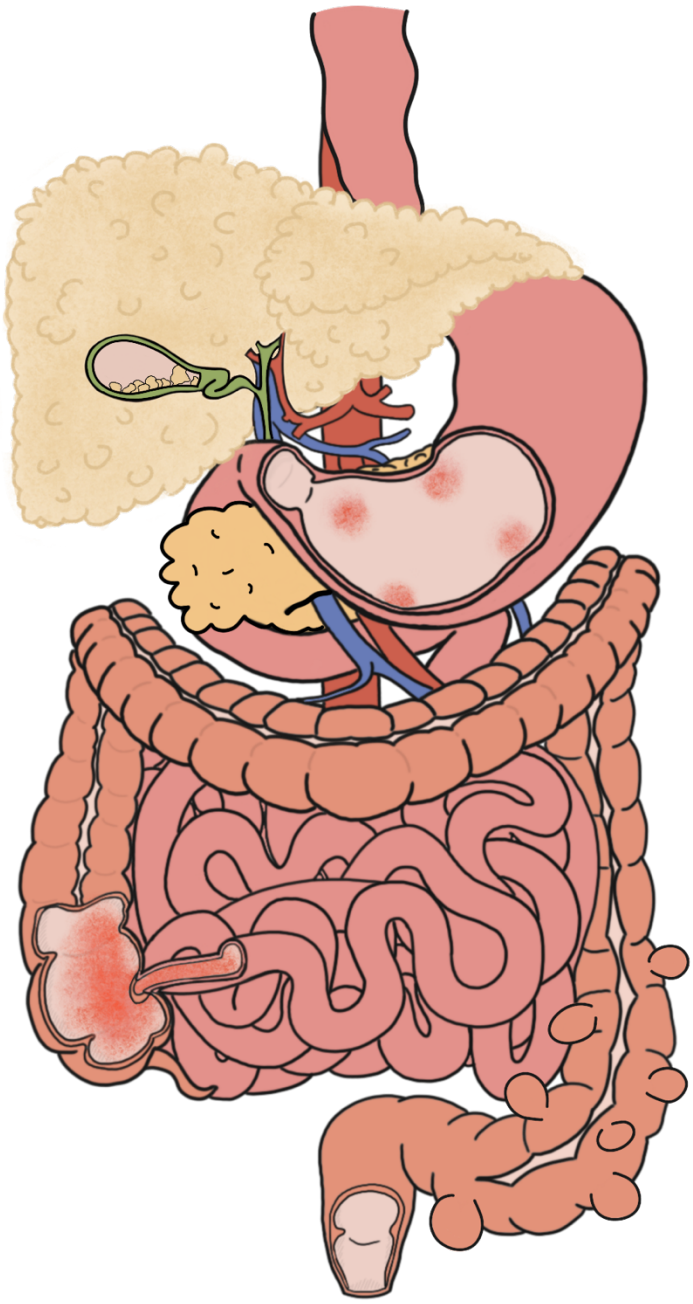

Gastrointestinal Pathology

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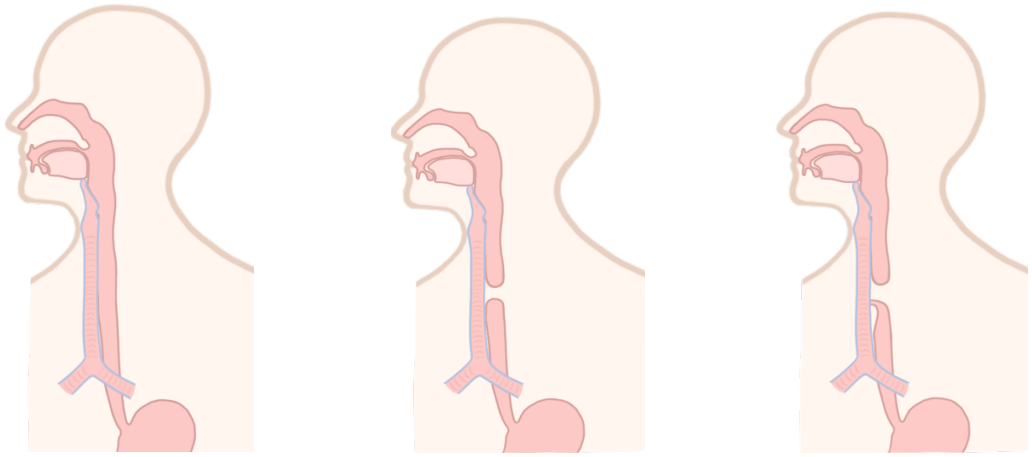
1.1 – Obstructive and Vascular Diseases of the Esophagus

1.1.1 – Congenital Esophageal Atresia



Normal anatomy

Pure esophageal atresia

Esophageal atresia with tracheoesophageal fistula (most common)

- Complete blockage of esophagus
- In most cases, esophageal atresia (EA) occurs with tracheoesophageal fistula (TEF), where a part of esophagus is connected with the trachea. This occurs at or near the tracheal bifurcation.

I. Clinical features

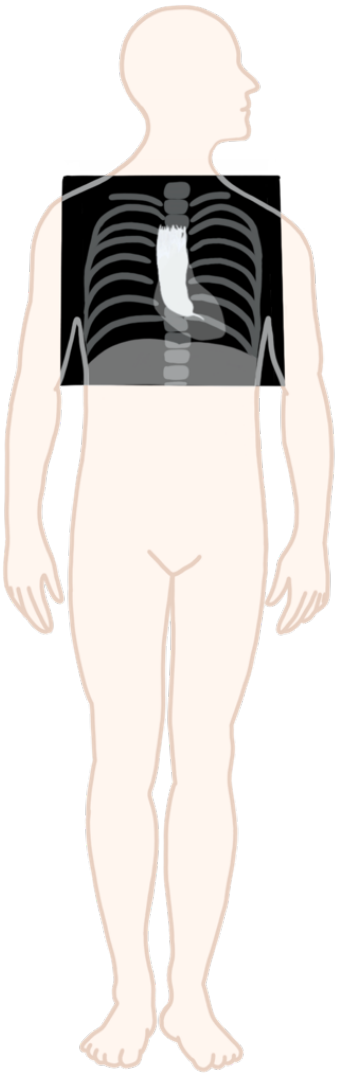
- Esophageal atresia presents with polyhydramnios in utero[1]. After birth, symptoms include regurgitation, choking and cyanosis during feeding.

II. Diagnosis

- Clinical tests include failure of passing a nasogastric tube into the stomach.
- The diagnosis is confirmed with chest X-ray.

[1]Excess amount of amniotic fluid present, due to fetus' inability to swallow amniotic fluid.

1.1.2 – Primary Esophageal Achalasia



I. Pathomechansim

- Primary achalasia is idiopathic.
- Normally, esophageal neurons relax the lower esophageal sphincter (LES) during swallowing by releasing nitric oxide (NO) and vasoactive intestinal peptide (VIP) from inhibitory neurons.
- Degeneration of inhibitory neurons → decreased release of NO → increased tension in LES
- Achalasia is characterized by
    1. Incomplete relaxation of LES
    2. Loss of esophageal peristalsis
    3. Increased LES pressure
- The dysfunctional LES will cause a functional obstruction at the gastroesophageal junction.

II. Symptoms

- Achalasia will present as *progressive dysphagia*, *regurgitation*, and *chest pain*.
- Often starts with a problem swallowing solid food which progresses to problems with swallowing liquids.

III. Diagnostics

- X-ray shows a characteristic dilated esophagus followed by a stenosis. This is called a "bird's beak" appearance.

IV. Complications

- Increased risk of gastroesophageal reflux disease and esophageal squamous cell carcinoma.

CLINICAL CORRELATION

Chagas disease

- Secondary esophageal achalasia caused by *Trypanosoma Cruzi* parasite infection.
- The parasite damages the neural plexuses of the esophagus giving similar symptoms as primary esophageal achalasia
- If left untreated, can cause heart failure, cardiac arrest and megacolon.

1.1.3 – Plummer-Vinson Syndrome

I. Overview

- Characterized by a triad of
    1. Dysphagia
    2. Iron deficiency anemia
    3. Esophageal webs[1]
- Most common in white women in 4th to 7th decade of life.

MNEMONIC – SYMPTOMS

Plumbers DIE
- **D** – Dysphagia
- **I** – Iron deficiency
- **E** – Esophageal webs

II. Clinical features

- Symptoms include burning sensation of lips & tongue, beefy red tongue and problem swallowing solids.
- Associated with an increased risk of esophageal squamous cell carcinoma.

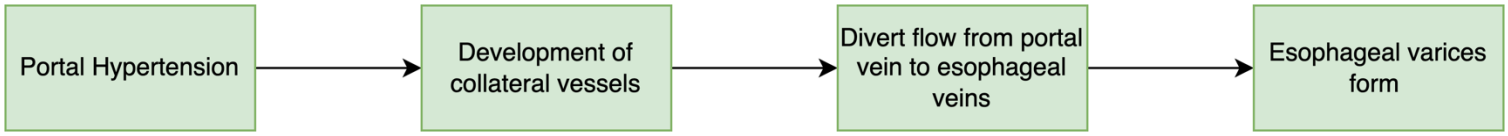
III. Treatment

- Treatment includes iron supplements and dilatation of esophageal webs.

[1]Web is an inward protrusion, here to the inner side of the esophagus. (In contrast, diverticulum is an outward protrusion.)

1.1.4 – Esophageal Varices

I. Pathogenesis



- Dilated lower esophageal veins located in the submucosa of the esophagus, secondary to portal hypertension.
- Very common in patients with liver cirrhosis, usually due to alcoholism.

II. Clinical presentation

- Most often patients exhibit no symptoms. However, if they rupture, they can lead to massive hematemesis[1] and death.
- Up to 50% die in first episode of bleeding, despite medical intervention. Rupture of esophageal varices is the most common cause of death in patients with cirrhosis.

[1]Hematemesis – vomiting of blood

1.2 – Esophagitis

1.2.1 – Mallory-Weiss Lacerations

- Longitudinal lacerations located at the lesser curvature of stomach or the gastroesophageal junction.
- Partial thickness lacerations: Confined to the mucosa or submucosa.
- Pathomechanism: Severe vomiting forcefully increases the pressure in the gastrointestinal tract, thus can result in lacerations.
- Occurs in vomiting disorders, such as alcoholism and eating disorders involving vomiting.
- Often presents with hematemesis.

MNEMONIC – DIRECTION OF LACERATIONS

MaLLory-Weiss is characterized by Longitudinal Lacerations

CLINICAL CORRELATION

Hiatal hernia

When the a part of the stomach "slips through" the diaphragm. Typically caused by situations in which the intraabdominal pressure is increased: Obesity, straining during defecation, frequent coughing.

Associated with reflux esophagitis

Sliding hernia: Most common. Protrusion of the stomach above the diaphragm, creating a bell shape.

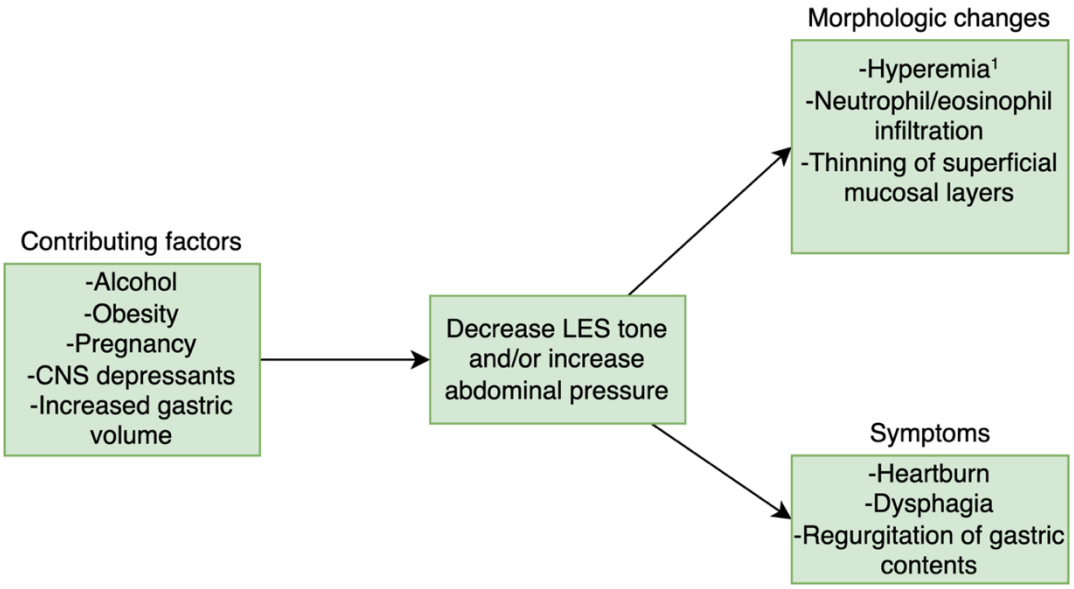
Paraesophageal hernia: A separate part of the stomach, usually the greater curvature, enters the thorax.

1.2.2 – Gastroesophageal Reflux Disease

- Most common in adults over 40 years.

I. Pathomechanism

- Reflux of gastric acid is the most common form and cause of esophagitis.
- The stratified squamous epithelium lining the esophagus is sensitive to acid. Decreased tone of LES allows for reflux of gastric contents into the esophagus which damage the epithelium. In many cases, no definitive cause is identified. However, there are several contributing factors.



[1]Hyperemia – increased blood flow causing redness.

II. Symptoms

- Difficulties and discomfort while swallowing, heart burn
- Pain may be similar to the signs of a myocardial infarction!
- The severity of symptoms is *not related to histology*
- Symptoms tend to worsen when lying down/at night and when eating large portions. *Eating large portions will increase abdominal pressure*.
- No gold standard exists for diagnosis, a mix of clinical symptoms, biopsies and intraesophageal pH monitoring is required for diagnosis

RECALL

Section 1.1.2 – Esophageal Achalasia

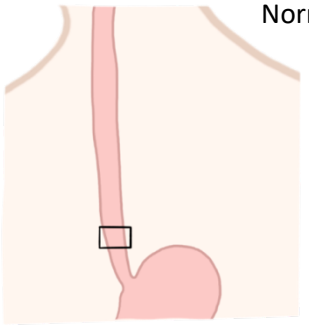
- Recall that in esophageal achalasia, there is failure of LES *relaxation*.
- In gastroesophageal reflux disease (GERD), there is failure of LES *contraction*.

III. Treatment

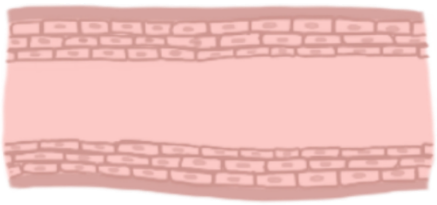
- Treatment includes eradication of H. Pylori with antibiotics and neutralizing gastric acid with proton pump inhibitors.

IV. Complications

- Ulceration and hematemesis
- Stricture
- Barrett's Esophagus

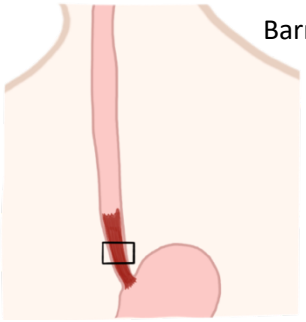


Normal esophagus

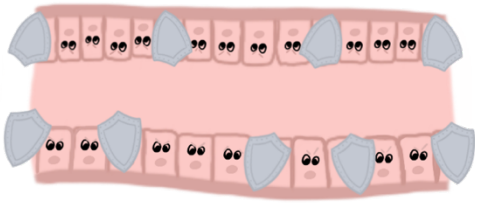


1.2.3 – Barrett Esophagus

- Barrett Esophagus is a complication of chronic GERD, occurring in about 10% of cases.
- <u>Defining feature:</u> Epithelial metaplasia above the gastroesophageal junction. The stratified, squamous epithelium is replaced to columnar epithelium due to recurrent exposure of gastric acid.



Barrett esophagus



- Considered a *precancerous* lesion with an increased risk of esophageal adenocarcinoma

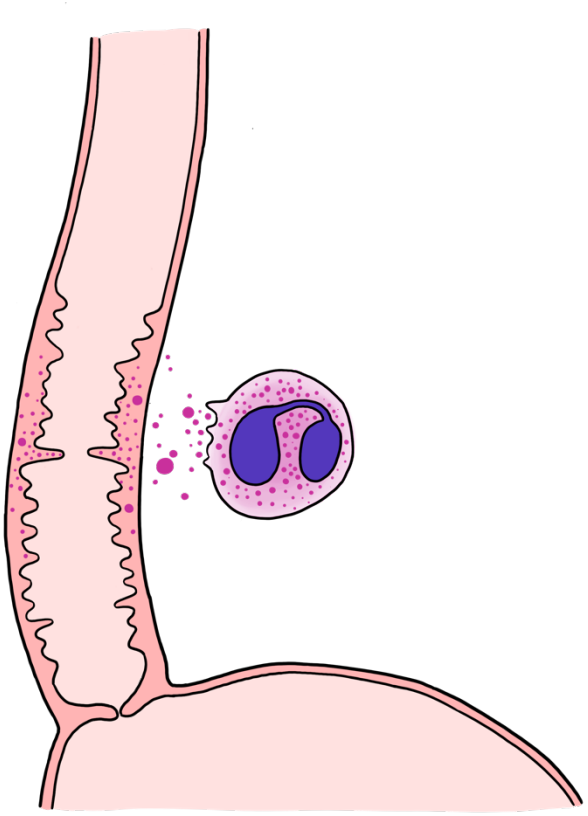
I. Morphological features

- Starting from the gastroesophageal junction, metaplastic columnar epithelium is spreading up from the stomach. Endoscopically, this is shown as red patches.
- Presence of goblet cells within the columnar epithelium is a defining feature epithelial metaplasia.
- A positive biopsy together with symptoms is required for diagnosis.

II. Symptoms

- Similar as in GERD
    1. Heartburn, dysphagia, regurgitation of gastric contents

1.2.4 – Eosinophilic Esophagitis



I. Morphology

- Gross: The esophagus will have stacked circular rings, showing a resemblance to the trachea on bronchoscopy
- Histology: Abundant eosinophilic infiltration located in upper and mid portions of esophagus, which differs from reflux esophagitis. The esophagus is normally void of eosinophils.

II. Clinical features

- Symptoms differ in children and adults:
    1. Children: Feeding intolerance and GERD-like symptoms
    2. Adults: Food impaction[1] and dysphagia
- An increased number of patients with eosinophilic esophagitis have a concomitant atopic disorder.

III. Treatment

- Treatment includes dietary restrictions to prevent exposure from allergens and corticosteroids.

[1] Food impaction = Food gets stuck

CLINICAL CORRELATION

Association with atopic disorders

- Atopic disorders include asthma, atopic dermatitis and allergic rhinitis.
- Inflammatory cells found in atopic disorders are similar to those in eosinophilic esophagitis, which are increased number of eosinophils and T cells.
- Every patient diagnosed with eosinophilic esophagitis should therefore be tested for concomitant atopic disorders.

1.3 – Malignant Esophageal Neoplasms

	Squamous cell carcinoma	Adenocarcinoma
Overview	- Arises from epithelial cells that line the esophagus - More common in men - Most common worldwide	- Arises from glandular cells present in esophagus[1] - More common in men - Most common in Western world, like America. - 95% arise in setting of Barrett's esophagus
Part of esophagus	Upper 2/3	Lower 1/3
Symptoms	- Iron deficiency - Respiratory fistulas Dysphagia - Weight loss - Hematemesis	- Chest pain - Vomiting - Dysphagia - Weight loss - Hematemesis
Risk factors[2]	- Alcohol - Hot liquids - Strictures - Smoking - Achalasia	- Chronic GERD - Barrett esophagus - Obesity - Smoking
Histological features	- Begins in situ as squamous dysplasia[3] - Early lesions are gray-white, mucosal thickenings - Expands as protruding lesions, which can ulcerate and lead to esophageal obstruction.	- Early lesions are flat or raised, surrounded by healthy mucosa. - Later, tumors form which may obstruct the lumen or infiltrate deeply. - Tumors typically form glands which produce mucin. - Barrett's esophagus is often present next to the tumor.

[1]Present due to intestinal metaplasia from Barrett's esophagus

[2]Remember that squamous cell carcinoma (SCC) often starts as an adaptation to chronic tissue damage; We can use this to remember that factors causing irritation of the fragile lining of the esophagus, like alcohol, smoking and hot liquids, are risk factors for SCC.

[3]Dysplasia – presence of abnormal cells

MNEMONIC - ADENOCARCINOMA

Adenocarcinoma is common in **A**merica, where **Obesity** is prevalent

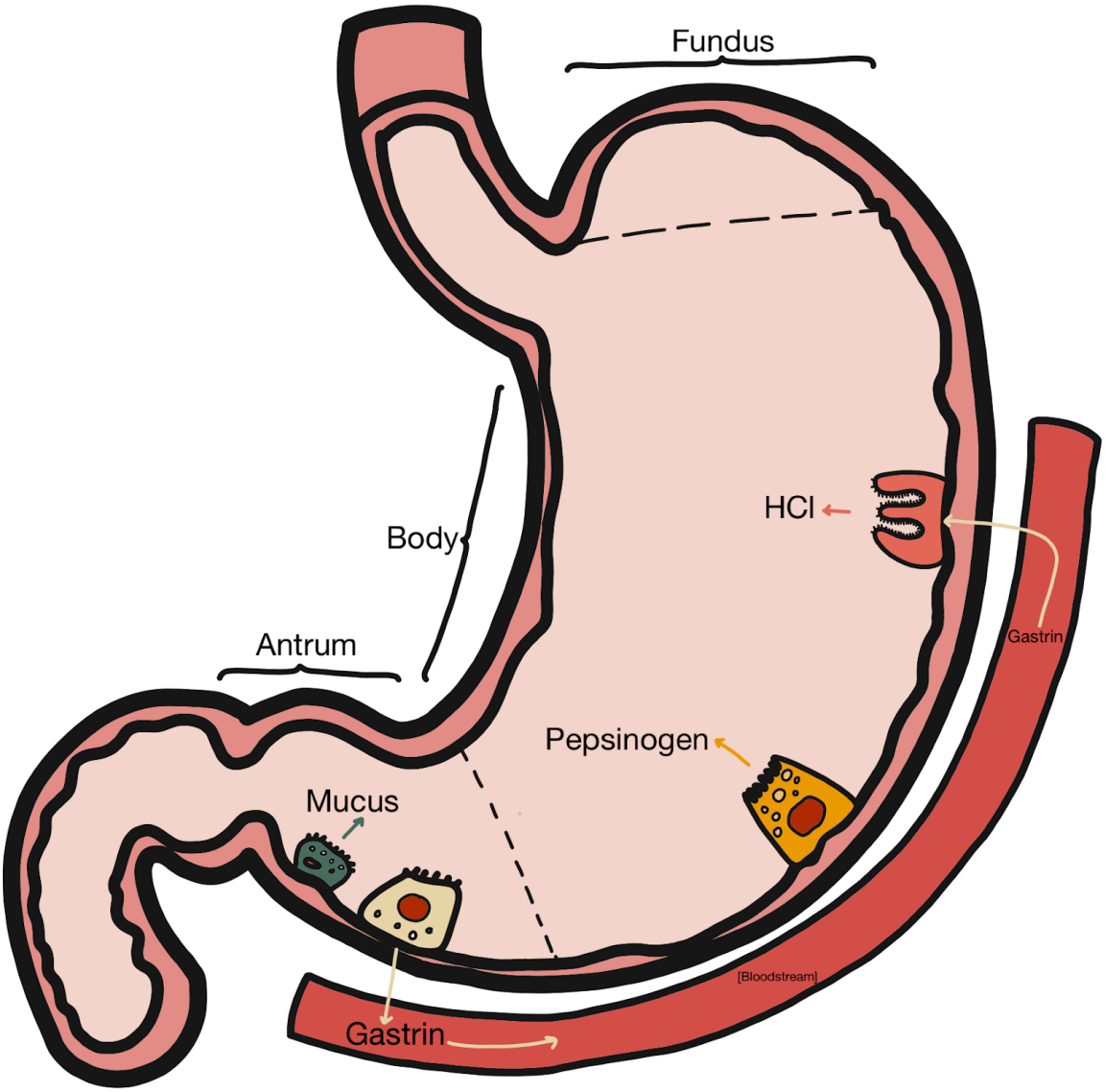
- Remember GERD and Barrett esophagus is a common result of obesity

1.4 – Gastritis

- Gastritis is when the mucosa of the stomach becomes inflamed: May be acute or chronic

Anatomy and histology of the stomach

Location	Cells	Secretions
Fundus, Body	Parietal cells	HCL, intrinsic factor
	Chief cells	Pepsinogen
Antrum	G-Cells	Gastrin (to circulation)
	Mucus cells	Mucus, pepsinogen
	D-cells (not in picture)	Somatostatin



1.4.1 – Acute Gastritis

- Gastritis is a consequence of an imbalance between damaging forces and protecting forces.

I. Symptoms

- Can vary from being asymptomatic to varying degrees of pain, nausea, and vomiting.
- Ulceration with hemorrhage presents with hematemesis or melena (dark, tarry looking stools).

II. Morphology

- Edema and hyperemia of mucosa.
- In *acute* gastritis, *neutrophils* invade the epithelium with superficial erosion.

III. Pathogenesis

- The gastric lumen has a pH close to 1 and is strongly acidic. The acidic environment aids in digestion, but can potentially damage the surrounding mucosa. Several mechanisms protecting the gastric mucosa has evolved, but disruption of these can lead to gastritis:

Protecting factors	Action	Damaging factors	Action
Mucin	Protects from acid secretion	NSAIDs[1]	Inhibit synthesis of protective prostaglandins
Bicarbonate secretion	Neutralize pH of mucosa	H. Pylori	Inhibit bicarbonate secretion
Blood supply	Acts as a buffer, by removing protons diffusing into the mucosa	Ischemia	Decreased gastric blood flow → hypoxic tissue injury → weakened mucosal barrier
		Increased intracranial pressure	Cause increased vagal stimulation which stimulates acid production in the stomach. This is called Cushing ulcer.

[1]Non-steroidal anti-inflammatory drugs

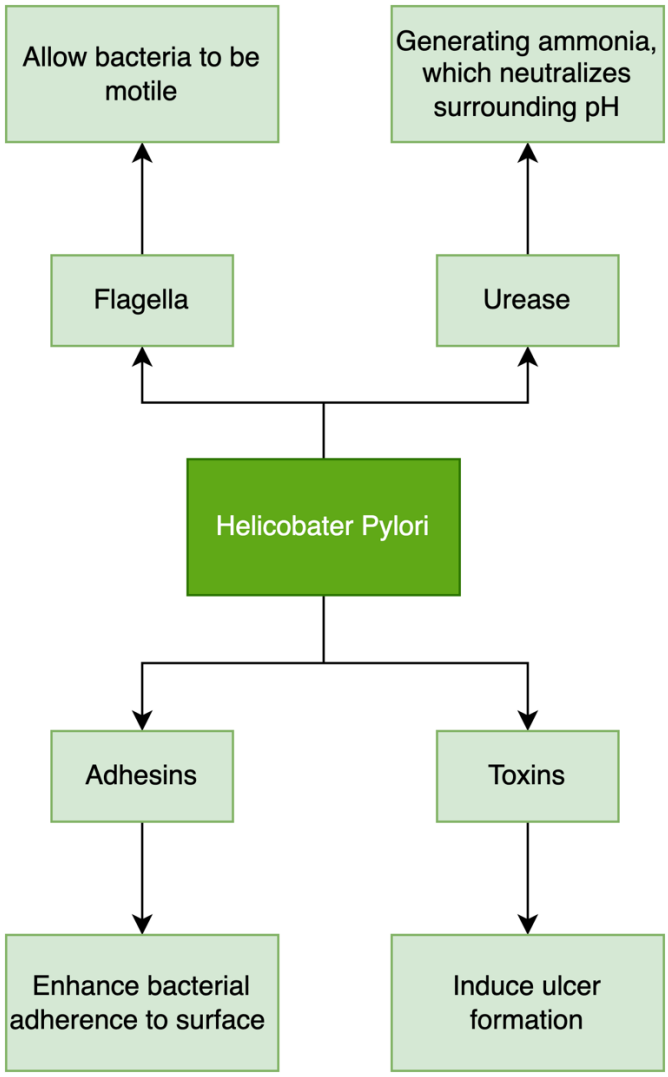
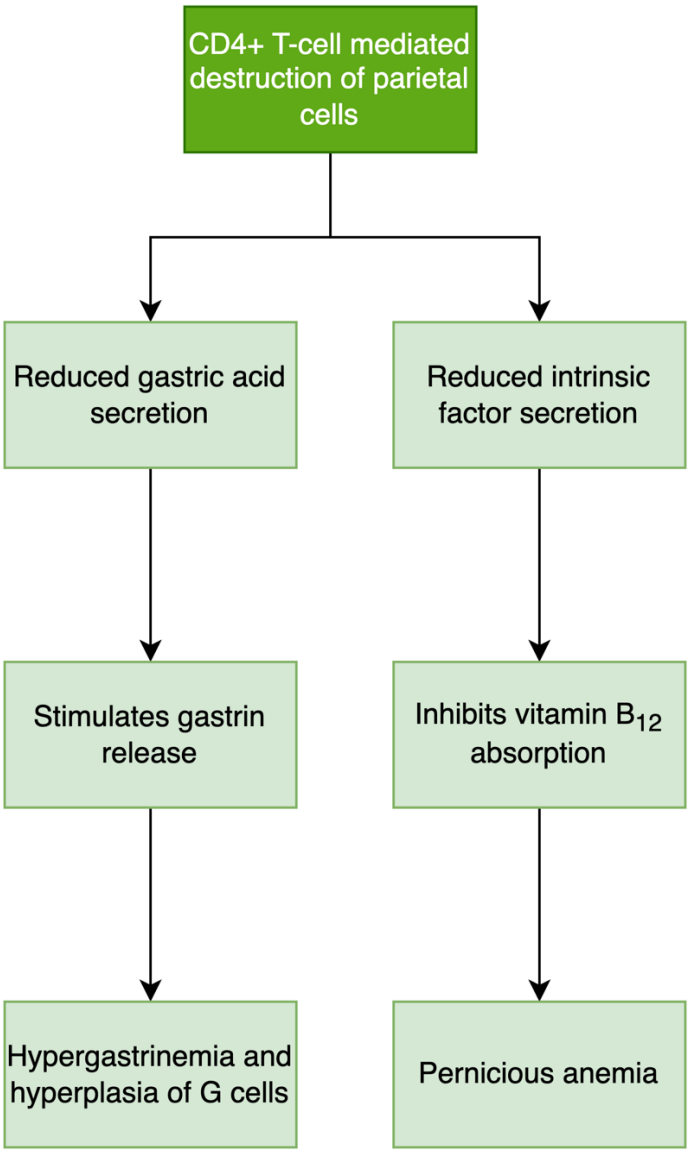
1.4.2 – Chronic Gastritis

Characteristics of chronic gastritis

	H. Pylori Gastritis	Autoimmune Gastritis
Overview	- Present in 90% of cases of chronic gastritis	- 10% of cases of chronic gastritis - Characterized by impaired gastric secretion
Location	Antrum	Body and fundus
Morphology	- Infected mucosa is erythematous and coarse - H. Pylori is found in the superficial mucus of the antrum. - Neutrophils are present - Diffuse mucosal atrophy with intestinal metaplasia	- Diffuse damage and atrophy[1] of oxyntic glands (produce acid). - Lymphocytes and macrophages present
Acid production	↑	↓
Gastrin	Normal	↑↑↑
Serology	Antibodies to H. Pylori	Antibodies to parietal cells and intrinsic factor
Complications	Peptic ulcers	Pernicious anemia
Associations	Low socioeconomic status	Autoimmune diseases

[1]Atrophy – thinning and loss of folds

Pathogenesis of chronic gastritis

H. Pylori Gastritis	Autoimmune Gastritis
Disruption of mucosal protection mechanisms by H. pylori virulence factors[1] 	

[1]Virulence factors – a pathogen's ability to infect or damage host tissues

1.4.3 – Peptic Ulcer Disease

I. Overview

- Complication of chronic gastritis
- Risk factors:
    1. H. pylori infection
    2. NSAIDs
    3. Cigarette smoking.
- The imbalance of damaging and protective forces responsible for chronic gastritis, are also responsible for peptic ulcer disease.

II. Pathogenesis

- Hyperacidity is the fundamental cause of peptic ulcer disease
- Some patients also have impaired secretion of bicarbonate in the duodenum

III. Morphology

- The ulcers[1] have well-demarcated borders and a smooth base
- Microscopically, granulation tissue and deep scarring is surrounding the ulcer.
- Most common location of ulcer is the first portion of the duodenum, but they can also be found in the gastric antrum.

IV. Clinical features

- In 80%, the ulcers are solitary.
- Often occurs in middle-aged to older adults.
- The most common symptom is epigastric burning or aching pain 1-3 hours after eating or at night.
- Complications include perforation, hemorrhage, and anemia
- Treatment: Eradication of H. Pylori with antibiotics and neutralizing gastric acid with proton pump inhibitors.

[1]Ulcer – Ulcer crosses the submucosa, an *erosion* does not.

CLINICAL CORRELATION

Pain in peptic ulcer disease

- The pain in peptic ulcer disease (PUD) is caused by acid present in the digestive tract.
- When eating, food is buffering the acid, making it less painful which may cause weight gain in some patients.

1.5 – Hypertrophic Gastropathies

- Cell injury and regeneration without presence of inflammatory cells.

1.5.1 – Menetrier Disease

- Hyperplasia of the foveolar layer, resulting in increased secretion of gastric mucosa
- Characterized by enlarged gastric mucosal folds due to hyperplasia of gastric mucosa, resembling the gyri of the brain.
- Leads to excessive mucous production, resulting in diminished acid secretion and protein loss causing hypoalbuminemia.

MNEMONIC – SYMPTOMS

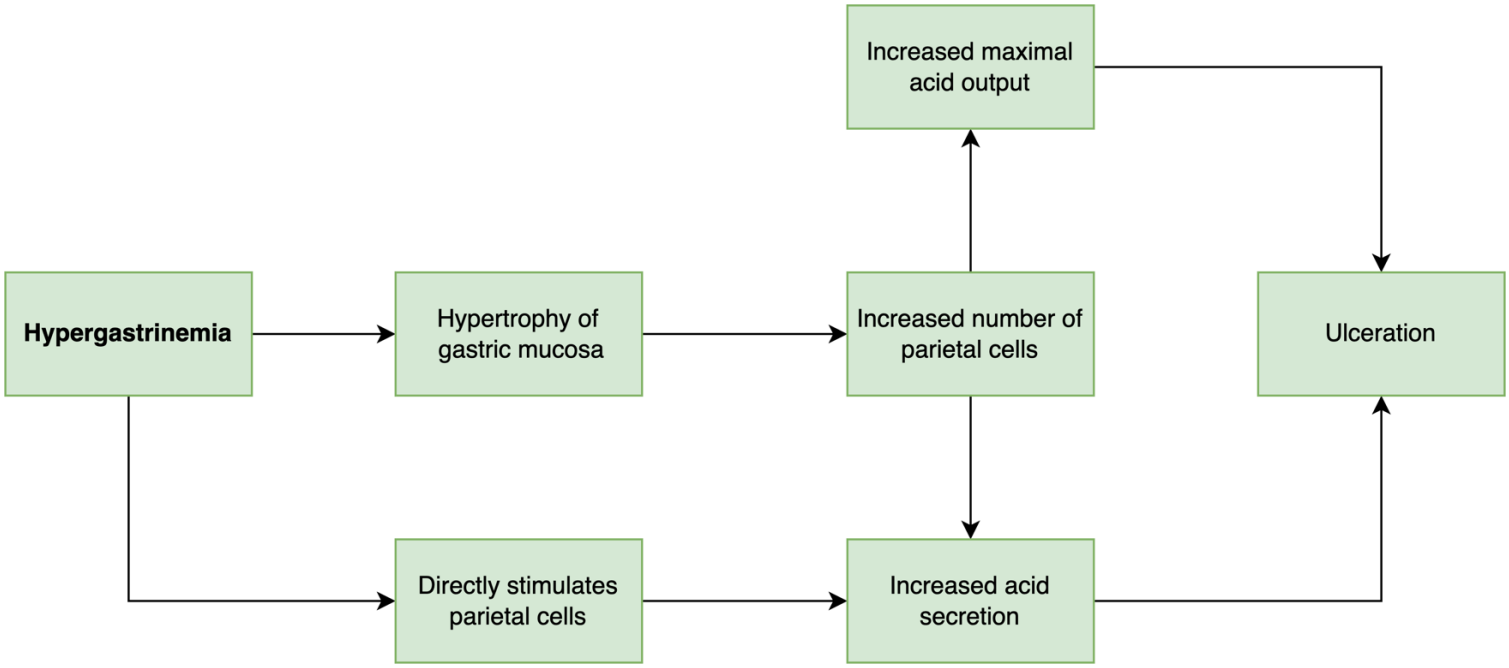
WAVEE
W – Weight loss
A – Anorexia
V – Vomiting
E – Epigastric pain
E – Edema

1.5.2 – Zollinger-Ellison Syndrome

I. Overview

- Hyperplasia of the glandular layer, resulting in increased secretion of acid.
- Zollinger-Ellison syndrome is caused by gastrinomas (gastrin-secreting tumors) located in the small bowel or pancreas.
- 75% of cases is sporadic.
- 60-90% of cases are malignant.

II. Pathophysiology



III. Clinical features

- Symptoms are related to ulceration due to increased acid production and include epigastric pain, diarrhea, and heartburn.
- Ulcers are often multiple and unresponsive to usual therapy.

IV. Diagnosis

- Zollinger-Ellison syndrome can be diagnosed using Secretin Stimulation test:
    1. Secretin, among other things, inhibits the secretion of gastrin.
    2. After administration of secretin, gastrin will remain elevated in patients with Zollinger-Ellison syndrome.

1.6 – Gastric Polyps and Tumors

1.6.1 – Gastric Polyps

	Inflammatory and hyperplastic polyps	Fundic gland polyps	Gastric Adenomas
	75% of gastric polyps where H. pylori is common	Most common polyps in areas with low H. pylori and frequent PPI use	10% of gastric polyps
Demographics	- Most common between age 50 and 60	- More common in women - Over age 50	- More common in males - Incidence increases with age
Association	Chronic gastritis	Sporadic or associated with polyposis syndromes, like FAP[1]	Associated with chronic gastritis
Characteristics	- < 1 cm - Multiple - Smooth surface	- Single or multiple - Well-circumscribed lesions	- < 2 cm - Solitary
Morphology	- Irregular, dilated, and elongated glands - Inflammation present	- Irregular, dilated, and elongated glands - No inflammation	- Flat or polypoid - 4 main types, the most common being intestinal type which is similar to colonic polyps
Dysplasia	- Risk correlates with size - Polyps >1.5 cm should be resected	- Almost never progress to become malignant	-All adenomas exhibit epithelial dysplasia - 30% may be malignant - Lesions >2cm should be resected

[1] Familial adenomatous polyposis (FAP) – inherited syndrome characterized by hundreds to thousands of colorectal polyps at an early age

1.6.2 – Gastric Adenocarcinoma

CLINICAL CORRELATION

The Virchow Node

- The Virchow node is a swollen left supraventricular node.
- This is the *most common site* of gastric cancer metastasis, as it is the first to receive lymph from, among other, the abdomen.

I. Overview

- Most common gastric malignancy, comprising more than 90% of all gastric cancers.
- The incidence in Japan and Eastern Europe is 20-fold greater than in North America and Sothern Europe.

II. Symptoms

- Early symptoms include dyspepsia, dysphagia, and nausea, resembling those of chronic gastritis.
- Therefore, the cancer is often diagnosed at advanced stages when more severe symptoms present, such as weight loss, anorexia, anemia, and hemorrhage.

III. Classification

	Intestinal	Diffuse
Location	Antrum > lesser curvature > greater curvature	
Pathogenesis	Associated with FAP	Mutations in CDH1, which encodes for a protein contributing to epithelial intracellular adhesion
Characteristics	- Predominates in high-risk countries - Mean age is 55 - More common in men	- Incidence is relatively similar between genders and countries
	Develops from precursor lesions (e.g. adenomas)	No precursor lesion
Morphology	- Typically localized - Form exophytic[1] tumors - Composed of cells that contain mucin vacuoles - Tumors contain glandular tissue	- No clear border - Composed of signet-ring cells[2] - Do not form tumors - Induce a fibrous desmoplastic response that changes the gastric appearance termed "linitis plastica[3]"
Complications	Skeleton, liver, lung, and brain are most commonly affected by hematogenous spread of gastric adenocarcinoma	
	–	Krukenberg tumor[4]

[1]Exophytic – protrudes out of the surface

[2]Signet-ring cells – cells with large vacuoles that push the nucleus to the periphery

[3]Linitis plastica – gastric wall becomes thickened and rigid. Means "leather bottle"

[4]Krukenberg tumor – bilateral metastatic tumor to the ovary, also with signet ring cells.

1.6.3 – Gastric Lymphoma

- Extranodal[1] lymphomas arise most commonly in the gastrointestinal tract, and especially the stomach. However, it can arise in any tissue.
- Most common type is MALToma (mucosa-associated lymphoid tissue) comprise 5% of gastric malignancies
- This is a tumor of mature B cells, expressing CD20.
- Often discovered incidentally in the setting of H. Pylori-induced gastritis.

I. Symptoms

- Patients typically present with dyspepsia and epigastric pain.
- Hematemesis, melena or weight loss can also occur.

II. Pathogenesis

- Tends to develop within tissues that are sites of chronic infection, such as H. Pylori.
- Eradication of H. pylori, often leads to regression of the tumor cells. However, a t(11;18), t(1;14) or t(14;18) translocation will make the tumor antibiotic-resistant, making treatment harder.

III. Morphology

- B cells infiltrate the epithelium of the stomach, collecting in small aggregates called lymphoepithelial lesions.

[1]Extranodal – lymphatic involvement of anatomic sites other than the lymph nodes

1.6.4 – Gastrointestinal Stromal Tumor

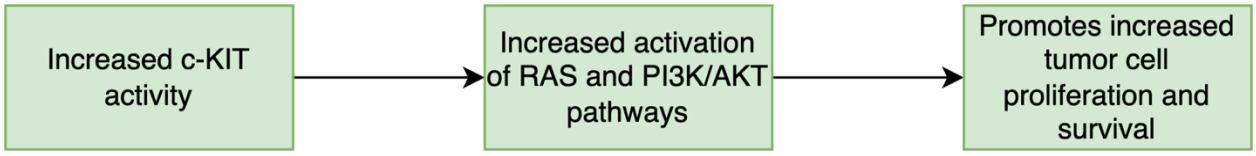
- Most common gastrointestinal mesenchymal tumor

I. Epidemiology

- Most common age of diagnosis is in the sixth decade.

II. Pathogenesis

- Arise from interstitial cells of Cajal[1] in the gut.
- Approximately 80% of all cases contain gain-of-function mutation in the gene coding for c-KIT.



III. Morphology

- Gastrointestinal stromal tumors (GIST) are solitary, well-circumscribed fleshy masses which can grow as large as 30 cm.
- Metastases may form multiple, small nodules or fewer large nodules in the liver. Metastases outside the abdomen is rare.
- Microscopically GISTs are composed of either
    1. Epithelioid cells, which are rounder or
    2. Spindle cells, which are thin and elongated

IV. Clinical features

- Symptoms are related to mass effects or blood loss.
- Surgical resection is the most common treatment for primary GIST.
- Metastases are rare when the tumor is <5 cm, but common when it is >10 cm.

[1]Interstital cells of Cajal – pacemaker cells for peristaltic motor activity of the gut

1.7 – Test Yourself

1) Indicate false statement regarding primary esophageal achalasia

a) Achalasia will often start with having problems swallowing solid food
b) Achalasia is characterized by decreased lower esophageal sphincter pressure
c) X-ray of the esophagus will show a bird's beak appearance
d) Patients with esophageal achalasia will have an increased risk of esophageal squamous cell carcinoma

2) What is a characteristic feature of Barrett's Esophagus?

a) It is a complication of chronic GERD
b) It often presents with hematemesis
c) The normal stratified, squamous epithelium is replaced to columnar epithelium.
d) Barrett's esophagus does not cause increased risk of cancer.
e) A and C is correct

3) Place the appropriate actions into the cells:

a) Inhibit synthesis of protective prostaglandins
b) Decreased gastric blood flow → hypoxic tissue injury → weakened mucosal barrier
c) Neutralize pH of mucosa
d) Inhibit bicarbonate secretion
e) Acts as a buffer, by removing protons diffusing into the mucosa
f) Cause increased vagal stimulation which stimulates acid production in the stomach.
g) Protects from acid secretion

Protecting factors	Action	Damaging factors	Action
Mucin		NSAIDs	
Bicarbonate secretion		H. Pylori	
Blood supply		Ischemia	
		Increased intracranial pressure	

4) Indicate the true statement regarding peptic ulcer disease

a) The ulcers are in most cases multiple

b) Peptic ulcer disease often occurs in the younger population

c) Nearly all peptic ulcers are associated with H.pylori infection, NSAID use and cigarette smoking

d) An ulcer does not cross the submucosa

5) Which of the following statement is false about gastric adenocarcinoma?

a) It is the most common gastric malignancy

b) Diagnosis is often made at an early stage

c) There are two types of gastric adenocarcinoma: intestinal type and diffuse type

d) Antrum is the most common location of gastric adenocarcinoma

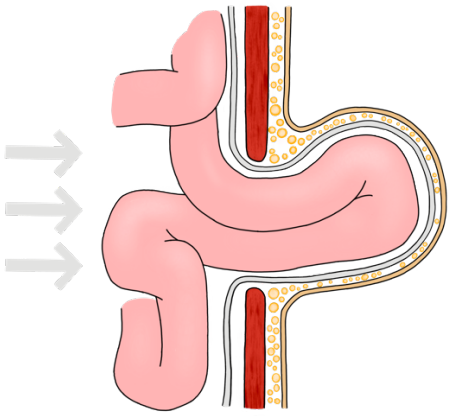
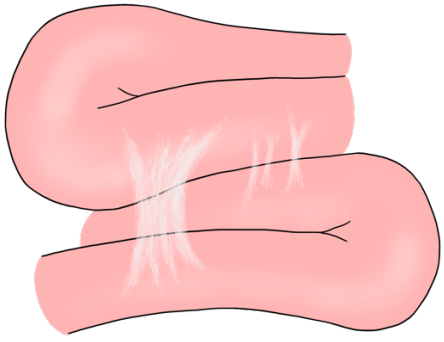
Section 2 – The Intestines

2.1 – Developmental Abnormalities and Malformations

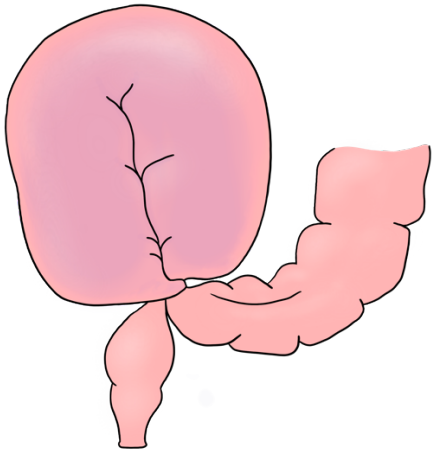
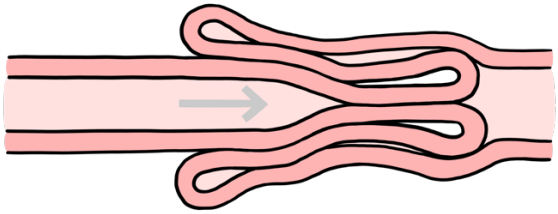
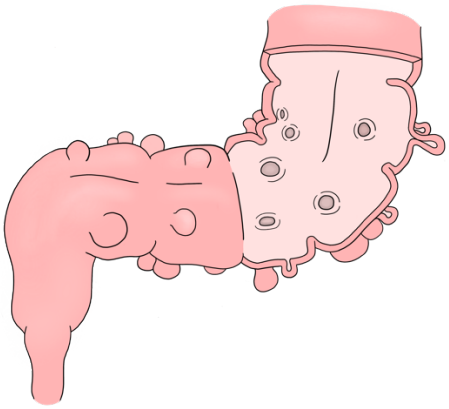
I. Atresia

- Anal atresia (imperforate anus) is the most common form of gastrointestinal atresia
    1. Male > Female
    2. May present as a single orifice for vagina, urinary tract and rectum in girls (cloaca)
    3. Strongly associated with defects in other organs
- Stenosis = Incomplete atresia
- Duodenum is typical, associated with Down syndrome
- Treatment: Surgery in the first few days of life

II. Intestinal obstructions

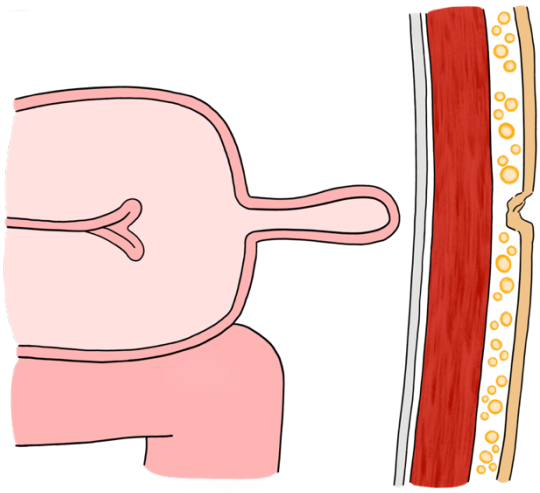
Types	Description	Illustrated Example
Hernia	An abnormal exit of the intestines through the wall of a cavity	
Adhesion	Bands of scar-like tissue that cause the intestines to stick together	

Intestinal obstructions continued

Types	Description	Illustrated Example
Volvulus	A loop of intestines that twist around itself and the supporting mesentery leading to ischemia	
Intussusception	When one part of the intestine slides inside another part (telescoping), leading to compression of mesenteric vessels pulled inside via peristalsis	
Diverticula	Bulging pouches that form in GI lining due to lack of muscular layer (false diverticula). Most common in large intestine	

2.1.1 – Meckel Diverticulum

- Most common congenital abnormality of GI
- Pathological diverticulum occurring in the distal Ileum
- Muscular layer is involved, making it a true diverticulum
- Pathomechanism: Improper obliteration of the vitelline duct[1] on the distal ileum
    1. Illustration shows the diverticulum behind the umbilicus
    2. Typical location is 30-90 cm distal to the ileocecal valve

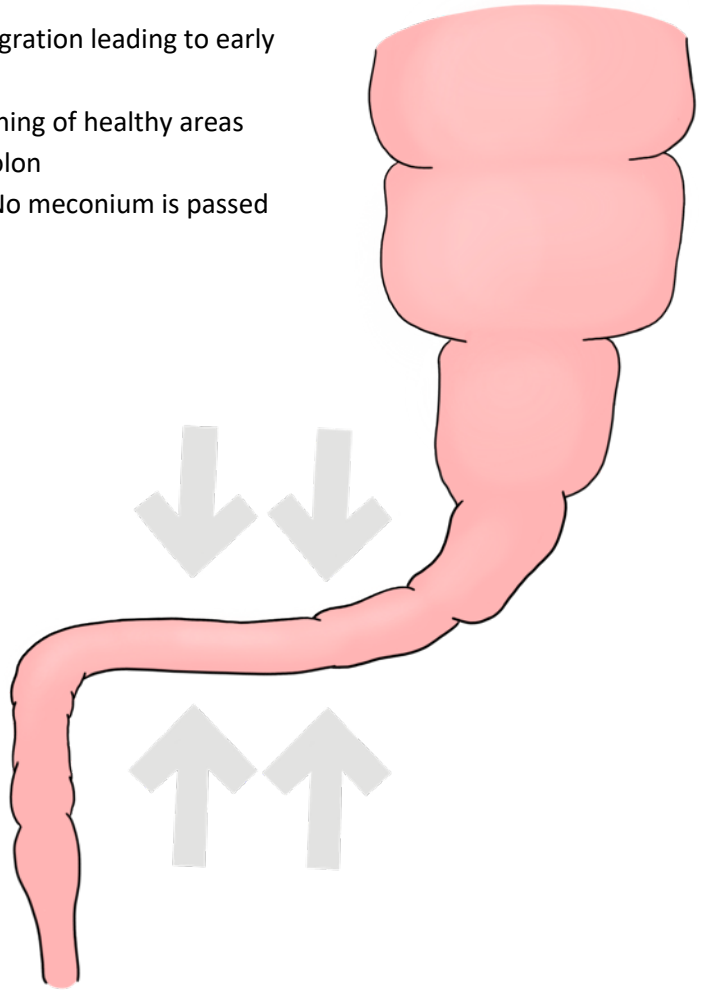


- Histology: Ectopic acid-secreting gastric mucosa and pancreatic tissue are common findings in the diverticulum
- Clinical features:
    1. Hematochezia/melena
    2. RLQ pain
    3. Intestinal obstructions
    4. Perforation of the bowel

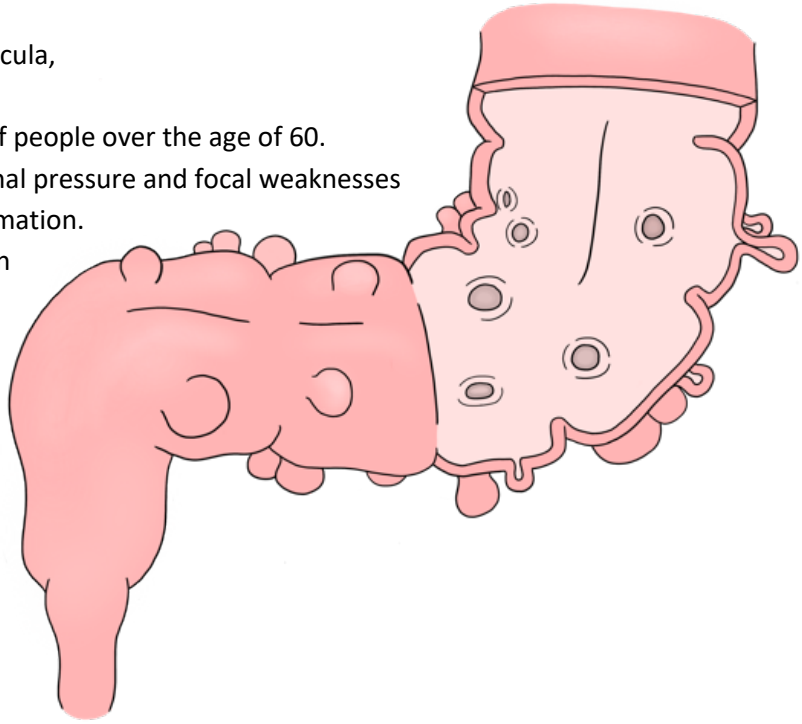
[1]Vitelline duct: Embryonic connection between yolk sac and midgut via the umbilicus

2.1.2 – Hirschsprung Disease

- Also called congenital megacolon
- Occurs when there are no enteric nerves in distal segment of colon
    1. Rectum always involved!
    2. May involve the entire colon
- Clinical picture:
    1. Present at birth
    2. Typically occurs in males
    3. Failure to pass meconium
- Pathomechanism: Defective neural crest migration leading to early death of ganglion cells.
- Narrowing of area with no nerves and widening of healthy areas proximal to the aganglionic section: megacolon
- Narrowing leads to neonatal constipation: No meconium is passed
- Associated with Down syndrome



2.1.3 – Diverticulosis



- Defined as the presence of many diverticula, most of which are in the sigmoid colon.
- Very common pathology found in half of people over the age of 60.
- Pathomechanism: Increase in intraluminal pressure and focal weaknesses in colonic wall leading to diverticula formation.
- Risk factors: Anything associated with an increase in intraluminal pressure increases chance of diverticula formation (e.g., obesity and low fiber diet).
- Not to be confused with diverticulitis, however diverticulitis can be a complication of diverticulosis

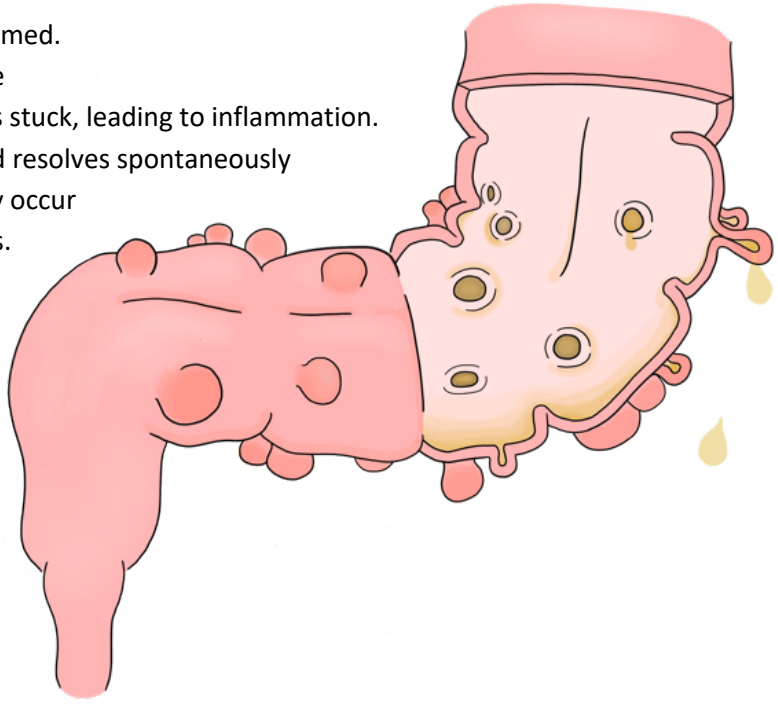
CLINICAL CORRELATION

Diverticulosis

It is good practice to recommend patients to avoid foods which can become stuck in diverticula (e.g., seeds, nuts)

2.2 – Inflammatory and Malnutrition Disorders

2.2.1 – Diverticulitis



- Occurs when diverticula become inflamed.
- Pathomechanism: Diverticula become filled with digestive material that gets stuck, leading to inflammation.
- Often does not require treatment and resolves spontaneously
    1. Perforations of the colon may occur
- Not to be confused with diverticulosis.

2.2.2 – Whipple Disease

- Men >> Women
- Infection with gram positive intracellular Tropheryma whipplei.
- Pathomechanism: Results in foamy macrophages in intestinal lamina propria that destroy infected cells.
- Can result in lymphatic obstruction leading to swollen mesenteric lymph nodes.
- The most distinctive sign of Whipple disease is malnutrition due to malabsorption; other symptoms include.
    1. Diarrhea
    2. Lymphadenopathy
    3. Arthritis
    4. Neurological symptoms

2.2.3 – Celiac Disease

- Autoimmune disease that targets gluten protein (gliadin) leading to intolerance.
- Occurs in 1 in 100 people.
- Associated genes: HLA-DQ2 and HLA -DQ8
- Associated autoimmune diseases: Sjogren's syndrome, thyroiditis, and type I diabetes.
- Pathomechanism: IgA anti-tissue transglutaminase (IgA tTG) is the primary responsible antibody.
    1. Production of the antibody results in atrophy of intestinal villus and loss of brush border resulting in malabsorption in the distal duodenum and proximal jejunum.
- Morphological features:
    1. Villous atrophy
    2. Crypt hyperplasia
    3. Intraepithelial lymphocytosis
- Symptoms:
    1. Malnutrition
    2. Diarrhea
    3. Dermatitis herpetiformis (type of dermatitis unique to celiac disease)
- There is a mild risk of T-cell lymphoma later in life
- The only treatment is a gluten free diet.

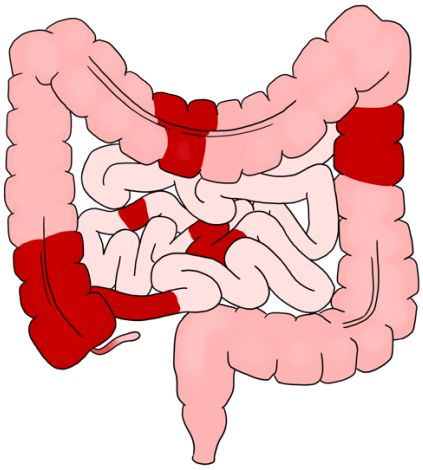
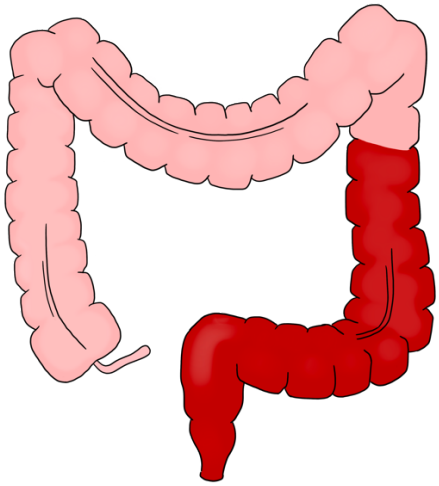
CLINICAL CORRELATION

Celiac Disease

This is the most common cause of pathologic malnutrition and should always be at the top of your differential diagnosis if malnutrition is seen in a clinical setting.

2.2.4 – Inflammatory Bowel Disease

- Inflammatory bowel disease (IBD) is split into 2 separate pathologies: Crohn disease and ulcerative colitis
- Both may present with extraintestinal symptoms like arthritis, cholangitis and uveitis

<table>
<tr><th></th><th>Crohn Disease</th><th>Ulcerative Colitis</th></tr>
<tr><td>Location</td><td>- Affects any portion of GI tract, including the oral cavity
- More commonly in terminal ileum and proximal colon
- Often multiple separate lesions throughout the GI (skip lesions)
  </td><td>- Lesions always start at rectum
- Lesions spread continuously along the colon
- Rectum involvement is required to make the diagnosis
  </td></tr>
<tr><td>Morphological features</td><td>- Lesions are transmural[1], resulting in fistulas, ulcers and fissures
- Granulomatous disease
- Cobblestone appearance of Mucosa
- Creeping fat leading to wall thickening</td><td>- Only mucosa and submucosa are inflamed leading to ulcerations
- Non-granulomatous disease
- Pseudopolyps may be present
- Loss of haustra giving “lead pipe” appearance</td></tr>
<tr><td rowspan="2">Complications</td><td>- May result in bloody diarrhea
- Fistulas
- Abscesses
- Strictures → Obstruction</td><td>- Always results in bloody diarrhea
- Perianal disease
- Fulminant colitis
- Toxic megacolon
- Perforation</td></tr>
<tr><td colspan="2">Malabsorption and increased colorectal cancer risk</td></tr>
</table>

[1]Transmural = Entire thickness of the bowel wall involved

MNEMONIC – CROHN DISEASE

Grandma creeping along the cobblestone deep into the night

Grandma – Granulomatous disease
Creeping – Creeping fat
Cobblestone – Cobblestone appearance
Deep – Entire thickness of intestinal wall affected; Transmural

CROHN OR CROHN'S DISEASE?

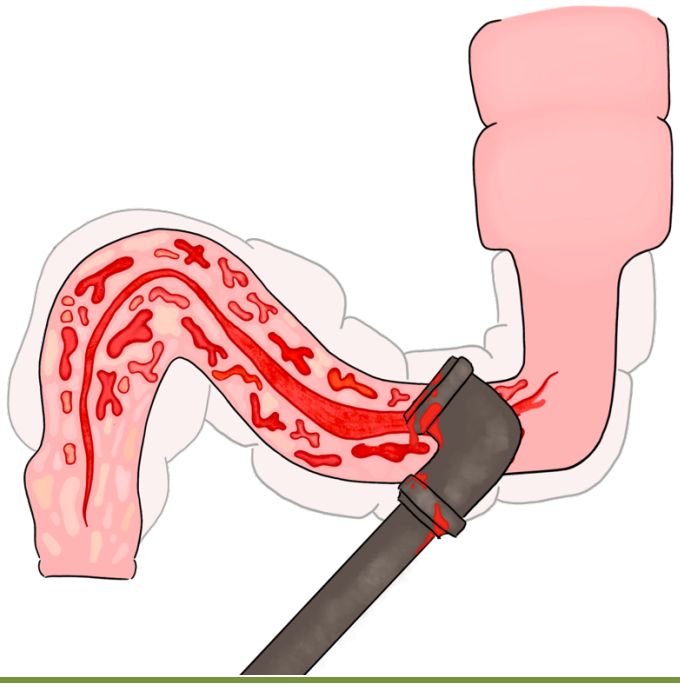
The medical community is divided; some say it is grammatically incorrect to leave out the apostrophe, but it is widely agreed that the apostrophe should only be used in cases where the disease was named after the *patient* in whom the disease was first described. In cases where it's named after the doctor, it should be left out.

In Poland, Crohn disease is known as Leśniowski-Crohn's disease because the first doctor to describe the disease was the Polish Dr. Antoni Leśniowski in 1904. The American Dr. Burrill Bernard Crohn described the disease almost 30 years later.

MNEMONIC – ULCERATIVE COLITIS

Bloody lead pipe scraping the wall

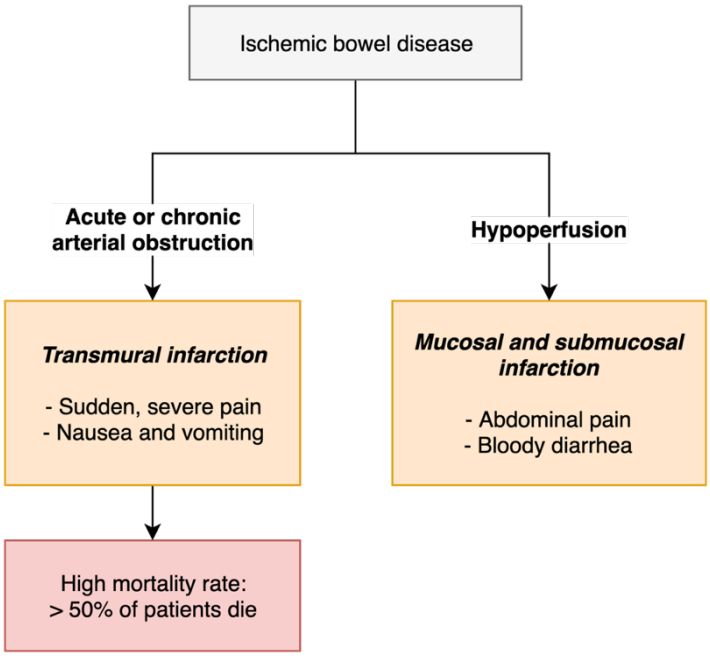
Bloody – Always results in bloody stool
Lead pipe – Lead pipe appearance
Scraping the wall – Only affects outer mucosa/submucosa



2.3 – Circulatory Disorders

2.3.1 – Ischemic Bowel Disease

- Defined as any bowel ischemia due to vascular compromise



I. Pathomechanism:

- Most common location for ischemia is the *splenic flexure* due to it being a so called "Watershed area", which is a part of an organ that is between two supplying arteries.

Acute mesenteric ischemia	Chronic mesenteric ischemia
- Embolic occlusion of superior mesenteric artery leads to small bowel necrosis - Typically present with extreme abdominal pain and red "currant jelly" stools may be present	- Atherosclerosis of either the celiac artery, superior mesenteric artery or inferior mesenteric artery - Hypoperfusion leads to epigastric pain, often referred to as "intestinal angina"

2.3.2 – Angiodysplasia

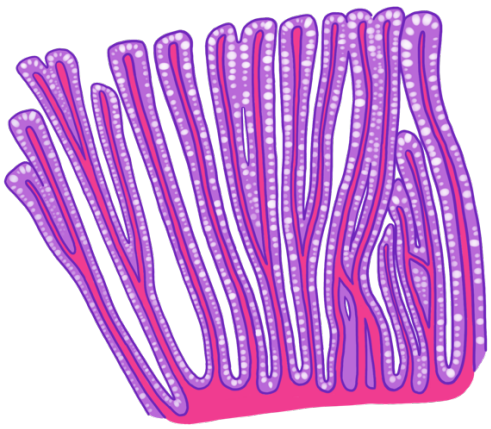
- More common on the right side of the colon in older patients
- Pathomechanism: Malformed submucosal and mucosal blood supply, most commonly the submucosal veins that are incredibly dilated
- Cause 20% of all lower GI bleeding

2.3.3 – Necrotizing Enterocolitis

- Occurs to premature formula fed children who have immature immune system and gastrointestinal tract
    1. Most common gastrointestinal emergency in neonates: Bloody stool, sepsis, shock
- Pathomechanism: Idiopathic Ischemic injury leading to transmural necrosis
    1. There are some potential triggers, like non-human milk, antibiotics, anemia
    2. May lead to complications due to perforation
- Most common in terminal ileus and ascending colon
- Complications:
    1. Strictures → Bowel obstruction
    2. Short bowel syndrome → Malabsorption

2.4 – Intestinal Cancer

2.4.1 – Colonic Polyps

<table>
<tr><th>Polyp type</th><th colspan="2">Description</th></tr>
<tr><td>Hyperplastic</td><td colspan="2">- Caused by decreased turnover of the epithelium
- Most common benign polyp of colon
- Found in rectosigmoid region
- No malignant potential</td></tr>
<tr><td rowspan="2">Hamartomatous[1]</td><td>Juvenile</td><td>Peutz-Jeghers syndrome</td></tr>
<tr><td>- Most common type of Hamartomatous polyp
- Occurs either sporadically in children < 5 years or due to the autosomal dominant juvenile polyposis syndrome (JPS).
- Each individual polyp is benign, but there is an increased risk of adenocarcinoma</td><td>- Autosomal dominant syndrome causing multiple non-malignant hamartomas throughout the GI.
- Mucocutaneous hyperpigmentation of mouth, lips, hands, and genitals also observed.
- Increased colorectal cancer risk as well as other cancers.</td></tr>
<tr><td>Adenomatous</td><td colspan="2">- Precancerous polyp with malignant risk: Malignant risk is higher with larger size and more dysplasia
- Commonly asymptomatic
- Two histological subtypes: Tubular and villous. Adenomas can be mostly tubular, mostly villous or both.
- The villous type is more malignant: “Villous is the villain”
Tubular
 
Villous
  </td></tr>
</table>

[1]Hamartomatous polyps: Tumor-like growths from tissue normally found at the site they grow in

2.4.2 – Colorectal Cancer

- Adenocarcinoma is the most common type of malignancy of the intestines
- Most commonly affects patients above the age of 50
- Patients with family history of colorectal cancer and those who inherit specific genetic syndromes are at increased risk. The most important syndromes are as follows:

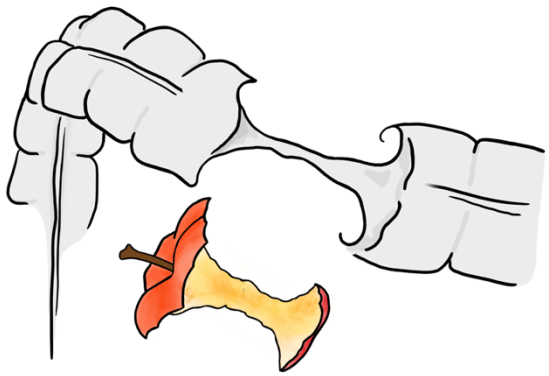
Genetic syndromes	Description
Familial adenomatous polyposis (FAP)	- Autosomal dominant disorder causing several colorectal adenomas to appear by the time the person is a teenager. - Mutation of APC gene leads to 100% chance of colorectal cancer (CRC) unless entire colon is resected.
Hereditary nonpolyposis colorectal cancer (HNPCC)	- Also known as Lynch syndrome - Autosomal dominant mutation of DNA mismatch repair genes. - 80% progress to CRC. - Proximal colon always involved. (right side) - May lead to several other types of cancers
Gardner syndrome	- Characteristics of FAP with osteomas of facial bones and long bones, epidermal cysts, fibromatosis and abnormal dentition - Congenital hyperpigmentation of retinal pigment epithelium is observed.
Turcot syndrome	- Characteristics of FAP with medulloblastomas

I. Risk factors

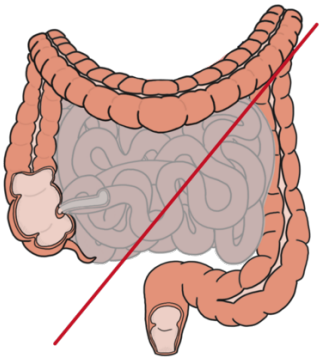
- IBD
- Tobacco
- Villous adenomas
- Juvenile polyposis syndrome
- Peutz-Jeghers syndrome

II. Clinical presentation

- Iron deficiency anemia due to bleeding
- Occult blood in stools
- Weight loss
- Imaging: X-ray studies with contrast may show the "*apple core sign*" indicating a lesion growing within the lumen, narrowing it.
- Clinical presentation depends on the location in the colon



Clinical features of colon cancer according to location

	Right-sided	Left-sided
		
Incidence	Less common	More common
Epidemiology	Women > Men	Men > Women
Prognosis	Worse	Better
Type	- Mucinous adenocarcinomas - Sessile serrated adenomas	Tubular and villous adenocarcinoma
Symptoms	- Anemia - Vomiting	- Change in bowel habits - Hematochezia[1]

[1]Hematochzia – Fresh, bright red blood in stool

III. Pathogenesis

- Loss of the APC gene is the initiating event for colorectal adenocarcinoma
- The APC gene is responsible for breakdown of beta-catenin, which normally stimulates cell proliferation and inhibits apoptosis
- The adenoma-carcinoma sequence is the most common pathway for sporadic colorectal carcinogenesis:

MNEMONIC

AK-53
APC → KRAS → P53

The adenoma-carcinoma sequence

Knudson two-hit hypothesis:
Both tumor-supressor alleles must be lost to cause cancer

First hit
Somatic or germline mutations in one allele of APC

Second hit
Mutation in the second APC allele

KRAS mutation

Loss of TP53

Normal colon → Mucosa at risk → Adenoma → Carcinoma

2.5 – Test Yourself

1) Indicate the false statement regarding inflammatory bowel disease
a) Crohn disease can cause lesions anywhere in the GI tract from mouth to anus
b) Ulcerative colitis most commonly occurs in the ileocecum junction
c) Crohn disease presents with multiple skip lesions
d) Fistulas are more commonly seen in Crohn disease compared to Ulcerative colitis
e) A and B are false

2) Patient presents to gastroenterology department presenting with abdominal pain and blood in stools, on X-ray barium contrast a single large diverticula is present located in the epigastric region. What is the most likely diagnosis?
a) Hirschsprung Disease
b) Diverticulitis
c) Diverticulosis
d) Whipple disease
e) Meckel Diverticulum

2) What disease is not associated with celiac disease?
a) T-Cell lymphoma
b) Sjogren's syndrome
c) Thyroiditis
d) Type II diabetes
e) Type I diabetes

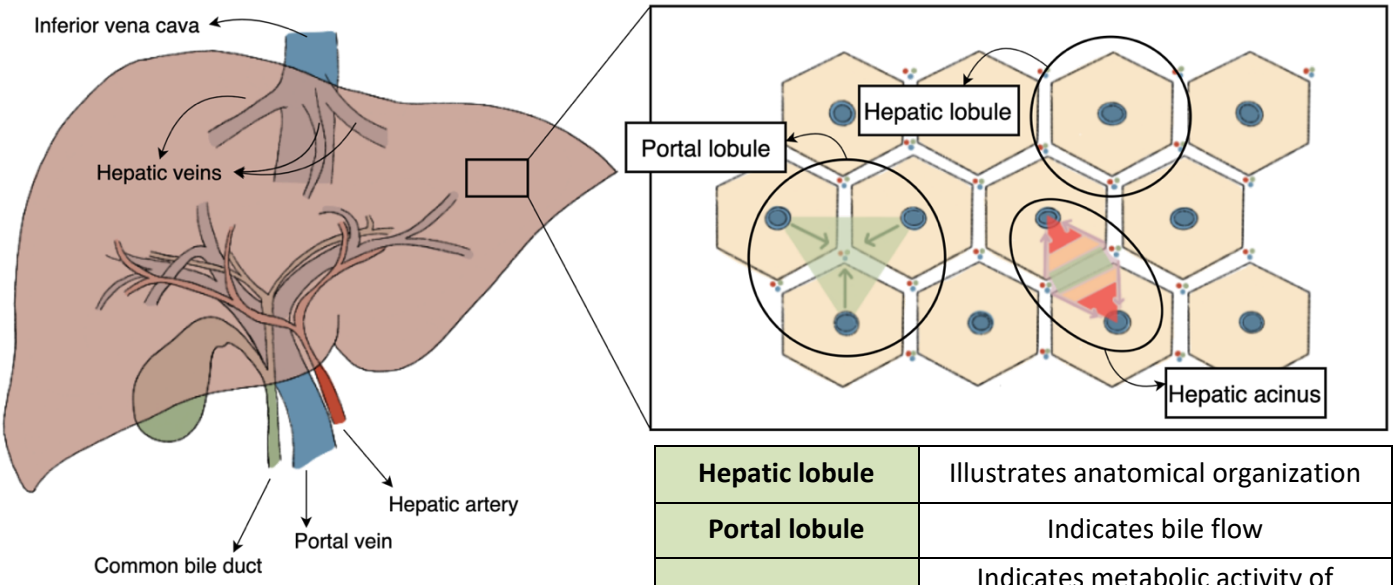
4) Most common benign polyp of intestines?
a) Adenomatous
b) Hyperplastic
c) Juvenile
d) Cystic
e) Non of the above

5) What features are characteristic of colorectal cancer?
a) Typically an adenocarcinoma
b) "Apple core" appearance on imaging
c) Iron deficiency anaemia
d Weight loss
e) All of the above

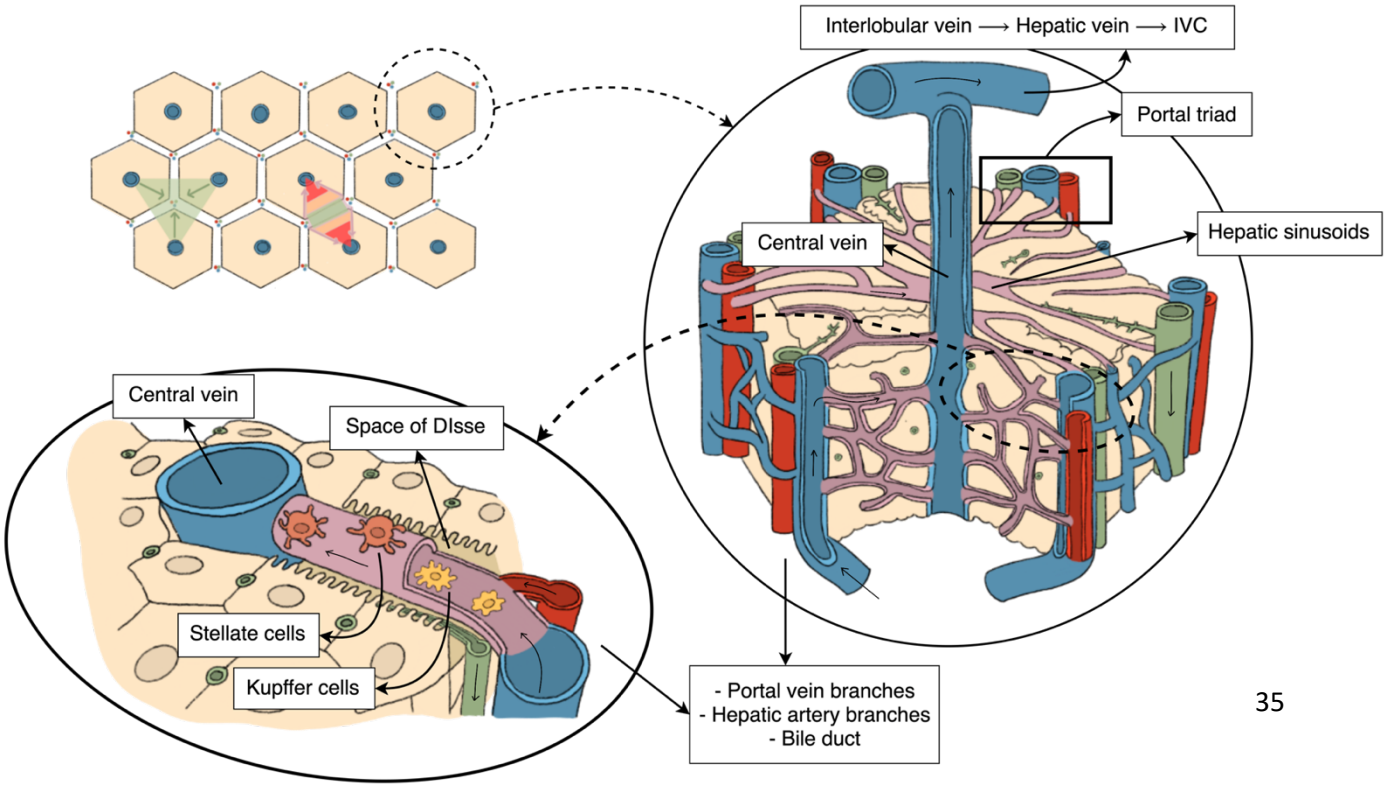
6) Indicate the correct statement regarding ischemic bowel disease
a) Most commonly seen in premature infants
b) Characterized by painless diarrhoea
c) Intestinal angina is a characteristic feature of acute mesenteric ischemia
d) Most common location for ischemia is the splenic flexure
e) None of the above

Section 3 - The Liver and Gallbladder

3.1 – Liver Anatomy and Histology



Hepatic lobule	Illustrates anatomical organization
Portal lobule	Indicates bile flow
Hepatic acinus	Indicates metabolic activity of hepatocytes



3.2 – Clinical Manifestations of Liver Disease

- The 3 major manifestations of liver disease are: Liver failure, portal hypertension and cholestasis

I. Understanding liver function tests

- Remember that most of the liver enzymes can indicate disease processes in other parts of the body, as they are produced in many tissues

Loss of hepatocyte integrity	
↑ AST[1] + ALT[2]	AST is located both in the mitochondria and cytoplasm, while ALT is mainly in the cytoplasm. Alcohol is a mitochondrial toxin → AST will be higher than ALT in alcoholic liver disease
Damage to bile canaliculus	
↑ Alkaline phosphatase (AP)	Also elevated in bone disease: *isolated* elevations in AP indicates bone disease. Unreliable in children as they have a high bone turnover.
↑ g-glutamyl transpeptidase (GGT)	Not released by bones; Used to confirm that elevated AP is due to biliary disease
Hepatocyte function	
↓ Serum albumin	Injured hepatocytes cannot produce albumin
↑ Prothrombin time (PT)	Injured hepatocytes cannot produce coagulation factors (V, VII, X), prothrombin or fibrinogen
↑ Serum ammonia	Inability to convert ammonia into urea for excretion
↓ Serum BUN[3]	

[1]AST: Aspartate aminotransferase, found in various tissues like liver, kidney, heart, muscle and RBCs

[2]ALT: Alanine aminotransferase, found mostly in liver and kidney

[3]BUN: Blood urea nitrogen

3.2.1 – Liver Failure

- > 80% of liver parenchyma is damaged → Inability to maintain homeostasis
- May be due to
    1. Sudden destruction of a large portion of the liver
    2. Result of end stage liver disease
- Transplantation is the only cure

Types of liver failure

	Description	Causes
Acute/fulminant liver failure	Massive necrosis of hepatocytes	**A** – Acetaminophen, Hepatitis A, Antimycobacterial drugs, Antidepressants **B** – Hepatitis B **C** – Cryptogenic[1], Hepatitis C **D** – Drugs/toxins, Death cap mushroom
Chronic liver disease	Cirrhosis	- Long standing liver disease - Hepatitis B or C
Acute-on-chronic liver failure	Minor precipitating factors may induce decompensation of a normally compensated patient.	- Heart failure - Sepsis - Drugs or toxins - Hepatitis D superinfection[2] - Malignancy
Microvesicular fatty change	Dysfunction of hepatocytes *without* necrosis	- Tetracyclines - Fatty liver of pregnancy - Reye syndrome[3]

[1]Cryptogenic = Unknown cause

[2]Coinfection with hepatitis B

[3]Occurs when you give aspirin to children with a viral infection

Clinical features of liver failure

Symptom	Mechanism
Jaundice	Decreased removal of bilirubin from the blood stream → hyperbilirubinemia
Hepatic encephalopathy (Confusion, asterixis, coma)	Hyperammonemia Triggered by *increased nitrogen delivery* to the liver from GI bleeding, constipation, infection or *decreased removal* due to kidney failure or diuretics
Peripheral edema	Hypoalbuminemia → Decreased oncotic pressure in vasculature
Gynecomastia, testicular atrophy, spider angiomas	↓ inactivation of estrogens in the liver → Hyperestrogenemia
Gastrointestinal bleeding	↓ Coagulation factors

- A late sign of liver failure is "Fetor hepaticus" described as the breath having a sweet, fecal smell similar to freshly mowed hay

3.2.2 – Cholestasis

- Disrupted formation and/or flow of bile
- Accumulation of bilirubin and other components of bile in the liver parenchyma

I. Morphology

- Bile pigment in hepatocytes, bile canaliculi and Kupffer cells
- Feathery degeneration of hepatocytes
- Proliferation of duct bile duct epithelial cells due to increased pressure from bile stasis

II. Signs of cholestasis

- Jaundice: Yellow discoloration of skin and/or sclera
- Pruritus: Itching due to bile salt accumulation in the skin
- Skin xanthomas: Accumulation of cholesterol in the skin
- Nutrition deficiencies: Fat soluble vitamins (A,D,E + K)

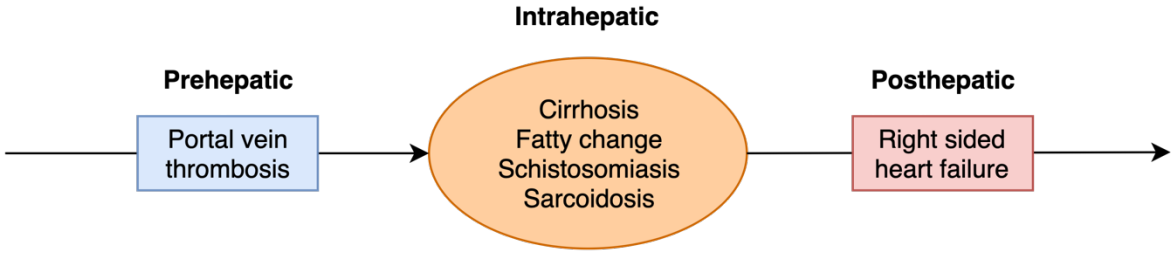
III. Lab findings supporting cholestasis

- Elevated AP and GGT

3.2.3 – Portal Hypertension

- Obstruction of portal blood flow at the level of hepatic sinusoids

Causes of portal hypertension



Clinical features of portal hypertension

Symptom	Mechanism
Ascites	Hepatic sinusoidal hypertension + retention of sodium and water by kidneys[1] → Lymph from liver and intestine leaks into peritoneal cavity
Varices in esophagus, stomach, rectum and umbilicus[2]	Portosystemic shunting: Blood flows into capillary beds that are shared by hepatic and systemic circulation Esophageal and gastric varices may lead to melena, or rupture and cause massive bleeding and death!
Splenomegaly	Long standing portal hypertension can cause blood to back up into the spleen
Hydrothorax	Fluid in the right pleural cavity via the transdiaphragmatic lymphatics

[1]Hepatorenal syndrome
[2]Umbilical varices are termed "caput medusae"

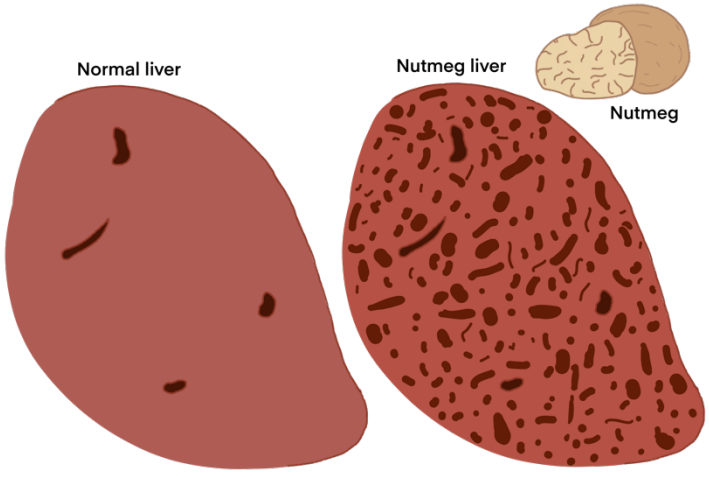
- Portal hypertension may also present with signs of liver failure described in the previous table

CLINICAL CORRELATION

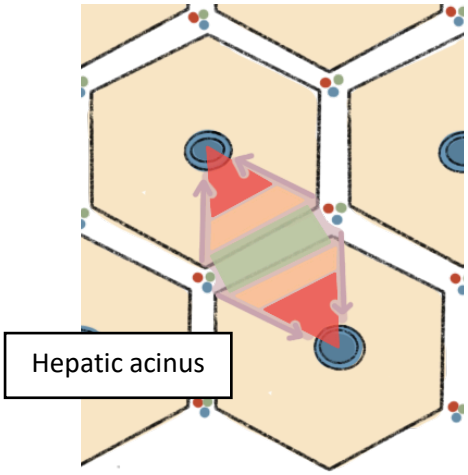
Nutmeg Liver

Passive congestion of the liver due to backup of venous blood flow (e.g. right sided heart failure).

The liver is tense and has a mottled and dark appearance due to centrilobular hemorrhagic necrosis. May progress to cirrhosis.



3.3 – Morphological Patterns of Liver Injury



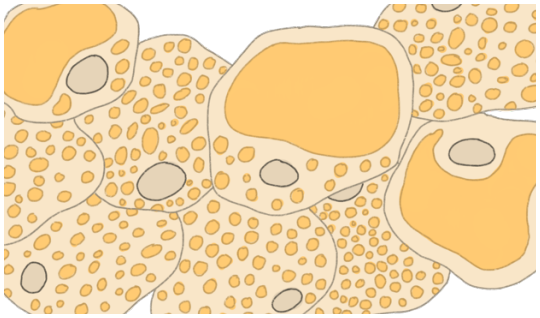
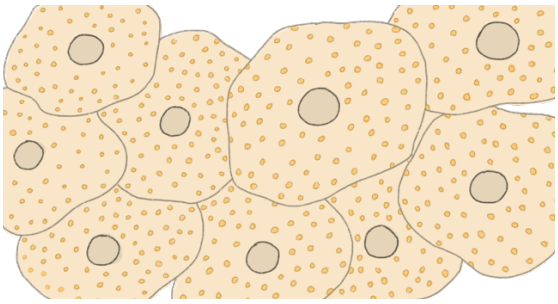
I. Zonal injury to hepatocytes

- Refers to the metabolic zones in the hepatic acinus
- Zone 1 (Green): Gestational eclampsia
- Zone 2 (Yellow): Yellow fever
- Zone 3 (Red, most common): Shock, passive congestion, toxins (Acetaminophen)

3.3.1 – Steatosis

- Fatty change of the liver: Buildup of triglycerides
- Liver is soft, large with a yellow and smooth surface

Types of steatosis

Macrovesicular	Microvesicular
- More common, less severe - Nuclei displaced by lipids	- Nuclei not displaced
- Obesity, unhealthy diet - Diabetes mellitus - Alcohol abuse 	- Alcohol abuse - Acute fatty liver of pregnancy - Reye syndrome 

CLINICAL CORRELATION

Reye Syndrome

- Edematous encephalopathy, lethargy, hepatomegaly and even coma due to mitochondrial dysfunction.
- Occurs in young children with a viral infection who are given aspirin.

I. Mechanism

- Defective assembly and secretion of lipoproteins
- Increased peripheral breakdown of fat
- Shunting of substrates towards lipid biosynthesis

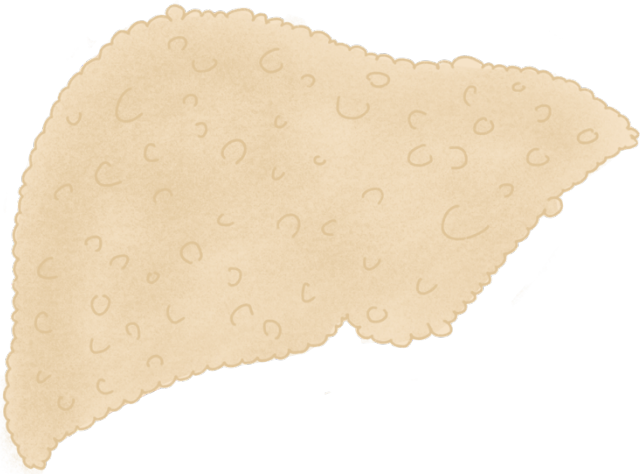
II. Clinical significance

- Depends on the degree of liver involvement
    1. < 33% → Mild steatosis with minimal effect on function
    2. 34-66% → Moderate
    3. > 66% → Severe steatosis that may impair cellular function

III. Histology

- Clear vacuoles within hepatocytes
- Orange/red color when stained with Oil Red O or Sudan IV

3.3.2 – Cirrhosis



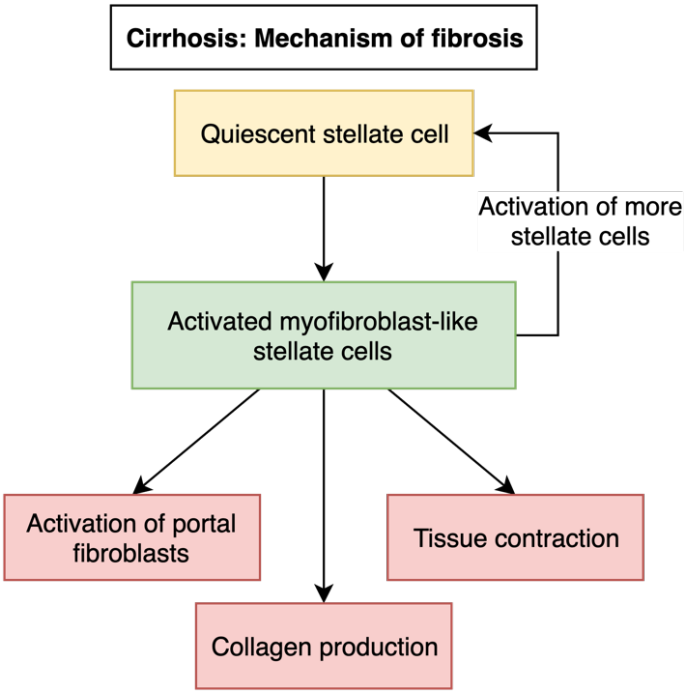
- The last stage of chronic liver disease
- Staining for fibrosis: Trichrome

I. Causes

- Alcohol abuse (60-70%)
- Viral hepatitis
- Idiopathic
- Hereditary diseases
- Non-alcoholic steatohepatitis

II. Morphology

- Diffuse injury
- Liver parenchyma is divided into regenerative nodules separated by fibrotic septa made from collagen type 1 and 2
- Abnormal connections between vascular in- and outflow of the liver



III. Clinical features

- Often clinically silent until late in the disease process
- Non-specific symptoms: Anorexia, weight loss, fatigue
- Liver failure

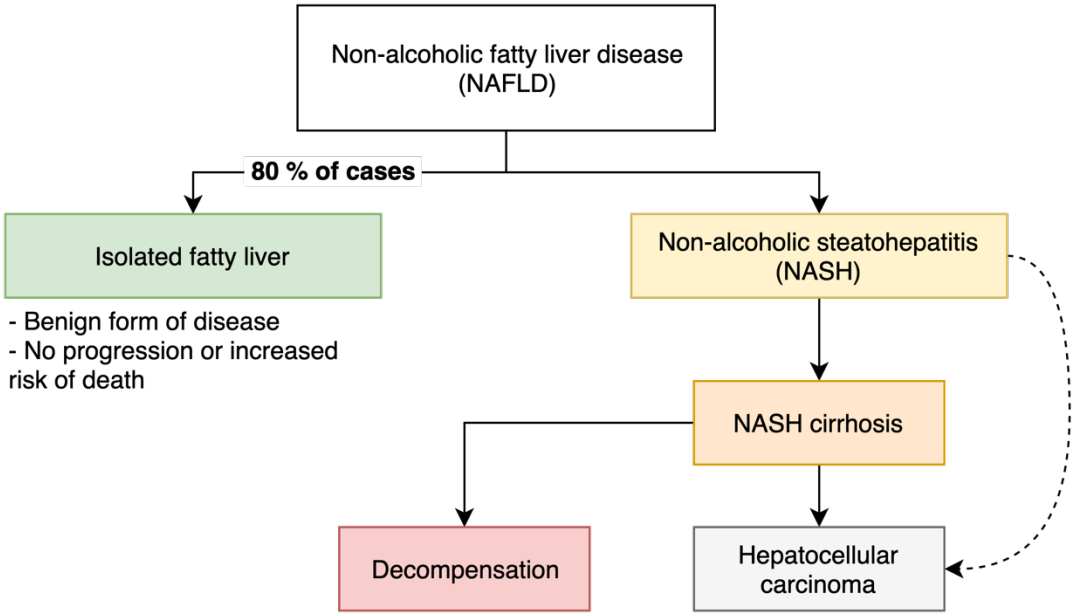
IV. Causes of death

- Hepatic coma
- Gastrointestinal tract bleeding
- Hepatorenal syndrome
- Hepatocellular carcinoma

3.4 – Fatty Liver Disease

3.4.1 – Non-Alcoholic Liver Disease

- Liver changes without history of alcohol consumption
- Treatment: Weight loss if patient is obese and correct hyperlipidemia



3.4.2 – Alcoholic Liver Disease

- Also called alcoholic hepatitis
- Not every alcoholic develops severe liver disease with cirrhosis, indicating that other factors play a role:
    1. Sex: Women > Men
    2. Genetic: African Americans > Caucasian Americans, polymorphisms in detoxifying enzymes
    3. Comorbidities: HCV, HBV, HIV, hemochromatosis etc.
- Clinical features:
    1. Alcoholic hepatitis: Acute liver failure with anorexia, tender hepatomegaly and fatigue. Associated with period of heavy drinking
    2. Hepatic steatosis: Hepatomegaly
    3. Cirrhosis: Only 10-15% of chronic alcoholics develop cirrhosis
- Treatment: Avoid alcohol, usually resolves on its own
- Morphology:
    1. Alcoholic hepatitis: Ballooning degeneration and Mallory-bodies
    2. Hepatic steatosis: Microvesicular lipid vacuoles within hepatocytes, *macrovesicular* if chronic

3.5 – Hepatitis

CLINICAL CORRELATION

Defining hepatitis severity
Intensity of inflammation (grade) = G1-4
Intensity of fibrosis = F1-4 (F4 = Cirrhosis)

I. Causes

- Viral: Hepatotropic viruses
- Autoimmune
- Systemic viral infections
    1. Usually Epstein-Barr virus (EBV)
    2. Rarely cytomegalovirus (CMV), rubella, adenovirus, herpesvirus

II. Morphology

- Acute hepatitis
    1. Eosinophilic hepatocytes with shrunken nuclei (representing apoptosis) and/or swollen hepatocytes (ballooning degeneration)
    2. Kupffer cell hyperplasia
    3. Inflammatory infiltrate of portal tract
- Chronic hepatitis: Inflammation of the portal tracts, that can progress and become cirrhosis

CLINICAL CORRELATION

Liver biopsy
Used to diagnose diffuse liver injury. A needle is guided by ultrasound through the abdominal skin and a sample of the liver tissue is taken.

Complications – The 3 B's
- **B**leeding, **B**ile leakage and **B**acteremia
- Injuries to nearby organs

3.5.1 – Viral Hepatitis

Possible outcomes of viral hepatitis

Acute asymptomatic infection with recovery	Most commonly HAV and HBV "subclinical"
Acute symptomatic infection with recovery	1) Incubation: 3 – 26 weeks 2) Asymptomatic pre-icteric phase 3) Symptomatic icteric phase 4) Convalescence
Acute liver failure	HAV, HBV and HEV. May resolve, if not: liver transplant is only option
Chronic hepatitis	HCV. Clinical, biochemical or serological evidence of disease > 6 months. Younger age at time of infection correlated with higher risk of progression to chronic disease.
Carrier state	Patient carries and transmits virus, but is asymptomatic
HIV and chronic hepatitis	Frequent coinfection due to similar modes of transmission and risk factors. More aggressive liver disease

I. Hepatitis A

- Think: "Hepatitis **A**cute"
- Outbreaks usually occur in schools, daycares, cruises – Any overcrowded space
- Typically causes a mild or asymptomatic, self-limited disease in children
    1. Jaundice, loss of appetite, fatigue
    2. Rare in adults
    3. People who smoke cigarettes may have a funny symptom: *Aversion to smoking*
- Virus is present in the stool a couple of weeks *before* *and* *after* the onset of jaundice!

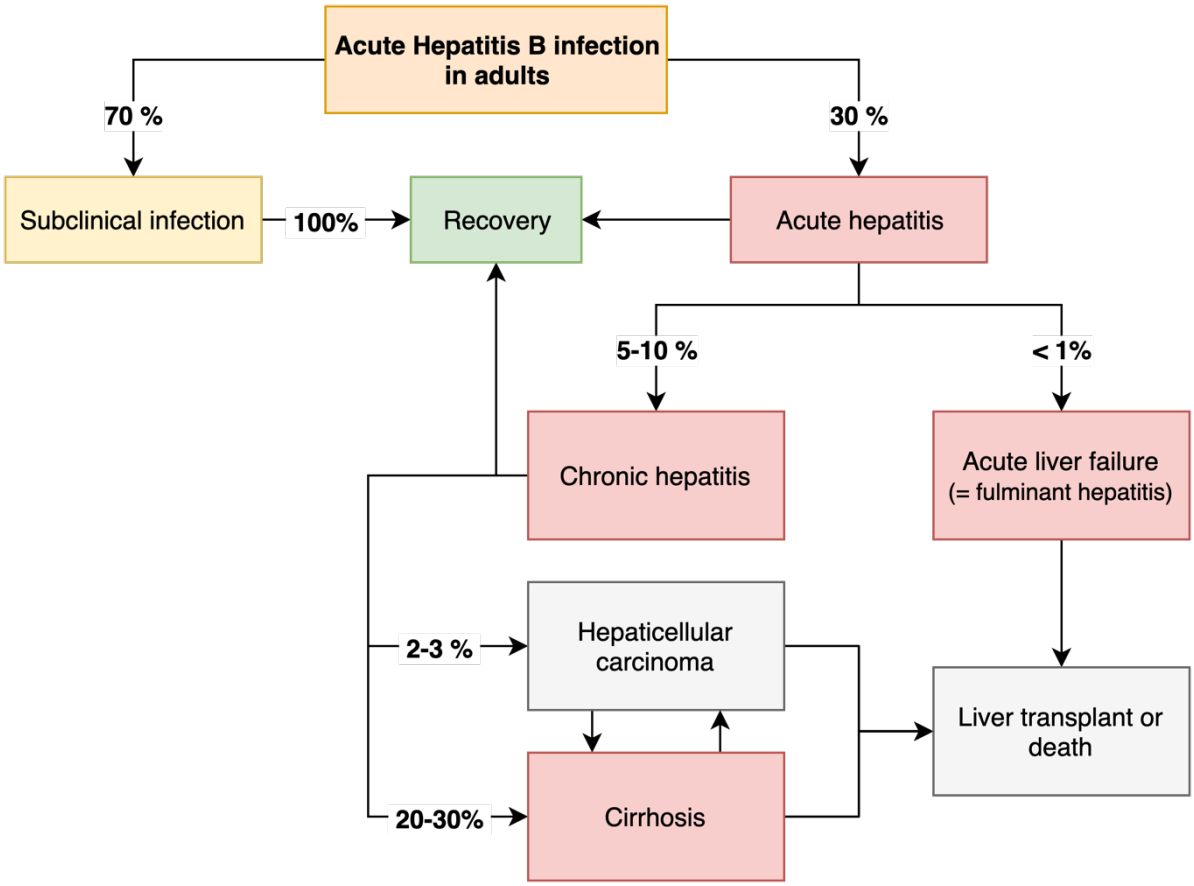
II. Hepatitis B

- Has 8 different genotypes
- Most cases causes a self-limited acute hepatitis which resolves without problems
- 5% become chronic → Significantly increased risk of hepatocellular carcinoma
- Mechanism of liver injury is by the cytotoxic action of $CD8^+$ T-cells (NOT the virus itself!)
- Carrier state with HBV: HBeAg is present, but serum HBV DNA is undetectable
- Morphology: Ground glass appearance of hepatocyte cytoplasm

HBV serology – Diagnosis

Serological marker	Notes
HBsAg	*Indicates active viral replication* - Symptoms are present - Used in the hepatitis B vaccine - Chronic infection defined by positive HBsAg > 6 months
HBV-DNA	*Indicates active viral replication*
HBeAg	*Indicates viral replication + high infectivity* - Symptoms are typically present
HBcAg	Not present in vaccinated patients
Anti-HBcAg	First antibody to appear, present in window period
Anti-HBsAg	*Indicates end of acute disease + immunity* - Can stay in the body for years, indicating immunity - A patient with anti-HBsAg alone has been immunized by *vaccine*, not by a past infection
Anti-HBeAg	*Indicates low infectivity*

Possible outcomes of hepatitis B infection in adults



III. Hepatitis C

- Think: "Hepatitis **C**hronic"
- Transmission: Needle stick injuries, perinatal, sex, surgery
- Antigenic variability: Makes it difficult for the immune system to get rid of it → High rate of progression to *chronic infection*: Around 85% turn chronic
    1. No vaccine available
- Acute infection is usually asymptomatic
    1. 20-30% of the patients develop cirrhosis, 5-20 years after acute infection
- Pathomechanism: Repeated periods of liver damage from reactivation of preexisting infection or newly mutated strains
- Morphology: Portal lymphoid aggregates, lobular areas of macrovesicular steatosis and reactive changes of the bile duct

CLINICAL CORRELATION

Hepatitis and the common cold

The lack of an available vaccine is something that Hepatitis C and the virus causing the common cold, Rhinovirus, have in common.

Both viruses present an amazing ability to frequently change their genome and antigens, making it extremely difficult for researchers to create an effective vaccine.

IV. Hepatitis D

- Requires Hepatitis B surface antigen to infect cells, hence the HBV vaccine is protective against HDV as well!
    1. Coinfection: HBV and HDV are transmitted together
    2. Superinfection: Chronic HBV carrier is exposed and infected by HDV
- Clinical presentation: Usually self-limited
    1. Coinfection: Indistinguishable from HBV infection
    2. Superinfection: Exacerbation of already existing hepatitis
- IgM antibodies against HDV indicates recent exposure

V. Hepatitis E

- Water-borne infection causing a self-limiting hepatitis
- Causes epidemics in Asia, Africa and Mexico, otherwise travelers are at risk
- No association with chronic hepatitis, but may cause fatal hepatitis in pregnant women

VI. Hepatitis G

- Not a hepatotropic virus (hence not in the table below)
- Replicates in bone marrow and spleen
- May co-infect HIV patients

Overview of the hepatotropic viruses

Virus	Type	Transmission	Incubation time	Chronic disease	Diagnosis
A	RNA	Fecal-oral	2-6 wk.	*No*	Serum IgM ab
B	Partially dsDNA	Parenteral, sexual contact, perinatal	*2-26 wk.*	5-10%	See own table
C	RNA	Parenteral	4-26 wk.	*>80%*	ELISA for antibodies or PCR for RNA
D	Circular defective ssRNA	Parenteral	2-26 wk.	Coinfection: 10% Superinfection: 90-100%	IgM or IgG Serum RNA HDAg in iver
E	ssRNA	Fecal-oral	4-5 wk.	Immunocompromised patients only	IgM and IgG PCR for RNA

MNEMONIC – FECAL-ORAL TRANSMISSION

Vowels

The hepatitis viruses that are *vowels* are the only ones with fecal-oral transmission

3.5.2 – Autoimmune Hepatitis

- Progressive, chronic liver disease with unknown etiology, associated with other autoimmune disease
- Females are more often affected, may present in childhood
- Clinical picture is similar to viral hepatitis, but absent serological markers of hepatitis viruses
    1. Autoantibodies against: Nuclear (ANA), smooth muscle (SMA), actin (AAA), soluble liver-pancreas antigens (SLA/LP) and liver-kidney microsome-1 (ALKM-1)
- Clinical presentation: Fulminant hepatitis is many cases with symptoms of liver failure
- Morphology: Periportal plasma cell clusters are characteristic
- Treatment: Immune suppression
- Prognosis: Poor with high mortality and high risk of cirrhosis if left untreated

3.5.3 – Drug- and Toxin-induced Liver Injury

- Drugs are the most common cause of fulminant hepatitis
- Injury from:
    1. Direct hepatocyte toxicity
    2. Conversion of substance into active toxin by hepatocytes
    3. Immune reaction (if substance is or is converted into an immunogenic substance)
- Examples: Antibiotics, chemotherapy, alcohol, contraceptives, acetaminophen

3.6 – Genetic Liver Disease

3.6.1 – Hemochromatosis

I. Pathogenesis

- Hepcidin normally regulates iron uptake
- Mutation in HFE gene → *decreased hepcidin expression*
- Hepcidin deficiency → Iron overload

II. Morphology

- Hemosiderin accumulation in different organs
- Micronodular cirrhosis without inflammation
- Liver becomes chocolate brown
- Pancreatic fibrosis

III. Clinical features

- Men > women (due to menstrual bleeding)
- Presents at age > 40y (later in women than men due to menstruation)
- Complications[1]
    1. Diabetes
    2. Skin pigmentation
    3. Hypogonadism
    4. Heart disease
- Causes of death
    1. Cirrhosis, cardiac involvement and hepatocellular carcinoma

[1]There are several other complications, these are most important

3.6.2 – Wilson Disease

I. Pathogenesis

- Mutation in the ATP7B gene
- Decreased copper excretion into bile
- Decreased incorporation of copper into ceruloplasmin
- Decreased ceruloplasmin secreted into blood

II. Morphology

- Liver damage can be anything from minor to massive changes
- Steatosis, Mallory bodies, necrosis
- Kayser-Fleischer rings: Copper deposits around cornea

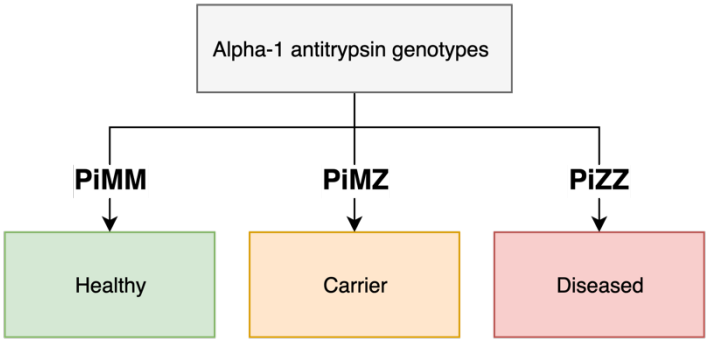
III. Clinical features

- Liver disease
- Neuropsychiatric disease

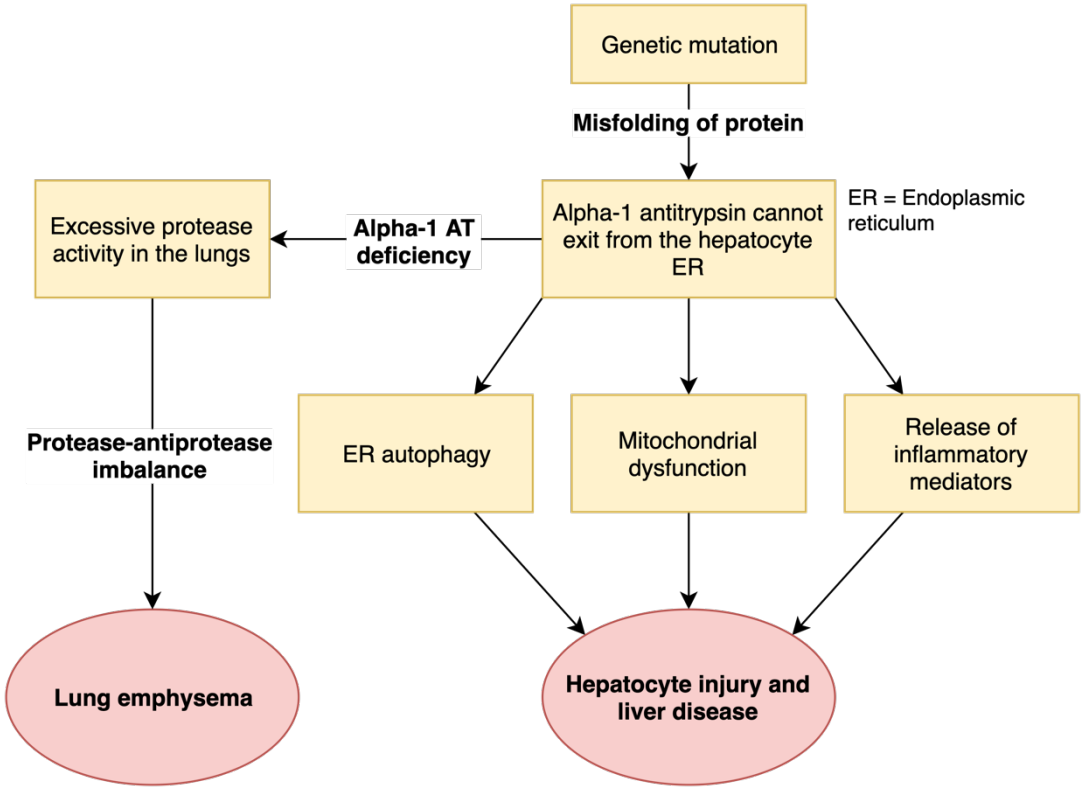
3.6.3 – α-1 Antitrypsin Deficiency

I. Genetics and pathomechanism

- Extremely polymorphic gene
- Severity of the disease depends on genotype
    1. Healthy genotype: M
    2. Mutated genotype[1]: Z
- α-1 antitrypsin is a *protease inhibitor*, explaining the "Pi" preceding the letters representing the genotypes



[1] This is only the *most common* mutated genotype, the others are low yield and therefore not mentioned here



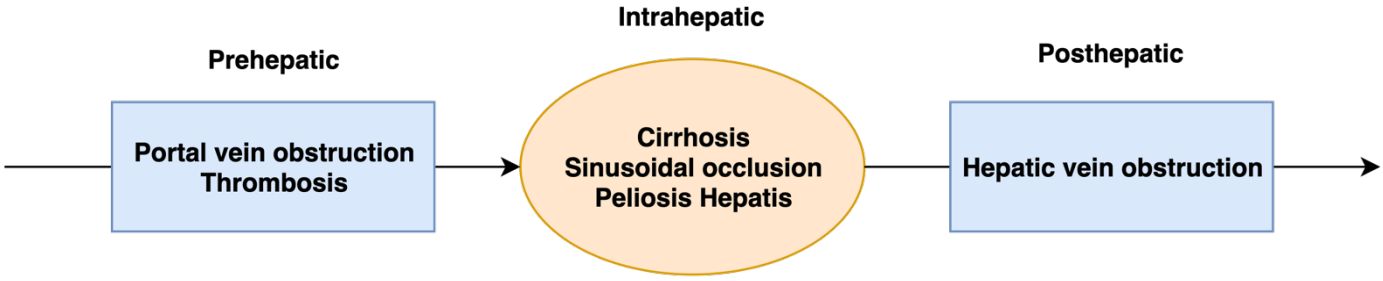
II. Morphology

- Periodic Acid-Schiff (PAS) positive globules in the cytoplasm of periportal hepatocytes

III. Clinical features

- Asymptomatic in many cases
- Hepatitis, cirrhosis
- Lung involvement *severely exacerbated by smoking*

3.7 – Circulatory Dysfunction



I. Prehepatic

- Portal vein obstruction
    1. May be mild or potentially lethal
    2. Various causes, some examples are neonatal umbilical vein infection or catheterization, coagulopathies, trauma
- Thrombosis of the hepatic artery
    1. Dual blood supply to the liver makes this rare

II. Intrahepatic

- Cirrhosis: Most important etiology
- Sinusoidal occlusion
    1. Sickle cell disease, DIC, tumors, eclampsia
- Peliosis hepatis
    1. Etiology is unknown
    2. Sinusoidal dilation due to malignancy, tuberculosis, immunodeficiency (e.g. AIDS), anabolic steroids or oral contraceptive pills.
    3. Reversible, and usually regresses when underlying cause is removed
    4. Histology: blood-filled cystic spaces

III. Posthepatic

- Hepatic vein obstruction
    1. May be due to a clot in the hepatic veins or inferior vena cava (IVC) thrombosis, associated with diseases that increases coagulability: Polycythemia vera, antiphospholipid syndrome, coagulopathies, hepatocellular carcinoma
    2. Called Budd-Chiari syndrome when there is liver enlargement, ascites and pain
    3. Gross appearance of the liver: Tense, swollen and red/purple in color

3.8 – The Gallbladder and Biliary Tree

3.8.1 – Autoimmune Biliary Disease

- Refers to the two most common autoimmune conditions of the intrahepatic biliary tree
    1. *Primary biliary cholangitis* (previously called primary biliary cirrhosis)
    2. P*rimary sclerosing cholangitis*
- Both are considered to have a progressive clinical course

MNEMONIC – AUTOIMMUNE CHOLANGITIS

Women first
Primary Biliary Cholangitis is more common in women, while primary sclerosing cholangitis is more common in men:
B (Biliary) is before S (Sclerosing) in the alphabet → *Women first*

	Primary *Biliary* Cholangitis	**Primary *Sclerosing* Cholangitis**
Epidemiology	Middle aged women with autoimmune disease	Middle aged men with inflammatory bowel disease (IBD)
Associated conditions	- Sjögren syndrome - Scleroderma - Thyroid disease	- IBD - Pancreatitis
Morphology	- Portal tract inflammation - Noncaseating granulomas - Upstream liver damage: cirrhosis	- Periductal inflammation - "Onion skin" fibrosis - Atrophy of bile duct lumen - Biliary cirrhosis → Liver failure
Radiology	Normal	Bead-like appearance of bile ducts
Autoantibodies[1]	AMA, ANA, ANCA	ANCA[2]
Clinical features	Signs of cholestasis and later cirrhosis	Signs of liver failure: ascites, variceal bleeding, weight loss Chronic pancreatitis

[1]ANCA = Anti-Neutrophil Cytoplasmic Antibody, AMA = Anti-Mitochondrial Antibody, ANA = Anti-Nuclear Antibody

[2]Some cases of PSC show positive titers of AMA/ANA, but ANCA dominates

3.8.2 – Gallstones

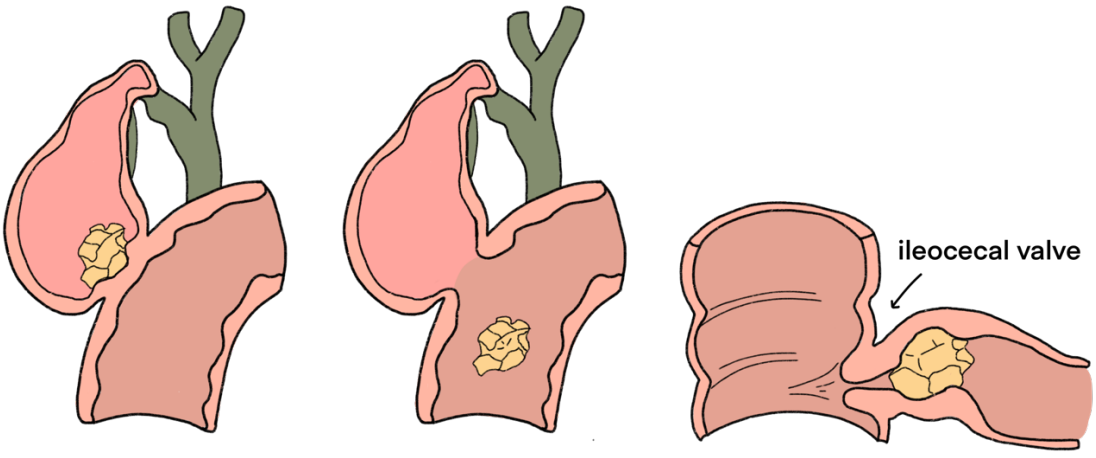
I. Cholesterol stones

- Majority of cases
- Supersaturation of cholesterol in the GB: Cholesterol concentration is higher than the capacity of the bile salts. Supersaturation + gallbladder hypomobility = Gallstones
- Risk factors: Fat, Female, Fertile, Forty
    1. Fat: Obesity
    2. Female: More common in women
    3. Fertile: Estrogen inhibits motility of smooth muscle → Decreased GB emptying
    4. Forty: More common in age > 40y
- Another risk factor is *rapid weight loss*

II. Pigment stones

- Due to increased unconjugated bilirubin in the setting of chronic hemolysis or biliary tract infections
    1. Hemolysis: Increased RBC turnover → Too much bilirubin for the liver to conjugate
    2. Infection: Pathogens promote deconjugation of bilirubin

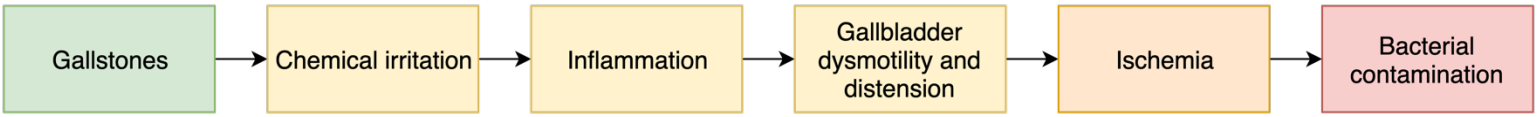
Complications of gallstones

Biliary colic	Colicky abdominal pain that occurs after meals, when the gallbladder contracts and a gallstone is forced into the cystic duct
Cholecystitis	Inflammation of the gallbladder due to obstruction of the cystic duct *(see below)*
Ascending cholangitis	Aka acute cholangitis. Biliary tree inflammation due to obstruction of the ducts by a stone. Leads to bacterial overgrowth and inflammation
Gallstone ileus	Gallstone may erode into adjacent small intestine, create a fistula, pass through and get stuck in the ileocecal valve 

3.8.3 – Cholecystitis

	Acute cholecystitis		Chronic cholecystitis
	Acalculous	*Calculous*	
Cause	Ischemia due to: - Sepsis with hypotension - Immunosuppression - Major trauma - Burns - Diabetes	Gallstones leading to bacterial contamination (see below)	- Repeated bouts of acute cholecystitis - Supersaturation of cholesterol, causing inflammation and dysmotility
Clinical features	Ranges from mild and asymptomatic to surgical emergency - Right upper quadrant (RUQ)/epigastric pain - Fever, anorexia, tachycardia, nausea and vomiting		- Recurrent attacks of constant or colicky RUQ/epigastric pain

Pathomechanism of calculous cholecystitis



3.9 – Neoplasia of the Liver and Gallbladder

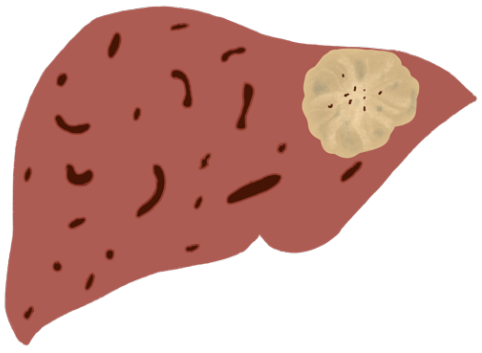
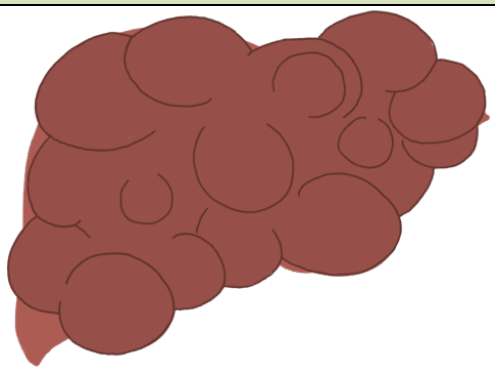
3.9.1 – Benign Neoplasms

I. Cavernous hemangioma

- Most common benign liver neoplasm
- Gross morphology:
    1. Soft, red-blue nodules located just below the liver capsule
    2. Size ranges from 1-20 cm
- Histology: Vascular channels within fibrous connective tissue
- Complications: Rupture due to trauma or spontaneously

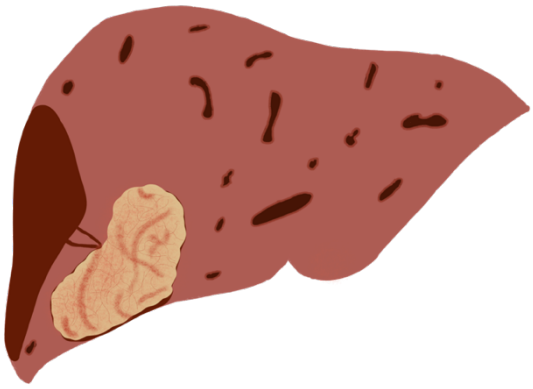
II. Nodular hyperplasia

- Two types, both related focal *obliteration of blood vessels in the liver*
- Not technically a neoplasm, rather a compensation by well perfused hepatocytes located next to poorly perfused hepatocytes

	Focal nodular hyperplasia	**Nodular regenerative hyperplasia**
		
Risk factors	- Oral contraceptive pills (OCPs) - Anabolic steroids	Conditions causing changes in intrahepatic blood flow: - Organ/bone marrow transplant - Vasculitis - HIV infection
Morphology	- Well demarcated, unencapsulated nodule with large arterial vessels - Central "Stellate" scar with radiating fibrous septa and lymphocytic infiltrate - No changes in the rest of the liver	- The entire liver is changed into nodules, *without fibrosis* - Plump hepatocytes surrounded by atrophic hepatocytes - May look like cirrhosis, but parenchyma is softer due to lack of fibrosis
Complications	–	Portal hypertension

III. Hepatic adenoma

- Seen in young women taking oral contraceptives; regresses upon discontinuation of OCPs
    1. The b-catenin mutation subtype is also associated with anabolic steroid use
- Gross morphology: Pale yellow nodule
- Histology:
    1. Sheets of normal hepatocytes and steatosis
    2. Absent portal tracts with prominent distribution of arteries and veins
- Complications:
    1. Rupture causing hemorrhage
    2. Transformation into hepatocellular carcinoma (HCC): Rare, associated with b-catenin gene mutations



3.9.2 – Malignant Neoplasms

I. Gallbladder Carcinoma

- Rare, typically affects elderly women and usually discovered late → Poor prognosis
- Risk factors: long standing gallstones, parasitic infections
- 80% are located in the fundus or neck of the gallbladder

II. Cholangiocarcinoma

Risk factors	- Primary sclerosing cholangitis - Congenital fibropolycystic diseases of the biliary system - Hepatitis C infection - Thorotrast exposure (radiocontrast agent no longer in use) *!! Most cases occur without a known risk factor being present !!*
Locations	- Perihilar (Klatskin tumor) and distal: May cause biliary obstruction and cholangitis, which allows for earlier detection - Intrahepatic: Detected late and is often unresectable at time of diagnosis
Prognosis	Very poor
Histology	- Arises from bile duct epithelium - Fibrous stroma separating neoplastic glands (desmoplastic)
Metastases	- Lung, bones - Vertebrae - Adrenals - Brain

III. Liver Metastases

- The most common liver tumor is metastases; The liver is the most common organ for metastases after lymph nodes
- Gastrointestinal tumors primarily spread to the liver, because blood from the gastrointestinal tract passes via the liver for detoxification

IV. Hepatoblastoma

- Most common tumor in children younger than 2 years with good prognosis *if treated*
- Clinical presentation: Usually asymptomatic, but increased abdominal circumference may be present
- Elevated alpha-fetoprotein
- Associated with tumor syndromes: FAP or Beckwith-Wiedemann

V. Angiosarcoma

- Aggressive, endothelial neoplasm associated with exposure to carcinogens
    1. Arsenic
    2. Thorotrast
    3. Polyvinal chloride (PVC, plastic)
- Long latency period between exposure and appearance of tumor
- Histology: Vascular spaces lined by atypical endothelial cells
    1. Positive for factor VIII related antigen, CD34 and CD31

VI. Hepatocellular Carcinoma

Epidemiology	- Male predominance - More frequent in countries with high rates of hepatitis B infections
Risk factors	- Chronic viral infection[1] - Chronic alcoholism - Non-alcoholic steatohepatitis - Some types of food (e.g. aflatoxin)
Gross morphology	Ranges from a single mass to diffuse infiltration and enlargement of the liver
Histology	- Tumor cells are arranged in nests and cords, and resemble hepatocytes. - May produce bile *Fibrolamellar HCC* - Occurs *without* the presence of chronic liver diseases and has a better prognosis - On histology one may find nests of cells separated by collagen bundles
Clinical features	- Hepatomegaly, pain in the right upper quadrant, elevated alpha-fetoprotein and weight loss. - Cause of death: Cachexia, variceal bleeding and rupture of the tumor with bleeding
Metastases	Lung, heart (May spread along the hepatic vein and reach the right atrium)

[1]Especially HBV infection transmitted perinatally or during infancy

3.10 – Test Yourself

1) Which of the following markers indicate loss of hepatocyte integrity?
a) Alkaline phosphatase
b) Alanine aminotransferase
c) Albumin
d) Blood urea nitrogen
e) g-glutamyl transpeptidase

2) What is the most common cause of liver cirrhosis?
a) Viral hepatitis
b) Genetic disease
c) Non-alcoholic steatohepatitis
d) Alcohol abuse
e) Vascular disease

3) Which of the following features are associated with alcoholic liver disease?
a) Mallory bodies
b) Hepatomegaly
c) Macrovesicular steatosis
d) Cirrhosis
e) All of the above

4) What does the serological marker anti-HBsAg indicate?
a) Immunity
b) Window period
c) Low infectivity
d) Chronic infection
e) a and b are correct

5) Which hepatitis virus is transmitted via fecal-oral transmission
a) HAV
b) HBV
c) HCV
d) HDV
e) HEV
f) HAV and HEV
g) HAV and HCV

6) Indicate the false sentence about genetic liver diseases:
a) Hemochromatosis is caused by decreased hepcidin expression
b) Wilson disease is associated with neuropsychiatric symptoms
c) Women are more likely than men to get severe hemochromatosis
d) Hemochromatosis can cause amenorrhea and/or loss of libido

7) What is the most important cause of intrahepatic circulatory insufficiency?

a) Peliosis hepatis
b) Hepatic vein obstruction
c) Sinusoidal occlusion
d) Cirrhosis
e) Thrombosis

8) The risk factors for gallstones are generally remembered as: "Fat, Female, Fertile, Forty", but there's another important risk factor. What is it?

a) Rapid weight gain
b) Rapid weight loss
c) Diabetes
d) Immunosuppression

9) Which hepatic neoplasm is associated with oral contraceptive pills?

a) Cavernous hemangioma
b) Focal nodular hyperplasia
c) Nodular regenerative hyperplasia
d) Hepatic adenoma
e) Hepatocellular carcinoma
f) b and d

Section 4 – The Pancreas

4.1 – Congenital Anomalies of the Pancreas

I. Pancreas divisum

- Most common congenital anomaly of the pancreas
- Pathogenesis: failure of fusion of the dorsal and ventral pancreatic buds
    1. The main pancreatic duct joins the bile duct proximal to the papilla of Vater and the accessory pancreatic duct (duct of Santorini)
    2. Pancreas drains mainly through the accessory pancreatic duct
- Main complication is the development of *chronic pancreatitis* though most are asymptomatic; consider evaluating for pancreas divisum in patients with idiopathic chronic pancreatitis!

II. Pancreatic agenesis

- Total absence of the pancreas
- Associated with other severe malformations
- Not compatible with life
- May result from mutations in PDX1 gene

III. Annular pancreas

- Ring of pancreatic tissue encircles the duodenum resulting in obstruction
- Contains large number of pancreatic polypeptide cells in an irregularly shaped islet
- Associated with Down syndrome
- Complications
    1. Symptoms associated with obstruction (e.g. abdominal pain and vomiting)
    2. Pancreatitis
    3. Peptic ulcer disease

IV. Ectopic pancreas

- Also known as heterotopic pancreas
- Common abnormality where pancreatic tissue is found outside the pancreas
- Pathomechanism: Displacement of pancreatic tissue during embryonic development
- Morphology:
    1. Gross: Resembles normal pancreas: Firm, yellow, well-circumscribed nodules, with or without central umbilication due to a central duct (can be detected radiographically)
    2. Histology: Acinar cells and ducts, islet cells are present in 1/3 of cases
- Common locations
    1. Gastric antrum, Gastroesophageal junction
    2. Duodenum, jejunum
    3. Meckel diverticulum
- Complications
    1. Inflammation and pain
    2. Ulceration
    3. Obstruction or intussusception
    4. Transformation into neuroendocrine tumor

V. Congenital cysts

- These cysts are benign and are a result of abnormal duct development
- May be due to polycystic disease which also presents with cysts in the liver and kidney
- Other associated diseases
    1. Von-Hippel-Lindau syndrome
    2. Oral-facial-digital syndrome
    3. Meckel-gruber syndrome
    4. Ivemark syndrome
    5. Trisomy 13, 14 and 15
    6. Tuberous sclerosis
- Morphological features
    1. Lined with uniform cuboidal cells or flattened epithelium
    2. Contained in a fibrous capsule
    3. Contain clear serous fluid (as opposed to mucinous fluid in neoplastic cysts)

4.2 – Pancreatitis

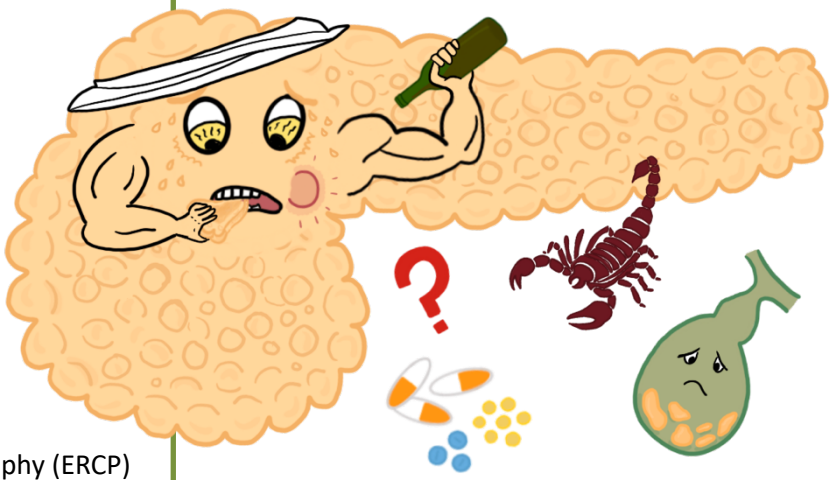
4.2.1 – Acute Pancreatitis

- The autodigestion of pancreas due to the over-secretion of pancreatic enzymes
- The majority of cases are due to gallstones or alcohol abuse

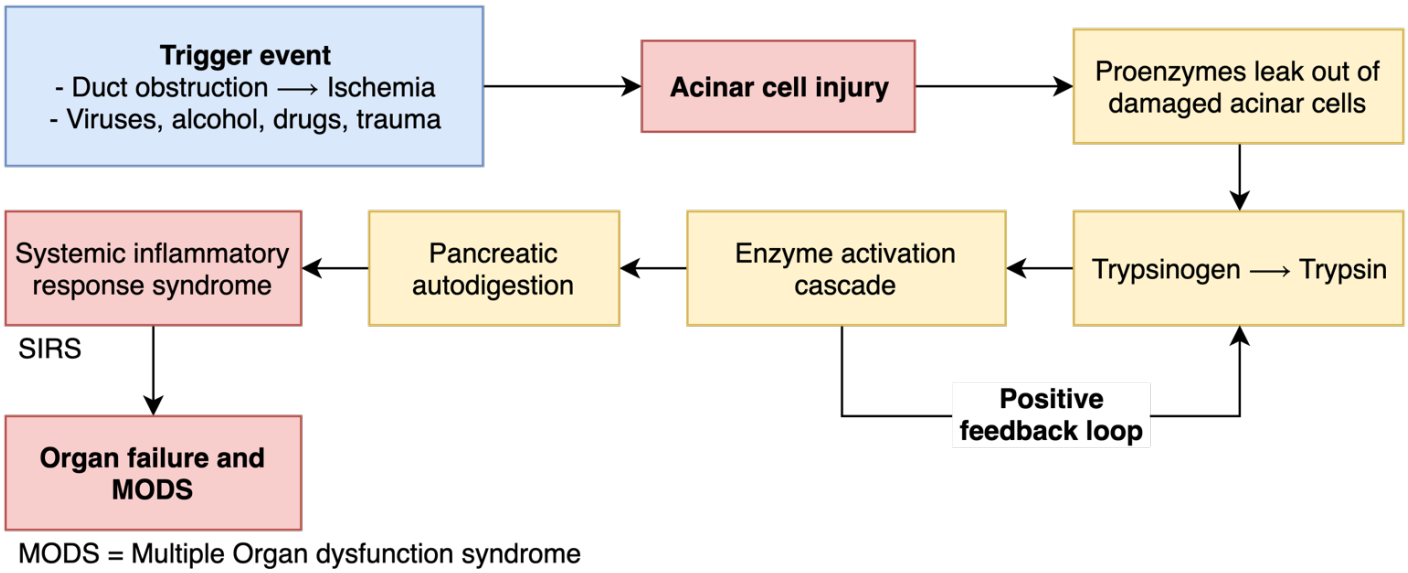
MNEMONIC – CAUSES OF ACUTE PANCREATITIS

I GET SMASHED

I - Idiopathic
G - Gallstones
E - Ethanol
T- Trauma
S - Steroids
M - Mumps
A - Autoimmune
S - Scorpions
H - Hypercalcemia/triglyceridemia
E - Endoscopic retrograde cholangiopancreatography (ERCP)
D - Drugs



I. Pathogenesis



MODS = Multiple Organ dysfunction syndrome

II. Subtypes

Acute interstitial: Edematous	Acute hemorrhagic: Necrotizing
- Acute pancreatic inflammation without damage to the microvasculature - Milder form of disease	- Acute pancreatic inflammation with damage to the microvasculature - Severe form of disease characterized by parenchymal necrosis and diffuse hemorrhage

III. Morphological features

- Microvascular leakage leading to edema
- Necrosis of fat cells
- Acute inflammation
- Destruction of the pancreatic parenchyma
- Destruction of blood vessels leading to interstitial hemorrhage

IV. Diagnostic criteria

- 2/3 required for diagnosis
    1. Acute epigastric pain that radiates to the back
    2. Increased serum lipase or amylase
    3. CT/USG showing edema and morphological changes

V. Complications

- Acute pancreatitis is a medical emergency: Pancreatic damage may disseminate into surrounding structures and/or cause bowel perforation
- Pseudocysts: Localized collections of pancreatic secretions surrounded by granulation tissue, *no epithelial lining*
- Hypocalcemia: Formation of calcium soaps
- Organ damage: Acute liver injury, ARDS, shock, renal failure
- Other: Abscess, necrosis, hemorrhage, infection, glycosuria

4.2.2 – Chronic Pancreatitis

- Chronic inflammation of the pancreas → Irreversible atrophy of parenchyma and fibrosis

I. Etiology

- Generally overlaps with acute pancreatitis, but chronic alcohol consumption is the leading cause
    1. 70% of cases are alcoholic males
- Genetic disorders: Cystic fibrosis

II. Morphological features

- Parenchymal fibrosis with sparing of the islet cells until late in the later stages
- Obstruction of pancreatic ducts
- Reduction in size and quantity of acini
- Alcohol abuse: Dilation of the pancreatic ducts with calcifications
- Ductal epithelium may be either be atrophic, hyperplastic, or undergo metaplasia

III. Clinical features

- Asymptomatic
- Recurrent episodes of epigastric pain with or without jaundice, triggered by heavy drinking, large meals and drugs (for example opioids)

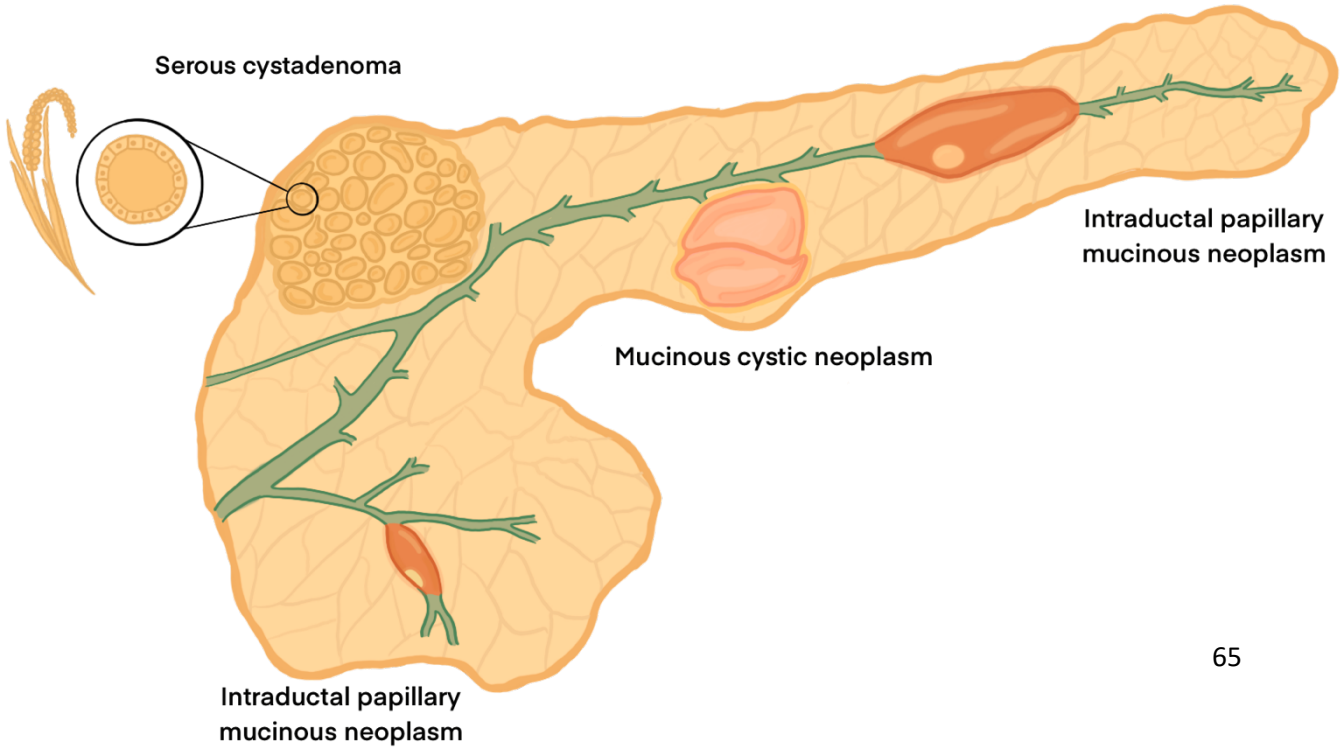
IV. Complications

- Pancreatic insufficiency → Malnutrition and diabetes
- Pseudocysts
- Pancreatic malignancy

4.3 – Neoplasia of the Pancreas

4.3.1 – Cystic Neoplasms

	Serous cystadenoma	Mucinous cystic neoplasms	Intraductal papillary mucinous neoplasms
Epidemiology	Women > Men (2:1) Typically occurs in 7th decade of life	95% arise in women	Men > Women
Location	Tail	Tail (most common) Head	- Head - Arises from the main pancreatic duct or one of its major branches - May be multifocal
Malignant potential	Benign	Painless, slow growing masses that can either be benign or malignant 1/3 are associated with *adenocarcinoma*	Varying grades of dysplasia <u>*Colloid carcinomas*</u> Highly dysplastic subtype associated with adenocarcinoma and large amounts of mucin production
Genetic abnormalities	Loss of function mutations in the von Hippel-Lindau (VHL) gene	- KRAS - TP53 - RNF43	- GNAS - KRAS - TP53
Histology	Glycogen rich cuboidal cells surrounding a clear straw-colored serous fluid	Columnar mucinous producing epithelium filled with thick mucin, within a dense stroma (ovary-like)	Similar to mucinous cystic neoplasms, but lack the dense stroma and involves larger ducts

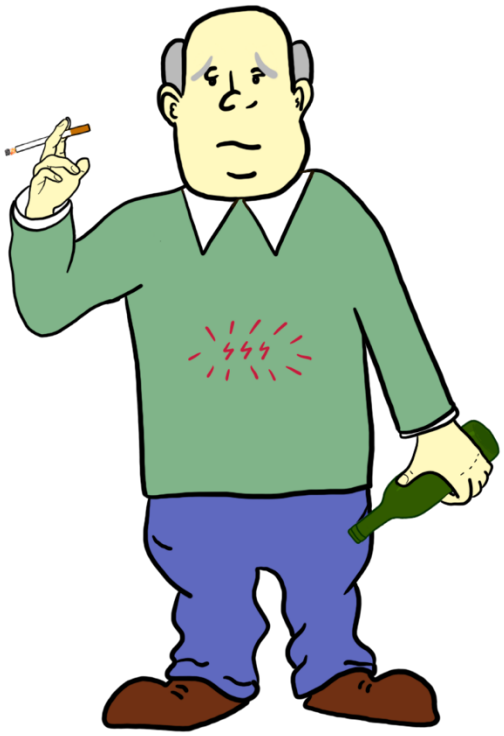


4.3.2 – Pancreatic Carcinoma

- Infiltrating ductal adenocarcinoma of the pancreas
- Typically occurs in older patients aged 60-80

I. Pathogenesis

- A combination of genetic mutations (KRAS, CDKN2A/p16, p53, BRCA2, and SMAD4) leads to progressive dysplasia culminating in invasive carcinoma
- Lesions most commonly begin in the smaller ducts as pancreatic intraepithelial neoplasia (PanIN)
- Metastasis to lymph nodes are very common at time of diagnosis → Poor prognosis



II. Histology

- Moderately to poorly differentiated adenocarcinoma
- Glands secreting mucin
- Deeply infiltrative growth pattern
- Dense stromal fibrosis
- The head of pancreas is the most common location

III. Risk factors

- Older age (>50)
- Smoking
- Chronic pancreatitis (alcohol use)
- Obesity
- Diabetes
- Familial syndromes (Peutz-Jeghers syndrome, ataxia telangiectasia, HNPCC)

IV. Clinical presentation

- Often goes undetected until late stage
- Abdominal pain radiating to back
- Malabsorption and anorexia → Weight loss
- Migratory thrombophlebitis
- Obstructive jaundice: Tumor in the head of the pancreas
- Chronic pancreatitis

V. Treatment

- The Whipple procedure (pancreaticoduodenectomy), however this is only possible in 15-20% of cases
- Chemotherapy and radiotherapy
- Metastases are usually already present at the time of diagnosis resulting in a very poor prognosis with a 4-8% 4 year survival rate

CLINICAL CORRELATION

Whipple procedure

A very complex operation. The head of pancreas, duodenum, gallbladder and bile duct are removed.

The stomach, bile ducts and the remaining part of the pancreas are subsequently reattached to the jejunum to allow passage of food, bile and pancreatic juices.

4.4 – Test Yourself

1) Which pancreatic congenital anomaly results in a ring of pancreatic tissue surrounding the duodenum resulting in obstruction?
a) Pancreatic agenesis
b) Annular Pancreas
c) Ectopic pancreas
d) Pancreas Divisum
e) Congenital pancreatic cysts

2) What features are characteristic of Acute Pancreatitis?
a) Acute epigastric pain radiating to the back
b) Increased serum Lipase or amylase
c) Decreased blood glucose
d) Hypercalcemia leading to urinary stone formation
e) A and B are correct

3) Which morphological feature is not present in Chronic pancreatitis?
a) Reduction in both size and quantity of acini
b) Islets of Langerhans are destroyed
c) Obstruction of Pancreatic duct
d) Parenchymal fibrosis
e) All of the above are present

4) Indicate the true statement regarding serous adenomas?
a) They are benign
b) More common in men
c) Made up of columnar mucinous epithelium
d) Has varying grades of dysplasia
e) All of the above are true

5) Indicate the false statement regarding pancreatic carcinoma?
a) Typically occurs in older patients
b) Glands may be present that secrete mucin
c) Most frequently located at the tail of the pancreas
d) Can lead to malabsorption and jaundice
e) Has one of the worst prognoses of all cancers

6) Which of the following pancreatic diseases may result in malabsorption?
a) Chronic pancreatitis
b) Pancreatic carcinoma
c) Annular pancreas
d) Ectopic pancreas
e) All of the above


studyaid