL-2 and interferon-γ and activate macrophages to synthesize TNF (tumor necrosis factor). All these substances might contribute to intestinal cell injury.

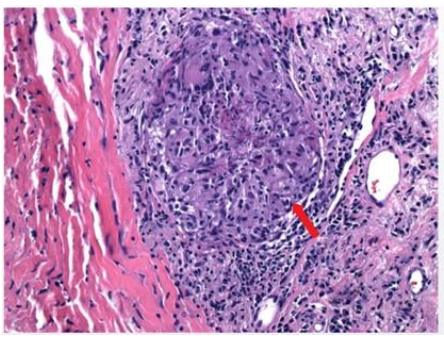
- Microscopic and macroscopic finding:

- Non-caseating granulomas (accumulation of epithelioid macrophages without central necrosis), like the one seen on the slide below, are characteristic of Crohn's disease.

- On light microscopy, non-caseating granulomas and an inflammatory infiltrate that involves all layers of the intestinal wall (transmural) are found.

- The affected bowel appears hyperemic and edematous on macroscopic examination. Mucosa of the involved area contains linear ulcers.

- Normal-looking mucosal areas intervene between the areas involved in pathologic process, leading to the classic "cobblestone appearance".



- Presentation:

- Typically, the disease presents insidiously over the course of years, marked by bouts of abdominal pain, non-bloody diarrhea, malaise, and fever.

- The most common presentation of Crohn's disease is abdominal pain, which represents transmural inflammation.

- Complication:

- Transmural inflammation explains the two most common complications of Crohn's disease (strictures, and fistulas):

  - The disease may progress to intestinal obstruction resulting from fibrotic narrowing of the intestinal lumen (as a result of bowel wall edema, fibrosis, and hypertrophy of the muscularis mucosae), requiring surgical bowel resection and placement of an ostomy (contrast barium studies may show the "string sign").

  - Because the lesions of Crohn's disease affect the entire thickness of the bowel wall, these patients are prone to developing fistulas and abscesses.

  - Fistulas occur when ulcers penetrate the entire thickness of the intestinal wall, leading to a sinus tract that communicates between multiple organs (enterovesicular, enterovaginal, enteroenteric).

  - Abscesses form when sinus tracts become walled off. They can also perforate, leading to diffuse peritonitis.

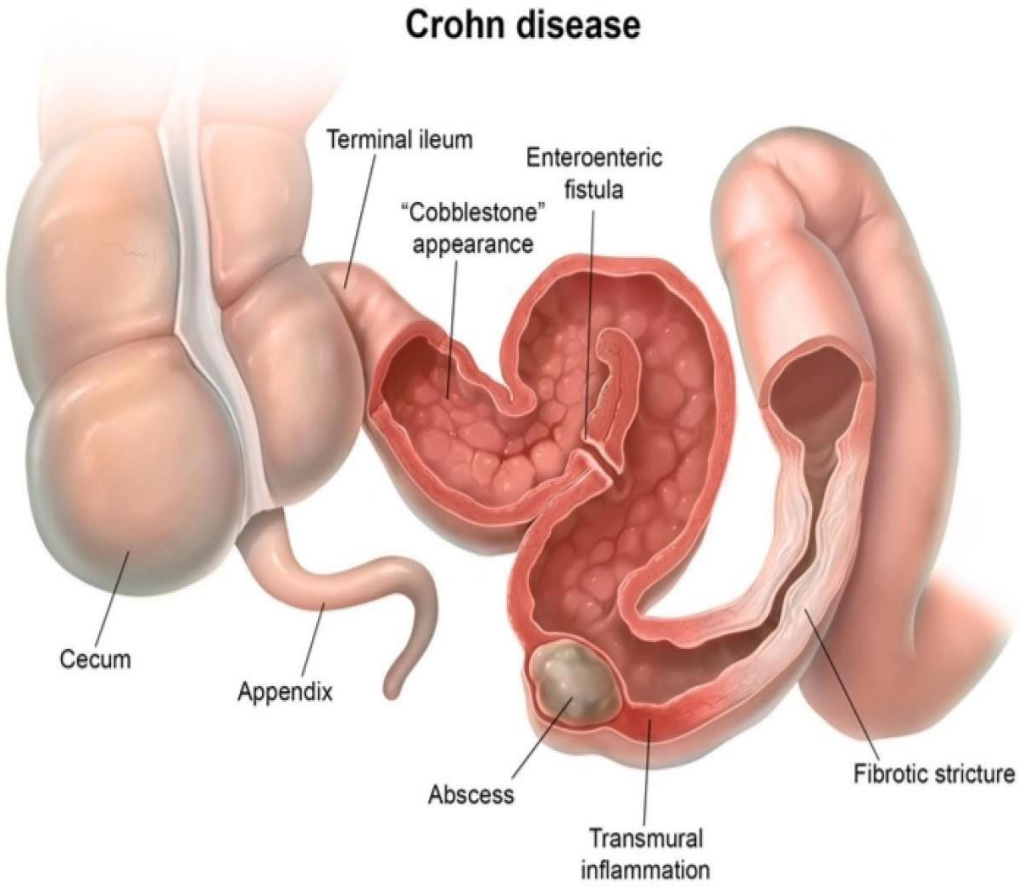
- Normally, the mucosa of the terminal ileum plays an important role in "recycling" bile acids that are necessary for the absorption of fat. Bile acids are produced in the liver, excreted with bile, and then reach the terminal ileum.

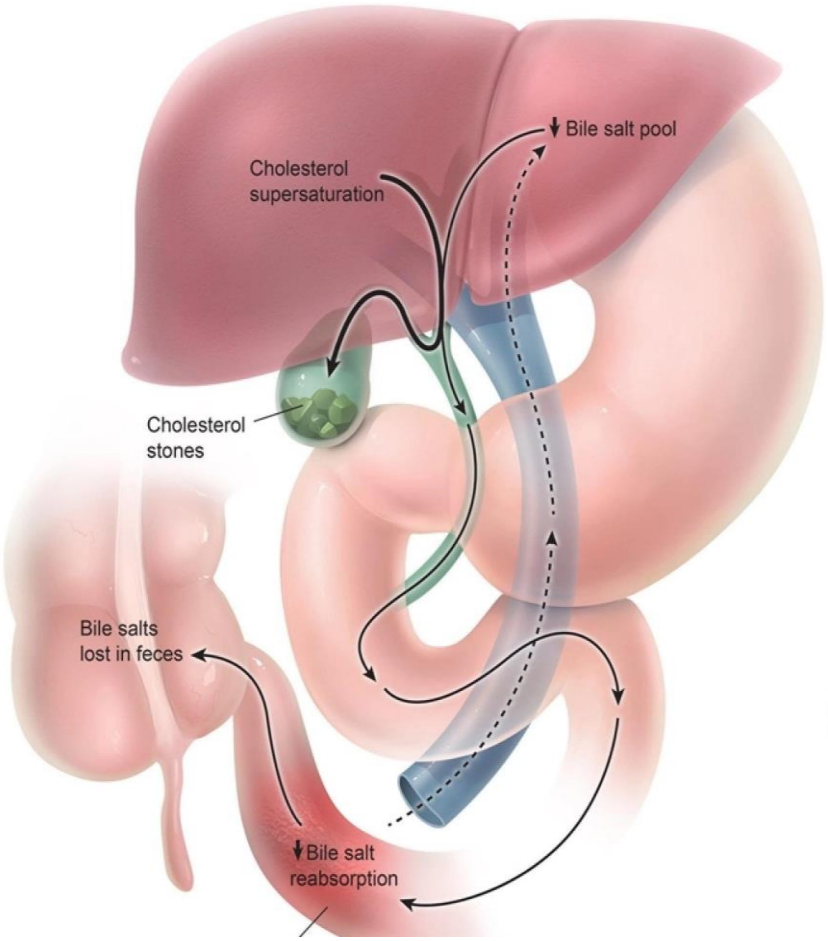
- There, they form micelles with fat droplets, are reabsorbed, and return to the liver to start a new cycle.

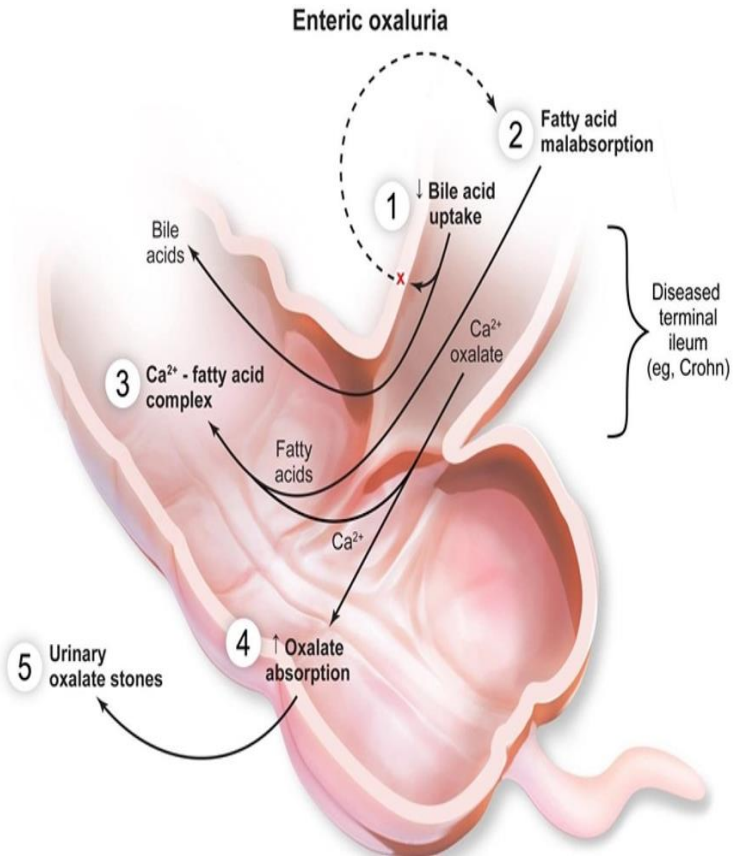
- When the mucosa of terminal ileum is inflamed (as in Crohn's disease), bile acids are not reabsorbed, becoming lost with feces. As a result, a lesser amount of bile acid is present in bile, and the ratio of cholesterol/bile acids increases → Cholesterol precipitates in bile of the gallbladder and forms gallstones.

- In the healthy bowel, dietary calcium binds to dietary oxalate, producing insoluble calcium oxalate salts and thus enabling oxalate excretion. In Crohn's disease, calcium binds instead to lipids, making it unavailable for complexing with oxalate. As a result, an increased amount of oxalate is absorbed, promoting the formation of urinary stones.

- Loss of bile acids causes fat malabsorption, which may lead to deficiencies in fat- soluble vitamins (A, D, E, K).

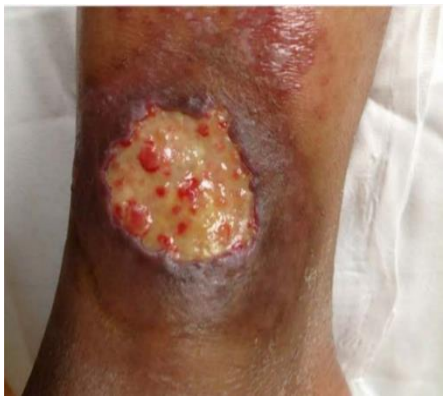

Crohn disease
Terminal ileum
Enteroenteric fistula
"Cobblestone" appearance
Cecum
Appendix
Abscess
Transmural inflammation
Fibrotic stricture

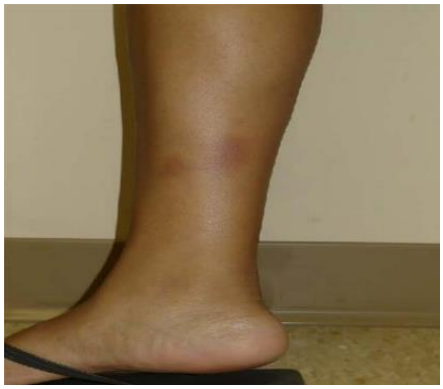

Bile salt pool
Cholesterol supersaturation
Cholesterol stones
Bile salts lost in feces
Bile salt reabsorption


Enteric oxaluria
2 Fatty acid malabsorption
1 ↓ Bile acid uptake
Bile acids
Diseased terminal ileum (eg, Crohn)
Ca2+ oxalate
3 Ca2+ - fatty acid complex
Fatty acids
Ca2+
4 ↑ Oxalate absorption
5 Urinary oxalate stones

- There are also a number of extraintestinal manifestations that are either immune-mediated or occur due to deficient absorption of nutrients. The most important complications of Crohn's disease are as follows:

1. Intestinal: fistulas, strictures, abscesses, perianal disease, increased risk of adenocarcinoma.
2. Skin: pyoderma gangrenosum (more common with ulcerative colitis), erythema nodosum.
3. Joints: arthritis, ankylosing spondylitis.
4. Eyes: iritis, uveitis, episcleritis.
5. Malabsorption: oxalate kidney stones, anemia, hypoproteinemia, B_{12} and folate deficiencies, gallstones.
6. Liver: primary sclerosing cholangitis (more common with ulcerative colitis), increased risk of cholangiocarcinoma.





Ulcerative colitis

- Ulcerative colitis has the following unique characteristics:

1. The rectum is always involved; involvement of other areas of the intestine is variable.

2. Inflammation is limited to the mucosa and submucosa only, so strictures and fistulas are not common.

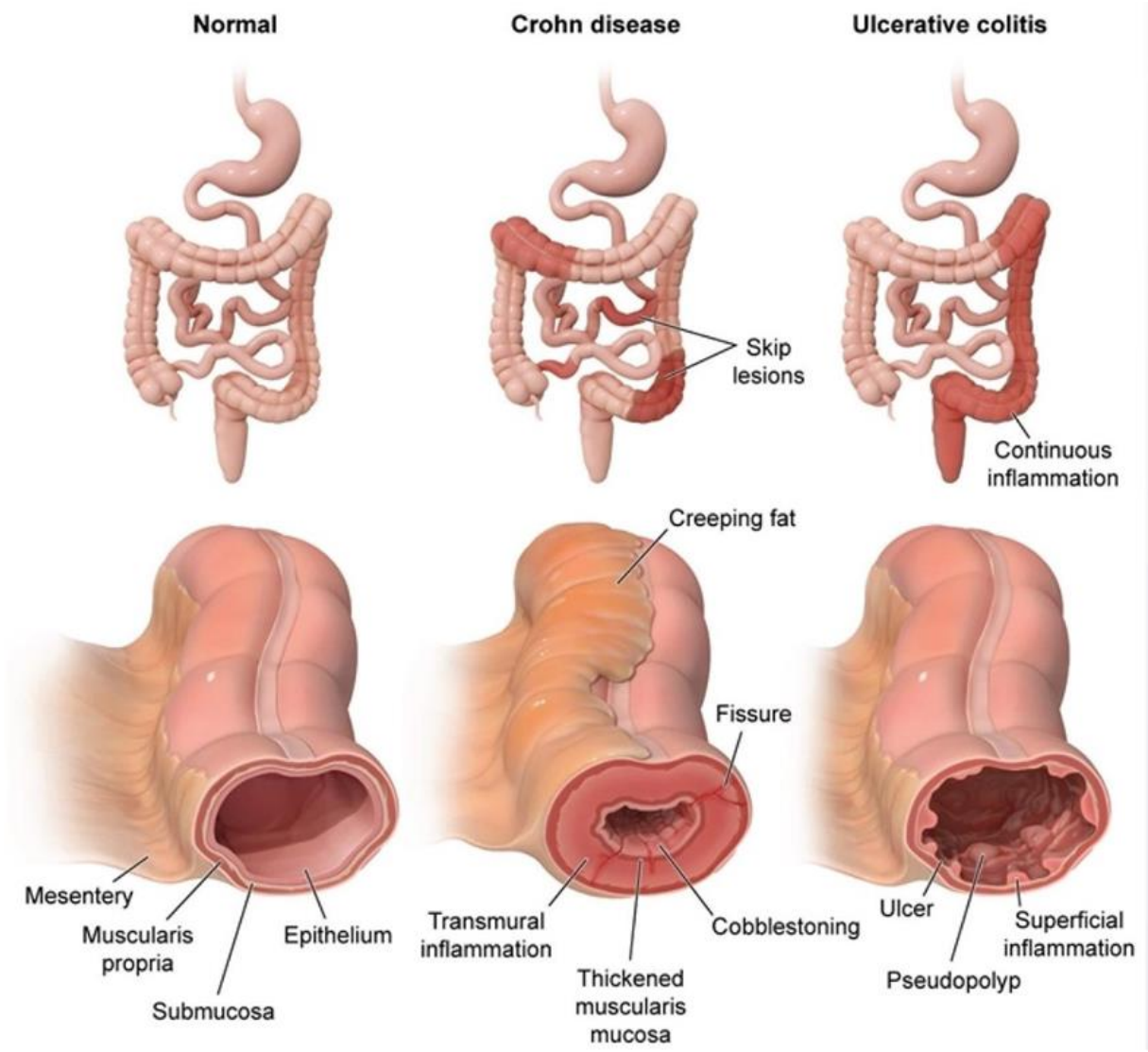
3. Mucosal damage is continuous. There are no areas of normal mucosa between the affected segments.

4. Bloody diarrhea, with or without abdominal pain, is the hallmark of ulcerative colitis (In Crohn's disease, there may also be bloody diarrhea, but abdominal pain is virtually always present).

- Ulcerative colitis has a number of complications:

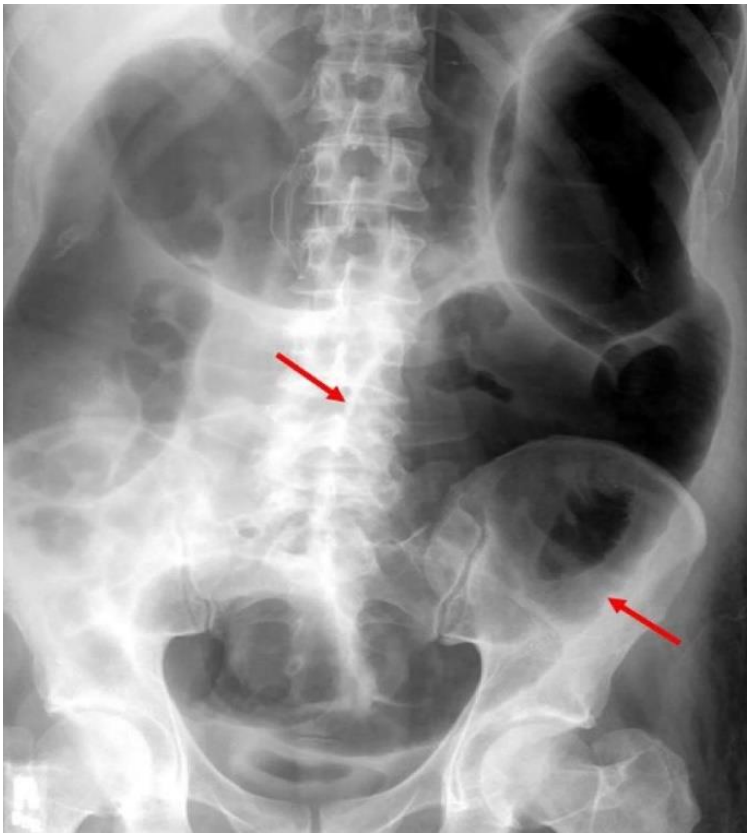
- The most dangerous is toxic megacolon (severe dilatation of the bowel), which can lead to perforation.

- Ulcerative colitis significantly increases the risk of adenocarcinoma of the colon.

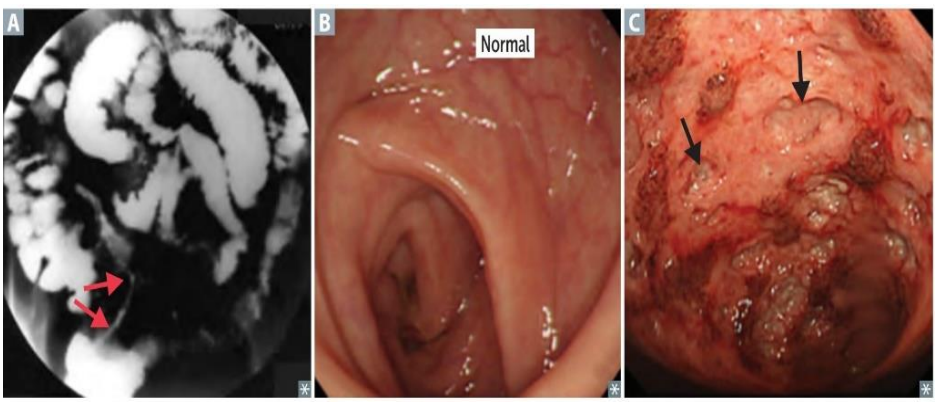


❖ Toxic megacolon:

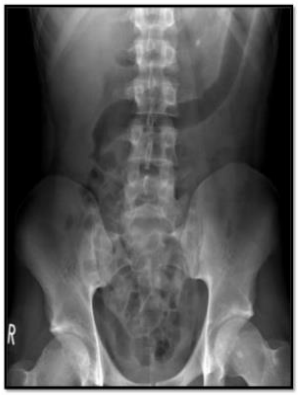
- Abdominal pain and distention, along with fever, diarrhea, and signs of shock (decreasing BP, increasing HR) in a patient with ulcerative colitis should alert the physician to the possibility of toxic megacolon.
- This is a common complication of inflammatory bowel disease and is seen much more often in ulcerative colitis than in Crohn's disease.
- Severe inflammation causes release of inflammatory mediators, bacterial products, and increased nitric oxide, which contribute to colonic smooth muscle paralysis.
- Complete cessation of neuromuscular activity in the intestinal wall is the first step in the pathogenesis of toxic megacolon. Rapid colonic distention ensues, which thins the intestinal wall, making it prone to rupture.
- Perforation is a life-threatening complication of megacolon, with a mortality rate> 50%.
- On physical examination, the classic acute abdomen will be present: marked distention with tenderness and tympany on percussion.
- Plain abdominal radiography is sufficient for diagnosis and will show colonic dilatation (especially in the transverse colon) with a >5.5cm diameter of the colon. Fluid levels might be seen in the large bowel.
- Barium contrast studies and colonoscopy are contraindicated due to risk of perforation.

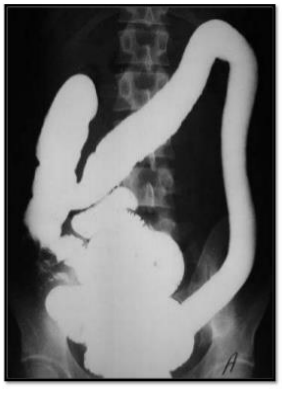


	Crohn disease	Ulcerative colitis
LOCATION	Any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal sparing.	Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.
GROSS MORPHOLOGY	Transmural inflammation → fistulas. Cobblestone mucosa, creeping fat, bowel wall thickening ("string sign" on barium swallow x-ray A), linear ulcers, fissures.	Mucosal and submucosal inflammation only. Friable mucosa with superficial and/or deep ulcerations (compare normal B with diseased C). Loss of haustra → "lead pipe" appearance on imaging.
MICROSCOPIC MORPHOLOGY	Noncaseating granulomas and lymphoid aggregates. Th1 mediated.	Crypt abscesses and ulcers, bleeding, no granulomas. Th2 mediated.
COMPLICATIONS	Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis).	
	Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.	Fulminant colitis, toxic megacolon, perforation.
INTESTINAL MANIFESTATION	Diarrhea that may or may not be bloody.	Bloody diarrhea.
EXTRAINTESTINAL MANIFESTATIONS	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).	
	Kidney stones (usually calcium oxalate), gallstones. May be ⊕ for anti-*Saccharomyces cerevisiae* antibodies (ASCA).	1° sclerosing cholangitis. Associated with p-ANCA.
TREATMENT	Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), biologics (eg, infliximab, adalimumab).	5-aminosalicylic preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.
	For Crohn, think of a fat granny and an old crone skipping down a cobblestone road away from the wreck (rectal sparing). Stones are more common in Crohns.	Ulcerative colitis causes ULCCCERS: Ulcers Large intestine Continuous, Colorectal carcinoma, Crypt abscesses Extends proximally Red diarrhea Sclerosing cholangitis



Lead pipe colon
This patient with ulcerative colitis has a featureless segment of transverse colon with shows loss of the normal haustral markings.





Irritable bowel syndrome

- Irritable bowel syndrome (IBS) is a pain syndrome that can have diarrhea, constipation, or both. There is no specific diagnostic test and it is a diagnosis of exclusion in association with a complex of symptoms.

- Recurrent abdominal pain associated with ≥ 2 of the following:

- Related to defecation.
- Change in stool frequency.
- Change in form (consistency) of stool.

- No structural abnormalities.

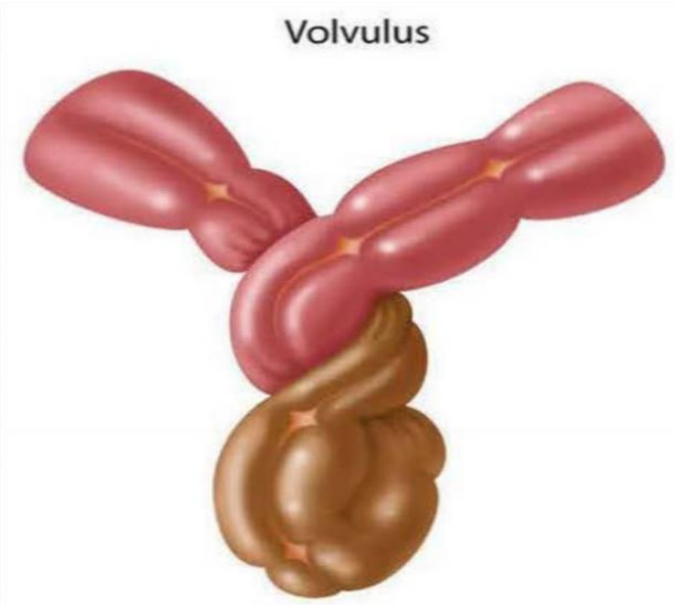
- Most common in middle-aged women.

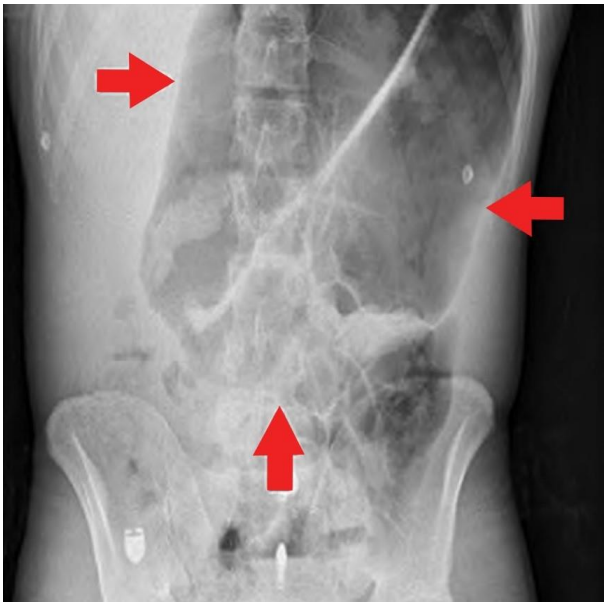
- Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.

- First-line treatment is lifestyle modification and dietary changes (Fiber in the diet).

Volvulus

- Twisting of bowel along its mesentery.
- Results in obstruction and disruption of the blood supply with infarction.
- Most common locations are sigmoid colon (elderly; coffee bean sign on x-ray) and cecum (young adults).
- In children, volvulus occurs in the midgut, with the majority being in the ileum. The primary predisposing factor for volvulus in children is malrotation of the midgut during early fetal development.



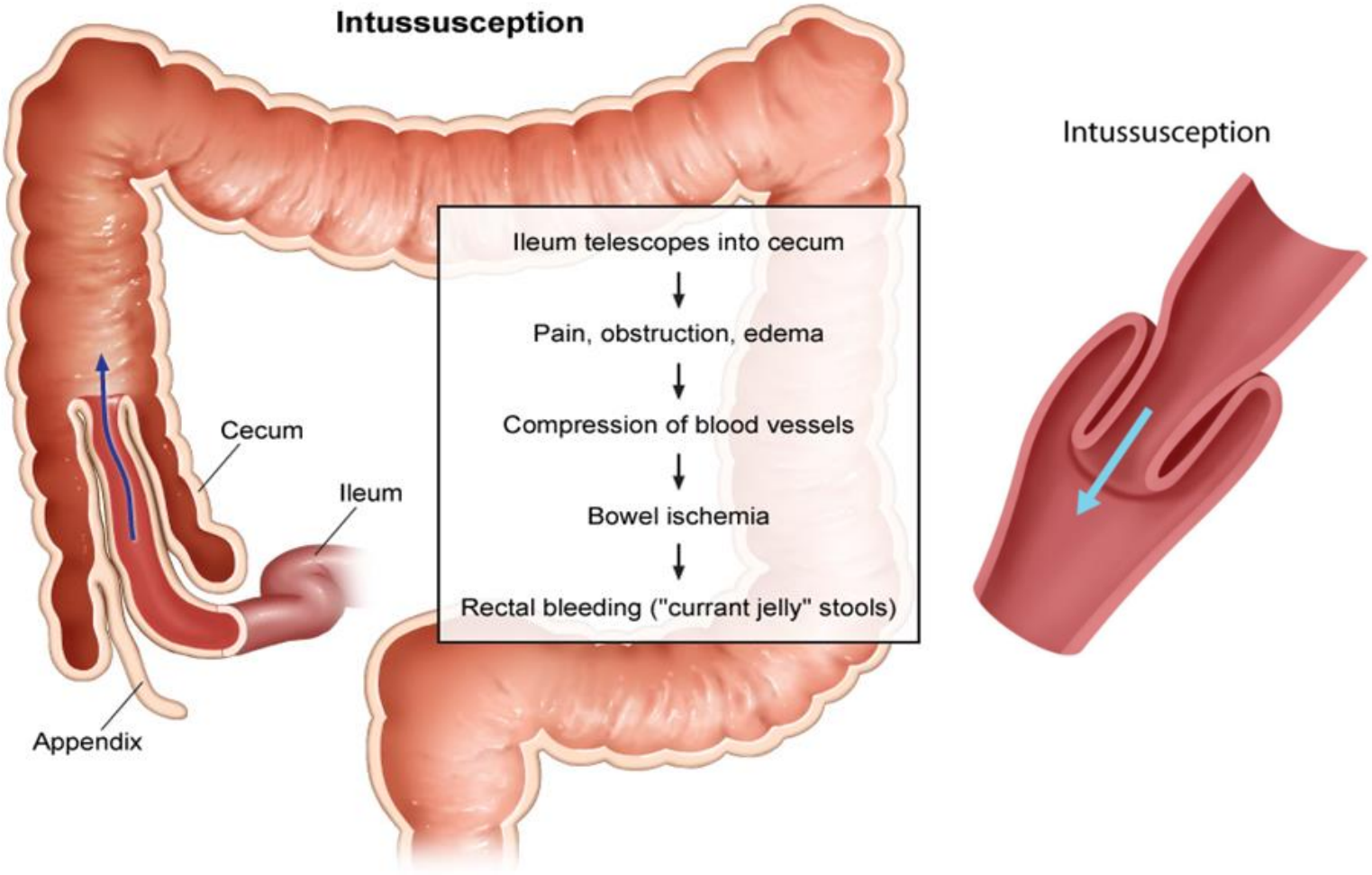


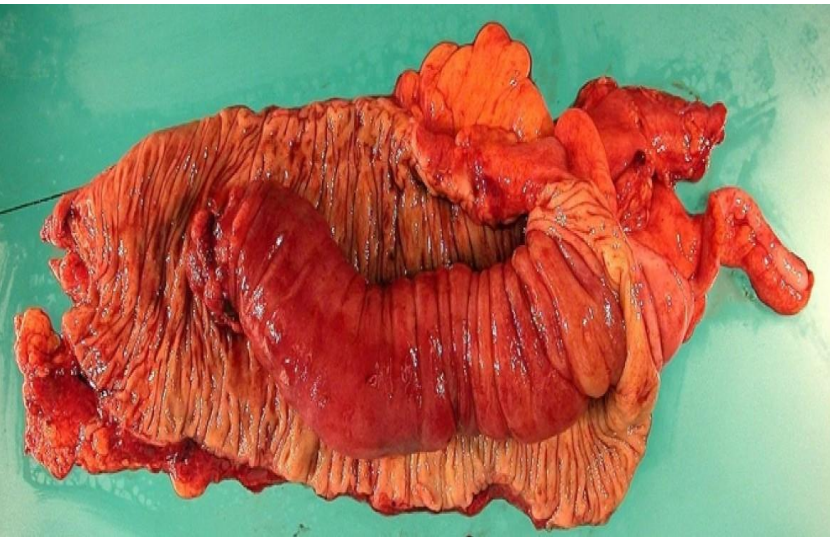
Intussusception

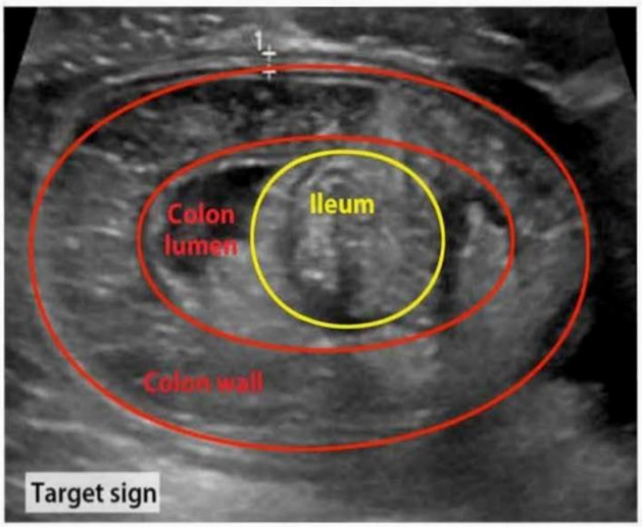
- Telescoping of proximal segment of bowel forward into distal segment (imagine a collapsed telescope).
- The most typical location for intussusception is at the ileocolic junction. The size differences in the adjacent segments of the intestine allow the small bowel to invaginate into the cecum.
- Majority of cases in children, unusual in adults.
- <u>Associated with a leading edge (focus of traction):</u>

- In children, the most common cause is lymphoid hyperplasia (due to rotavirus); usually arises in the terminal ileum, leading to intussusception into the cecum.
- In patients older than 2 years of age, a lead point, such as Meckel diverticulum, foreign body, or intestinal tumor, should be sought.

- Telescoped segment is pulled forward by peristalsis, resulting in obstruction and disruption of blood supply with infarction.
- Intussusception leads to impaired venous return from the invaginated segment of the bowel, which can cause ischemia and subsequent necrosis of the intestinal wall.
- Clinical presentation is colicky, intermittent abdominal pain, nausea, vomiting, and "currant jelly" stools (that contain blood and mucus).
- Occasionally, the intussusception is palpable as a tubular "sausage-shaped" mass in the right upper quadrant (the invagination of the ileum into the colon causes the obstructive mass to be found in the right upper quadrant).
- Imaging: Ultrasound/CT may show a doughnut sign or target sign, which is generated by concentric alternating echogenic (mucosa) and hypoechogenic (submucosa) bands.
- Barium enema is diagnostic and may be therapeutic.
- If the intussusception does not resolve with barium enema, surgical intervention is mandated.







Intestinal Adhesion

- Fibrous band of scar tissue; commonly forms after surgery.
- They may be congenital in children (Ladd's bands), but typically result from abdominal operations or inflammatory processes.
- Most common cause of small bowel obstruction, demonstrated by multiple dilated small bowel loops on x-ray.
- <u>Other causes of mechanical intestinal obstruction:</u>

- Incarcerated Hernias.
- Crohn disease.
- Neoplasms.
- Intussusception.
- Volvulus.
- Foreign bodies.
- Intestinal atresia.

- <u>Signs and Symptoms:</u>

- Severe waves of intermittent crampy abdominal pain.
- Nausea and vomiting.
- Hyperactive bowel sounds.
- Early on, High-pitched “tinkling” sounds indicate that the intestinal fluid and air are under high pressure in the bowel (after a few days there is silence).
- Hypovolemia due to third spacing.

Paralytic (adynamic) ileus

- Ileus is a functional defect in bowel motility without an associated physical obstruction.
- Ileus is most commonly due to abdominal surgery but can also be seen in other conditions such as retroperitoneal/abdominal hemorrhage or inflammation, intestinal ischemia and electrolyte abnormalities (hypokalemia).
- Contributors to the pathophysiology of ileus include increased splanchnic nerve sympathetic tone following peritoneal instrumentation, local release of inflammatory mediators, and postoperative opiate analgesic use (which causes decreased gastrointestinal motility and disordered peristalsis).
- Signs and symptoms of ileus include nausea, vomiting, abdominal distension, failure to pass flatus or stool (obstipation) and hypoactive or absent bowel sounds.
- Some degree of ileus occurs following most abdominal procedures; however, persistence of the signs and symptoms (>3-5 days postoperatively) is termed prolonged (or "pathologic") postoperative ileus (PPI).
- The diagnosis is clinical, but abdominal x-rays (classically revealing dilated gas-filled loops of bowel with no transition point) can be helpful in confirmation.
- Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility) and treatment of secondary causes.

Small bowel obstruction versus ileus

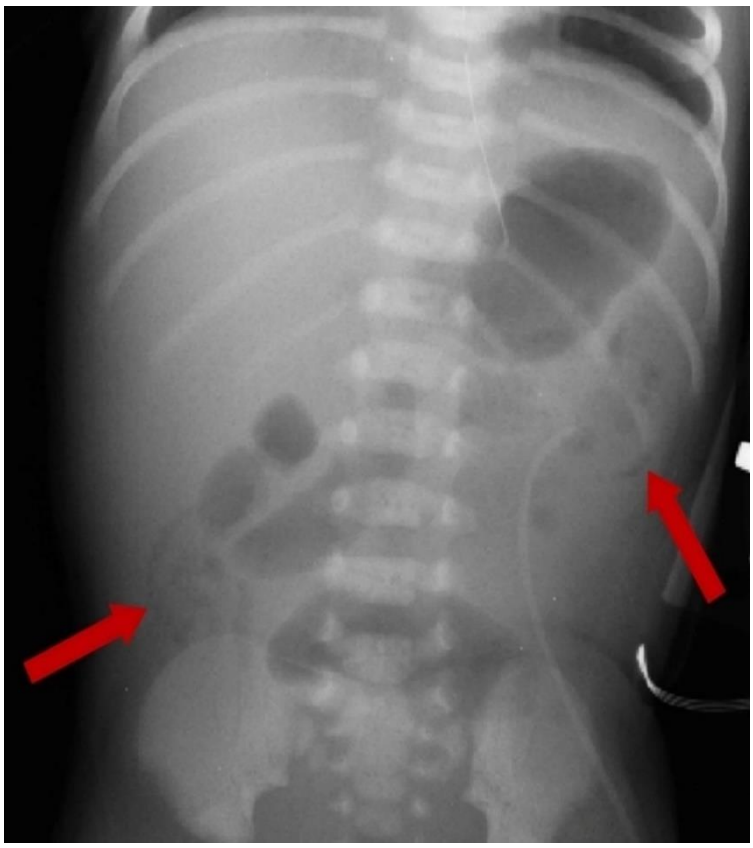
	Small bowel obstruction	Ileus
Etiology	• Prior surgery (weeks to years)	• Recent surgery (hours to days) • Metabolic (eg, hypokalemia) • Medication induced
Abdominal examination	• Distension • Increased bowel sounds	• Possible distension • Reduced/absent bowel sounds
Small bowel dilation	Present	Present
Large bowel dilation	Absent	Present

Meconium ileus

- Meconium ileus is virtually diagnostic for cystic fibrosis (CF).
- Although only 20% of patients with CF develop meconium ileus almost all newborns with meconium ileus have CF.
- A mutation in the CF transmembrane conductance regulator gene results in abnormal chloride and sodium transport and thick, viscous secretions in multiple organs.
- Thick, inspissated meconium is difficult to propel, resulting in obstruction at the level of the ileum and a narrow, underdeveloped colon (microcolon).
- Administration of hyperosmolar enema (Gastrografin) can potentially break up the inspissated meconium and dissolve the obstruction.
- Surgery is required if therapeutic enema is unsuccessful.

Necrotizing enterocolitis

- Necrotizing enterocolitis is one of the most common gastrointestinal emergencies affecting newborns.
- It occurs predominantly in preterm infants secondary to gastrointestinal and immunologic immaturity.
- Upon initiation of enteral feeding, bacteria are introduced into the bowel where they proliferate excessively due to compromised immune clearance.
- Impaired mucosal barrier function allows the bacteria to invade the bowel wall, causing inflammation and ischemic necrosis of the terminal ilium and colon.
- Typical symptoms include abdominal distension, gastric retention, tenderness, rectal bleeding, and visible intestinal loops lacking peristalsis.
- As the disease progresses, the bowel becomes congested and gangrenous with the formation of intramural gas collections.
- Abdominal x-ray showing pneumatosis intestinalis (air in the bowel wall) confirms the diagnosis.
- Up to 30% of affected neonates die, especially when disease is complicated by intestinal perforation.
- Survivors are at risk for strictures and bowel obstruction secondary to fibrosis that occurs as the inflammation subsides.



Appendix

Acute appendicitis

- Pathogenesis:

- Acute inflammation of the appendix, can be due to obstruction by fecalith (in adults) or lymphoid hyperplasia (in children).

- Obstruction by foreign bodies, nematodes, and carcinoids may also cause acute appendicitis.

- Retained mucus causes the appendicular wall to distend, which impairs venous outflow. The resulting hypoxia causes ischemia and associated bacterial invasion.

- Proximal obstruction of appendiceal lumen produces closed-loop obstruction → ↑ intraluminal pressure → stimulation of visceral afferent nerve fibers at T8-T10 → initial diffuse periumbilical pain → inflammation extends to serosa and irritates parietal peritoneum.

- Presentation:

- Typical features include migratory (vague periumbilical visceral pain caused by stretching of the appendiceal wall) abdominal pain, fever, nausea, vomiting, and anorexia.

- Eventually the peritoneum becomes inflamed and the pain becomes sharp and localizes to the RLQ. Patients typically will have pain with palpation at McBumey point (1/3 the distance from right anterior superior iliac spine to umbilicus) and Rovsing sign (RLQ pain with deep palpation of the LLQ).

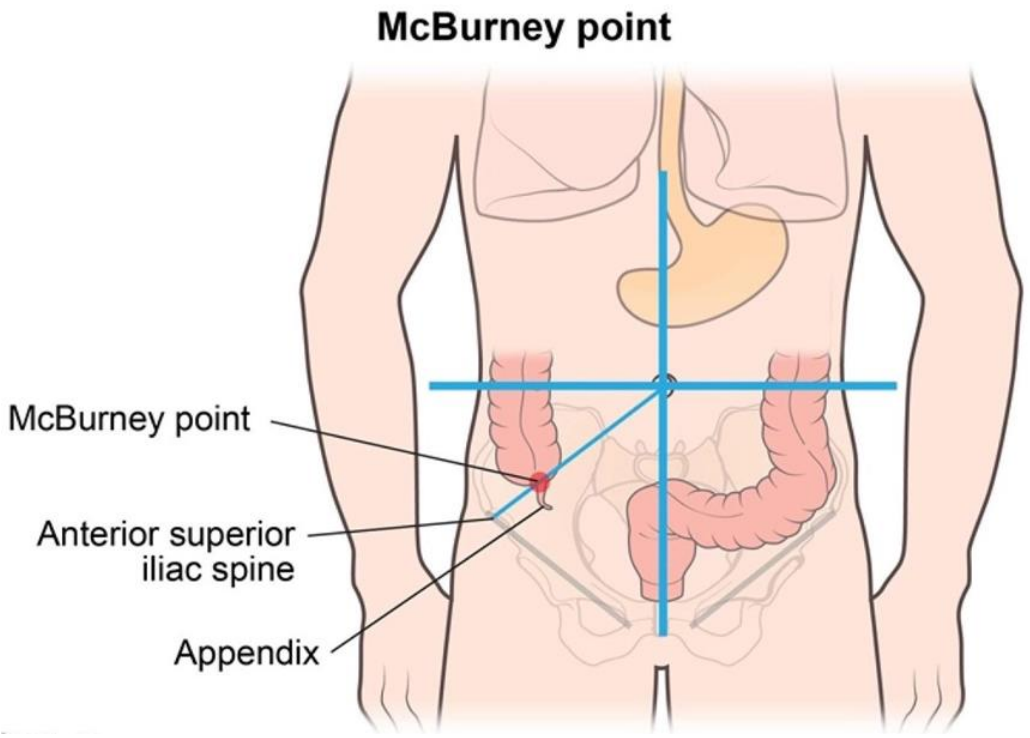
- Acute appendicitis is a clinical diagnosis, and patients with a classic presentation (migratory pain, nausea, vomiting, fever, leukocytosis, McBumey point tenderness and Rovsing sign) should have an immediate appendectomy to prevent appendiceal rupture.

- Inflammation and edema of the appendicular wall occur, causing further distention. Necrosis of the wall with rupture may follow. In this case, inflammatory fluid and bacterial contents spill into the peritoneal cavity, causing peritonitis.

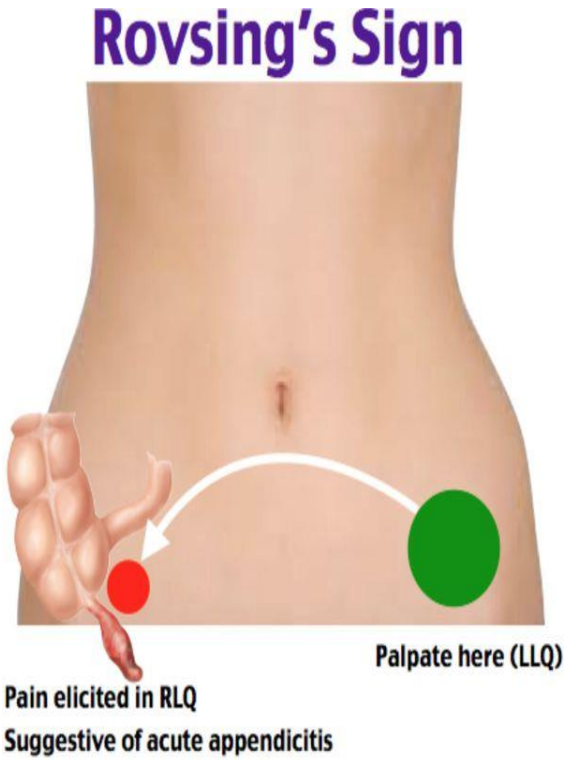
- Patients who have a delayed presentation with a longer duration of symptoms (>5 days) often have appendiceal rupture with a contained abscess. These patients will generally have significant fever and leukocytosis, but findings on anterior palpation of the abdomen may be unrevealing.

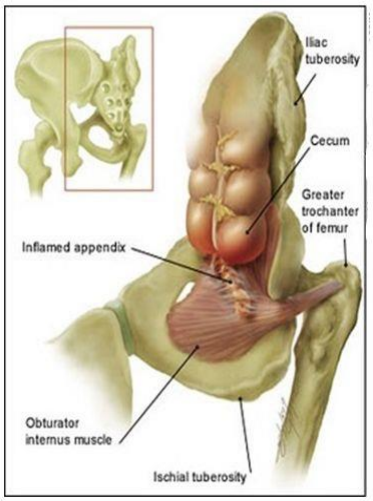
- In such cases, maneuvers that assess the deep abdominal spaces (psoas sign, obturator sign, rectal examination) may be more informative.

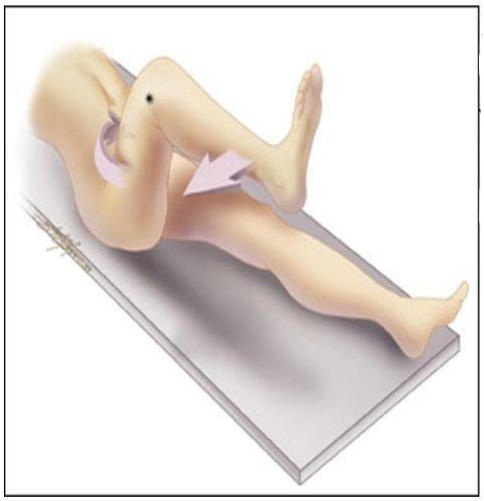
- Differential: diverticulitis (elderly), ectopic pregnancy (use hCG to rule out), pseudoappendicitis.

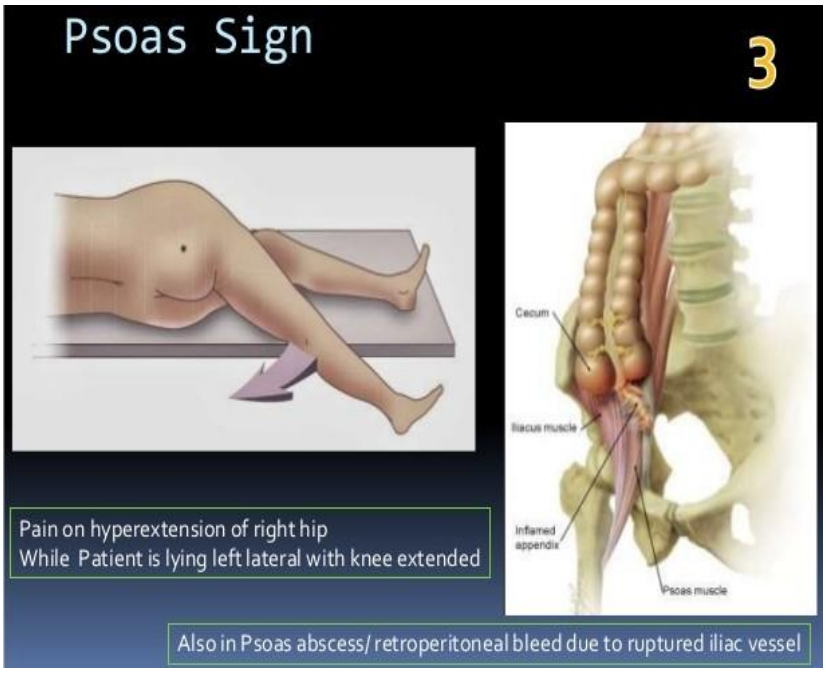


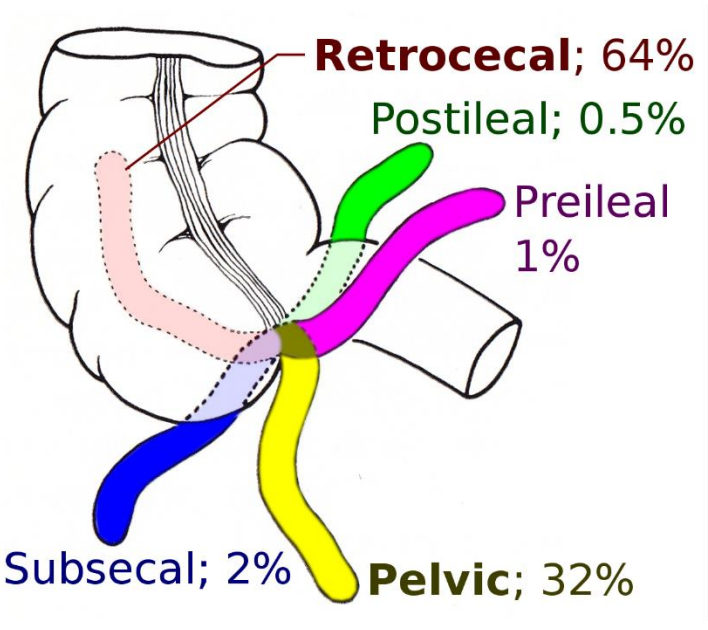
Examination signs in appendicitis		
Sign	**Findings**	**Significance**
Peritoneal signs • Rebound tenderness • Involuntary guarding • Abdominal rigidity	Acute increase in pain after removing the hand from applying pressure Tensing of abdominal wall muscles during palpation of abdomen Persistent tension of abdominal wall muscles	Peritoneal irritation (rupture or impending rupture)
Psoas sign	RLQ pain with extension of right thigh	Abscess adjacent to psoas or retrocecal appendix
Obturator sign	RLQ pain with internal rotation of right thigh	Pelvic appendix or abscess
Rovsing's sign	RLQ pain with LLQ palpation & retropulsion of colonic contents	Acute appendicitis
Rectal tenderness	Right pelvic pain during rectal examination, especially with pressure on right rectal wall	Pelvic appendix or abscess


Rovsing's Sign
Palpate here (LLQ)
Pain elicited in RLQ
Suggestive of acute appendicitis


Obturator Sign
Iliac tuberosity
Cecum
Greater trochanter of femur
Inflamed appendix
Obturator internus muscle
Ischial tuberosity




Psoas Sign
3
Pain on hyperextension of right hip
While Patient is lying left lateral with knee extended
Cecum
Iliacus muscle
Inflamed appendix
Psoas muscle
Also in Psoas abscess/ retroperitoneal bleed due to ruptured iliac vessel


Retrocecal; 64%
Postileal; 0.5%
Preileal 1%
Subsecal; 2%
Pelvic; 32%

Carcinoid tumor

- Intestinal carcinoids are malignant transformations of enterochromaffin (endocrine) cells of the intestinal mucosa.

- These cells are a part of the APUD-system (Amine Precursor Uptake and Decarboxylation). APUD or enterochromaffin cells are found in many organs and tissues, where they secrete a number of hormone-like substances that play an important role in regulating organ function. The most common location of intestinal carcinoids is the ileum. They also frequently occur in the appendix and rectum.

- Carcinoids are the most common appendiceal tumors.

- When the tumor is confined to the intestine, its secretory products are metabolized by the liver, and patients do not develop clinical manifestations.

- If intestinal carcinoids metastasize to the liver, their secretory products are not degraded, and they enter the systemic circulation. In this case, carcinoid syndrome develops. Symptoms include:

1. Vasomotor instability: cutaneous flushing, dizziness.

2. Gastrointestinal symptoms: secretory diarrhea, crampy abdominal pain.

3. Bronchoconstriction: dyspnea with wheezing.

4. Right-sided (pulmonary, tricuspid) valvular heart disease:

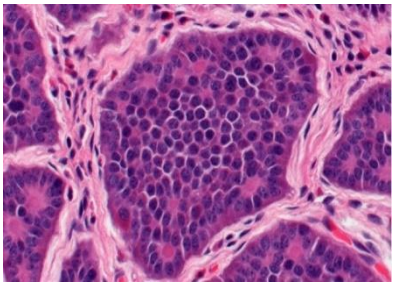
- Fibrous intimal thickening with endocardial plaques limited to the right heart are characteristic of carcinoid heart disease associated with carcinoid syndrome.

- The degree of endocardial fibrosis seen in this syndrome correlates with plasma levels of serotonin and urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid.

- This fibrosis is generally limited to the right heart because both serotonin and bradykinin in the blood are inactivated distally by pulmonary vascular endothelial monoamine oxidase.

- Pulmonic stenosis and restrictive cardiomyopathy may ultimately result from this condition.

- Carcinoid tumors are composed of islands or sheets of uniform cells with eosinophilic cytoplasm and oval- to-round stippled nuclei.



- Increased level of the serotonin metabolite 5-HIAA (5-hydroxyindoleacetic acid) in a 24-hour urine sample is the most useful initial test (Serotonin is metabolized by liver monoamine oxidase (MAO) into 5-HIAA).

- Carcinoid syndrome can occur even without liver metastasis-but only if the primary tumor is outside of the intestine, such as in the lung (The vasoactive substances secreted by tumors in extra-intestinal locations are not filtered by the liver).

- The most definitive treatment for serotonin syndrome is surgical excision of the tumor.

- When there is disseminated disease, medical therapy with octreotide is used to control the symptoms.

- Octreotide is a synthetic analog of somatostatin with a longer half-life. It acts on somatostatin receptors and inhibits secretion of many hormones and hormone-like substances.

Colon

Acute mesenteric ischemia

- Acute mesenteric ischemia is the acute occlusion of mesenteric arteries, most commonly the superior mesenteric artery.

- AMI is most commonly due to abrupt arterial occlusion from either of the following:
  - Cardiac embolic events in the setting of atrial fibrillation, valvular disease (infective endocarditis), or cardiovascular aneurysms.
  - Acute thrombosis due to rupture of atheromatous plaque.
  - Low cardiac output states.

- Acute mesenteric ischemia classically presents with acute-onset, severe, midabdominal pain out of proportion to physical examination findings.

- If bowel infarction occurs, patients may develop more focal abdominal tenderness (due to local inflammation/infarction), peritoneal signs (guarding, rebound tenderness), rectal bleeding, and sepsis.

- Labs may show increased lactic acid and leukocytosis.

Chronic mesenteric ischemia

- Chronic mesenteric ischemia results from atherosclerotic disease of 2 or more mesenteric vessels. Most cases are due to atherosclerotic changes of the celiac or superior mesenteric arteries.

- CMI commonly presents with crampy postprandial epigastric pain (intestinal angina), food aversion, and weight loss (many patients avoid the pain associated with eating). Patients may also report nausea, early satiety, and diarrhea.

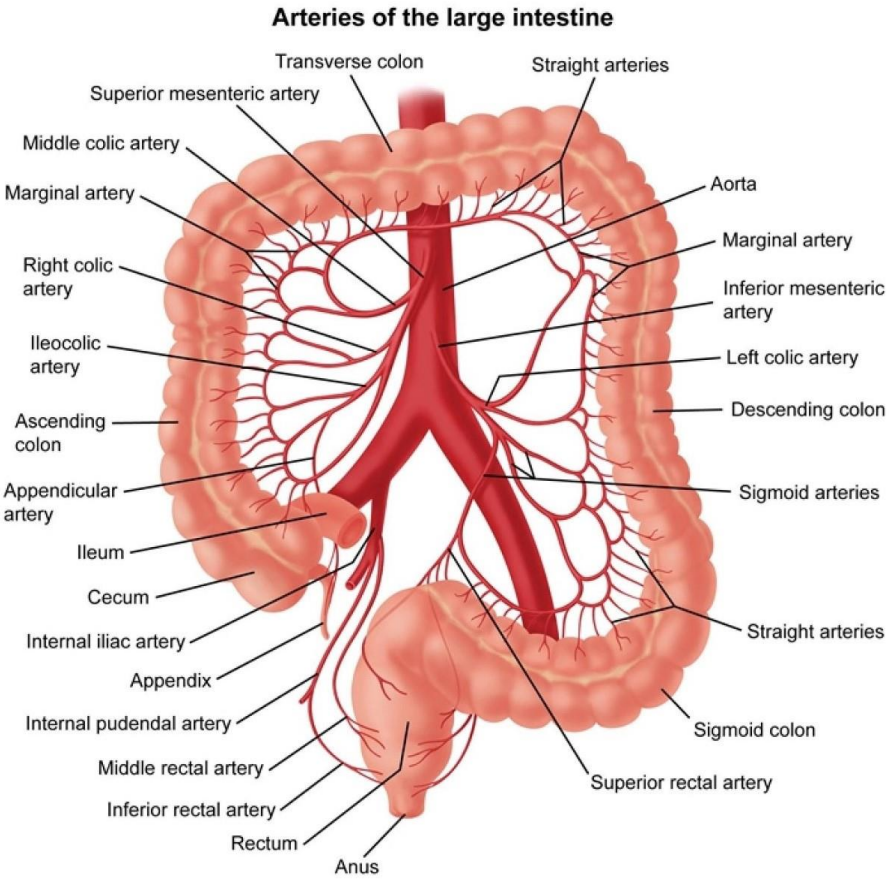
- The anginal pain frequently starts within the first hour of eating and slowly resolves over the next 2 hours.

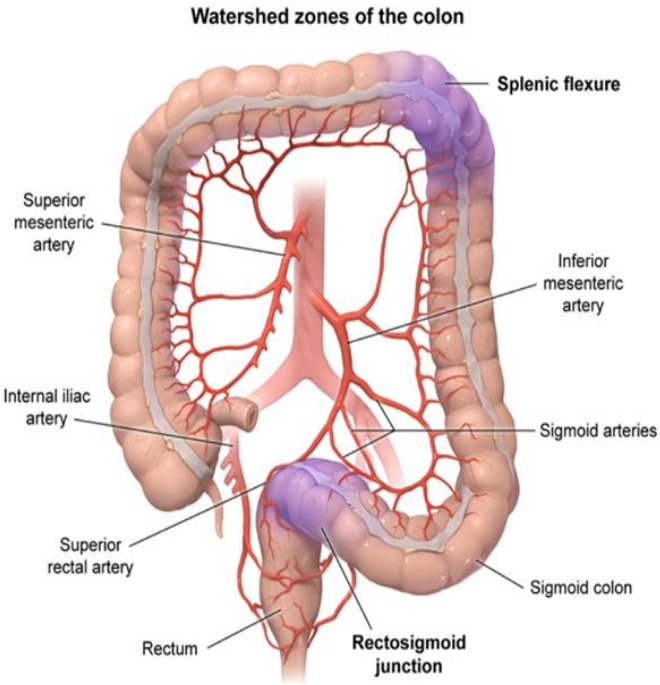
- The pathophysiology of the pain is most likely related to shunting of blood away from the small intestine to meet the increased demand of the stomach.

- It is analogous to angina of the heart but affects only the gut. In intestinal ischemia, eating is the equivalent of exertion in “chest pain with exertion”.

Colonic ischemia

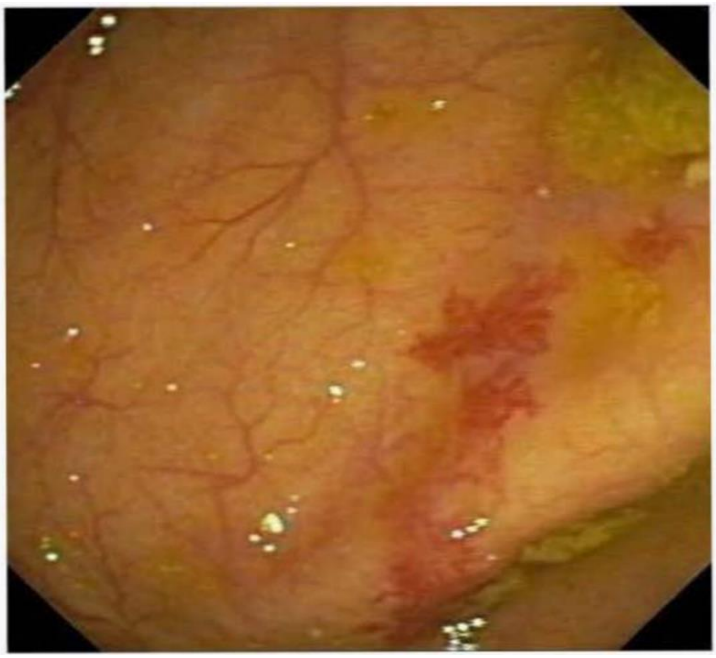
- Ischemic colitis is characterized by acute abdominal pain and lower gastrointestinal bleeding (hematochezia).
- It typically follows an episode of hypotension and most commonly affects arterial watershed areas at the splenic flexure and rectosigmoid junction.
- Ischemic colitis is a common complication of vascular surgery (Repair of an abdominal aortic aneurysm), as patients are often older and have extensive underlying atherosclerosis. Contributing factors may include loss of collateral circulation, manipulation of vessels with surgical Instruments, prolonged aortic clamping, and impaired blood flow through the inferior mesenteric artery.
- The most commonly involved segments of the colon include the splenic flexure at the "watershed" line between the territory of the superior and inferior mesenteric arteries and the rectosigmoid junction at the watershed between the sigmoid artery and superior rectal artery.





Angiodysplasia

- Tortuous dilation of vessels → hematochezia (due to rupture).
- It is a common cause of recurrent, painless gastrointestinal bleeding.
- Most often found in the right-sided colon due to high wall tension.
- More common in older patients.
- Confirmed by angiography.
- Associated with aortic stenosis, advanced renal disease and von Willebrand disease (possibly due to the bleeding tendency associated with these disorders)



Colonic diverticula

- Outpouchings of mucosa and submucosa through the muscularis propria (false diverticulum).
- Related to wall stress. This is attributed to increased intraluminal pressure that occurs when one strains during a bowel movement, most commonly due to constipation, straining, and diet high in red meat & fat & low in fibers; commonly seen in older adults (risk increases with age).
- Arise where the vasa recta traverse the muscularis propria (weak point in colonic wall); sigmoid colon is the most common location.
- Colonic diverticula, therefore, are pulsion by mechanism, and false by structure.

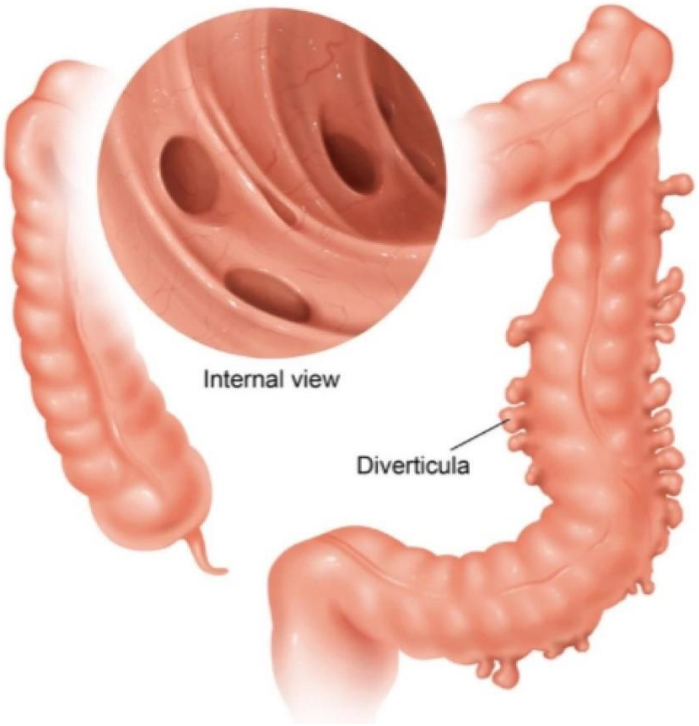
- Usually asymptomatic; complications include:

- Painless rectal bleeding (hematochezia): This bleeding occurs due to the disruption of the arterioles adjacent to a diverticulum.

- Diverticulitis: due to obstructing fecal material; presents with appendicitis-like symptoms in the left lower quadrant.

- Fistula: Inflamed diverticulum ruptures and attaches to a local structure. Colovesicular fistula presents with air (or stool) in urine (pneumaturia).

Diverticulosis



Diverticular disease	
Etiology	• Diverticulosis: ↑ Intraluminal pressure causing herniation through points of weakness (vasa recta penetration) • Diverticular bleeding: Injury to exposed vasa recta • Diverticulitis: Trapped food particles & ↑ intraluminal pressure causing microperforation
Symptoms	• Diverticulosis: None • Diverticular bleeding: Painless hematochezia • Diverticulitis: Left lower quadrant pain, nausea, vomiting, fever
Risk factors	• Diet high in red meat & fat & low in fiber • Obesity, physical inactivity, smoking

Acute diverticulitis	
Pathogenesis	• Trapped food particles & ↑ intracolonic pressure causing microperforation of colonic diverticula
Clinical presentation	• Abdominal pain (usually left lower quadrant) • Nausea, vomiting, change in bowel habits • Tenderness ± palpable mass • Leukocytosis
Diagnosis	• Abdominal CT (oral & intravenous contrast)

Colonic polyps

- Raised protrusions of colonic mucosa.

- Colonic polyps may be differentiated as non-neoplastic and neoplastic. Most are non-neoplastic and do not increase the risk of colon adenocarcinoma; such types include:

1. Hyperplastic polyps: composed of well-differentiated mucosal cells that form glands and crypts. Occasionally evolves into serrated polyps and more advanced lesions.

2. Hamartomatous polyps: consist of mucosal glands, smooth muscle and connective tissue. They may occur sporadically or in Peutz-Jeghers syndrome or juvenile polyposis.

3. Inflammatory pseudopolyps: are seen in ulcerative colitis and Crohn disease. They are composed of regenerating intestinal mucosa.

4. Mucosal polyps: Small, usually < 5 mm. Look similar to normal mucosa. Clinically insignificant.

5. Submucosal polyps: are typically composed of lipomas or lymphoid aggregates that bulge up into the mucosa.

- Neoplastic polyps include adenomatous polyps (tubular, villous, tubulovillous) and serrated polyps (sessile serrated polyp, traditional serrated adenoma). These polyps have the potential to transform into colonic adenocarcinoma.

- Colonic adenomatous polyps are divided into three types according to their histologic appearance:

A. Tubular adenomas: composed of dysplastic colonic mucosal cells that form tubular-shaped glands.

B. Villous adenomas: dysplastic epithelial cells form villi-like projections that extend from the polyp surface down to the stroma.

C. Tubulo-villous adenomas: show a mixture of the two patterns.

- Unlike non-neoplastic polyps, adenomatous polyps contain dysplastic mucosal cells and can transform into adenocarcinoma via the adenoma-carcinoma sequence. The following criteria determine the malignant potential of adenomatous polyps:

1. Degree of dysplasia.

2. Histologic pattern: villous adenomas are more likely to undergo malignant transformation than tubular adenomas.

3. Size: adenomas >4 cm have 40% risk of becoming malignant; those <1 cm are most likely benign.

- Greatest risk for progression from adenoma to carcinoma is related to size > 2 cm, sessile growth, and villous histology.

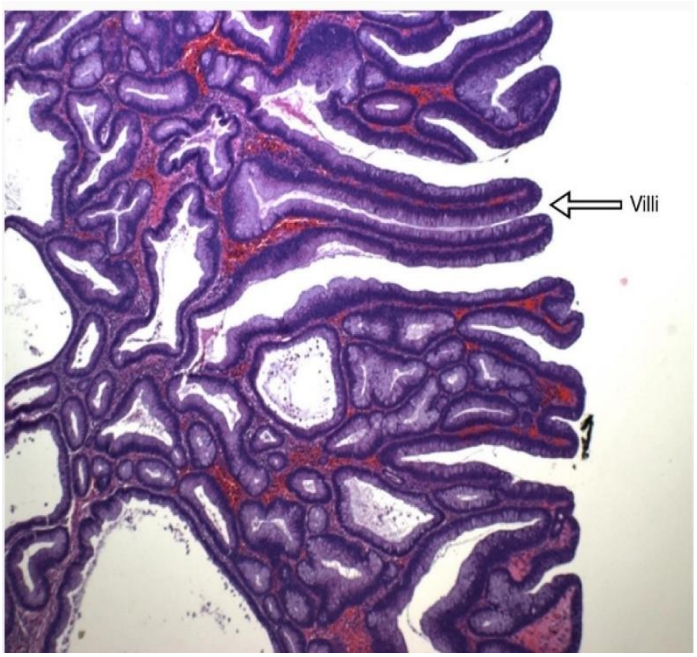
- Although most of colon adenomas are asymptomatic, larger ones can cause a number of symptoms:

1. Lower intestinal bleeding causes guaiac-positive stool (fecal occult blood testing) and microcytic hypochromic anemia. The bleeding is usually unknown to the patient, but overt bleeding may also occur.

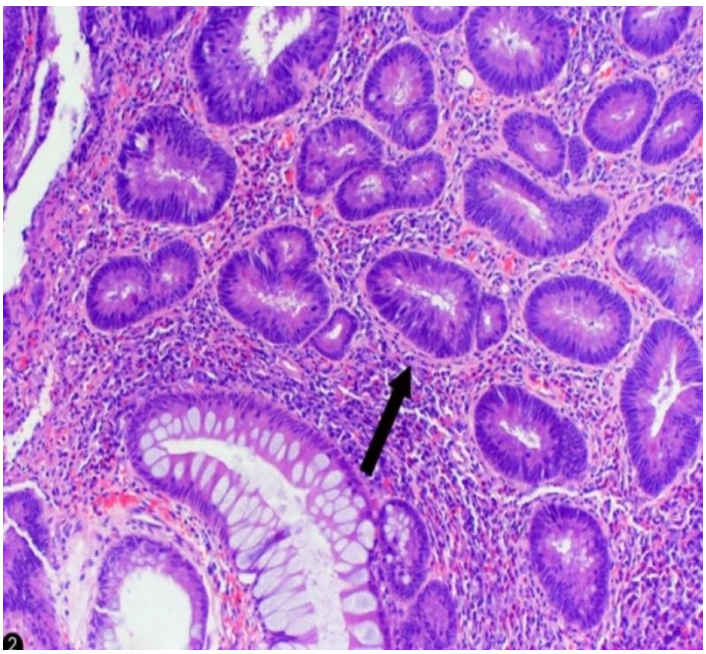
2. Partial intestinal obstruction can manifest with bowel habit changes, crampy abdominal pain, constipation, and abdominal distention.

3. Villous adenomas may secrete large amounts of mucus, leading to secretory diarrhea. If the stool volume is large, diarrhea may cause hypovolemia and electrolyte imbalances.

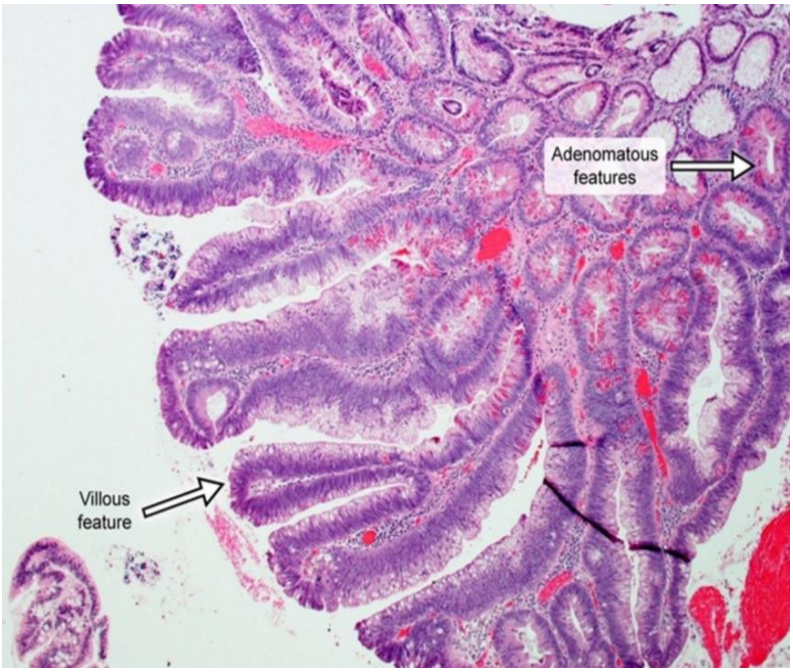
4. Villous adenomas have a high risk of progression to adenocarcinoma.



Villous Adenoma



Tubular Adenoma



Tubullovillous Adenoma

Adenoma to carcinoma sequence

- Adenoma-carcinoma sequence describes the molecular progression from normal colonic mucosa to adenomatous polyp to carcinoma.

- Stepwise progression to adenocarcinoma proceeds as other mutations occur in genes such as APC, K-ras, p53, and DCC.

- This accumulation of gene mutations is called the "adenoma-to-carcinorna sequence":

A. Progression from normal mucosa to a small polyp:

- The initial appearance of small adenomatous polyps is attributed to the mutation of the APC tumor suppressor gene (regulates cell growth and adhesion).

- APC is located on chromosome 5, and its mutation leads to uncontrolled cell proliferation.

B. Increase in the size of the polyps:

- Mutation of the K-ras protooncogene is thought to facilitate this step.

- This mutation leads to the appearance of a protein that stimulates unregulated cell growth.

C. Malignant transformation of adenoma into carcinoma requires mutation of two genes (p53 and DCC):

- Sometimes called a "molecular policeman", p53 is an anti-oncogene.

- It codes for protein p53, which triggers apoptosis of cells with damaged DNA.

- Mutation of p53 allows cells with genomic errors to enter the cell cycle.

- This mutation is considered the last hit in the adenoma to-carcinoma sequence.

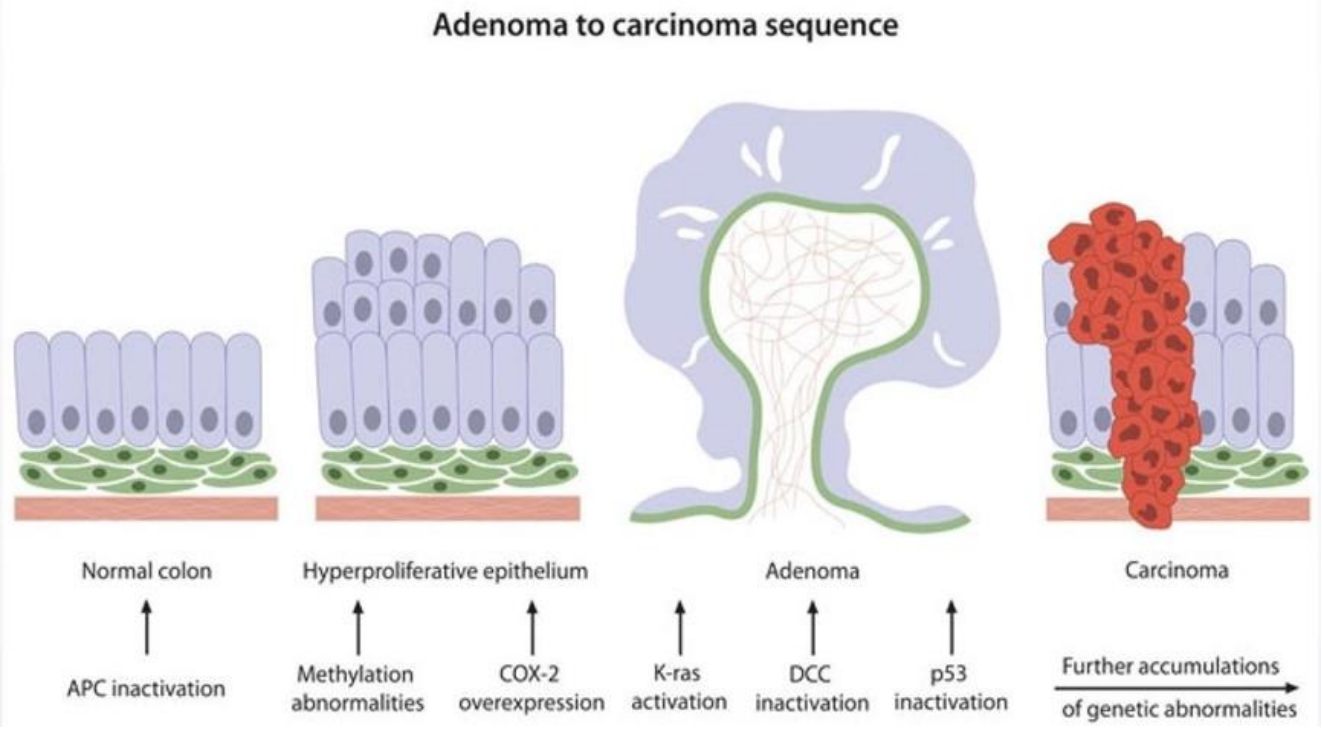
- Increased activity of the enzyme cyclooxygenase-2 (COX-2) has been found in many forms of colon adenocarcinoma and in inherited polyposes syndromes. This may be due to the need for COX-induced prostaglandin production, which leads to epithelial proliferation. Regular aspirin (a COX inhibitor) intake has been associated with lower rates of colonic adenoma and adenocarcinoma.

- Screening for polyps is performed by colonoscopy and testing for fecal occult blood; polyps are usually clinically silent, but can bleed.

- Patients should have a colonoscopy every 10 years beginning at age 50.

- Goal is to remove adenomatous polyps before progression to carcinoma.

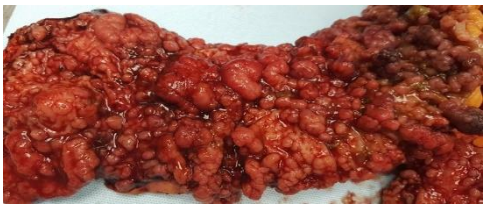
- On colonoscopy, hyperplastic and adenomatous polyps look identical. Hence, all polyps are removed and examined microscopically.


Adenoma to carcinoma sequence
Normal colon
Hyperproliferative epithelium
Adenoma
Carcinoma
APC inactivation
Methylation abnormalities
COX-2 overexpression
K-ras activation
DCC inactivation
p53 inactivation
Further accumulations of genetic abnormalities

Polyposis syndromes

1. **Familial adenomatous polyposis:**

- FAP is caused by a germline mutation (autosomal dominant) to the tumor suppressor gene adenomatous polyposis coli (APC) on chromosome 5.
- 2-hit hypothesis (inherit a mutation in one allele of the gene; and mutation of the second allele occurs during adult life).
- Thousands of adenomatous polyps arise starting after puberty; pancolonic; always involves rectum.
- Colon and rectum are removed prophylactically; otherwise, almost all patients develop carcinoma by 40 years of age (The lifetime risk that >1 of these polyps will transform to invasive colon cancer is nearly 100%).



2. **Gardner syndrome:**

- Gardner syndrome is FAP with fibromatosis and osteomas.
- Fibromatosis is a neoplastic proliferation of fibroblasts; arises in retroperitoneum (desmoid) and locally destroys tissue
- Osteoma is a benign tumor of bone that usually arises in the skull.

3. **Turcot syndrome:**

- FAP or Lynch syndrome + malignant CNS tumor (medulloblastoma, glioma). Turcot = Turban.

4. **Peutz-Jeghers syndrome:**

- Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented macules (freckle-like spots) on mouth, lips, hands, genitalia.
- Associated with ↑ risk of breast and GI cancers (colorectal, stomach, small bowel, pancreatic).

5. **Juvenile polyposis syndrome:**

- Autosomal dominant syndrome in children (typically < 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel.
- Usually presents as a solitary rectal polyp that prolapses and bleeds.
- Juvenile polyposis is characterized by multiple juvenile polyps in the stomach and colon; large numbers of juvenile polyps increase the risk of progression to carcinoma.

Lynch syndrome

- Previously known as hereditary nonpolyposis colorectal cancer (HNPCC).
- Autosomal dominant mutation of DNA mismatch repair genes (MSH2, MLH1) with subsequent microsatellite instability.
- Unlike sporadic colon cancer, HNPCC does not involve mutations of proto-oncogenes or anti-oncogenes. Instead, there is an inherited mutation in one of the four genes responsible for DNA mismatch repair.
- Microsatellites are repeating sequences of noncoding DNA; integrity of sequence (stability) is maintained during cell division.
- Instability indicates defective DNA copy mechanisms (DNA mismatch repair enzymes).
- Hereditary nonpolyposis colorectal carcinoma (HNPCC) is due to inherited mutations in DNA mismatch repair enzymes.
- Colorectal carcinoma arises de novo (not from adenomatous polyps) at a relatively early age (<50 years old).
- 80% progress to CRC.
- Proximal colon is always involved.
- Associated with endometrial, ovarian, and skin cancers.

Syndromes that increase colon cancer risk			
Syndrome	**Gene mutation**	**Colon cancer risk**	**Other associated neoplasms**
Familial adenomatous polyposis	*APC*	100%	Upper gastrointestinal Thyroid Desmoids/osteomas
Lynch syndrome	*MSH2/6, MLH1*	50%-80%	Endometrial Ovarian
Peutz-Jeghers syndrome	*STK11*	39%	Upper gastrointestinal Pancreatic Breast

Colorectal carcinoma

- Carcinoma arising from colonic or rectal mucosa; 3rd most common site of cancer and 3rd most common cause of cancer-related death.
- Peak incidence is 60-70 years of age.
- Most commonly arises from adenoma-carcinoma sequence; a second important molecular pathway is microsatellite instability (MSI).
- Most cases of sporadic colon adenocarcinoma arise from preexisting adenomatous polyps.
- Colon cancer may be completely asymptomatic and is often found on screening colonoscopy.
- The most common location for this malignancy is the rectosigmoid colon.
- The ascending colon is the second most common location of colorectal carcinomas.

Rectosigmoid > ascending > descending

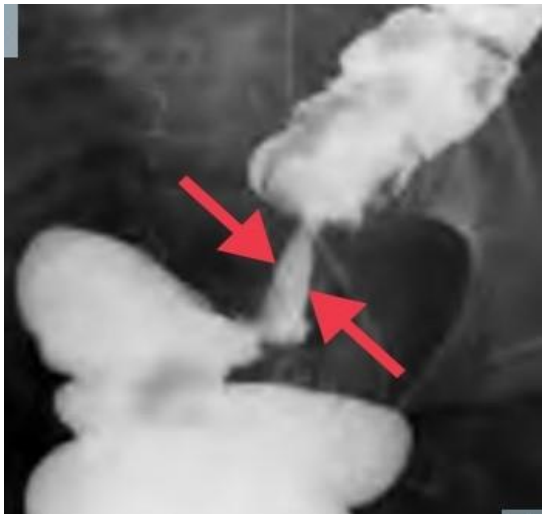
- <u>The location of colon adenocarcinomas influences clinical manifestation:</u>

- Left-sided colon cancers (rectosigmoid colon) tend to infiltrate the intestinal wall and encircle the lumen; hence, they present with symptoms of partial intestinal obstruction. Change in the stool caliber, constipation, cramping abdominal pain, abdominal distention, nausea, and vomiting occur.

- Right-sided colon cancers (ascending colon) usually grow as exophytic masses. Patients generally do not develop intestinal obstruction because the right-sided colon has a larger caliber than the left. Right-sided colon cancers usually present with manifestations of iron deficiency anemia (fatigue and pallor) due to the ongoing blood loss.

Right side bleeds; left side obstructs (narrower lumen)

- Screening for colorectal carcinoma occurs via endoscopy and fecal occult blood testing; begins at 50 years of age. Goal is to remove adenomatous polyps before carcinoma develops and to detect cancer early (before clinical symptoms arise).
- Colonic carcinoma is associated with an increased risk for Streptococcus bovis endocarditis.
- "Apple core" lesion seen on barium enema x-ray



- Staging:

- T: depth of invasion; tumors limited to the mucosa generally do not spread due to lack of lymphatics in the mucosa.

- N: spread to regional lymph nodes.

- M: distant spread; most commonly involves the liver.

- CEA is a serum tumor marker that is useful for assessing treatment response and detecting recurrence; not useful for screening.

- Colorectal carcinoma (CRC) is the most common type of malignancy in patients suffering from inflammatory bowel disease (IBD), particularly ulcerative colitis.

- There are some important differentiating features between colitis-associated carcinoma and sporadic colorectal carcinoma. Colitis-associated carcinoma is more likely to:

- Affect younger patients.

- Progress from flat and non-polypoid dysplasia.

- Histologically appear mucinous and/or have signet ring morphology.

- Develop early p53 mutations and late APC gene mutations, opposite that of sporadic disease.

- Be distributed within the proximal colon (especially with Crohn's disease or concurrent primary sclerosing cholangitis).

- Be multifocal in nature.

- Long-standing ulcerative colitis is associated with an increased risk of colorectal cancer. The duration and extent of colitis are the most significant risk factors.

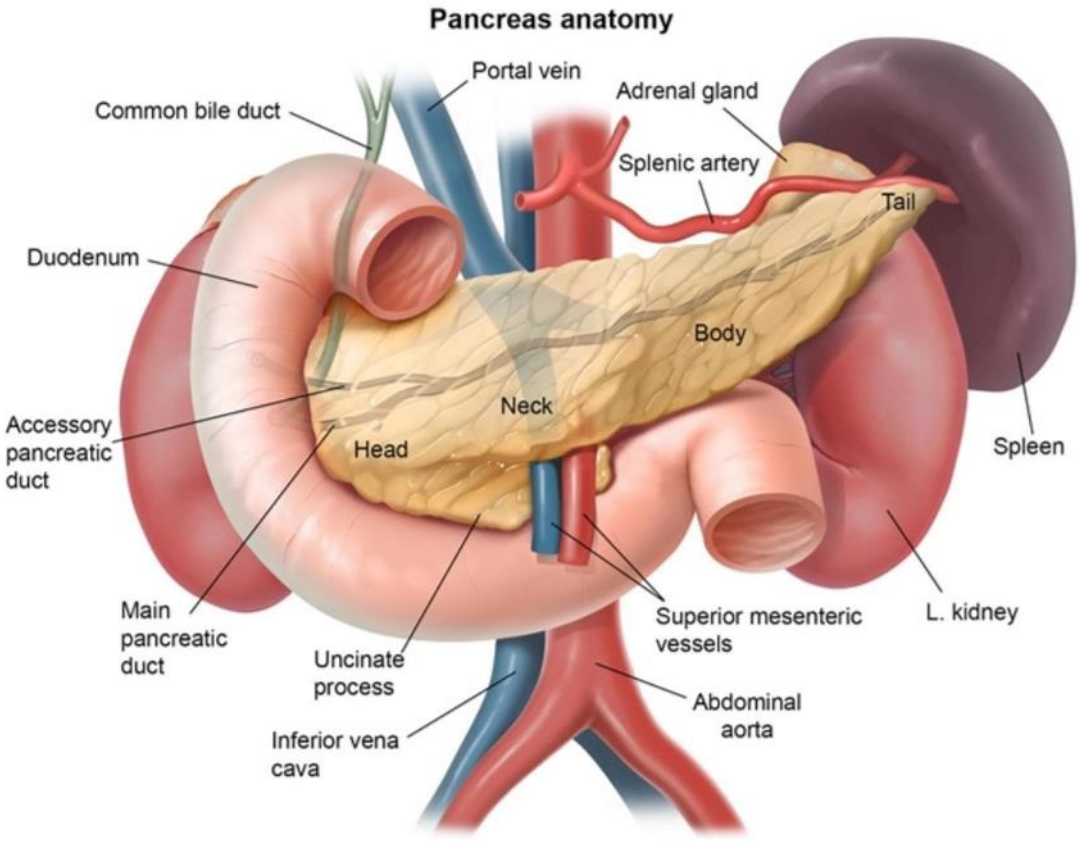
- Colorectal carcinoma in IBD patients usually develops after 10 years of colitis. Pancolitis is associated with the highest risk of CRC. Given their high risk for CRC, it is important for the physician to monitor and evaluate IBD patients for malignancy on a regular basis. Patients should be monitored regularly via colonoscopy with random biopsies.

Colitis-associated vs sporadic colorectal cancer

	Colitis-associated	Sporadic
Age	• Younger (age 40-55)	• Older (age >60)
Origin of dysplasia	• Flat (nonpolypoid) lesions	• Polypoid lesions
Location	• Proximal > distal (particularly with CD)	• Distal > proximal
Tumors	• Multifocal	• Singular
Histology	• Mucinous and/or signet ring cells • Poorly differentiated	• Rarely mucinous • Well differentiated
Mutations	• Early *p53* mutation • Late *APC* gene mutation	• Early *APC* gene mutation • Late *p53* mutation

APC = adenomatous polyposis coli; **CD** = Crohn disease.

Pancreas



- Most pancreatic enzymes are synthesized by pancreatic acinar cells as inactive enzyme precursors called zymogens.
- After traversing the pancreatic duct system, they drain through the ampulla of Vater into the descending part of the duodenum.
- There, the enzyme enterokinase (secreted from intestinal mucosa) cleaves trypsinogen into trypsin, its active form.
- Once a small quantity of trypsin is produced, it activates most of the other zymogens through proteolytic cleavage, including chymotrypsin, elastase, carboxypeptidase, etc.
- Trypsin can also cleave trypsinogen to produce more trypsin. The ability to self-activate allows trypsin to maintain a self-supporting cycle of proteolytic enzyme activation in the duodenum.

Pancreatic secretions

- Isotonic fluid; low flow → high Cl, high flow → high HCO_3.

A. **α-amylase:**
- Starch digestion.

- Secreted in active form.

B. **Lipases:** Fat digestion.

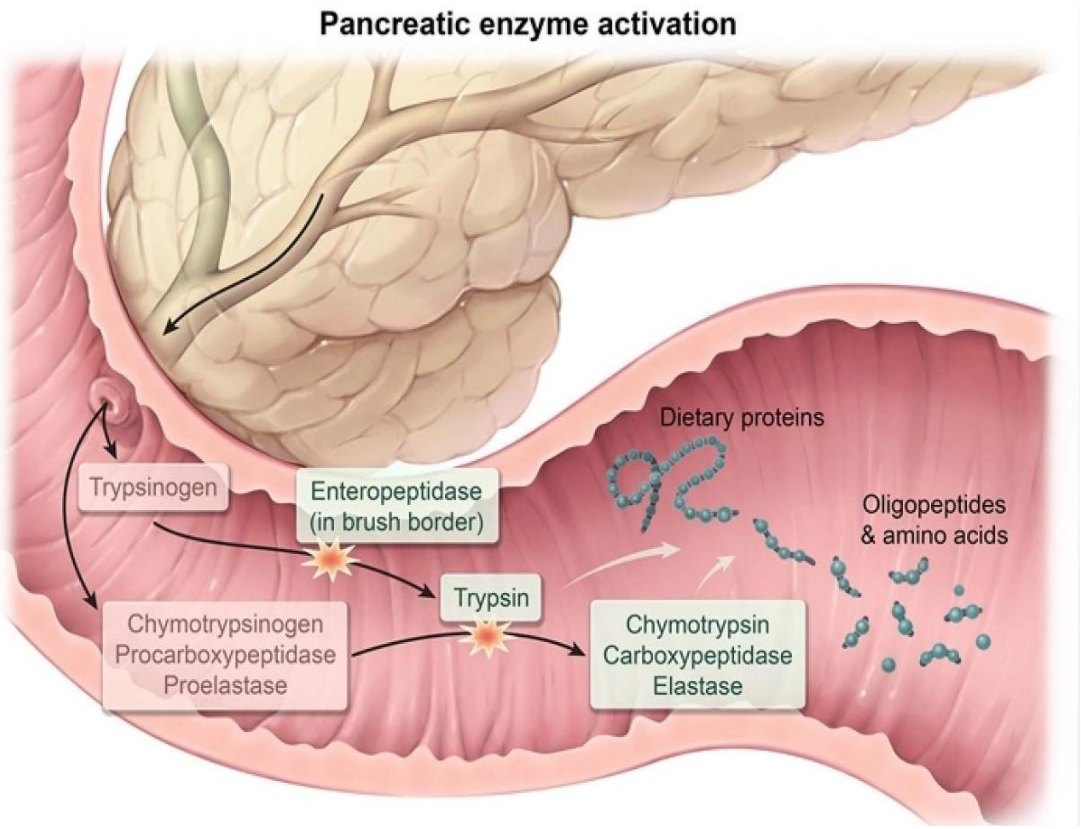
C. **Proteases:**
- Protein digestion.

- Includes trypsin, chymotrypsin, elastase, carboxypeptidases.

- Secreted as proenzymes also known as zymogens.

D. **Trypsinogen:**
- Converted to trypsin by enterokinase/enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa.

- Converted to active enzyme trypsin → activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop).



Acute pancreatitis

- Definition: Inflammation and hemorrhage of the pancreas due to autodigestion of pancreas by pancreatic enzymes.

- Pathogenesis:

- The pathogenesis of acute pancreatitis begins with damage to the pancreatic acinar cells either through a direct toxic insult or ischemia resulting from pancreatic ductal obstruction.

- This triggers the abnormal premature activation of trypsin inside the acinar cells by lysosomal enzymes. Trypsin then activates the other proteolytic enzymes and starts a self-sustaining cycle of pancreatic autodigestion (autolysis) with further release of active digestive enzymes.

- Results in liquefactive hemorrhagic necrosis of the pancreas and fat necrosis of the peripancreatic fat.

- Destruction of blood vessel walls can cause hemorrhage into the necrotic areas.

- Causes:

- Most commonly due to alcohol and gallstones (80%).

- Ethanol induces pancreatic secretions with a high protein concentration and low fluid content. These viscous secretions are prone to precipitate and form plugs that can obstruct the lumina of the pancreatic ductules. Alcohol also causes spasm of the sphincter of Oddi and has a direct toxic effect on the acinar cells.

- Less common causes of acute pancreatitis (20%):

1. Recent endoscopic retrograde cholangiopancreatography (ERCP) procedure.

2. Drugs (azathioprine, sulfasalazine, furosemide, valproic acid).

3. Infections (mumps, Coxsackie virus, Mycoplasma pneumoniae).

4. Hypertriglyceridemia:
   - High levels of circulating triglycerides lead to increased production of free fatty acids within the pancreatic capillaries by pancreatic lipase. Normally, fatty acids exist in serum bound to albumin.
   - However, if serum triglyceride levels rise to >1000 mg/dl, the concentration of free fatty acids exceeds the binding capacity of albumin and leads to direct injury to the pancreatic acinar cells. Thus, hypertriglyceridemia causes acute pancreatitis via direct tissue toxicity.

5. Hypercalcemia.

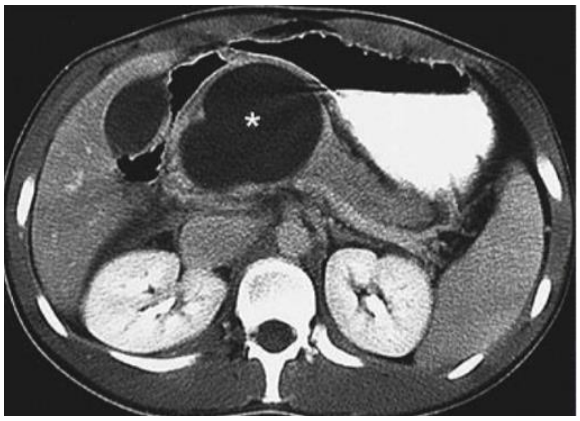
6. Structural abnormalities of the pancreatic duct (strictures, cancer, pancreas divisum) or of the ampullary region (choledochal cyst, stenosis of sphincter of Oddi).

- Clinical features:

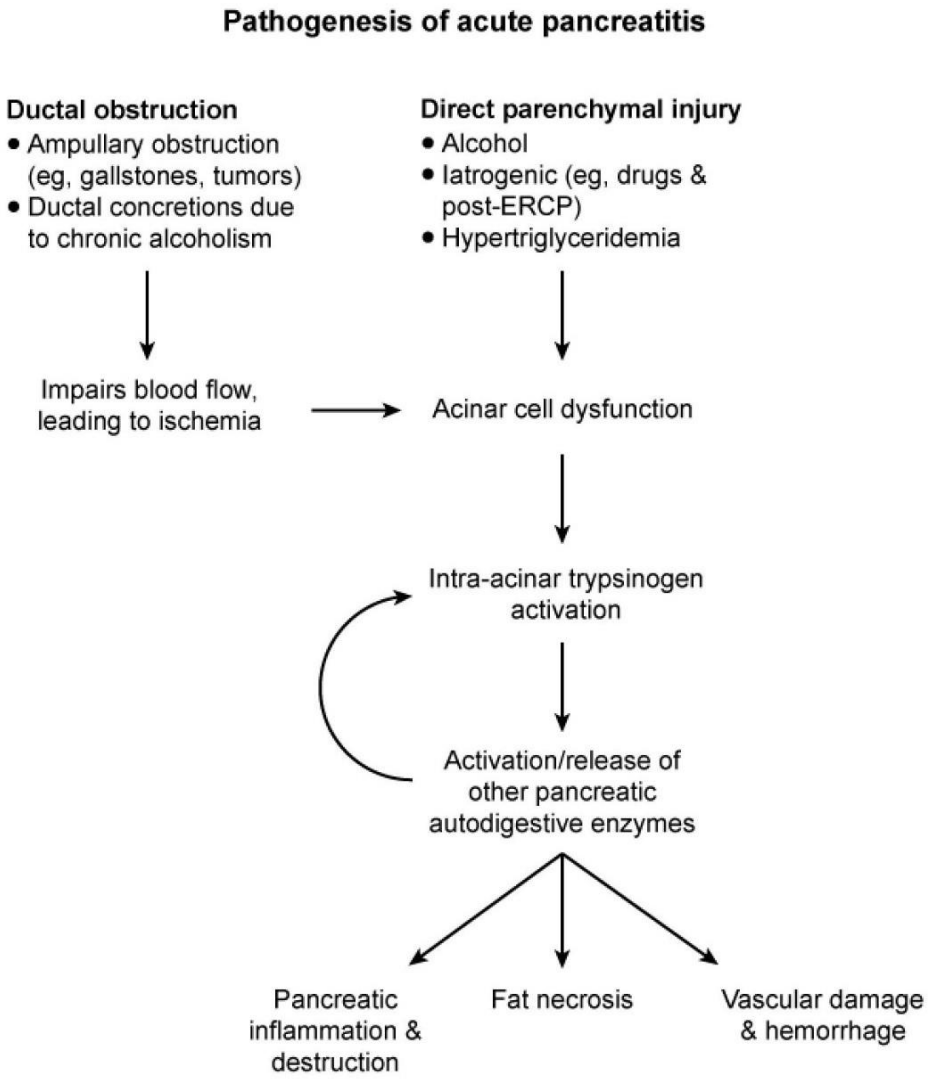
- Epigastric abdominal pain that radiates to the back.
- Nausea and vomiting.
- Periumbilical and flank hemorrhage (necrosis spreads into the periumbilical soft tissue and retroperitoneum).
- Elevated serum lipase and amylase; lipase is more specific for pancreatic damage.
- Hypocalcemia (calcium is consumed due to formation of fatty acids that bind calcium ions and precipitate as insoluble calcium salts).

- Complications:

- Shock: due to peripancreatic hemorrhage and fluid sequestration.
- Pancreatic pseudocyst:
  - It is a collection of fluid rich in enzymes and inflammatory debris. Its walls consist of granulation tissue and fibrosis. Unlike true cysts, pseudocysts are not lined by epithelium.
  - Presents as an abdominal mass with persistently elevated serum amylase.
  - Rupture is associated with release of enzymes into the abdominal cavity and hemorrhage.



- Pancreatic abscess: often due to Ecoli; presents with abdominal pain, high fever, and persistently elevated amylase.
- DIC and ARDS.



❖ N.B:

- Premature activation of trypsinogen before it reaches the duodenal lumen can result in autodigestion of the pancreatic tissues.
- Multiple inhibitory mechanisms exist to reduce the premature activation of trypsinogen, including cleavage inactivation of trypsin by trypsin itself. Gene mutations that render trypsin insensitive to cleavage inactivation cause hereditary pancreatitis.
- Because of trypsin's central role in the activation of pancreatic digestive proenzymes, multiple protective mechanisms exist to limit the amount of trypsinogen that becomes prematurely activated:

A. Serine peptidase inhibitor Kazal type 1(SPINK1) is secreted by pancreatic acinar cells and functions as a trypsin inhibitor.

- It impedes the activity of trypsinogen molecules that become prematurely activated within the pancreas, preventing trypsin-mediated activation of other proteolytic enzymes and autodigestion of pancreatic tissue.

B. In addition to functioning as its own activator, trypsin can also serve as its own inhibitor by cleaving other trypsin molecules (rendering them inactive).

- This process is critical in preventing large amounts of trypsin from forming within pancreatic tissue.

Chronic pancreatitis

- Fibrosis of pancreatic parenchyma, chronic inflammation, atrophy, calcification of the pancreas, most often secondary to recurrent acute pancreatitis.

- Most commonly due to alcohol (adults) and cystic fibrosis (children); however, many cases are idiopathic.

- Clinical features:

- Epigastric abdominal pain that radiates to the back.

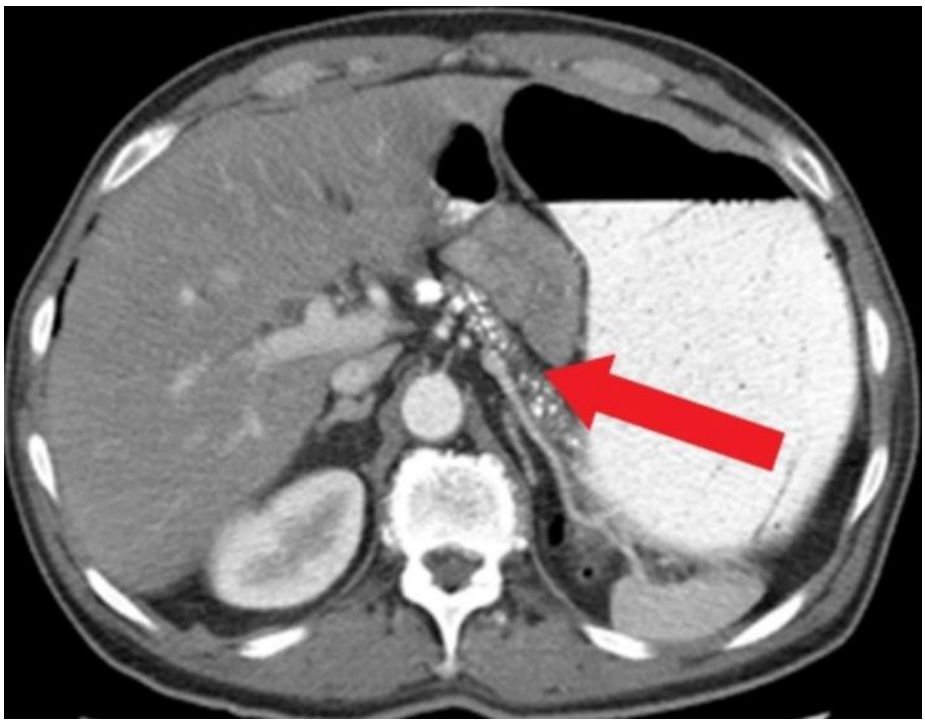
- Pancreatic insufficiency: results in malabsorption with steatorrhea and fat-soluble vitamin deficiencies.

- Amylase and lipase are not useful serologic markers of chronic pancreatitis (almost always elevated in acute pancreatitis)

- Dystrophic calcification of pancreatic parenchyma on imaging; contrast studies reveal a 'chain of lakes' pattern due to dilatation of pancreatic ducts.

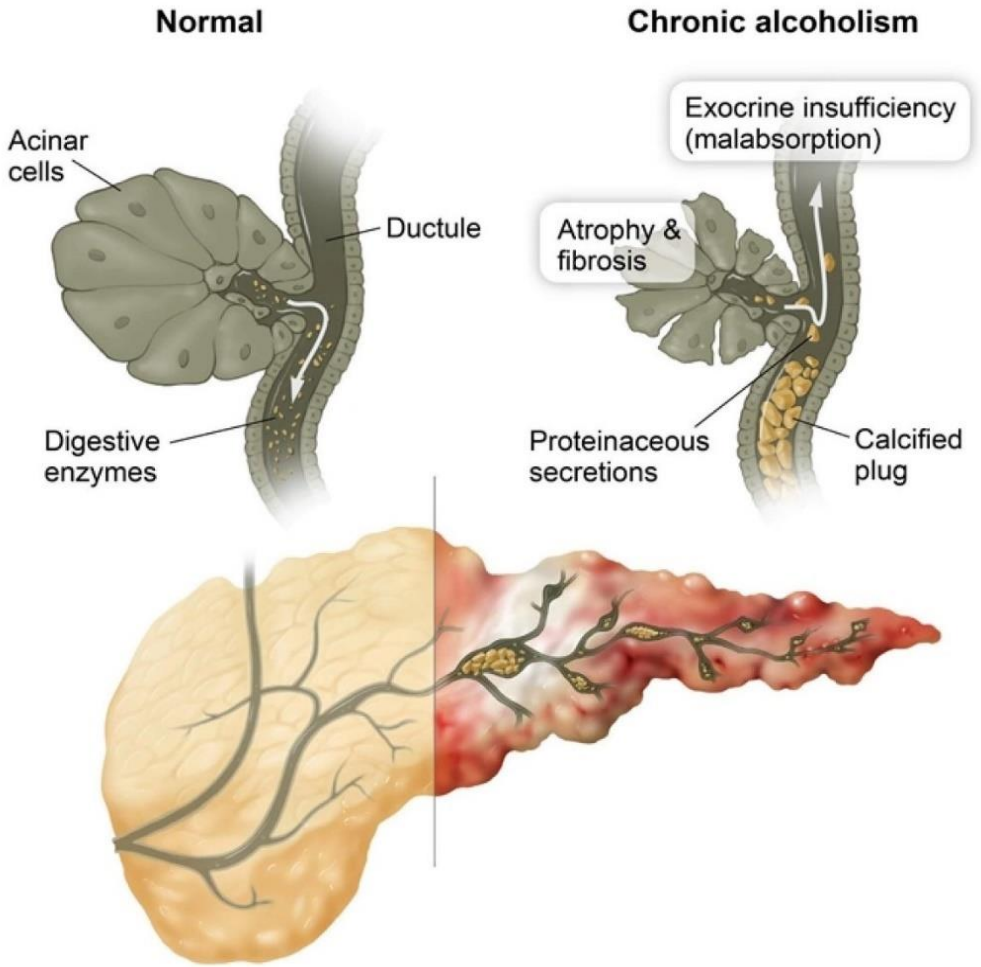
- Secondary diabetes mellitus: late complication due to destruction of islets.

- Increased risk for pancreatic carcinoma.



❖ N.B:

- It is thought that alcohol-related chronic pancreatitis may develop secondary to alcohol-induced protein precipitation within the pancreatic ducts.
- These proteins form ductal plugs which may calcify, forming calculi consisting in part of calcium carbonate.
- Ductal obstruction by such concretions may cause exocrine insufficiency due to atrophy of the pancreatic acinar cells and pancreatic fibrosis.
- Pancreatic exocrine insufficiency (failure to secrete adequate amylases, proteases and lipases) leads to malabsorption with consequent diarrhea/steatorrhea.
- Diarrhea, weight loss, and epigastric region calcifications in a patient with chronic alcoholism suggest chronic pancreatitis with resulting pancreatic exocrine insufficiency and malabsorption.



Pancreatic carcinoma

- Adenocarcinoma arising from the pancreatic ducts.

- The following are risk factors for this malignancy:

- Age: the highest incidence is in those age 65-75 years.

- Smoking: the most important environmental risk factor for pancreatic cancer; it doubles the risk.

- Diabetes mellitus: the risk of pancreatic cancer increases with the duration of diabetes.

- Chronic pancreatitis: the risk of pancreatic cancer increases with the duration of the disease. The risk is highest after 20 years of chronic pancreatitis.

- Genetic predisposition: hereditary pancreatitis, MEN syndromes, hereditary nonpolyposis colon cancer, and familial adenomatous polyposis syndromes can be associated with an increased risk of pancreatic cancer.

- Clinical features (usually occur late in disease):

- Epigastric abdominal pain and weight loss.

- Obstructive jaundice with pale stools and palpable gallbladder; associated with tumors that arise in the head of the pancreas (most common location).

- Secondary diabetes mellites; associated with tumors that arise in the body or tail.

- Migratory thrombophlebitis (Trousseau sign); presents as swelling, erythema, and tenderness in the extremities (seen in 10% of patients).

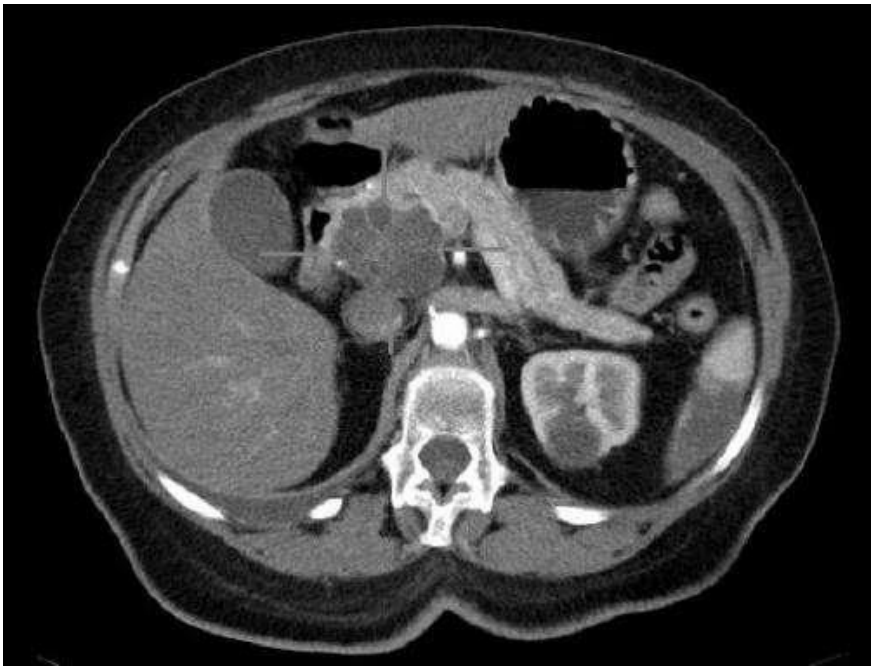
- A palpable but nontender gallbladder (Courvoisier sign), weight loss, and obstructive jaundice (associated with pruritus, dark urine, and pale stools) are indicative of an adenocarcinoma at the head of the pancreas compressing the common bile duct.

- Cancers of the body and tail of the pancreas do not obstruct the common bile duct, and thus they usually do not produce symptoms until they invade the splanchnic plexus and cause mid-epigastric abdominal pain.

- Serum tumor marker is CA 19-9.

- Because pancreatic cancer is a malignancy that manifests late, most tumors are unresectable at the time of diagnosis. Surgical resection involves en bloc removal of the head and neck of pancreas, proximal duodenum, and gallbladder (Whipple procedure).

- Very poor prognosis; 1-year survival is < 10%.



Liver

Bile

- Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions.

- Cholesterol 7α-hydroxylase catalyzes rate-limiting step of bile acid synthesis.

- <u>Functions:</u>

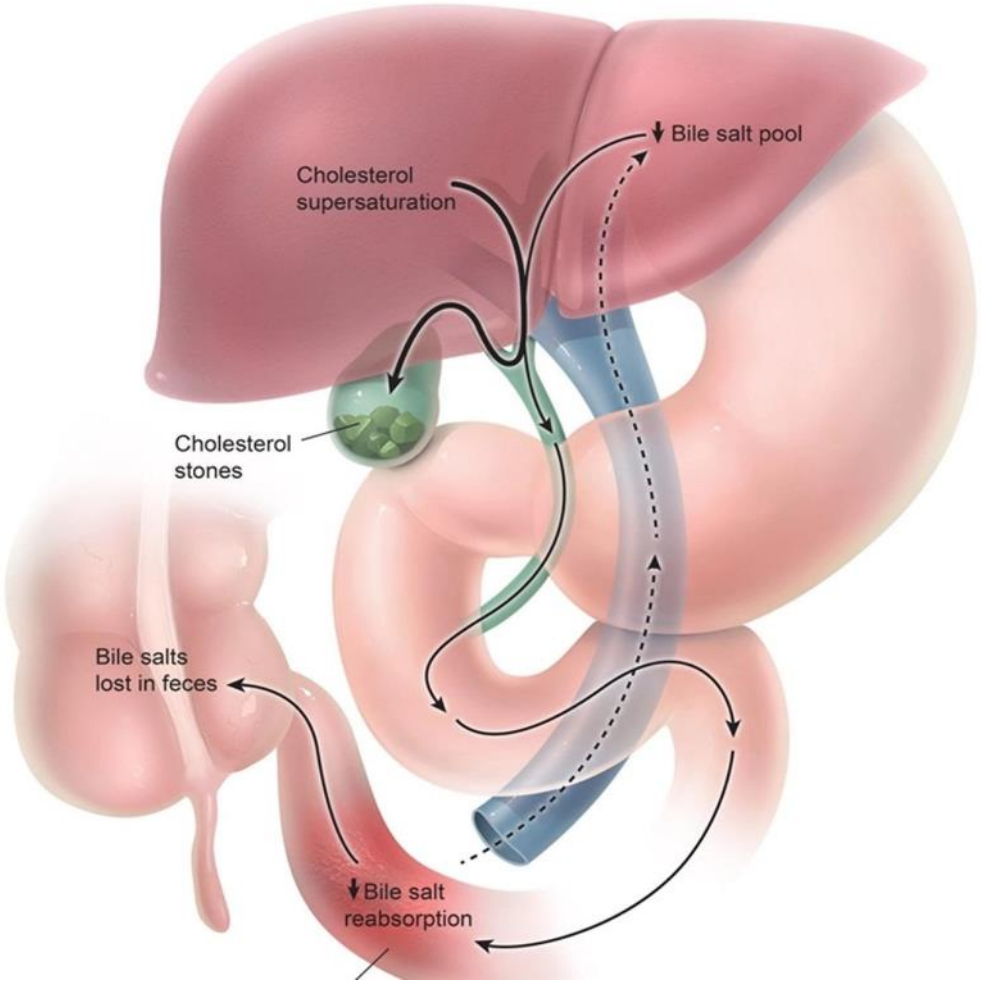
- Digestion and absorption of lipids and fat-soluble vitamins.

- Cholesterol excretion (body's 1° means of eliminating cholesterol).

- Antimicrobial activity (via membrane disruption).

- ↓ absorption of enteric bile salts at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption.

- Calcium, which normally binds oxalate, binds fat instead, so free oxalate is absorbed by gut → ↑ frequency of calcium oxalate kidney stones.



Liver cirrhosis

- The end stage of many chronic liver diseases, cirrhosis is characterized by diffuse hepatic fibrosis (via stellate cells) with replacement of the normal lobular architecture by fibrous-lined parenchymal nodules ("nodular parenchymal regeneration").

- Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

- Clinical features of cirrhosis:

- Cirrhosis of any type results in the progressive loss of liver functionality.

- The concentration of sex hormone-binding globulin also rises, which results in a higher binding of testosterone, decreasing the ratio of free testosterone to estrogen. This essentially creates an estrogen-excess state:
  - In the cirrhotic patient, gynecomastia arises from hyperestrinism secondary to the damaged liver's inability to metabolize circulating estrogens (specifically, androstenedione is not catabolized, resulting in increased estradiol levels).

  - Other manifestations of hyperestrinism in the cirrhotic patient include spider angiomata and, in males, testicular atrophy and decreased body hair.

- In advanced disease, portal blood has an increasingly difficult time passing through the liver because the vasculature becomes compromised by the progressive fibrosis, causing portal hypertension:
  - The effects of prolonged portal hypertension include varices at the sites of portocaval anastomoses (esophagus, rectum, umbilicus), as well as ascites.

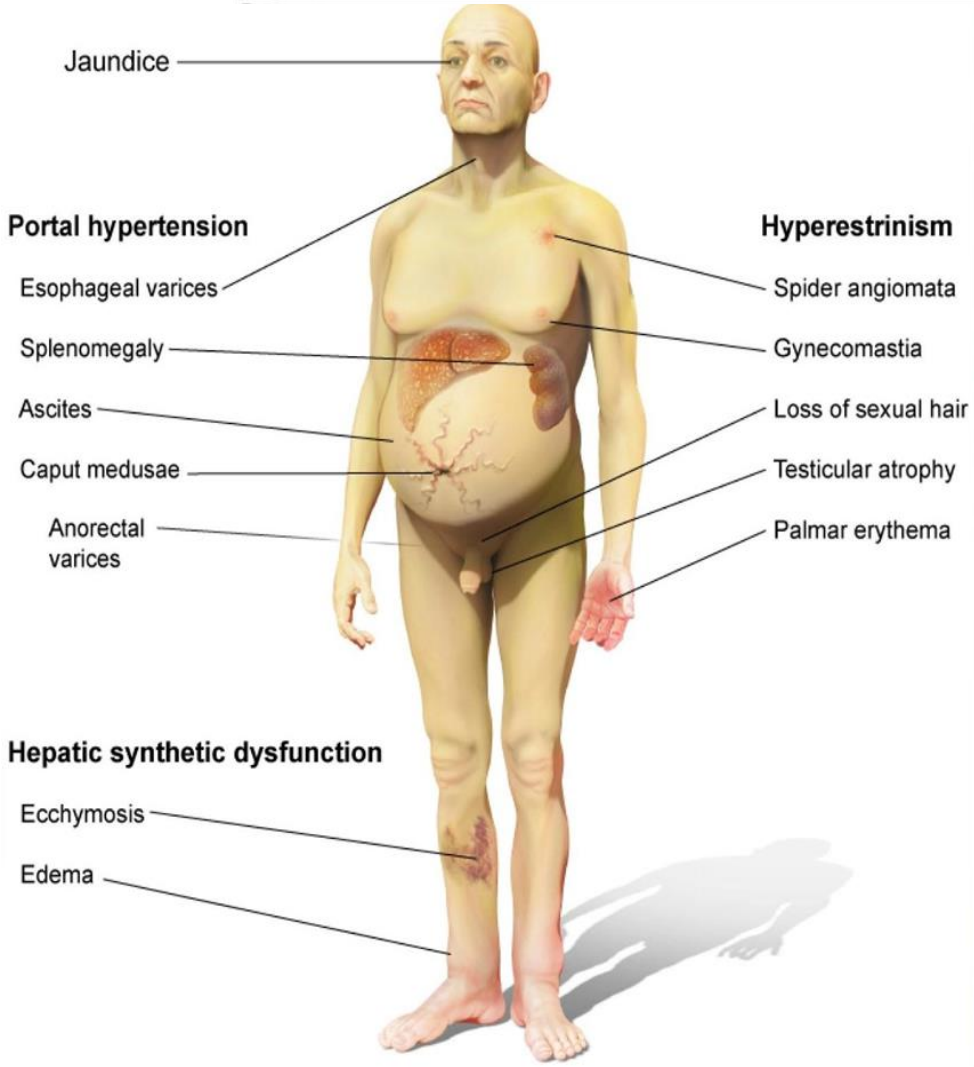
  - Etiologies of portal hypertension include cirrhosis (most common cause in Western countries), vascular obstruction (portal vein thrombosis, Budd Chiari syndrome), schistosomiasis.

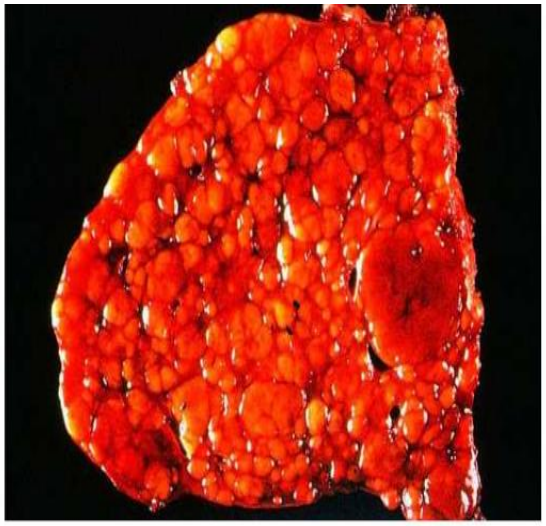
  - The pathogenesis of ascites in patients with cirrhosis is complex. In addition to mechanical compromise of portal vein flow by fibrotic tissue, vasoactive agents also play a role by causing dilatation of the splanchnic arterial vasculature and further intrahepatic vasoconstriction.

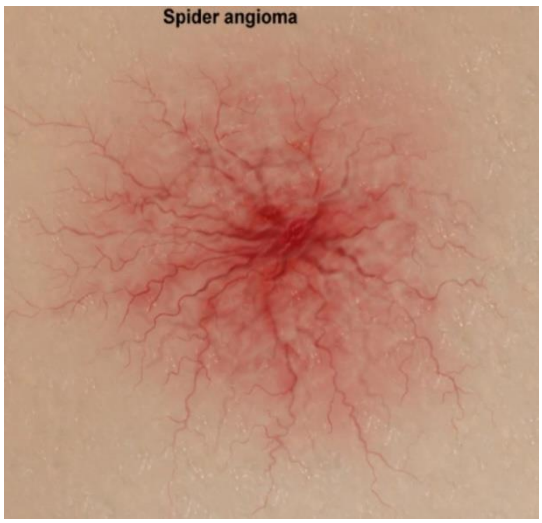
  - These processes result in increased portal vein hydrostatic pressure leading to ascitic fluid formation, as well as decreased systemic perfusion pressure. The kidney senses the decreased perfusion pressure (accentuated by renal vasoconstriction in hepatorenal syndrome) and responds with avid retention of sodium and water, thus promoting further increase in ascitic fluid formation.

  - Treatment of ascites secondary to cirrhosis involves restriction of sodium intake combined with diuretics. The most commonly prescribed initial therapy is a combination of furosemide and spironolactone.

Clinical features of cirrhosis	
Symptoms	• Nonspecific symptoms (eg, anorexia, fatigue, muscle cramps) • Jaundice & pruritus • Upper gastrointestinal bleeding • Encephalopathy (eg, confusion, sleep disturbances) • **Women**: Amenorrhea, irregular menses, anovulation • **Men**: Hypogonadism (eg, decreased libido, erectile dysfunction, loss of axillary & pubic hair)
Physical examination	• **Skin**: Telangiectasias, caput medusae • **Breast**: Gynecomastia (usually bilateral but can be unilateral) • **Abdomen**: Ascites, firm or nodular liver, splenomegaly • **Genitourinary**: Testicular atrophy • **Extremities**: Palmar erythema, Muehrcke &/or Terry nails, Dupuytren contracture, clubbing







Serum markers of liver pathology

- Laboratory findings in cirrhosis reflect both hepatocellular/biliary injury and loss of hepatic function.
- Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are indicators of hepatocellular damage, and increased alkaline phosphatase and gamma-glutamyl transpeptidase indicate biliary injury.
- Although these laboratory studies are indicative of ongoing hepatobiliary injury, they do not provide information on the liver's functional reserve, a key determinant of prognosis in patients with cirrhosis.
- Serum albumin levels, bilirubin levels, and prothrombin time are reflective of liver function and are of greatest prognostic significance in patients with cirrhosis. Hypoalbuminemia, elevated bilirubin levels, and prolonged PT are signs of inadequate liver function (liver failure) and indicate a poor prognosis in cirrhotic patients.

Serum markers of liver pathology

ENZYMES RELEASED IN LIVER DAMAGE	
Aspartate aminotransferase and alanine aminotransferase	↑ in most liver disease: ALT > AST ↑ in alcoholic liver disease: AST > ALT (AST usually will not exceed 500 U/L in alcoholic hepatitis) AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis ↑↑↑ aminotransferases (>1000 U/L): differential includes drug-induced liver injury (eg, acetaminophen toxicity), ischemic hepatitis, acute viral hepatitis
Alkaline phosphatase	↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease
γ-glutamyl transpeptidase	↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use
FUNCTIONAL LIVER MARKERS	
Bilirubin	↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis
Albumin	↓ in advanced liver disease (marker of liver's biosynthetic function)
Prothrombin time	↑ in advanced liver disease (↓ production of clotting factors, thereby measuring the liver's biosynthetic function)
Platelets	↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)

Hepatic encephalopathy

- Hepatic encephalopathy refers to a reversible decline in neurologic function that occurs due to failure of the liver to metabolize waste products such as ammonia.

- Ammonia is normally produced by the GI tract as a result of enterocytic catabolism of glutamine and colonic bacterial catabolism of dietary protein.

- Triggers:

- ↑ NH_3 production and absorption (due to GI bleed, constipation, infection).
- ↓ NH_3 removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).

- GI bleeding causes increased nitrogen delivery to the gut in the form of hemoglobin, which is then converted into ammonia and absorbed into the bloodstream. The ammonia then enters the liver through the portal vein and is detoxified to urea.

- In chronic liver failure, hepatocyte dysfunction and the shunting of blood through portosystemic collaterals impair the liver's detoxification ability.

- This leads to accumulation of ammonia and other neurotoxins in the circulation, causing altered amino acid transport across the blood-brain barrier, impaired neurotransmitter metabolism, and depressed cerebral glucose metabolism.

- These and other factors result in increased inhibitory neurotransmission (γ-aminobutyric acid [GABA]) and impaired excitatory neurotransmitter release (glutamate, catecholamines).

- In patients with hepatic encephalopathy, lowering of blood ammonia levels is typically accomplished with oral administration of a disaccharide (lactulose) and rifaxamine or neomycin (nonabsorbable antibiotic) which cause destruction of gut bacteria → less conversion of dietary protein to ammonia.

- Bacterial action on lactulose results in acidification of colonic contents, which then converts absorbable ammonia into nonabsorbable ammonium ions, trapping the ammonia in the stool and increasing fecal nitrogen excretion.

Hepatic encephalopathy	
Precipitating factors	• Drugs (eg, sedatives, narcotics) • Hypovolemia (eg, diarrhea) • Electrolyte changes (eg, hypokalemia) • ↑ Nitrogen load (eg, GI bleeding) • Infection (eg, pneumonia, UTI, SBP) • Portosystemic shunting (eg, TIPS)
Clinical presentation	• Sleep pattern changes • Altered mental status • Ataxia • Asterixis
Treatment	• Correct precipitating causes (eg, fluids, antibiotics) • ↓ Blood ammonia concentration (eg, lactulose, rifaximin)

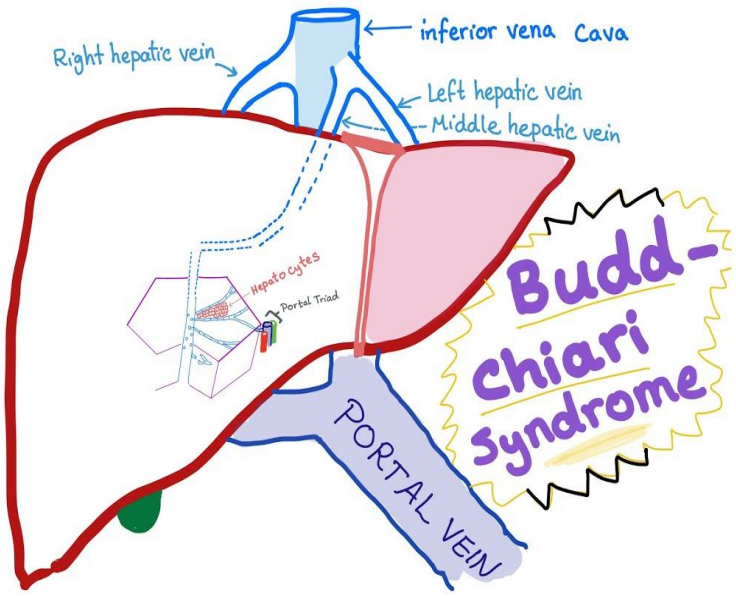
GI = gastrointestinal; **SBP** = spontaneous bacterial peritonitis; **TIPS** = transjugular intrahepatic portosystemic shunt; **UTI** = urinary tract infection.

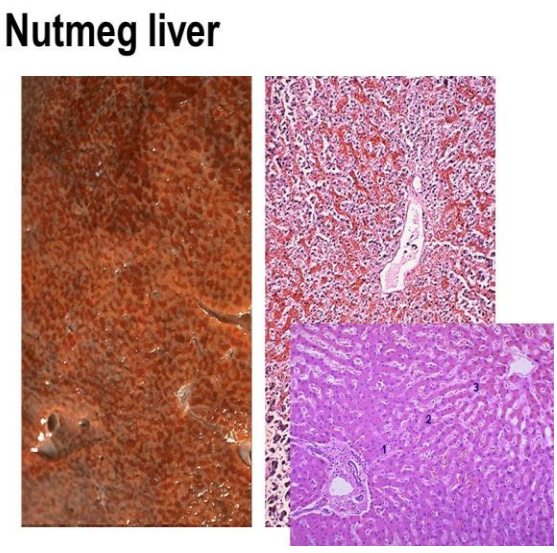
Spontaneous bacterial peritonitis

- Acute bacterial infection of the ascitic fluid without obvious focal source. Also known as 1° bacterial peritonitis.
- Common and potentially fatal bacterial infection in patients with cirrhosis and ascites (up to 20% of patients with ascites).
- Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy.
- Commonly caused by aerobic gram ⊖ organisms (E coli, Klebsiella) or less commonly gram ⊕ Streptococcus.
- Diagnosis: Paracentesis with ascitic fluid absolute neutrophil count (ANC) > 250 cells/mm^3.
- Empiric first-line treatment is 3rd generation cephalosporin (cefotaxime).

Budd-Chiari syndrome

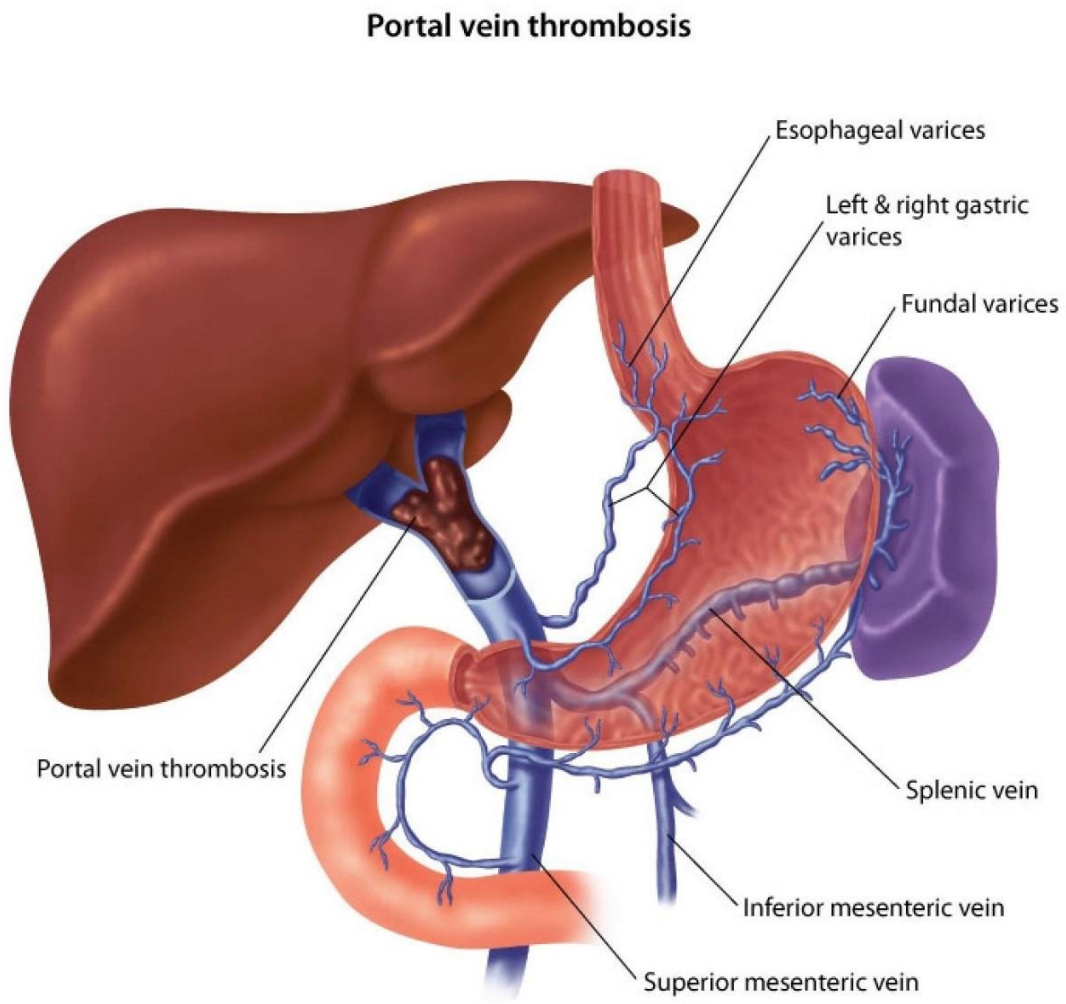
- Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure).
- Absence of JVD.
- Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC.
- May cause nutmeg liver (mottled appearance of the liver as a result of hepatic venous congestion).





Portal vein thrombosis

- Portal vein thrombosis causes portal hypertension, splenomegaly, and varicosities at portocaval anastomoses.
- Portal vein thrombosis causes obstruction in portal venous flow upstream from the liver, causing portal hypertension while leaving the liver unaffected.
- Ascites is uncommon with portal vein thrombosis since sinusoidal hypertension does not develop.
- Varices form in portal hypertension due to increased hydrostatic pressure in the portal system that causes blood to be shunted through portocaval anastomoses.



Reye syndrome

- Rare, often fatal childhood hepatic encephalopathy.
- Associated with viral infection (especially VZV and influenza) that has been treated with aspirin.
- Aspirin metabolites ↓ β-oxidation by reversible inhibition of mitochondrial enzymes.
- The pathogenesis of this condition is still unclear, but it is hypothesized that affected children have some inborn metabolic error that renders them sensitive to the toxic effects of salicylates.
- It is especially pronounced in viral-infected cells and causes mitochondrial dysfunction. The two components of Reye's syndrome include:

1. Hepatic dysfunction manifests with vomiting and hepatomegaly, hypoglycemia, but jaundice is rare:

- Liver function tests reveal increased levels of ALT, AST, ammonia, and bilirubin, and a prolonged PT and PTT.
- Light microscopy of a liver biopsy shows microvesicular steatosis, the presence of small fat vacuoles in the cytoplasm of hepatocytes.
- No necrosis or inflammation is present in the liver. Electron microscopy findings include swelling, a decreased number of mitochondria and glycogen depletion.

2. Encephalopathy of Reye syndrome is attributed to hepatic dysfunction and the toxic effect of hyperammonemia on the CNS leading to cerebral edema.

- To avoid the possibility of inducing Reye syndrome, aspirin should not be administered to children under the age of sixteen except for very specific circumstances where it is indicated for the treatment of a serious illness such as in Kawasaki disease where salicylates are a mainstay of treatment.
- Salicylates aren't a ray (Reye) of sunSHINE for kids:

- Steatosis of liver/hepatocytes.
- Hypoglycemia/Hepatomegaly.
- Infection (VZV, influenza).
- Not awake (coma).
- Encephalopathy.

Alcohol-related liver disease

A. Hepatic steatosis:

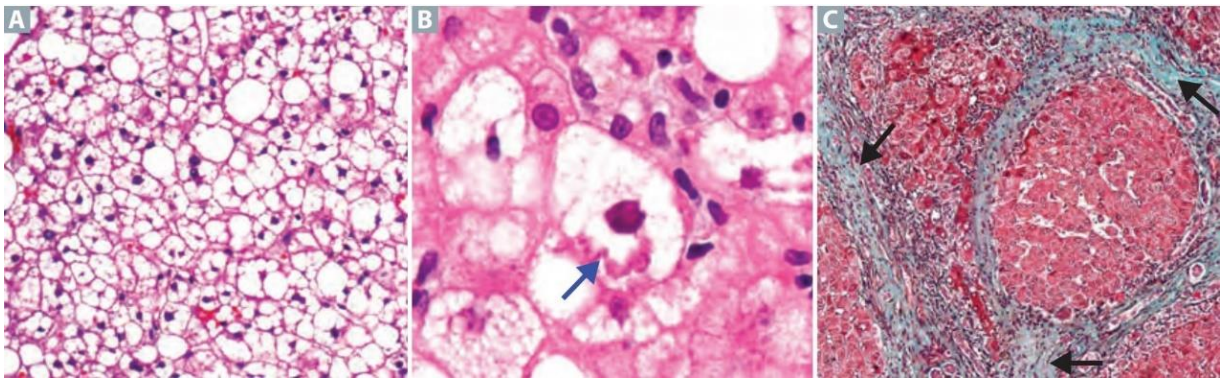
- Macrovesicular fatty change (A) that may be reversible with alcohol cessation.
- The pathogenesis of alcohol-induced hepatic steatosis appears related primarily to a decrease in free fatty acid oxidation secondary to excess NADH production by the 2 major alcohol metabolism enzymes, alcohol dehydrogenase and aldehyde dehydrogenase.

B. Alcoholic hepatitis:

- Requires sustained, long-term consumption.
- Swollen and necrotic hepatocytes with neutrophilic infiltration.
- Mallory bodies (B) (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).
- Make a toAST with alcohol: AST > ALT (ratio usually > 2:1).

C. Alcoholic cirrhosis:

- Final and usually irreversible form.
- Sclerosis around central vein (arrows in C) may be seen in early disease.
- Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease.



Nonalcoholic fatty liver disease

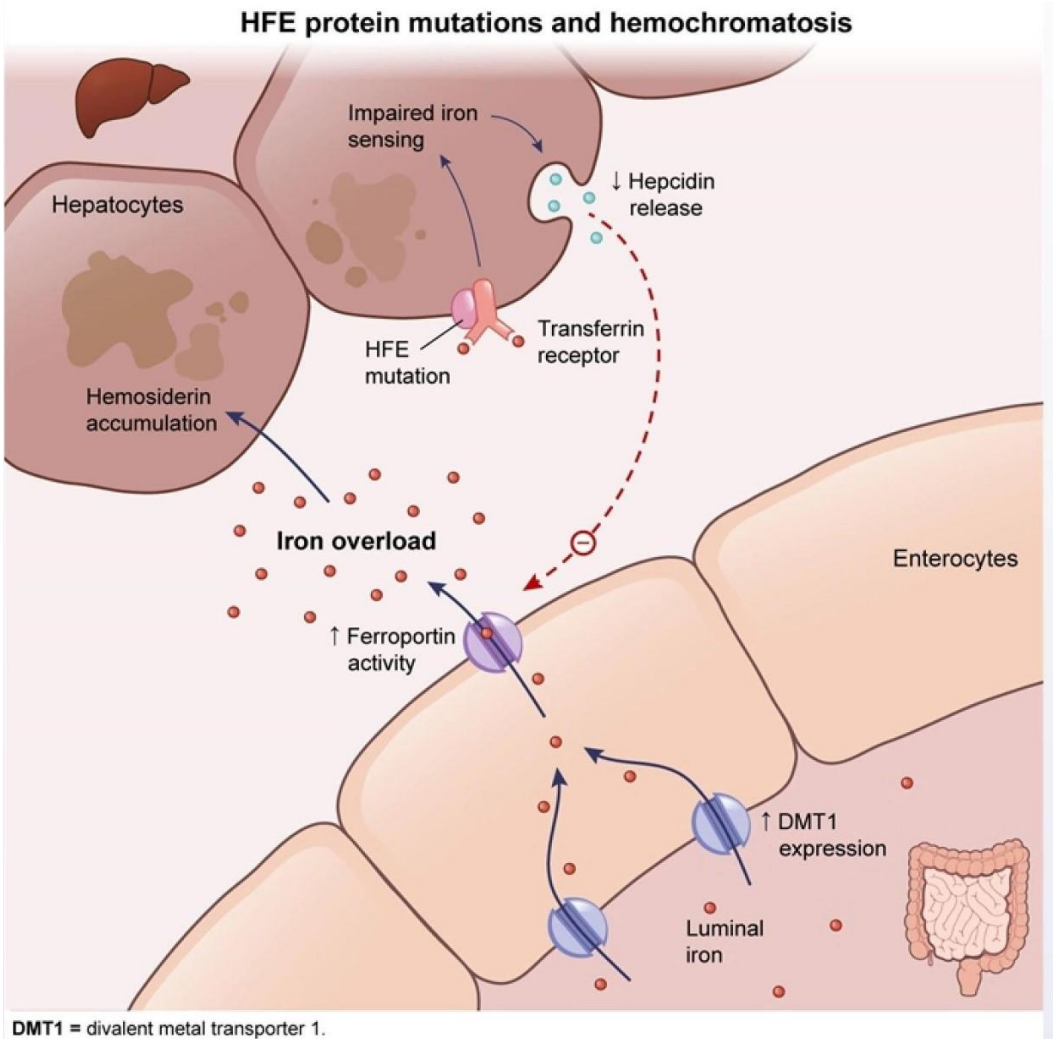
- Fatty change, hepatitis, and/or cirrhosis that develop without exposure to alcohol (or other known insult).
- Metabolic syndrome (insulin resistance); obesity → fatty infiltration of hepatocytes → cellular "ballooning" and eventual necrosis.

Hemochromatosis

- Excess body iron leading to deposition in tissues (hemosiderosis) and organ damage (hemochromatosis).
- Total iron stores within the body are normally closely regulated, with gastrointestinal absorption of iron adjusted to match the daily losses of iron.
- Due to autosomal recessive defect in iron absorption (primary) characterized by abnormally high iron gastrointestinal absorption that causes an iron overload, primarily in parenchymal organs such as the heart, pancreas, skin, pituitary, joints and liver or chronic transfusions (secondary).
- Primary hemochromatosis (hereditary hemochromatosis) is due to mutations in the HFE gene, usually C282Y (cysteine is replaced by tyrosine at amino acid 282). Presents in late adulthood.
- Mutations that inactivate the HFE protein cause enterocytes and hepatocytes to detect falsely low iron levels. This increases iron accumulation in the body through the following 2 mechanisms:

1. Enterocytes respond by increasing apical expression of divalent metal transporter 1 (DMT1), increasing iron absorption from the intestinal lumen.
2. Hepatocytes respond by decreasing hepcidin synthesis; low hepcidin levels result in increased ferroportin expression on the basolateral surface of enterocytes.

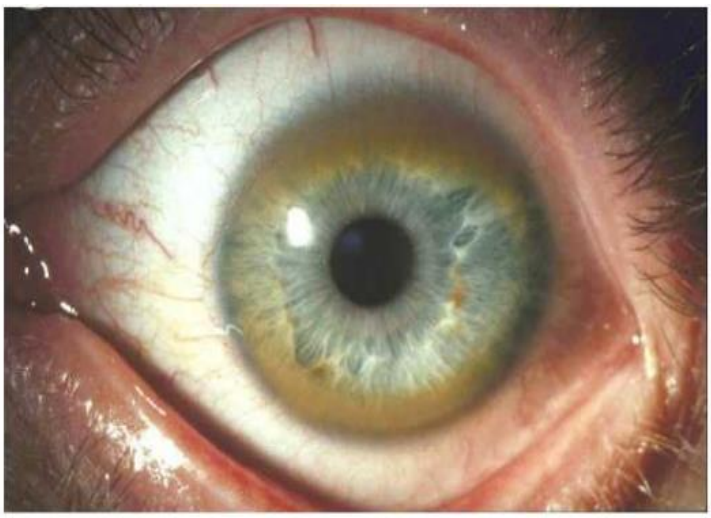
- This allows increased iron secretion into the circulation, leading to iron overload.
- Tissue damage is mediated by generation of free radicals.
- Presents after age 40 when body iron levels exceed 20g, patients typically develop the classic triad of micronodular cirrhosis, diabetes mellitus, and skin pigmentation ("bronze diabetes").
- These patients are at an increased risk for hepatocellular carcinoma, congestive heart failure, and testicular atrophy/hypogonadism.
- Women tend to present significantly later secondary to the protective effects of blood (iron) loss during menstruation and pregnancy. Physiologic iron loss through menstruation and pregnancy slows the progression of hemochromatosis in women.
- Labs show ↑ ferritin, ↓ TIBC, ↑ serum iron, and ↑ % saturation.
- Liver biopsy reveals accumulation of brown pigment in hepatocytes; Prussian blue stain distinguishes iron (blue) from lipofuscin. Lipofuscin is a brown pigment that is a by-product from the turnover ('wear and tear') of peroxidized lipids; it is commonly present in hepatocytes.
- Increased risk of hepatocellular carcinoma.
- Treatment: repeated phlebotomy, iron (Fe) chelation with deferasirox, deferoxamine, deferiprone.



Clinical manifestations of hereditary hemochromatosis	
Skin	Hyperpigmentation (bronze diabetes)
Musculoskeletal	Arthralgia, arthropathy & chondrocalcinosis
Gastrointestinal	Elevated hepatic enzymes with hepatomegaly (early), cirrhosis (later) & increased risk of hepatocellular carcinoma
Endocrine	Diabetes mellitus, secondary hypogonadism & hypothyroidism
Cardiac	Restrictive or dilated cardiomyopathy & conduction abnormalities
Infections	Increased susceptibility to *Listeria*, *Vibrio vulnificus* & *Yersinia enterocolitica*

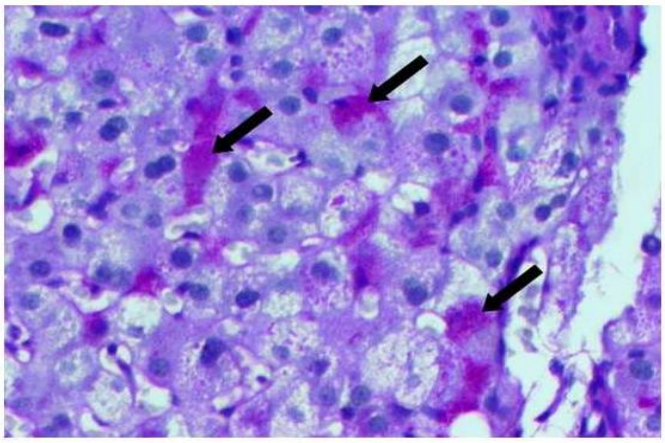
Wilson disease

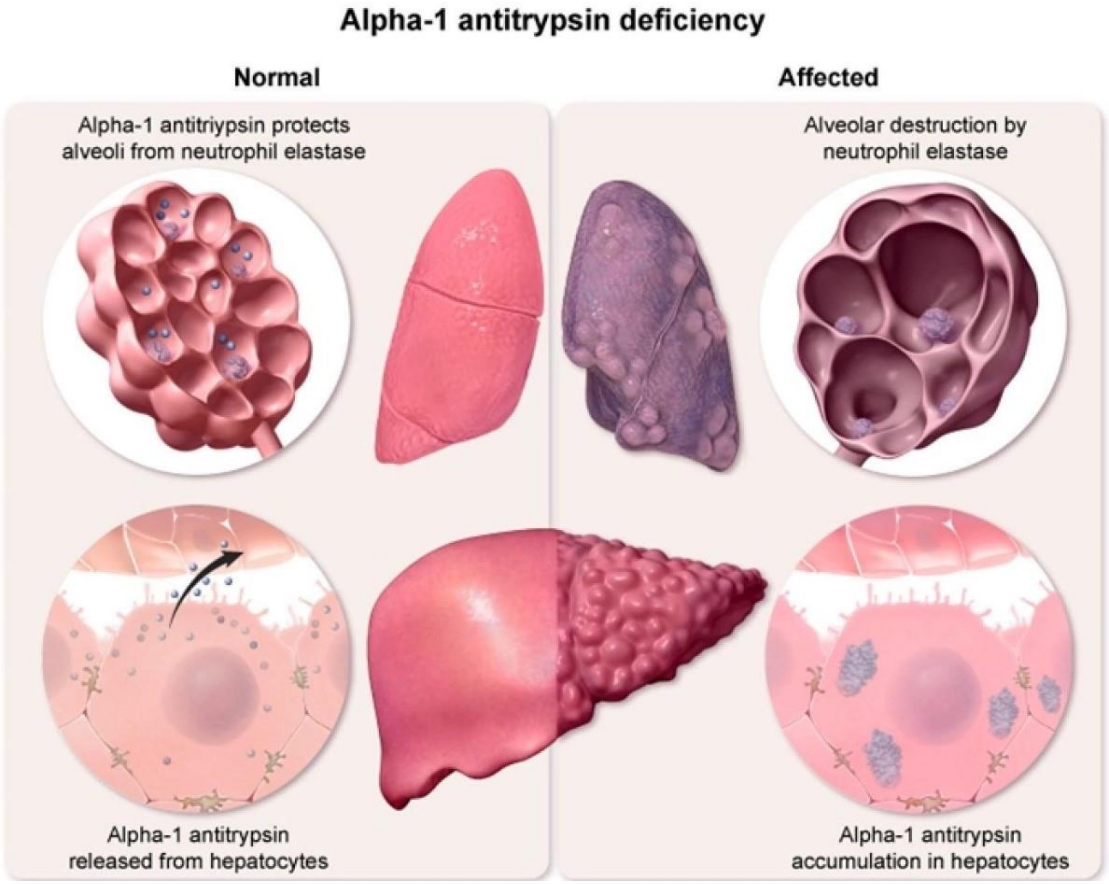
- Also known as hepatolenticular degeneration. Wilson disease is a rare, autosomal recessive disease most often identified in younger individuals aged 5 to 40 years.
- The mutation of gene ATP7B (ATP-mediated hepatocyte copper transport) on chromosome 13 is associated with Wilson disease and hinders copper metabolism by reducing the formation and secretion of ceruloplasmin and by decreasing the secretion of copper into the biliary system.
- Copper is a pro-oxidant and causes damage to the hepatic tissue through the generation of free radicals.
- Presents before age 40 with liver disease (hepatitis, acute liver failure, cirrhosis)
- Eventually, copper leaks from injured hepatocytes into the blood to be deposited in various tissues, including the cornea and basal ganglia. Atrophy of the basal ganglia then ensues.
- Advanced Wilson disease is often characterized by neuropsychiatric symptoms (behavioral changes, dementia, chorea, and Parkinsonian symptoms due to deposition of copper in basal ganglia). Almost all patients with neuropsychiatric involvement will also have Kayser-Fleischer rings, which can be identified on slit lamp examination. The rings are formed through the granular deposition of copper within Descemet's membrane in the cornea.
- Labs show ↑ urinary copper, ↓ serum ceruloplasmin, and ↑ copper on liver biopsy.
- Increased risk of hepatocellular carcinoma.
- Treatment is life-long and focuses on removing accumulated copper in the tissues and preventing its re-accumulation. First-line medications include copper chelators such as D-penicillamine and trientine.



Alpha-1 antitrypsin (A1AT) deficiency

- Alpha-1 antitrypsin (A1AT) deficiency is an autosomal co-dominant disorder that can affect the lungs and liver.
- Produced primarily in the liver, A1AT is a serum protein that inhibits several different proteolytic enzymes (including neutrophil elastase), thereby reducing tissue damage caused during inflammation.
- Approximately 75%-85% of individuals with A1AT deficiency eventually develop severe panacinar emphysema (without a history of smoking) due to the destruction of alveolar walls (which contain large amounts of elastin).
- Smoking plays a synergistic role in the disease process by permanently inactivating A1AT. Thus, smokers with A1AT deficiency tend to develop dyspnea at a median age of 36 years versus a median age of 51 years in nonsmokers.
- Because pulmonary dysfunction takes decades to develop, liver involvement is of greater concern during the first 2 decades of life. Liver disease develops in approximately 10%-15% of affected individuals due to intra-hepatocyte accumulation of polymerized A1AT molecules.
- Those affected typically demonstrate hepatomegaly or hepatosplenomegaly, cholestasis, and elevation of the hepatocellular enzymes. Neonatal hepatitis with cholestatic jaundice is common. Attacks of hepatitis in childhood and adolescence may appear to completely resolve or may become chronic and silently progressive.
- The most serious consequences of liver involvement include cirrhosis (the second most common cause of death in this population) and hepatocellular carcinoma.
- Histologically, intracellular granules representing globules of unsecreted A1AT are seen within the periportal hepatocytes of afflicted individuals. These globules stain reddish-pink with the periodic acid-Schiff reaction (arrows) and resist digestion by diastase.
- The diagnosis of A1AT deficiency is established by measurement of the serum A1AT level, followed by confirmatory genetic testing.





Hepatocellular carcinoma

- Most common 1° malignant tumor of liver in adults.

- Risk factors include:

- Chronic hepatitis (HBV and HCV). Hepatocellular carcinoma is strongly associated with HBV infection. Integration of viral DNA into the genome of host hepatocytes triggers neoplastic changes. Universal vaccination of children against HBV would likely cause a steep decline in the worldwide incidence of hepatocellular carcinoma.

- Cirrhosis (alcohol, nonalcoholic fatty liver disease, hemochromatosis, Wilson disease, and A1AT deficiency).

- Anatoxins derived from Aspergillus:
  - High levels of dietary aflatoxin intake have been strongly associated with hepatocellular carcinoma.
  - In certain areas within Asia and Africa where aflatoxin exposure is high, p53 mutations have been identified in most individuals who developed hepatocellular carcinoma.

- Increased risk for Budd-Chiari syndrome.

- Liver infarction secondary to hepatic vein obstruction.

- Presents with painful hepatomegaly and ascites.

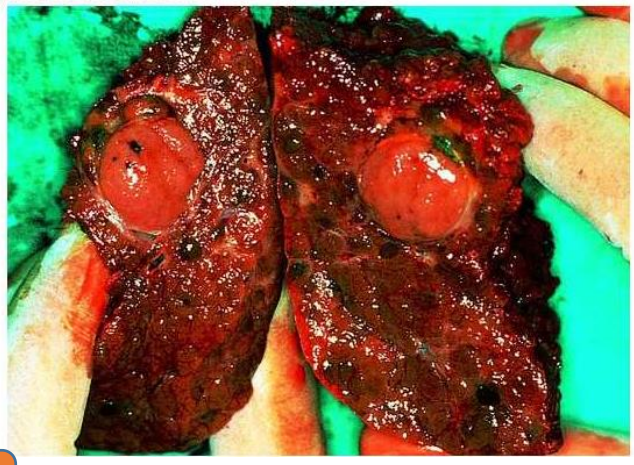
- Diagnosis of hepatocellular carcinoma can be challenging, as the clinical manifestations of HCC overlap with those of cirrhosis or chronic hepatitis; most patients complain of upper abdominal pain, malaise, fatigue, weight loss, and sometimes a sensation of abdominal fullness.

- Individuals with stable, compensated cirrhosis who suddenly decompensate without apparent reason should be carefully evaluated for hepatocellular carcinoma, especially when serum AFP levels are also elevated.

- Serum tumor marker is alpha-fetoprotein. A liver mass associated with an increased alpha-fetoprotein level is a typical presentation of hepatocellular carcinoma.

- This serum marker is not without clinical limitations, as serum AFP levels do not correlate well with the size, stage, or prognosis of HCC. Moreover, an elevated serum AFP is associated with numerous other conditions, including pregnancy, tumors of gonadal origin, and chronic liver disease (viral hepatitis).

- Despite these limitations, AFP is a useful marker in the evaluation of cirrhotic patients who are at increased risk for developing HCC.



Other liver tumors

A. Metastasis to liver:

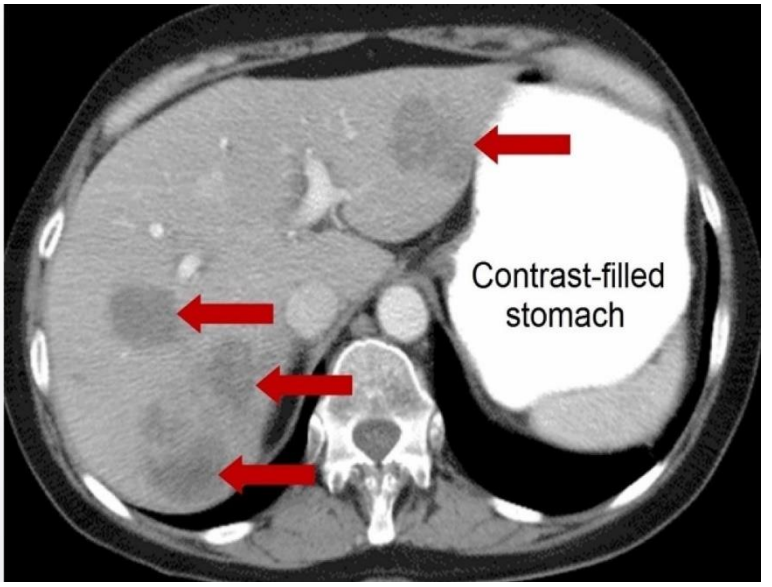
- Metastases are the most common malignant neoplasms of the adult liver and are 20 times more common than hepatocellular carcinoma; most common sources include colon, pancreas, lung, and breast carcinomas.

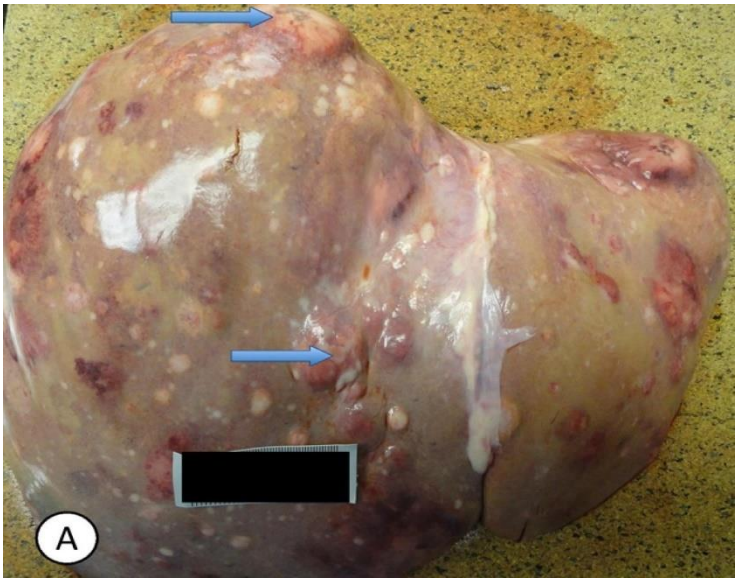
- The liver is the second most common site of metastatic spread (after the lymph nodes) because of its large size, dual blood supply, high perfusion rate, and the filtration function of Kupffer cells.

- Patients with liver metastases typically have multiple nodules throughout the liver that may replace more than 80% of the hepatic parenchyma, often resulting in marked hepatomegaly.

- The nodules frequently outgrow their vascular supply and become centrally necrotic and umbilicated.

- The below contrast-enhanced CT scan shows multiple hypodense masses in the liver (arrows) consistent with metastatic liver disease.



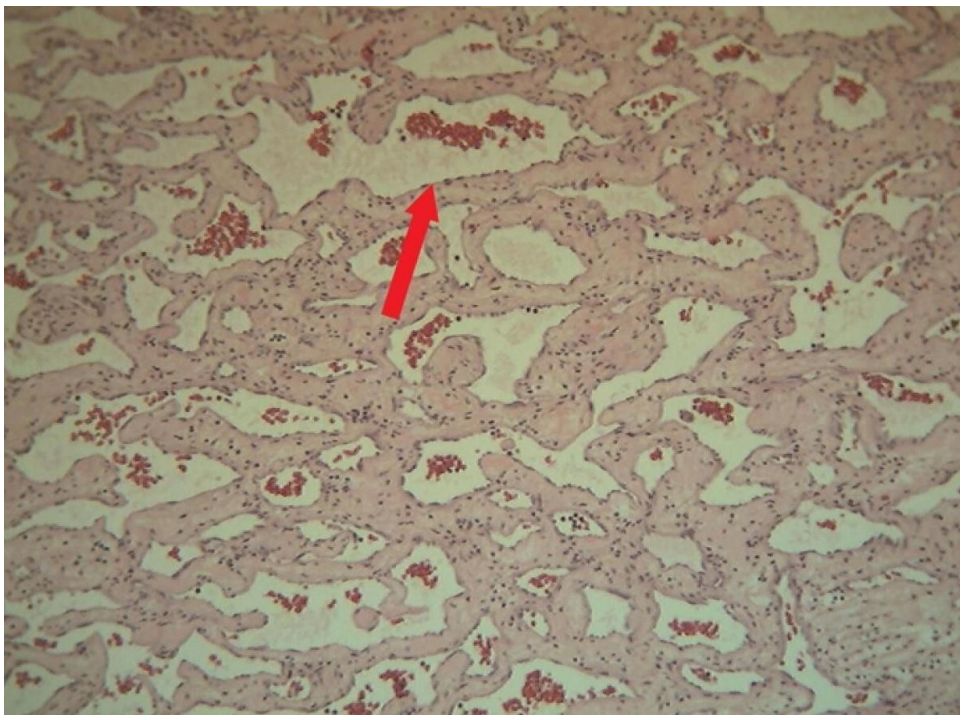


B. Hepatic adenoma:

- Benign tumor of hepatocytes.
- Tumors are subcapsular and grow with exposure to estrogen.
- Associated with oral contraceptive use; regresses upon cessation of drug.
- Risk of rupture and intraperitoneal bleeding, especially during pregnancy.

C. Cavernous hemangioma:

- Cavernous hemangioma is the most common benign liver tumor, typically presenting in adults 30-50 years of age.
- These benign tumors are thought to be congenital malformations that enlarge by ectasia, not hyperplasia or hypertrophy.
- Microscopically, these tumors consist of cavernous, blood-filled vascular spaces of variable size lined by a single epithelial layer (arrow).
- Most patients are asymptomatic, although some will complain of abdominal pain and right upper quadrant fullness.
- Prognosis is usually excellent, with surgical resection an option for those patients who are symptomatic or who have compression of adjacent structures.
- The biopsy of a suspected hemangioma is not advisable, as the procedure has been known to cause fatal hemorrhage and is of low diagnostic yield.

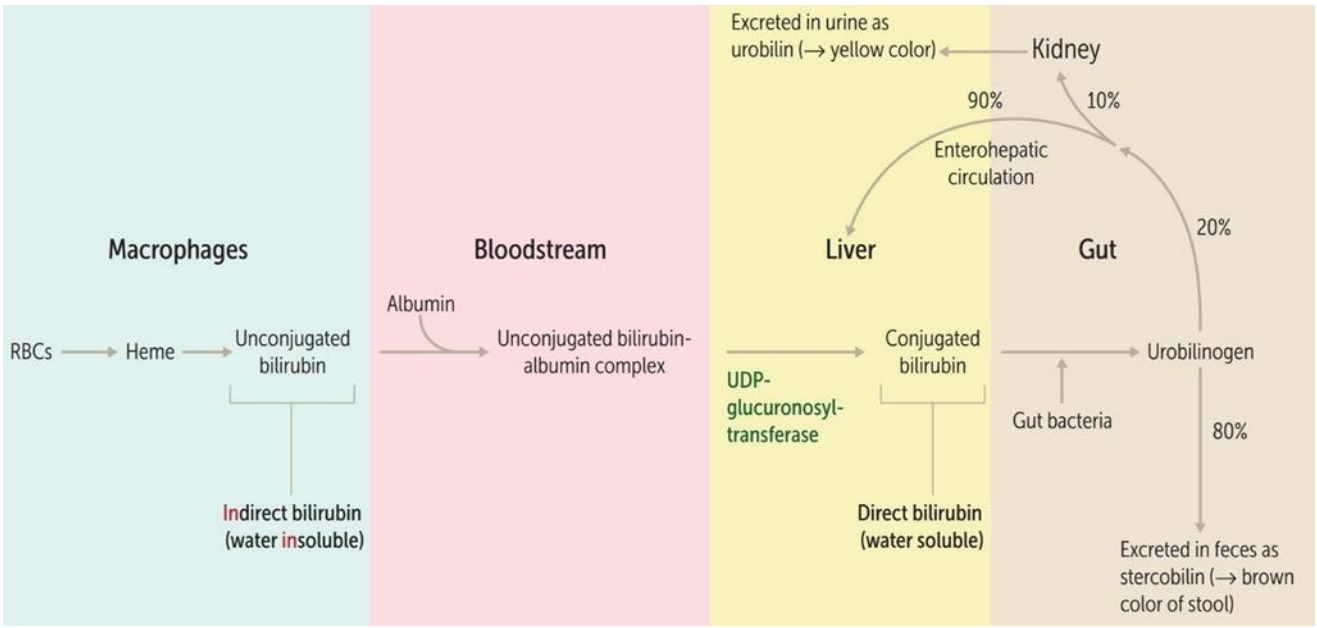


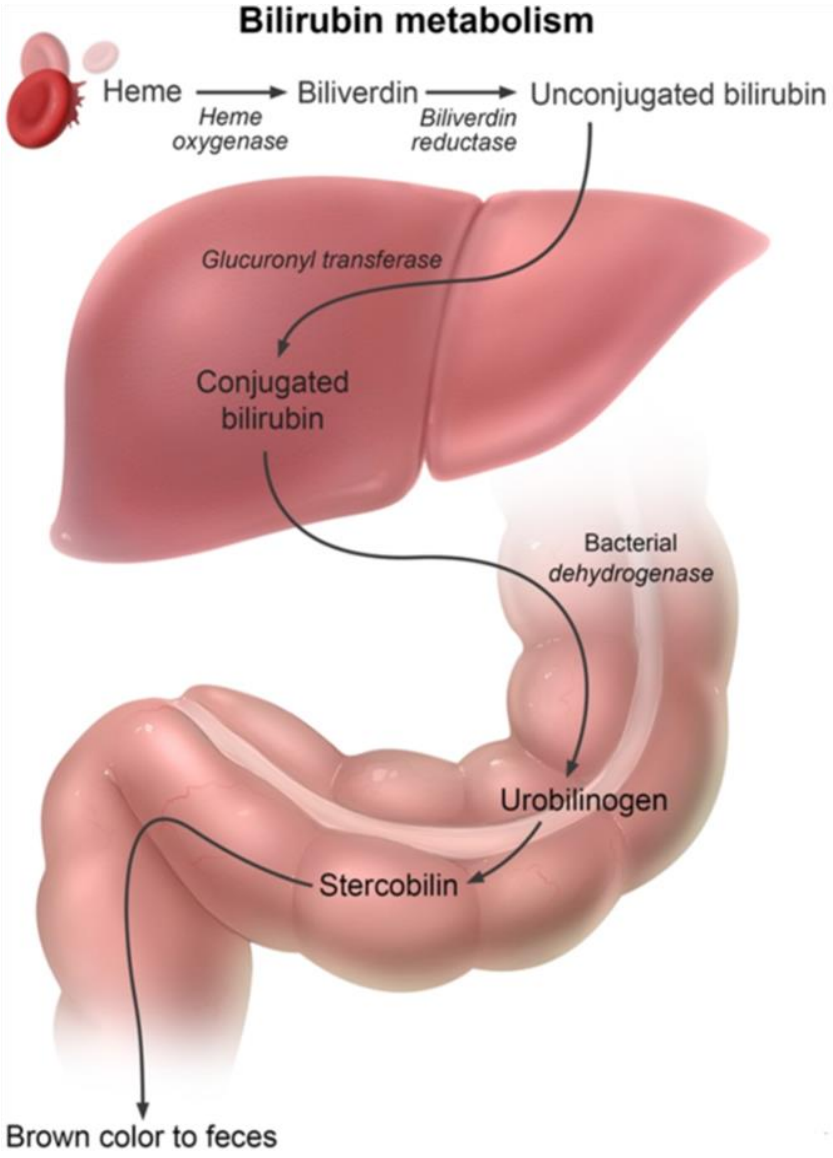
D. Angiosarcoma: Malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.

Jaundice

- Yellow discoloration of the skin; earliest sign is scleral icterus (yellow discoloration of the sclera).
- Due to ↑ serum bilirubin, usually > 2,5 mg/dL.
- Arises with disturbances in bilirubin metabolism.
- <u>Normal bilirubin metabolism:</u>

- RBCs are consumed by macrophages of the reticuloendothelial system.
- Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin.
- Albumin carries UCB to the liver.
- Uridine glucuronyl transferase (UGT) in hepatocytes conjugates bilirubin.
- Conjugated bilirubin (CB) is transferred to bile canaliculi to form bile, which is stored in the gallbladder.
- Bile is released into the small bowel to aid in digestion.
- Intestinal flora convert CB to urobilinogen, which makes the stool brown.
- Urobilinogen is also partially reabsorbed into the blood and filtered by the kidney, making the urine yellow.
- Direct bilirubin: conjugated with glucuronic acid; water soluble.
- Indirect bilirubin: unconjugated; water insoluble.





A. Conjugated (direct) hyperbilirubinemia:

- Biliary tract obstruction: Gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke.

- Biliary tract disease:
  - Primary sclerosing cholangitis.
  - Primary biliary cholangitis.

- Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

B. Unconjugated (indirect) hyperbilirubinemia: Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.

C. Mixed (direct and indirect) hyperbilirubinemia: Hepatitis, cirrhosis.

Hereditary hyperbilirubinemias

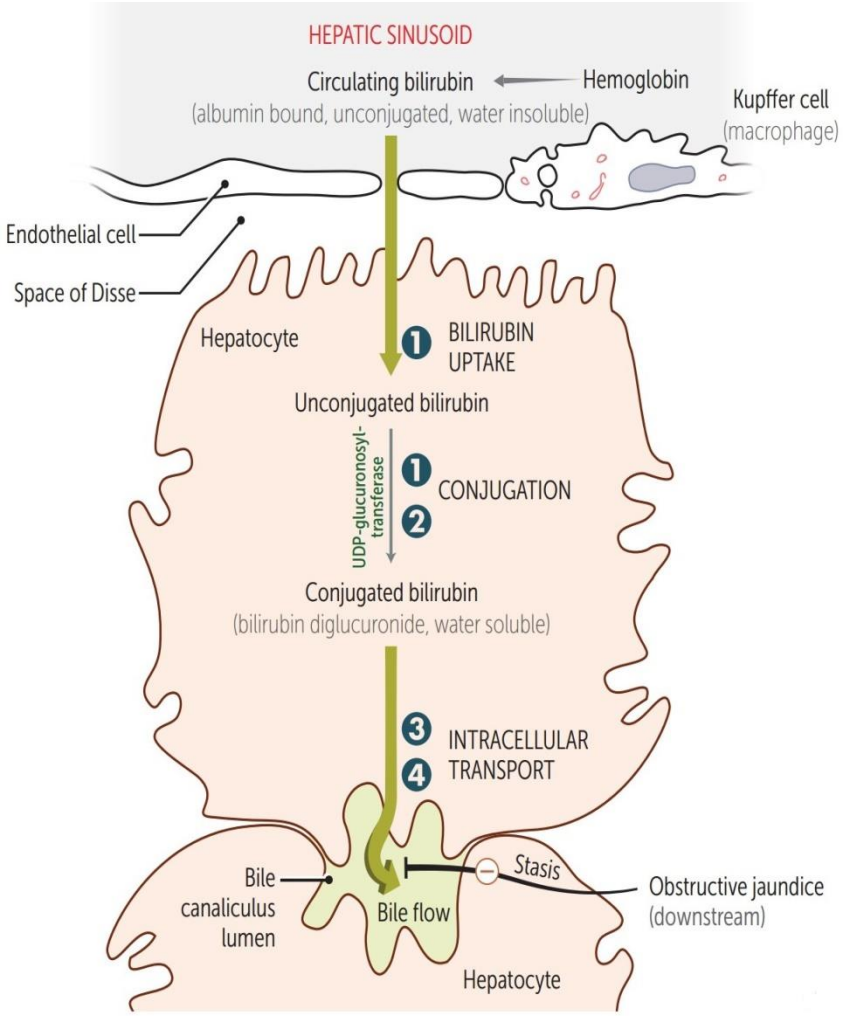
- <u>The hepatic processing of bilirubin is accomplished in three key steps:</u>

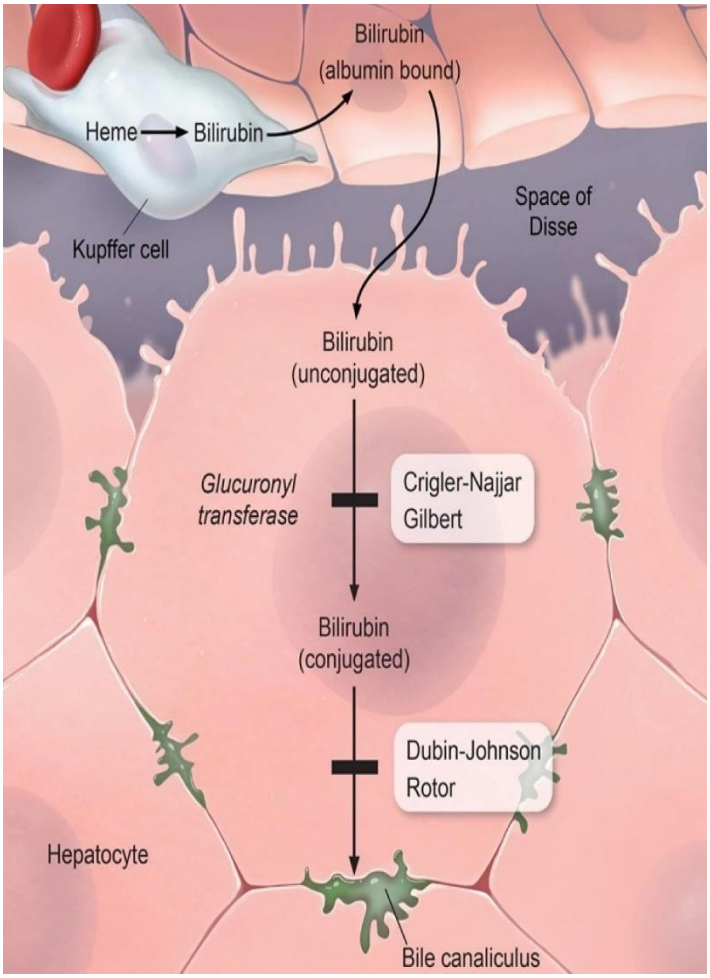
1. Carrier-mediated uptake of bilirubin at the sinusoidal membrane.

2. Conjugation of bilirubin with glucuronic acid by UGT (uridine diphosphate glucuronyl transferase) in the endoplasmic reticulum.

3. Biliary excretion of the water-soluble, nontoxic bilirubin glucuronides. Disruption of this process can be fatal, as seen with Crigler-Najjar syndrome.

- In the normal individual, serum total bilirubin is 0.2-1 mg/dL, of which < 0.2 mg/dL is the direct fraction.





1. Gilbert syndrome:

- Gilbert syndrome is a common familial disorder of bilirubin glucuronidation in which the production of UDP glucuronyl transferases (enzymes that mediate glucuronidation of various substances) is reduced and impaired bilirubin uptake.

- The diagnosis is suggested in those patients with no apparent liver disease and without overt hemolysis who have mild unconjugated hyperbilirubinemia thought to be provoked by one of the classic triggers.

- Examples of such triggers include fasting, physical exertion, febrile illness, stress, and fatigue.

- Relatively common, benign condition.

2. Crigler-Najjar syndrome:

- Crigler-Najjar syndrome type 1 is an autosomal recessive disorder of bilirubin metabolism caused by a genetic lack of the UGT enzyme needed to catalyze bile glucuronidation (Absent UDP-glucuronosyltransferase).

- When bilirubin is not correctly enzymatically processed by the liver, unconjugated hyperbilirubinemia develops.

- Indirect bilirubin levels typically approximate 20-25 mg/dl in these infants, but can rise to as high as 50 mg/dL.

- The unconjugated bilirubin is gradually deposited into various tissues, including the brain. These deposits can cause kernicterus (bilirubin encephalopathy), which is a potentially fatal condition characterized by severe jaundice and neurologic impairment.

- Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.

- Treatment:

- Plasmapheresis and phototherapy (does not conjugate UCB; but does ↑ polarity and ↑ water solubility to allow excretion).

- Liver transplant is curative.

3. Dubin-Johnson syndrome:

- Dubin-Johnson syndrome is characterized by a defect in the hepatic excretion of bilirubin glucuronides across the canalicular membrane.

- Individuals with this rare, benign condition have predominantly conjugated chronic hyperbilirubinemia.

- Grossly, the liver is strikingly black (Dark). Histological features are normal, though a dense pigment composed of epinephrine metabolites within the lysosomes can be seen.

4. Rotor syndrome:

- It is similar to dubin johnson syndrome, but milder in presentation without black (Regular) liver.
- Due to impaired hepatic uptake and excretion.

Physiologic neonatal jaundice

- At birth, immature UDP-glucuronosyltransferase → unconjugated hyperbilirubinemia → jaundice/kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).
- Occurs after first 24 hours of life and usually resolves without treatment in 1–2 weeks.
- Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.

❖ N.B:

- Heme oxygenase converts heme to biliverdin, a pigment that causes the greenish color to develop in bruises several days after an injury.

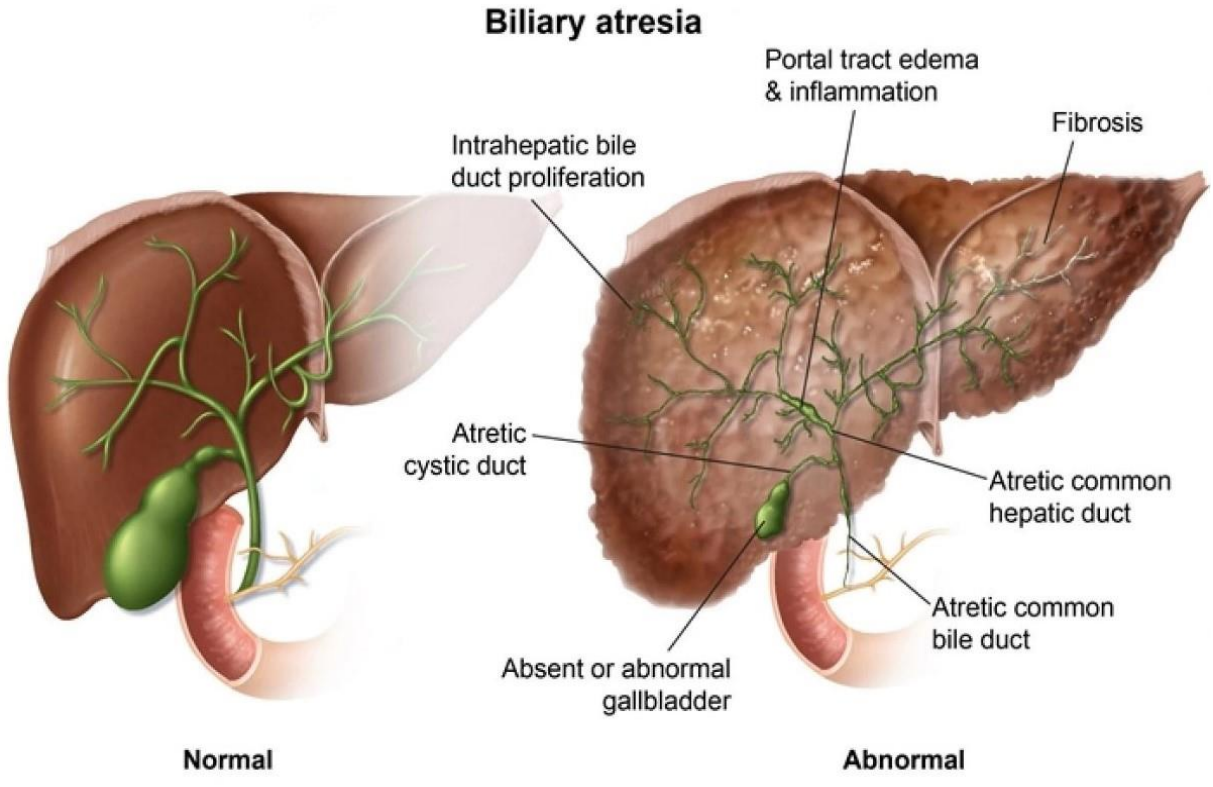
Gall bladder and biliary tract

Biliary atresia

- Biliary atresia is caused by progressive obliteration of the extrahepatic biliary ducts connecting the liver to the small bowel. It is the most common indication for pediatric liver transplantation.
- By the 3rd week of life, there is total obstruction.
- Affected children will have the characteristic cholestatic picture of acholic (light) stools and dark urine. On physical examination there is a firm, enlarged liver.
- Laboratory findings include increased levels of direct bilirubin, alkaline phosphatase, and gamma-glutamyl transferase.
- Liver biopsy is usually diagnostic, showing:

1. Marked intrahepatic bile ductule proliferation.
2. Portal tract edema and fibrosis.
3. Parenchymal cholestasis.

- If biliary drainage is not restored surgically, bile stasis will cause development of biliary cirrhosis by 6 months of life.
- Newborns with conjugated hyperbilirubinemia and hepatomegaly require immediate evaluation for biliary atresia.



Cholelithiasis (Gallstones)

- Solid, round stones in the gallbladder.
- Classically, cholelithiasis (gallstone disease) is most common in those who are "fat, fertile, female, and forty".
- The gallstones are formed by the aggregation of bile constituents and are categorized as cholesterol stones, pigment stones, or mixed stones.
- Due to precipitation of cholesterol (cholesterol stones) or bilirubin (bilirubin stones) in bile.
- Arises with:
  - Supersaturation of cholesterol or bilirubin.
  - Decreased phospholipids (lecithin) or bile acids (normally increase solubility).
  - Stasis.
- Cholesterol stones (yellow):
  - The most common type (90%), especially in the U.S.
  - Usually radiolucent (10% are radiopaque due to associated calcium).
  - Risk factors include age (40s), estrogen (female gender, obesity, multiple pregnancies and oral contraceptives), fibrate, Native American ethnicity, Crohn disease, and cirrhosis.
  - Estrogenic influence increases cholesterol synthesis by upregulating hepatic HMG-CoA reductase activity, which causes the bile to become supersaturated with cholesterol.
  - Progesterone reduces bile acid secretion and slows gallbladder emptying. When the gallbladder is hypomotile or there is more cholesterol than bile salts, the cholesterol precipitates into insoluble crystals that eventually form to make gallstones.
  - Estrogen-induced cholesterol hypersecretion and progesterone-induced gallbladder hypomotility are responsible for the increased incidence of cholelithiasis in women who are pregnant or using oral contraceptives.
  - Suppression of cholesterol 7α-hydroxylase activity (through fibrate medications such as bezafibrate, fenofibrate, and ciprofibrate) reduces the conversion of cholesterol into bile acids, resulting in an increased concentration of cholesterol within the bile.
  - When the gallbladder is hypomotile or there is more cholesterol than can dissolve into the bile salts, the cholesterol precipitates into insoluble crystals that eventually form to make gallstones.

- Bilirubin stones (pigmented):

- Composed of bilirubin.

- Usually radiopaque.

- Risk factors include extravascular hemolysis (increased bilirubin in bile) and biliary tract infection (E coli, Ascaris lumbricoides, and Clonorchis sinensis).

- Pigment stones are most common in rural Asian populations (accounting for only 10-25% of gallstones in the United States), with an increased incidence in women and the elderly.

- Brown pigment stones typically arise secondary to infection of the biliary tract, which results in the release of β-glucuronidase by injured hepatocytes and bacteria.

- The presence of this enzyme contributes to the hydrolysis of bilirubin glucuronides and increases the amount of unconjugated bilirubin in bile. Therefore, biliary infection with Escherichia coli, Ascaris lumbricoides, or clonorchis sinensis significantly elevates the risk of developing brown pigment stones.

- Black pigment stones form within the gallbladder when increased unconjugated bilirubin precipitates in bile as calcium bilirubinate.

- Elevated levels of circulating unconjugated bilirubin are primarily associated with chronic extravascular hemolysis (sickle cell anemia, B-thalassemia, hereditary spherocytosis).

- Diagnosis of cholelithiasis in all patients is best confirmed with ultrasound.

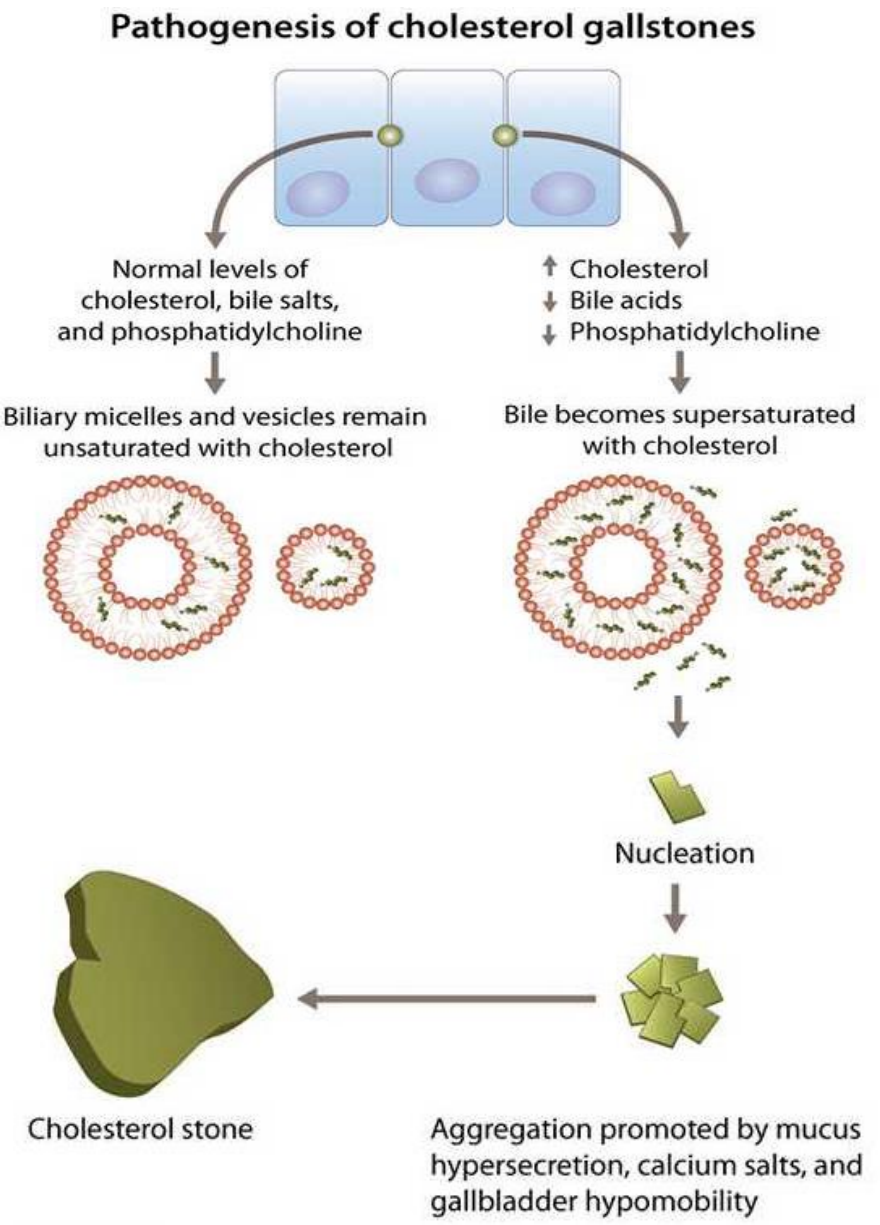
- Asymptomatic patients do not require intervention, but symptomatic cholelithiasis is usually treated with laparoscopic cholecystectomy.

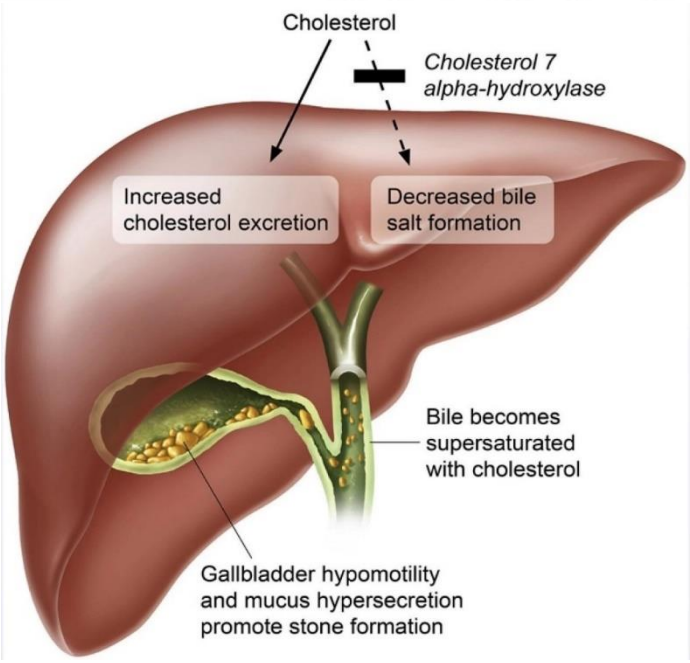
- Gallstones are usually asymptomatic; complications include biliary colic, acute and chronic cholecystitis, ascending cholangitis, gallstone ileus, and gallbladder cancer.

❖ N.B:

1. Removal of excess cholesterol from the body occurs by 2 mechanisms: Intact excretion of free cholesterol into the bile and conversion of cholesterol into bile acids.

- In the liver, free cholesterol is converted into cholic and chenodeoxycholic acids through a series of chemical reactions beginning with cholesterol 7α-hydroxylase (the rate-limiting step in bile acid synthesis).
- These bile acids are then conjugated to either glycine or taurine (improving solubility and emulsifying ability) to create the bile salts that are actively secreted into the bile canaliculi.
- As water-insoluble cholesterol is secreted in bile, it is rendered soluble in small amounts by the detergent action of these amphipathic (both hydrophobic and hydrophilic) bile salts and phosphatidylcholine (a phospholipid).
- When there is more cholesterol than can be made soluble, the cholesterol precipitates into crystals that eventually grow and merge to form gallstones. Gallbladder hypomotility further promotes cholesterol nucleation and gallstone formation.


Pathogenesis of cholesterol gallstones
Normal levels of cholesterol, bile salts, and phosphatidylcholine
↑ Cholesterol
↓ Bile acids
↓ Phosphatidylcholine
Biliary micelles and vesicles remain unsaturated with cholesterol
Bile becomes supersaturated with cholesterol
Nucleation
Cholesterol stone
Aggregation promoted by mucus hypersecretion, calcium salts, and gallbladder hypomobility


Cholesterol
Cholesterol 7 alpha-hydroxylase
Increased cholesterol excretion
Decreased bile salt formation
Bile becomes supersaturated with cholesterol
Gallbladder hypomotility and mucus hypersecretion promote stone formation

2. A prolonged course of total parenteral nutrition (TPN) is often complicated by the formation of gallstones, with one study suggesting the incidence is as high as 44 % in this patient population.

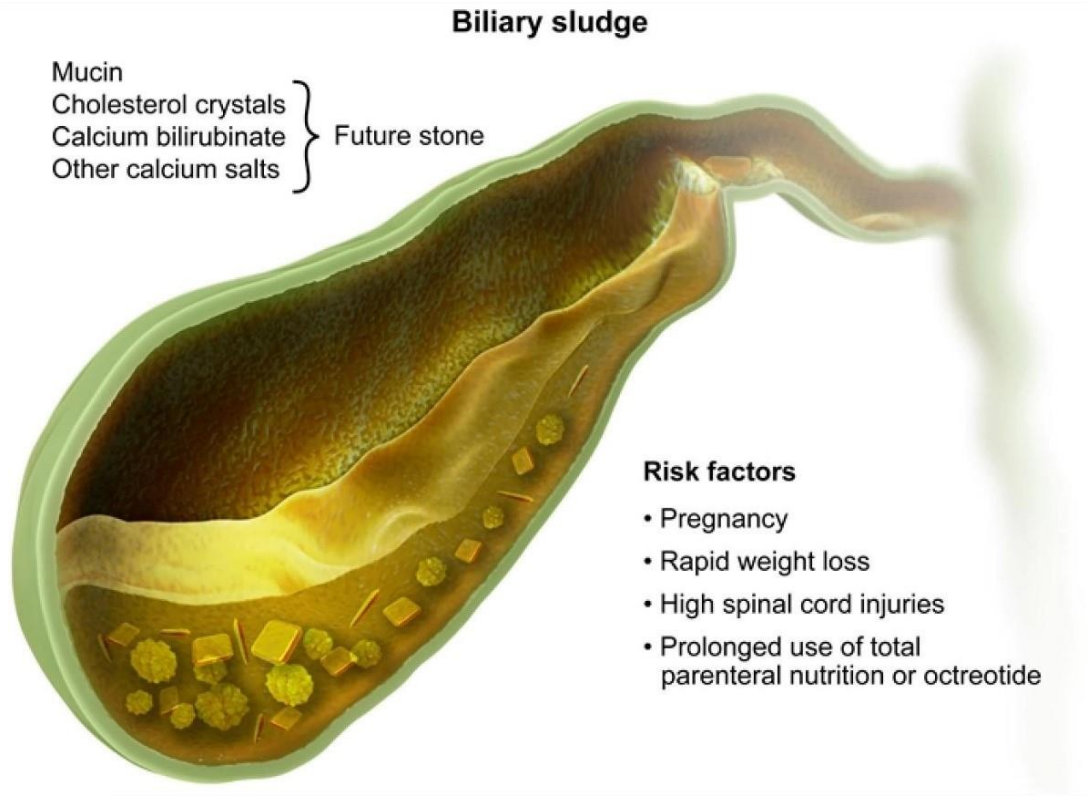
- The pathogenesis of TPN-induced gallstones is thought to include:

1. Biliary stasis from absent enteral stimulation secondary to decreased cholecystokinin release.
2. In those with ileal resection, disturbance of the enterohepatic bile acid circulation resulting in supersaturation of hepatic bile with cholesterol.

- Exogenous cholecystokinin administration will typically prevent gallstone formation in patients on TPN.

3. Gallbladder hypomotility (slow or incomplete gallbladder emptying in response to cholecystokinin stimulation) is a common occurrence in the Western world.

- Risk factors for this condition include pregnancy, rapid weight loss, prolonged use of total parenteral nutrition or octreotide, and high spinal cord injuries.
- One of the more frequent consequences of gallbladder hypomotility is the formation of biliary sludge, which results from bile precipitation.
- Biliary sludge typically contains cholesterol monohydrate crystals, calcium bilirubinate, and mucus and is a known precursor to stone formation.
- Complications such as acute cholecystitis occur in up to 20% of patients with biliary sludge.



4. Cholecystectomy is the preferred treatment for symptomatic gallstones.

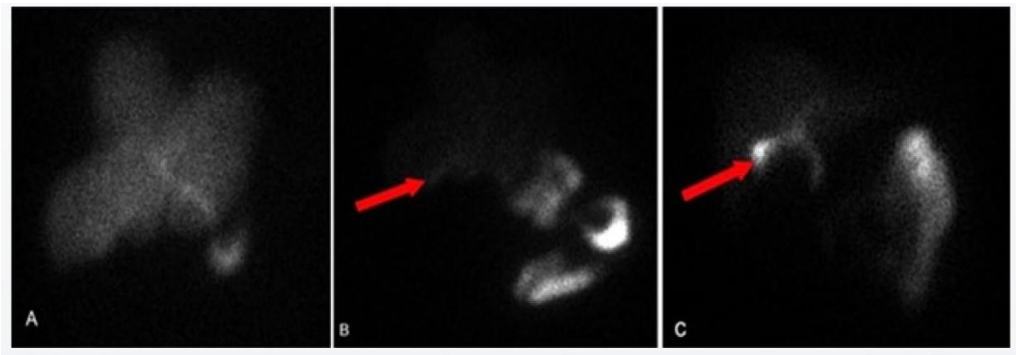
- Medical therapy to dissolve cholesterol gallstones is an option in patients refusing cholecystectomy or with high surgical risk. Hydrophilic bile acids (ursodeoxycholic acid) improve cholesterol solubility by reducing the amount of cholesterol secreted into the bile and increasing biliary bile acid concentration.

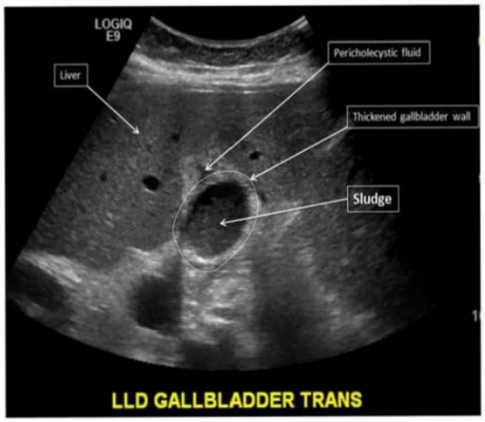
Biliary colic

- Biliary colic occurs when a stone temporarily occludes the cystic duct.
- Biliary colic occurs due to increased intra-gallbladder pressure that is created when the gallbladder contracts against an obstructed cystic duct.
- This causes colicky pain in the right upper quadrant radiating to the right shoulder and back, often triggered by ingestion of fatty food, accompanied by nausea and vomiting, but without signs of peritoneal irritation or systemic signs of inflammatory process.
- Fatty foods increase CCK production and pain occurs when an inflamed and/or obstructed gallbladder contract.
- The episode is self-limited (10, 20, maybe 30 minutes), or easily aborted by anticholinergics.

Acute calculous cholecystitis

- Acute calculous cholecystitis (ACC) is characterized by acute inflammation of the gallbladder, initiated 90% of the time by obstruction of the gallbladder neck or cystic duct.
- ACC typically results from chemical irritation and inflammation caused by the presence of stones in the gallbladder. The stones disrupt the protective mucus layer, leaving the epithelium exposed to the detergent action of the bile salts.
- Prostaglandins released in the gallbladder wall further incite inflammation of the mucosa and deeper tissues.
- The increasing distention and internal pressure within the gallbladder eventually result in ischemia. Finally, bacteria invade the injured and necrotic tissue, causing an infection.
- Typical features include acute right upper quadrant pain and tenderness, fever, vomiting, and leukocytosis.
- The pain may radiate to the right shoulder (due to irritation of phrenic nerve) or be accompanied by Murphy's sign, described as worsening of right upper quadrant pain with inspiration that sometimes causes the patient to suddenly hold their breath.
- Potential complications include gangrene and perforation, with generalized peritonitis or a well-circumscribed abscess being a more common outcome. Other potential complications include cholangitis and chronic cholecystitis.
- U/S is diagnostic in most cases (gallstones, thick-walled gallbladder, and pericholecystic fluid). In equivocal cases, a radionuclide scan (HIDA) might be needed, and would show tracer uptake in the liver, common duct, and duodenum, but not in the occluded gallbladder.





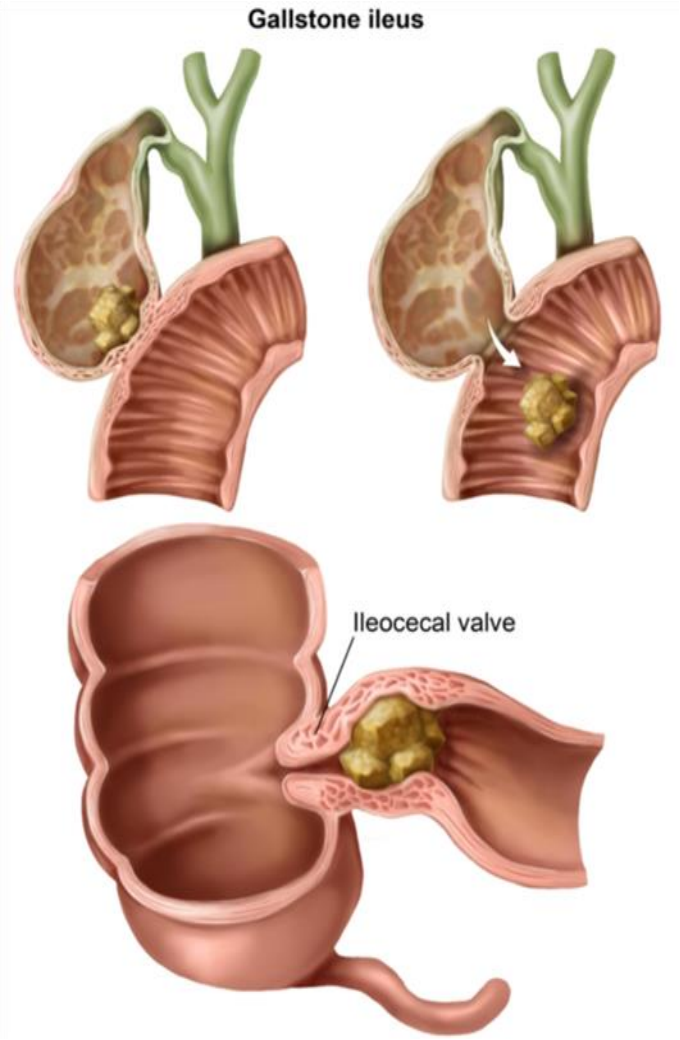
Acute acalculous cholecystitis

- Acute acalculous cholecystitis is an acute inflammation of the gallbladder in the absence of gallstones.
- It is most commonly seen in hospitalized and severely ill patients.
- Common predisposing conditions Include recent surgery (particularly cardiopulmonary, aortic, or abdominal), severe trauma, extensive bums, sepsis or shock, prolonged fasting or total parenteral nutrition, or critical illness requiring mechanical intubation.
- The condition is thought to arise secondary to gallbladder stasis and ischemia, which cause inflammation and injury to the gallbladder wall.
- Clinical manifestations may be subtle, especially in those who are sedated or intubated. Fever, severe right upper quadrant abdominal pain, a positive Murphy's sign, leukocytosis, and abnormal liver function tests are often present.
- Potential complications include gangrene and perforation. It is crucial to have a high index of suspicion for acalculous cholecystitis when managing those patients at increased risk, as an insidious presentation is linked to higher rates of gangrene and perforation.
- Mortality rates range widely from 10-90%, depending on patient condition and how quickly the diagnosis is established.
- Management of acalculous cholecystitis should include prompt administration of intravenous broad-spectrum antibiotics and a cholecystectomy with drainage of any abscess.

Gallstone ileus

- Gallstone ileus is an uncommon complication of longstanding cholelithiasis that usually occurs in elderly women.
- A large (typically >2.5 cm) gallstone causes formation of a cholecystoenteric fistula between the gallbladder and adjoining gut (most often the duodenum) due to pressure necrosis and erosion of these tissues.

- Fistula formation allows passage of the gallstone into the small bowel, where it travels freely until it becomes trapped in the ileum, the narrowest portion of the intestine.
- Patients consequently develop symptoms/signs of small bowel obstruction, including abdominal pain/distension, nausea/vomiting, high- pitched (tinkling) bowel sounds, and tenderness to palpation.
- Abdominal x-ray may reveal dilated loops of bowel with air-fluid levels due to intestinal obstruction.
- Communication between the intestine and gallbladder may also allow gas to enter the biliary tree (pneumobilia).



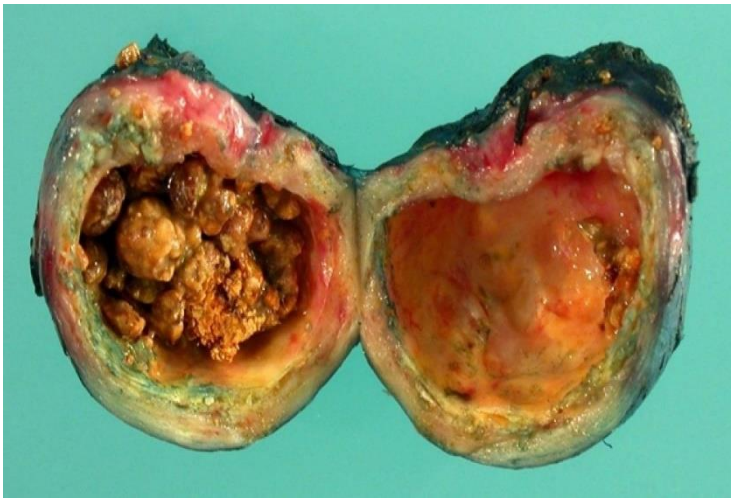
Porcelain gallbladder

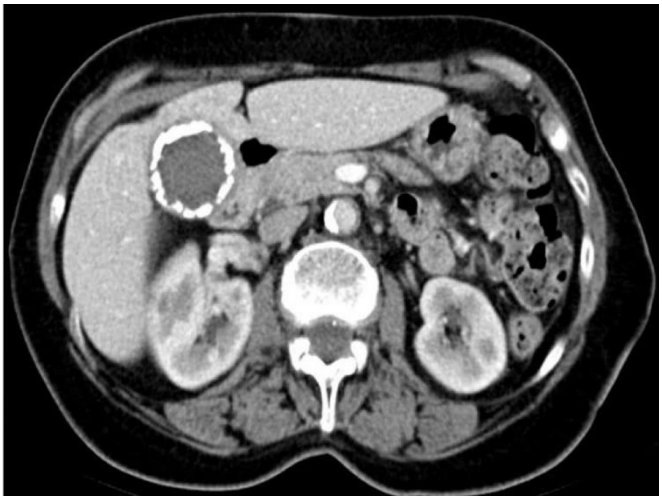
- Porcelain gallbladder is a term used to describe the calcium-laden gallbladder wall with bluish color and brittle consistency often associated with chronic cholecystitis.
- The pathogenesis of the condition remains unclear, but it is thought that calcium salts are deposited intramurally due to the natural progression of chronic inflammation or chronic irritation from gallstones.

- Patients can be asymptomatic, have right upper quadrant pain, or have a firm and nontender right upper quadrant mass on examination.

- Plain x-rays can show a rim-like calcification in the area of the gallbladder.

- Cholecystectomy is recommended for those with porcelain gallbladders because 11-33% of this patient population will eventually develop gallbladder carcinoma.





Ascending cholangitis

- Acute ascending cholangitis is a far more deadly disease, in which stones have reached the common bile duct (Choledocholithiasis) producing partial obstruction and ascending infection.

- Biliary stasis predisposes to AC and the most common causes are due to bile duct obstruction from gallstones, malignancy, or stenosis. In the setting of stasis, the bile-blood barrier can be disrupted, allowing bacteria and toxins from the hepatobiliary system to translocate into the blood stream.

- Fever, jaundice, and right upper quadrant abdominal pain (Charcot triad) are consistent with acute cholangitis. Confusion and hypotension (Reynolds pentad) are also sometimes seen in severe AC If not treated promptly. AC can lead to septic shock.

- Laboratory results usually show leukocytosis and neutrophilia in addition to elevations in alkaline phosphatase, gamma-glutamyl transpeptidase, and direct bilirubin.

❖ N.B:

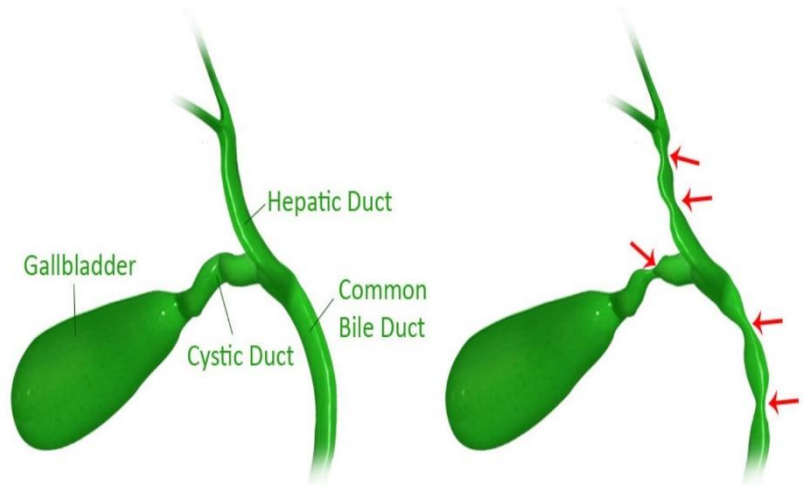
- Administration of mu opioid analgesics, such as morphine, can cause contraction of smooth muscle cells in the sphincter of Oddi, leading to spasm and an increase in common bile duct pressures.
- Although uncommon, pressures in the gallbladder can also increase, potentially leading to biliary colic. Patients who develop biliary colic will have severe pain and cramping in the right upper abdomen.
- Management involves discontinuation of mu opioid analgesics and pain control with alternative agents such as nonsteroidal anti-inflammatory drugs (ketorolac, diclofenac).

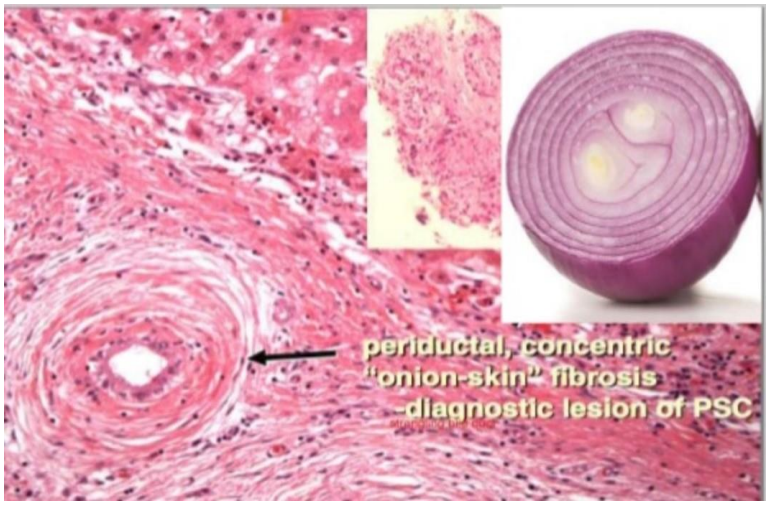
Biliary tract disease

- May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly.
- Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP).

Primary sclerosing cholangitis

- Pathology:
  - Unknown cause of concentric "onion skin" bile duct fibrosis → alternating strictures and dilation with "beading" of intra- and extrahepatic bile ducts on ERCP, magnetic resonance cholangiopancreatography (MRCP).
- Epidemiology:
  - Classically in middle-aged men with IBD.
- Additional features:
  - Associated with ulcerative colitis. p-ANCA ⊕. ↑ IgM.
  - Can lead to 2° biliary cholangitis.
  - ↑ risk of cholangiocarcinoma and gallbladder cancer.





Primary biliary cholangitis

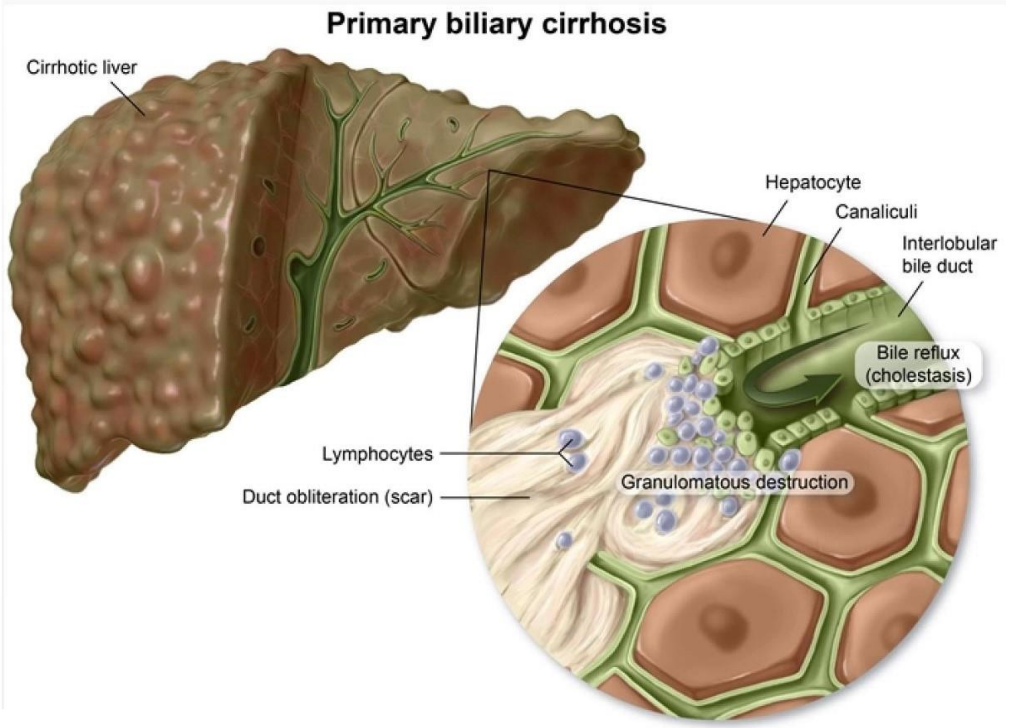
- Previously known as primary biliary cirrhosis.
- Pathology:
  - Autoimmune reaction → lymphocytic infiltrate + granulomas → destruction of the intrahepatic bile ducts and cholestasis.

- Epidemiology:
- Classically in middle-aged women.

- Additional features:
- Anti-mitochondrial antibody ⊕, ↑ IgM.

- Associated with other autoimmune conditions (Hashimoto thyroiditis, rheumatoid arthritis, celiac disease).

- Treatment:
- Ursodiol.



Secondary biliary cholangitis

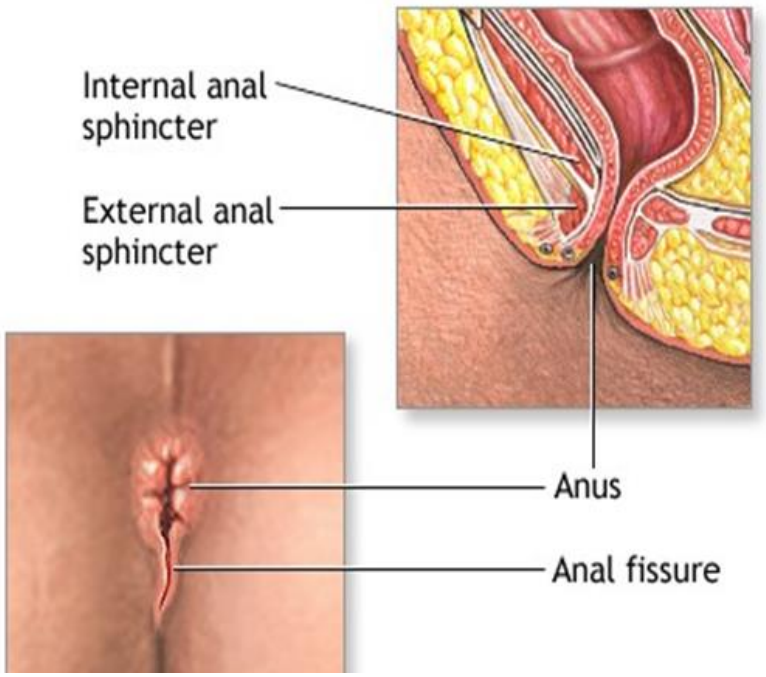
- Pathology:
- Extrahepatic biliary obstruction → ↑ pressure in intrahepatic ducts → injury/ fibrosis and bile stasis.

- Epidemiology:
- Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma).

- Additional features:
- May be complicated by ascending cholangitis.

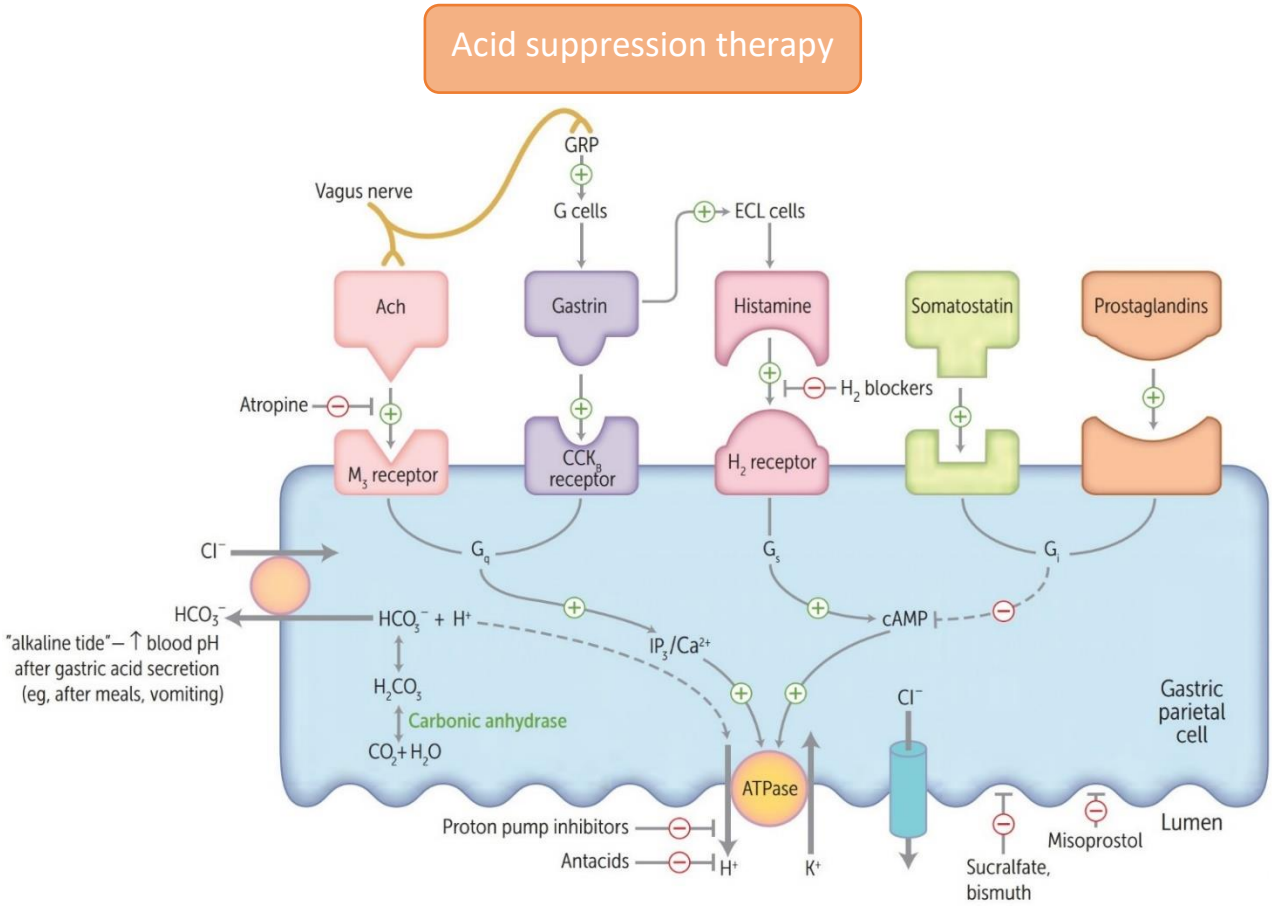
Anal fissure

- Anal fissure happens to young women.
- Anal fissures are characterized by longitudinal tears in the anal canal distal to the dentate line and are most common at the posterior midline.
- Most fissures are related to chronic constipation with high anal pressures and passage of hard stools. They can also be seen with frequent diarrhea or anal sexual intercourse.
- There is exquisite pain with defecation and blood streaks covering the stools.
- The fear of pain is so intense that patients avoid bowel movements (and get constipated) and may even refuse proper physical examination of the area.
- Initial treatment of anal fissures includes dietary modification (high-fiber diet, increased fluid intake). Topical anesthetics (lidocaine) can enhance comfort. In addition, topical vasodilators (nifedipine, nitroglycerin) can be used to reduce pressure in, and increase blood flow to, the anal sphincter, facilitating healing.



CHAPTER 4

Pharmacology



- <u>Gastric parietal cells secrete hydrochloric acid (HCl) in response to 3 major stimulants (histamine, vagal output, and gastrin):</u>

1. Vagal stimulation causes acetylcholine release, which directly stimulates HCl secretion by binding to parietal cell muscarinic (M_3) receptors. In addition, vagal stimulation indirectly promotes HCl secretion via gastrin-releasing peptide (GRP), which stimulates gastrin release from G cells.

2. G cells also release gastrin in response to protein-rich meals. Gastrin primarily stimulates HCl secretion by binding to ECL cells (promotes histamine release which binds to H_2 receptors on the basolateral parietal cell membrane). It also directly binds to the CCK_B receptor on parietal cells, but this mechanism is less significant for acid secretion.

- Synthesis of HCl by parietal cells of the gastric mucosa is dependent on the H/K ATPase, which is known as a proton pump.

- This carrier transports hydrogen ions into the gastric lumen in exchange for potassium ions.

- Omeprazole and other proton pump inhibitors inhibit the H/K ATPase, thus decreasing the concentration of HCl in the gastric lumen. These medications are used for treatment of peptic ulcer disease, gastroesophageal reflux disease (GERD), and diseases associated with increased gastrin secretion such as the Zollinger-Ellison syndrome.

Histamine H_2 blockers

- Drugs:

- Cimetidine, ranitidine, famotidine, nizatidine. Take H_2 blockers before you dine.

- Think "table for 2" to remember H_2.

- Mechanism of action:

- Reversible block of histamine H_2-receptors → ↓ H secretion by parietal cells.

- Clinical Use:

- Peptic ulcer, gastritis, mild esophageal reflux.

- Adverse effects:

- Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions).

- It also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males).

- Can cross blood-brain barrier (confusion, dizziness, headaches) and placenta.

- Both cimetidine and ranitidine ↓ renal excretion of creatinine. Other H_2 blockers are relatively free of these effects.

Proton pump inhibitors

- Drugs:

- Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.

- Mechanism of action:

- Irreversibly inhibit H/K ATPase in stomach parietal cells.

- Clinical Use:

- Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for H pylori, stress ulcer prophylaxis.

- Adverse effects:

- ↑ risk of C difficile infection, pneumonia, acute interstitial nephritis.

- ↓ serum Mg and ↓ Ca absorption (potentially leading to increased fracture risk in elderly).

Antacid use

- Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.

- All can cause hypokalemia via alkalinzation of the blood.

- Overuse can also cause the following problems:

A. Aluminum hydroxide:

- Constipation, Hypophosphatemia; Osteodystrophy, Proximal muscle weakness, Seizures.

- CHOPS.

- Aluminimum amount of feces.

B. Calcium carbonate:

- Hypercalcemia (milk-alkali syndrome), rebound acid ↑.

- Can chelate and ↓ effectiveness of other drugs (tetracycline).

C. Magnesium hydroxide:

- Diarrhea, hyporeflexia, hypotension, cardiac arrest.

- Mg^2 = Must go to the bathroom.

❖ N.B:

- Magnesium hydroxide and aluminum hydroxide are weak alkali mineral salts.
- They temporarily increase the gastric pH by neutralizing hydrochloric acid, helping to relieve gastroesophageal reflux symptoms.
- Aluminum hydroxide has a tendency to cause constipation due to interactions with intestinal secretions that form insoluble salts. In contrast, magnesium hydroxide cause osmotic diarrhea.
- Therefore, the two medications are combined to offset the adverse effects of the individual medications.
- Patients with reflux symptoms and chronic constipation may benefit from magnesium salt monotherapy, whereas aluminum hydroxide monotherapy may be of value in patients with chronic diarrhea.

Bismuth, sucralfate

- Mechanism of action:
- Bind to ulcer base, providing physical protection and allowing HCO_3 secretion to reestablish pH gradient in the mucous layer.
- Sucralfate requires acidic environment, not given with PPIs/H_2 blockers.
- Clinical Use:
- ↑ ulcer healing, travelers' diarrhea (bismuth).
- Bismuth also used in quadruple therapy for H pylori gastritis.

Misoprostol

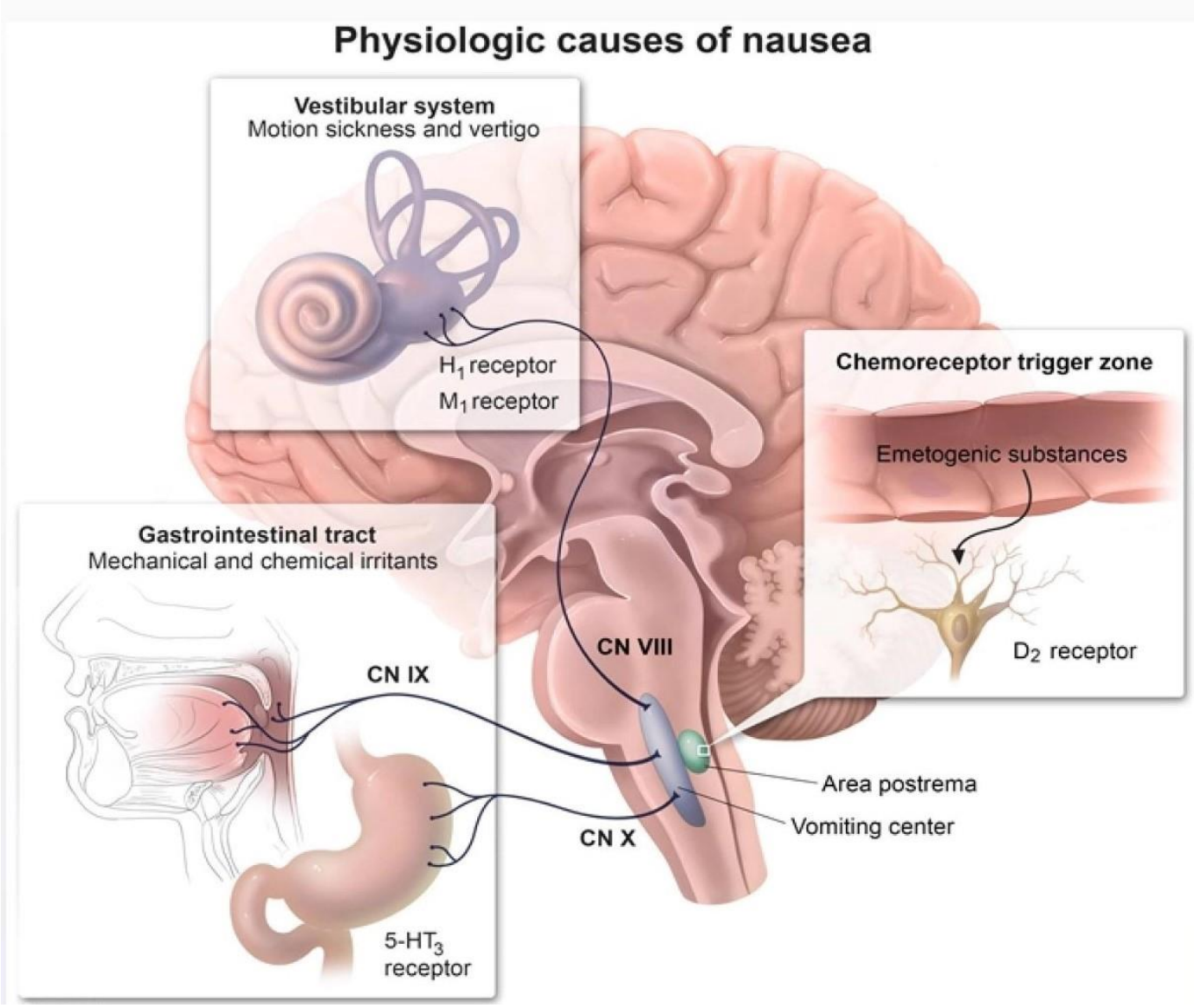
- Mechanism of action:
- A PGE1 analog.
- ↑ production and secretion of gastric mucous barrier, ↓ acid production.
- Clinical Use:
- Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE1 production).
- Maintenance of a PDA.
- Also used off-label for induction of labor (ripens cervix).
- Adverse effects:
- Diarrhea.
- Contraindicated in women of childbearing potential (abortifacient).

Octreotide

- Mechanism of action:
- Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones.
- Clinical Use:
- Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.
- Adverse effects:
- Nausea, cramps, steatorrhea. ↑ risk of cholelithiasis due to CCK inhibition.

❖ N.B:

- The vomiting reflex can be activated by either humoral or neuronal stimuli.
- The nucleus tractus solitarius (NTS) in the medulla receives information from the area postrema, gastrointestinal (GI) tract via the vagus nerve, vestibular system, and central nervous system (meninges, hypothalamus). Neurons from the NTS project to other medullary nuclei and coordinate the vomiting process.
- The area postrema in the fourth ventricle has a chemoreceptor trigger zone that can respond to many neurotransmitters, drugs, or toxins.
- The 5 major receptors involved in stimulating the vomiting reflex in the area postrema and adjacent vomiting center nuclei are M_1 muscarinic, D_2 dopaminergic, H_1 histaminic, 5-HT_3 serotonergic, and neurokinin 1 (NK1) receptors.
- 5-HT_3 receptor antagonists are useful for the treatment of visceral nausea due to gastrointestinal insults, such as gastroenteritis, chemotherapy, and general anesthesia. Antihistamines and anticholinergics are recommended for vestibular nausea. Dopamine antagonists are useful for nausea associated with migraine.



Ondansetron

- Mechanism of action:
- 5-HT_3 antagonist; ↓ vagal stimulation.

- Powerful central-acting antiemetic.

- Clinical Use:
- Control vomiting postoperatively and in patients undergoing cancer chemotherapy.

- Adverse effects:
- Headache, constipation, QT interval prolongation, serotonin syndrome.

Metoclopramide

- Mechanism of action:
- D_2 receptor antagonist.

- ↑ resting tone, contractility, LES tone, motility.

- Does not influence colon transport time.

- Clinical Use:
- Diabetic and postoperative gastroparesis, antiemetic, persistent GERD.

- Adverse effects:
- ↑ parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents.

- Contraindicated in patients with small bowel obstruction or Parkinson disease (due to D_2-receptor blockade).

Aprepitant

- Mechanism of action:
- Substance P antagonist.

- Blocks NK1 (neurokinin-1) receptors in brain.

- Clinical Use:
- Antiemetic for chemotherapy-induced nausea and vomiting.

Characteristics of antiemetic drugs		
Drug class	**Examples**	**Clinical uses**
Antimuscarinics (anticholinergics)	• Scopolamine	Motion sickness Hyperemesis gravidarum (promethazine)
Antihistamines	• Diphenhydramine • Meclizine • Promethazine	
Dopamine receptor antagonists	• Prochlorperazine • Metoclopramide	Chemotherapy-induced emesis
Serotonin (5-HT_3) receptor antagonists	• Ondansetron • Granisetron	
Neurokinin 1 (NK1) receptor antagonists	• Aprepitant • Fosaprepitant	

Laxatives

- Constipation is common in elderly, debilitated patients as well as those on chronic opiate therapy.

A. Bulk-forming laxatives:

- Examples: Psyllium, methylcellulose.

- Mechanism of action: Soluble fibers draw water into gut lumen, forming a viscous liquid that promotes peristalsis.

- Adverse effects: Bloating.

B. Osmotic laxatives:

- Examples: Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose.

- Mechanism of action:

- Osmotic laxatives are nonabsorbable or poorly absorbable substances that attract water into the intestinal lumen, thus distending the intestinal wall and increasing peristalsis. The laxative effect is usually fairly rapid.

- Lactulose also treats hepatic encephalopathy: gut flora degrade lactulose into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as NH_4.

- Adverse effects: Diarrhea, dehydration; may be abused by bulimics.

C. Stimulants:

- Examples:
  - Senna.

- Mechanism of action:
  - Enteric nerve stimulation → colonic contraction.

- Adverse effects:
  - Diarrhea, melanosis coli.

D. Emollients (stool softeners):

- Examples:
  - Docusate.

- Mechanism of action:
  - Promotes incorporation of water and fat into stool.

- Adverse effects:
  - Diarrhea.

Loperamide

- Mechanism of action:
  - Agonist at μ-opioid receptors; slows gut motility.
  - Poor CNS penetration (low addictive potential).

- Clinical Use:
  - Diarrhea.

- Adverse effects:
  - Constipation, nausea.

Sulfasalazine

- Mechanism of action:
  - A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory).
  - Activated by colonic bacteria.

- Clinical Use:
  - Ulcerative colitis, Crohn disease (colitis component).

- Adverse effects: Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

Orlistat

- Mechanism of action:
  - Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats.

- Clinical Use:
  - Weight loss.

- Adverse effects:
  - Abdominal pain, flatulence, bowel urgency/frequent bowel movements, steatorrhea; ↓ absorption of fat-soluble vitamins

Ursodiol (ursodeoxycholic acid)

- Mechanism of action:
  - Ursodeoxycholic acid improve cholesterol solubility by reducing the amount of cholesterol secreted into the bile and increasing biliary bile acid concentration.

- Clinical Use:
  - Primary biliary cirrhosis, gallstone prevention or dissolution.