

GASTROINTESTINAL

THE ESOPHAGUS

NORMAL STRUCTURE:

- Three areas of narrowing:
 - Cricopharyngeus muscle
 - Compression near the arch of the aorta
 - At the esophageal hiatus (diaphragm)
- Musculature:
 - Upper Third: Skeletal Muscle
 - Middle Third: Skeletal + Smooth
 - Lower Third: Smooth Muscle
- Layers of the Esophagus:
 - **Non-Keratinized Squamous Epithelium**
 - Lamina Propria
 - Muscularis Mucosa
 - Submucosa
 - **Submucosal Plexus**
 - Muscularis Externa
 - Muscularis Circularis
 - **Myenteric Plexus**
 - Muscularis Longitudinalis
 - Adventitia

CONGENITAL DISORDERS:

- **TRACHEO-ESOPHAGEAL FISTULA:**
 - PATHOGENESIS: Congenital anomaly, often associated with Esophageal Atresia and congenital heart disease
 - THREE FORMS:
 - Most Common Form (90%): Upper esophagus ends in blind non-descript pouch. Lower esophagus is then connected to trachea.
 - CLINICAL: Associated with high mortality.
 - COMPLICATION: **Aspiration Pneumonia** in the infant is worse complication. Milk is regurgitated and then aspirated.
 - TREATMENT: Surgery is sometimes possible.

RINGS and WEBS:

- **PLUMMER-VINSON (PATERSON-KELLY) SYNDROME:**
 - PATHOLOGY: **Cervical Esophageal Web** is an indentation of esophageal mucosa in neck, impeding flow.
 - Will also find glossitis; mucosal lesions of mouth and pharynx.
 - Iron-deficiency anemia is almost always also found.
 - CLINICAL:
 - **Dysphagia** is most common symptom.
 - COMPLICATION: **Carcinoma** of the mouth and oropharynx is common.
- **SCHATZKI RING:** Narrowing at gastroesophageal junction (between squamous and columnar epithelium). It is only rarely symptomatic.

ESOPHAGEAL DIVERTICULA:

- **ZENKER DIVERTICULUM:** Outpocketing of the upper esophagus between cricopharyngeus and pharyngeus muscles.
 - **CLINICAL:** Outpocketing creates a blind pouch, which accumulates food -----> **halitosis**.
 - Usually seen in elderly patients.
- **TRACTION DIVERTICULUM:** Pulling of the esophagus, caused by scars or fibrosis.
- **EPIPHRENIC DIVERTICULUM:**

MOTOR DISORDERS:

- **ACHALASIA:** Stenosis of the Lower Esophageal Sphincter -----> **Megaesophagus**.
 - **PATHOGENESIS:** Thought to be a congenital degeneration of the **Myenteric (Auerbach's) Plexus**, such that the lower esophagus is unable to fully relax.
 - Three characteristic abnormalities:
 - Increased LES Pressure.
 - Inability for lower esophagus to relax.
 - Aperistalsis of lower esophagus.
 - Acquired Megaesophagus can be caused by the parasite ***Trypanosoma Cruzi*** (Chagas Disease)
 - **CLINICAL:** Symptoms are dysphagia, regurgitation, megaesophagus, and aspiration pneumonia.
- **SCLERODERMA:** Effects principally the lower esophageal sphincter.

HIATAL HERNIA:

- **PATHOGENESIS:**
 - **SLIDING HERNIA:** Standard hiatal hernia. Slippage of the gastric cardia upward through the Esophageal Hiatus.
 - **PARA-ESOPHAGEAL HERNIA:** Herniation of the gastric cardia through a defect in the diaphragmatic membrane (next to the esophagus), rather than through the Hiatus itself.
- **CLINICAL:** Hiatal hernias usually present as GERD. They don't know whether the GERD causes the hernia, or vice-versa. Each one begets the other.

ESOPHAGITIS:

- **PATHOGENESIS:** Multiple causes
 - **GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD):** Incompetent lower esophageal sphincter; regurgitation of stomach contents.
 - **INFECTIOUS AGENTS:** Can be seen in immunocompromised: AIDS, Diabetes, Lymphomas.
 - **Candida** is most common.
 - Can visualize it by using a **silver stain**, which colors the candidal hyphae black.
 - CMV is second most common.
 - Herpes Zoster, HSV can also be seen.
 - **Uremia**
 - Iatrogenic: Radiation, chemotherapy, prolonged intubation.
 - **CHEMICAL:** Acids or bases can damage the esophageal epithelium, but particularly bases, **lye**, causes the worst damage.
 - **Alkaline Injury:** Produces liquefactive necrosis, thrombosis, and saponification of lipids in the region.
- **PATHOLOGY:**
 - **Basal Zone Hyperplasia:** Basal zone proliferates, going from 10% to ~20% of esophageal mucosa.
 - **Elongated Papillae**
 - **Inflammatory Cells:** Eosinophils are almost always found between epithelia. PMN's may or may not be found.
 - **Leukoplakia:** General thickening of the epithelium, seen as white patches.
- **COMPLICATIONS:**
 - **Ulceration:** Ulcers can heal, leaving behind scars and possibly strictures.
 - **Strictures** can occur with chronic esophagitis -----> scarring.

- **BARRETT ESOPHAGUS: Squamous -----> Columnar Metaplasia** of esophageal epithelium.
 - **Esophageal Adenocarcinoma** develops in 5-10% of people with Barrett Esophagus.
 - Esophageal epithelium can change to gastric or intestinal epithelium. **Intestinal** epithelium carries a higher chance of becoming cancerous.

ESOPHAGEAL VARICES: Lower Esophagus. Portal-caval anastomoses of the esophageal arteries, which become dilated in portal hypertension, and often rupture.

ESOPHAGEAL CANCER:

- **EPIDEMIOLOGY:** Most prevalent in **China**. 60% of all cases come from China.
- **PATHOGENESIS:** Long list of predisposing conditions and risk-factors.
 - **RISK-FACTORS: Alcoholism and Smoking** are the big ones.
 - Nitrosamines: maybe, but evidence is lacking.
 - Diet: Low in fresh fruits and vegetables. Again, this is possible, but evidence lacks.
 - **PREDISPOSING CONDITIONS:**
 - **Chronic Esophagitis:** Anything causing chronic esophagitis can lead to cancer.
 - GERD
 - **Plummer Vinson Syndrome**
 - **Achalasia**
 - Esophageal Stricture
 - Rings and Webs.
 - **Barrett Esophagus:** Columnar dysplasia is a risk-factor for development of adenocarcinoma *only*.
 - **Squamous Dysplasia:** Pre-cancerous epithelium at risk for turning into squamous cell carcinoma *only*.
- **CLINICAL:** Very poor survival due to late detection. Once it becomes symptomatic, cancer has usually already spread to lymph nodes.
- **SQUAMOUS CARCINOMA:** Most common type. 70-90%
 - **CLINICAL:** Can treat with radiation therapy.
 - **PATHOLOGY:** Three morphological types:
 - **Polypoid:** Projects into esophageal lumen.
 - **Ulcerating**
 - **Infiltrating:** Spreads through esophageal wall.
- **ADENOCARCINOMA:** Next most common type. 10-20%
 - **CLINICAL:** Radiation therapy doesn't really help that much.
 - **PATHOGENESIS:** Almost always arise from **Barrett Esophagus**. Barrett esophagus can lead to adenocarcinoma -- but not squamous!
- **OTHER CANCERS:** Very rarely seen
 - OAT CELL CARCINOMA
 - MELANOMA

THE STOMACH

NORMAL STRUCTURE:

- **BODY / FUNDUS:** The pits are short and the glands are long and straight. High gland:pit ratio.
 - **Parietal Cells** which secrete acid are found mostly in the body of the stomach.
 - Also contains Chief Cells (secreting Pepsin)
- **ANTRUM:** The pits are long and the glands are short. Small gland:pit ratio.
 - Contains Chief Cells, but very few Parietal Cells.

CONGENITAL DISORDERS:

- **CONGENITAL PYLORIC STENOSIS:**
 - **EPIDEMIOLOGY:** Fairly common. Male:female ratio of 4:1.

- **PATHOGENESIS:** Congenital hypertrophy and hyperplasia of the smooth muscle of the pyloric sphincter, resulting in little or no gastric emptying.
- **SYMPTOMS:** Symptoms appear by 3-4 weeks of age.
 - **Projectile Vomiting:** The vomit does not contain bile (it never reaches duodenum).
 - **Voracious Appetite.**
 - **Hypochloremic Alkalosis:** Low HCl with metabolic alkalosis, due to loss of gastric juices because of vomiting.
 - Visible peristaltic movements can be seen, and a palpable lump is felt near the pylorus.
- **TREATMENT: Pyloromyotomy.** Surgical incision made along the length of the pylorus. Usually curative.

GASTRITIS:

- **ACUTE (EROSIVE) GASTRITIS:** Short-term, reversible necrosis in the stomach.
 - **PATHOGENESIS:** Long list of causative agents.
 - Alcohol
 - **NSAID's:** Inhibit prostaglandins -----> lost protection of gastric mucosa.
 - **CUSHING ULCER:** Trauma to CNS, or CNS surgery. Ulcers are typically deep and can perforate.
 - **CURLING ULCER:** Gastric ulcer from extensive third-degree burns.
 - Shock or sepsis -----> gastric ischemia -----> acute ulcer.
 - **PATHOLOGY:** **Patchy** mucosal necrosis. Ulcers vary in size and distribution.
- **CHRONIC (NON-EROSIVE) GASTRITIS:**
 - **PATHOLOGY:** Three progressive stages of chronic gastritis, common to both forms.
 - **Superficial Gastritis:** Just superficial mucosa.
 - **Atrophic Gastritis:** Inflammation becomes transluminal, and mucosa becomes flattened. The inflammatory cells can leave, leaving behind a thin mucosa -----> Gastric "atrophy"
 - **Intestinal Metaplasia:** Similar to Barrett Esophagus, this metaplasia is pre-cancerous.
 - **SYMPTOM:** **Dyspepsia** is the common symptom of chronic gastritis. It is a very non-specific finding.
 - **AUTOIMMUNE GASTRITIS:**
 - **PATHOGENESIS:** Autoantibodies against parietal cells, against intrinsic factor, or against both.
 - **PATHOLOGY:** Typically involves the fundus of the stomach (where the Parietal cells are). **The antrum is spared.**
 - **CLINICAL:**
 - **Pernicious (Megaloblastic) Anemia** is seen, due to loss of intrinsic factor -----> no absorption of Vit B-12 in ileum.
 - **Hypergastrinemia:** Acid secretion is deficient, and Gastrin levels are therefore elevated.
 - **CHRONIC ANTRAL (IDIOPATHIC) GASTRITIS:** Chronic gastritis of unknown cause. *Chronic idiopathic gastritis is a risk-factor for Stomach Cancer.*
 - **PATHOGENESIS:** Idiopathic.
 - **PATHOLOGY:** Inflammation starts at the **antrum** and spreads proximally. Degree of inflammation varies from superficial to gastric atrophy.
 - **CLINICAL:**
 - No pernicious anemia is seen.
 - May see an excess or deficiency of HCl.
 - Gastrin levels and acid secretion are normal.
 - **INFECTIOUS GASTRITIS:** Usually caused by *H. Pylori*, it is a precursor to Peptic Ulcer Disease of either the stomach or duodenum (see PUD).

MENETRIER'S DISEASE (HYPERTROPHIC GASTROPATHY):

- **EPIDEMIOLOGY:** Rare. 4 times more common in men.
- **PATHOGENESIS:** Idiopathic.
- **PATHOLOGY:** Extra large rugae (folds) in the stomach lead to a loss of plasma proteins through the stomach mucosa.
 - May see cystic dilatation of foveolae.
- **SYMPTOMS:** Sometimes present as postprandial pain.
 - May see symptoms similar to cancer (due to loss of plasma proteins): Cachexia, weight loss, edema.
 - **COMPLICATION:** *Increased risk of Gastric cancer* occurs with Menetrier's Disease.

PEPTIC ULCER DISEASE (PUD): Breaks in the mucosa of the antrum, pylorus, or proximal duodenum, caused by gastric secretions.

- **PATHOGENESIS:** *Helicobacter Pylori* is the cause in the majority of cases.
 - Gastric acid secretion is required to cause it. Thus Autoimmune Gastritis never leads to PUD!
 - **RISK-FACTORS:** Things that are associated with PUD
 - Smoking and alcohol
 - NSAID's and corticosteroids.
 - Blood Type O
 - **PREDISPOSING CONDITIONS:** Diseases associated with PUD
 - **Zollinger-Ellison Syndrome:** Hypergastrinemia causes PUD
 - **Hyperparathyroidism** -----> increased Ca^{+2} -----> increased Gastrin and PUD
 - **COPD** -----> increased pCO_2 -----> increased Gastrin and PUD
- **PATHOLOGY:** Ulcers occur in both duodenum and stomach.
 - **MORPHOLOGY:** Grossly, you see sharp, clean borders with "punched out" appearance. *This distinguishes an ulcer from an ulcerating, malignant carcinoma.* Histologically, there are four layers:
 - **Fibrinous Exudate** is the inner layer, on luminal surface.
 - **Inflammatory cells** and PMN's are beneath this.
 - **Granulation tissue** is found next
 - **Fibrotic tissue** is found at the base of the ulcer, with various levels of chronic inflammation.
 - **DUODENAL ULCERS:**
 - *H. Pylori* is always found in duodenal ulcers. It is a necessary condition for duodenal ulcers.
 - The bugs are found in islands of gastric mucosa within the duodenal bulb. They are thought to induce gastric metaplasia in the duodenum, and then subsequently infect the metaplastic area.
 - *Duodenal ulcers never become malignant.*
 - **GASTRIC ULCERS:** *H. Pylori* may or may not be found in gastric ulcers.
- **CLINICAL:**
 - **SYMPTOMS:** Patient will have epigastric pain made worse by food, aspirin, and alcohol.
 - May have hematochezia (occult blood in stool) or hematemesis.
 - GI blood is possible.
 - **COMPLICATIONS:**
 - **Pyloric Obstruction** is a possible complication, in which case patient will have anorexia, early satiety, and a succussion splash during fasting.
 - **Perforation** of ulcer has high mortality.
 - PUD do not become malignant, particularly in the duodenum.

BENIGN NEOPLASMS:

- **LEIOMYOMA:** Benign smooth muscle tumor.
- **EPITHELIAL POLYPS:**
 - **HYPERPLASTIC POLYPS:** The vast majority of gastric polyps are hyperplastic. Their origin is uncertain (sometimes from chronic inflammation), and they have no malignant potential.
 - **HAMARTOMATOUS POLYPS:** Mixed-tissue polyps with no malignant potential.
 - **ADENOMATOUS POLYPS:** They do have malignant potential and are similar to adenomatous polyps in the colon.
 - **Villous Adenomas:** Finger-like structure. They tend to become malignant more often than the tubular adenomas.
 - **Tubular Adenomas:** Pedunculated, gland (acinar)-like structure.

MALIGNANT NEOPLASMS:

- **ADENOCARCINOMA of the STOMACH:**
 - **EPIDEMIOLOGY:** Incidence is high in **Japanese** population. It used to be high in U.S. but is now continually decreasing.
 - **PATHOGENESIS:**
 - **RISK-FACTORS:**
 - Genetic predisposition.

- Blood Group A
 - Nitrosamines
 - **PRE-DISPOSING CONDITIONS:** The same conditions that cause **intestinal metaplasia** may lead to gastric cancer.
 - **Chronic Gastritis:** Either Idiopathic or Autoimmune.
 - **Menetrier's Disease:** Hypertrophic gastropathy
 - **Partial Gastrectomy:** The gastric stump is at risk of becoming malignant.
 - Gastric adenomatous polyps (but not hyperplastic polyps)
- **PATHOLOGY:**
 - Multiple types of gastric tumors
 - **Polypoid Adenocarcinoma:** Solid mass projects into lumen of stomach.
 - **Ulcerating Adenocarcinoma:** Tumor forms an ulcer, with epithelium "overgrowing" around the edges.
 - This must be distinguished with a benign ulcer, which has sharp, "punched-out" edges.
 - **Diffuse (Infiltrating) Adenocarcinoma:** No solid tumor, but instead neoplasm infiltrates throughout the mucosa of the stomach, making the stomach wall thicker.
 - Invading tumor cells cause intense fibrosis of the stomach, and cause the wall to become very thick.
 - **LINITIS PLASTICA:** "Leather-bottle stomach," when the entire stomach is subjected to infiltrating carcinoma.
 - **Signet Ring Cell:** Gastric tumor cells have lots of mucin, which displaces the nucleus to the periphery, giving it this characteristic appearance.
- **CLINICAL:**
 - **COMPLICATIONS:**
 - **KRUKENBERG TUMOR:** Metastases to the ovaries. The metastases can come from any primary site, but often originates as a gastric adenocarcinoma.
- **OTHER CARCINOMAS:** Much rarer
 - ADENOSQUAMOUS CARCINOMA
 - ENDOCRINE-CELL TUMORS
 - CHORIO-CARCINOMA:
- **GASTRIC LYMPHOMA:**

THE SMALL INTESTINE

CONGENITAL DISORDERS:

- **ATRESIA AND STENOSIS:**
 - **ATRESIA:** Complete occlusion of the intestinal lumen. Three subtypes:
 - **Fibrous Diaphragm** forms in the lumen of the bowel, creating a complete obstruction.
 - **Complete Fibrosis** of a segment of the bowel can leave the surrounding segments connected by a string-like cord.
 - **Complete Separation** between two sections of bowel. Walls completely close off each end.
 - **STENOSIS:** Narrowing or stricture of the intestinal lumen.
 - **CLINICAL:** Babies with congenital atresia or stenosis will have failure to pass meconium.
 - **TREATMENT:** Surgery is usually curative, but other anomalies can coexist.
- **MECKEL DIVERTICULUM:** Most common congenital anomaly of small intestine.
 - **CLINICAL: RULE of 2's**
 - 2 inches long
 - 2% of population (some say 10%)
 - 2 feet proximal to the ileocecal junction
 - **COMPLICATIONS:** Diverticulum can contain ectopic secretory tissue: gastric tissue, endocrine tissue, biliary tissue, pancreatic, etc.
 - Gastric metaplasia -----> secrete Gastrin -----> ulcer at the site of the Diverticulum.
- **MECONIUM ILEUS:**

INFECTIONS:

- BACTERIAL DIARRHEA:
- VIRAL GASTROENTERITIS:
- TUBERCULOSIS:
- PARASITIC INFECTIONS:

VASCULAR DISEASES:

- **ACUTE INTESTINAL ISCHEMIA:** Often caused by mechanical obstruction, but can be caused by other things, too.
 - **PATHOGENESIS:** Mechanical obstruction is one main cause. Other causes:
 - Thromboembolism to bowel.
 - Arteritis, vasculitis
- **CHRONIC INTESTINAL ISCHEMIA:** Caused by hypotension or atherosclerotic narrowing of splanchnic arteries.

MALABSORPTION:

- **PATHOGENESIS:**
 - **Luminal-Phase Malabsorption:** Failure to digest food in the lumen, caused by pancreatic insufficiency, bile obstruction or biliary insufficiency (fail to absorb fats), bacterial overgrowth.
 - **Intestinal Phase Malabsorption:** Failure to absorb nutrients at the brush border, caused by Celiac Disease, Tropical Sprue, Whipple Disease, and Lactase Deficiency.
- **CELIAC DISEASE (CELIAC SPRUE):** Also known as **Gluten-Sensitive Enteropathy**
 - **PATHOGENESIS:** Antibodies to **gliadin**, the breakdown byproduct of **gluten** which is found in wheat and rye.
 - **IMMUNITY:** Genetic predisposition, plus exposure to a virus (Adenovirus 12) causes antibodies to be formed against gliadin.
 - **GENETIC PREDISPOSITION:** **HLA-B8** (class I) and **HLA-DR3, HLA-DQw2** (class II) are found in high percentage in patients with the disease.
 - **PATHOLOGY:** Autoimmune attack against Gliadin -----> loss of intestinal villi and flattening of mucosa - ----> malabsorption at the brush border.
 - Flattened, blunted villi.
 - Hyperplastic crypts, with chronic inflammatory cells found between the crypts.
 - No glycocalyx border.
 - **CLINICAL:** Diarrhea, malabsorption, anemia, weight loss.
 - **DIAGNOSIS: D-Xylose Absorption Test.** Give 25 gms of xylose orally and measure urinary excretion of xylose in the next 5 hours. Should be at least 5 grams of xylose excreted, but it is lower in sprue and other malabsorptive syndromes.
 - **TREATMENT:** Withhold gluten from diet.
- **TROPICAL SPRUE:** Progressive malabsorption of obscure etiology.
 - **PATHOGENESIS:** Enterotoxigenic *E.Coli* (ETEC) and Folate Deficiency have been implicated in pathogenesis.
 - **TREATMENT:** Give tetracycline (for the bugs) and folate.
- **WHIPPLE DISEASE:** Infection with *Tropheryma Whipplei*.
 - **CLINICAL:** Symptoms are arthritis, joint swelling, fever, weight loss, diarrhea
 - **PATHOLOGY: Foamy macrophages** in the intestinal brush-border are the pathognomonic sign of Whipple Disease.
 - Macrophages have a basophilic, granular cytoplasm and are filled with the *T. Whipplei*, intracellular parasites.
- **LACTASE DEFICIENCY:**

MECHANICAL OBSTRUCTION: Mechanical obstructions can lead to ischemic bowel disease.

- **INTUSSUSCEPTION:** Occlusion in which a segment of bowel protrudes distally into the outer portion of the next segment of bowel, just like the segments of a telescope.
 - **COMPLICATION:** Can lead to ischemic bowel injury.

- **VOLVULUS:** A segment of gut twists on its mesentery, cutting off the blood supply and resulting in acute ischemia.
 - **PATHOGENESIS:** Consequence of underlying congenital abnormality.
 - **CLINICAL:** Presents as acute abdomen, with a cut off blood supply.

BENIGN NEOPLASMS:

- **ADENOMAS**
- **PEUTZ-JEGHERS SYNDROME:**
 - **PATHOGENESIS:** Autosomal dominant hereditary disorder.
 - **PATHOLOGY:**
 - **Hamartomatous Polyps:** Benign polyps, consisting of glandular epithelium and smooth muscle.
 - **CLINICAL:**
 - **SYMPTOMS:** **Mucocutaneous Pigmentation** of the skin is seen in face, buccal mucosa, hands, feet, and perineum.
 - **COMPLICATIONS:** 2% of patients will develop adenocarcinoma of the stomach, breast, or ovary.

MALIGNANT NEOPLASMS:

- **ADENOCARCINOMA:** The tumors are often annulars, thus the symptoms are often those of progressive bowel obstruction.
- **PRIMARY LYMPHOMA:**
 - **PATHOGENESIS:** Associated with Celiac Disease is well established.
 - **CLINICAL:** **Mediterranean Lymphoma**
- **CARCINOID TUMOR:** Ectopic, secretory tumor found in small intestine, appendix, or colon.
 - **CLINICAL:** **Carcinoid Syndrome** results from excessive secretion of serotonin and/or bradykinin from the tumor.
 - Right Heart Failure
 - Sweating, flushing
 - Cyanosis
 - Hypertension
 - Diarrhea
 - **DIAGNOSIS:** Look for **5-hydroxy-indole acetic acid** in urine, a metabolite of serotonin.
- **MEDITERRANEAN LYMPHOMA:** Immuno-proliferative disorder of the small intestine in which the plasmacytoid lymphocytes synthesize one of the heavy chains of the immunoglobulins (commonly it is the alpha chain, hence called alpha chain disease)

THE APPENDIX:

- **ACUTE APPENDICITIS:**
 - **PATHOGENESIS:** **Intestinal ischemia** in the appendix is often the cause of the infection. Content increase the pressure in appendix -----> cut off blood supply -----> ischemia, which predisposes to infection.
 - **PATHOLOGY:** Infected appendix is covered with fibrinous exudate when removed.
 - **CLINICAL:** Presents as acute abdomen. Sharp RLQ pain, leukocytosis with left shift.
- **MUCOCELE:** Distended appendix with lots of mucus inside.
 - **PATHOLOGY:** Can be benign or malignant. Look at underlying epithelium to distinguish.
 - **COMPLICATION:** **Pseudomyxoma Peritonei** occurs when the mucocoele leaks into the peritoneum. Epithelial cells can seed in the peritoneal wall and create these little polyps of mucus-secreting tumor cells.

THE LARGE INTESTINE

CONGENITAL DISORDERS:

- **HIRSCHSPRUNG DISEASE (CONGENITAL MEGACOLON):**
 - PATHOGENESIS: Defect in the innervation of the rectum, resulting in failure of relaxation of the anal sphincter. Very similar to Achalasia.
 - Acquired Megacolon can be caused by the parasite *Trypanosoma Cruzi* (Chagas Disease)
- ANORECTAL MALFORMATIONS:

INFECTIONS:

- **PSEUDOMEMBRANOUS COLITIS:** *Clostridium Difficile* infection resulting from antibiotic therapy.
 - PATHOGENESIS: The inflammation is caused by a **toxin** elaborated by *C. Difficile* -- not by the bug itself.
 - Antibiotics kill intestinal flora, resulting in overgrowth of *C. Difficile*. Suspect antibiotics:
 - Clindamycin
 - Penicillins
 - Cephalosporins
 - Aminoglycosides
 - PATHOLOGY: Multiple dot-like
- **NEONATAL NECROTIZING ENTEROCOLITIS:** *Clostridium Perfringens*

DIVERTICULAR DISEASE:

- **DIVERTICULOSIS:** Herniation of mucosa and submucosa through the muscular layers of the colon.
 - PATHOGENESIS: **Lack of fiber** in diet is believed to be a strong causative factor.
 - PATHOLOGY: Almost always occurs in sigmoid colon.
- **DIVERTICULITIS:** Inflammation at the base of a diverticulum.
 - PATHOGENESIS: Presumed to be caused from retained fecal material in a diverticulum.
 - CLINICAL: **Perforation** is very common, but it usually only leads to a localized abscess (restricted by neighboring organs, the mesentery, or adhesions). It can, however, lead to generalized peritonitis.

INFLAMMATORY BOWEL DISEASE:

- EPIDEMIOLOGY: Highest prevalence in U.S. and European countries. Incidence has increased in modern times, pointing to dietary and environmental factors as causative factors.
 - Age-Distribution: Peak around 20-25 years of age, with another peak in the 60's.
 - Seen more frequently in whites than in blacks.
- PATHOGENESIS: Diseases are idiopathic, with environmental and possible immune factors playing a role.
 - General risk-factors for inflammatory bowel disease
 - Stress of urban life style.
 - Smoking has been found to have a *beneficial* effect for Ulcerative Colitis, statistically. However, for Crohn's Disease it was found to be detrimental.
- **CROHN DISEASE:** Chronic granulomatous inflammation of the bowel wall, with unknown etiology.
 - PATHOLOGY: **Transmural inflammation** of the bowel wall occurs.
 - **Skip-Lesions** are found, where normal sections of intestine are interspersed with inflamed sections. Inflammation is interspersed and periodic.
 - **Non-caseating granulomas** are found in Crohn's Disease
 - Anatomic distribution is variable: can be found anywhere from mouth to anus.
 - 45%: Terminal ileum and colon.
 - 33%: Small bowel alone
 - 25%: Colon alone
 - CLINICAL: Symptoms are abdominal pain and diarrhea, possible fever.
 - COMPLICATIONS:
 - **Strictures** may result from the transmural inflammation.
 - **Gallstones:** Crohn's Disease in the Ileum -----> poor reabsorption of bile salts -----> deficient bile salts and gallstones.

- **Hydronephrosis:** Can result from involvement of ureter in the stricture.
 - **CANCER:** Increased risk for **Squamous Carcinoma** of anus and **Adenocarcinoma** of colon.
- **ULCERATIVE COLITIS:** Chronic inflammation of the colon, essentially limited to the colonic mucosa.
 - **PATHOLOGY:**
 - **Anatomic Distribution:** Ulcerative Colitis always starts in the rectum and works its way proximally, often extending through sigmoid and left colon.
 - **Inflammation is consistent throughout the mucosa:** edema, denudation, and ulceration is seen throughout.
 - **Crypt Abscesses** are common.
 - **CLINICAL:** Rectal bleeding is very common. Fever, diarrhea, abdominal pain. Moderate anemia from blood loss.
 - **COMPLICATIONS:**
 - **Toxic Megacolon:** Extensive dilatation of colon, where wall is thin, friable, and subject to perforation.
 - **Colonic Carcinoma:** Increased risk for cancer with prolonged disease. Occurs because of continual regeneration of epithelia -----> **intestinal dysplasia.**
 - Usually occurs after 10 years with Ulcerative Colitis.
 - The type of cancer is different than colonic adenocarcinoma arising from polyps: they are often multiple and are flat lesions rather than polypoid.
- **INDETERMINATE COLITIS:**
- **SYSTEMIC COMPLICATIONS:** Inflammatory Bowel Diseases in general can present with several systemic complications:
 - Immune-mediated complications:
 - Erythema Nodosum
 - Pyoderma Gangrenosum
 - Uveitis: in eyes
 - Aphthous Stomatitis: inflammation in mouth.
 - Ankylosing Spondylitis
 - **Primary Sclerosing Cholangitis** is a long-term complication, which can lead to **cholangiocarcinoma.**
 - **Adenocarcinoma:** Crohn's leads to intestinal carcinoma, and UC leads to colonic carcinoma.

| | CROHN DISEASE | ULCERATIVE COLITIS |
|-----------------------------------|---|---|
| Anatomic Distribution | <i>Rectal sparing.</i> Terminal Ileum is often involved and is very important. | <i>Rectum is always involved.</i> Terminal ileum is rarely involved. |
| Type of Inflammation | Transmural | Strictly mucosal |
| Distribution of Inflammation | Periodic Skip-lesions: Discrete ulcers with islands of normal mucosa. | No skip lesions. Diffuse inflammation and edema throughout, leading to edema and ulceration. |
| Microscopic Pathological Features | Non-caseating granulomas | Crypt Abscesses |
| Macroscopic Pathological Features | Fissures piercing through wall, which can lead to fistulas. | Thickened colonic wall early on. Can see thin, atrophic wall in case of toxic megacolon. Pseudopolyps are common. |
| Complications | May see strictures Gallstones | No strictures are seen. Toxic Megacolon. |

| | | |
|--------|---|---|
| | Hydronephrosis from ureter involvement. | Many systemic complications. |
| Cancer | Intestinal Adenocarcinoma Overall risk is slim compared to Ulcerative Colitis. | Risk for diffuse Colonic Adenocarcinoma (not arising from discrete polyps) Increased risk for cholangiocarcinoma |

VASCULAR DISEASES:

- ISCHEMIC COLITIS:
- **ANGIODYSPLASIA:** Malformed vessels in the submucosa, in the cecum and ascending colon.
 - **PATHOGENESIS:** Degenerative process often found in elderly. Should always be part of the differential for bloody stools in the elderly.
- HEMORRHOIDS:

POLYPS of the COLON:

- BENIGN POLYPS:
 - **HYPERPLASTIC POLYPS:**
 - **PATHOLOGY:** **Serrated** appearance of crypts, frequent in rectosigmoid area. Distinguished by the proliferation in the crypts.
 - **CLINICAL:** They are not themselves neoplastic, but they are often found concurrently with colon cancers.
 - **JUVENILE POLYPS:** Non-neoplastic polyp which can undergo torsion and cause rectal bleeding in children.
 - **PATHOLOGY:** They are hamartomas and they are never cancerous.
 - **INFLAMMATORY POLYPS:** "Pseudopolyps," often found in Ulcerative Colitis.
- **ADENOMATOUS POLYPS:** Extensions of colonic epithelia, which may become cancerous.
 - **PATHOGENESIS:** They are thought to result from an over-proliferation of crypt cells. Crypts cells normally grow up the colonic villus as part of the process of normal cell-turnover. When this process grows out of control, polyps result.
 - **PATHOLOGY:** Two different forms.
 - **TUBULAR ADENOMAS:** Pedunculated, gland-like structures.
 - They are easier to fix with surgical resection. They come off easier.
 - **VILLOUS ADENOMAS:** Extensions of mucosal surface, **cauliflower**-like surface. More finger-like structure.
 - Generally, *Villous Adenomas are more likely to progress to cancer.*
 - **CLINICAL:** They are pre-cancerous. The size of the polyp correlates with the risk for cancer.
- POLYPOSIS SYNDROMES:
 - **ADENOMATOUS POLYPOSIS COLI (APC):** Autosomal Dominant, progressive development of lots of adenomatous polyps in the colon.
 - **CLINICAL:** *Progression to colonic adenocarcinoma is inevitable.*
 - **GARDNER SYNDROME:** Autosomal dominant disease.
 - **CLASSICAL SYMPTOMS:**
 - Polyposis of GI tract, especially in colon, but it also occurs in stomach and the Ampulla of Vater.
 - Osteomas of skull, mandible, long bones.
 - Soft tissue tumors of the skin.
 - **CLINICAL:** Gardner Syndrome progresses to Colon Cancer.

ADENOCARCINOMA of the COLON:

- **PATHOGENESIS:**
 - Classically, step-wise progression to cancer. Multiple genetic mutations are thought to have to occur, before a polyp becomes malignant. Genes involved:
 - **ras gene:** Oncogene that becomes cancerous when a point mutation is introduced.

- **p53 gene:** Tumor-suppressor gene.
 - DCC gene: Tumor suppressor gene; "deleted in colon cancer"
 - **PREDISPOSING CONDITIONS:**
 - Inflammatory bowel disease
 - Congenital polyposis syndromes
 - **PATHOLOGY:**
 - **Napkin-Ring Tumors:** Constricting-type tumors, most common in the left colon. The wall thickens, narrowing the colonic lumen.
 - Often present with constipation due to narrowed lumen.
 - **Cauliflower Tumors:** More prevalent in the right colon. Tumors may ulcerate.
 - Usually presents with rectal bleeding.
 - **CLINICAL:**
 - Progression of disease
 - **EARLY:** Asymptomatic. May find occult blood in stool if you test for it.
 - **MIDDLE:** Rectal bleeding and change in bowel habits. Possible palpable mass.
 - **LATE:** Fatigue, abdominal pain, pallor, cachexia, hepatomegaly.
 - **DUKE'S CLASSIFICATION:** Clinical staging of colonic tumor
 - **STAGE A:** Mildest; best prognosis. Tumor confined to mucosa.
 - **STAGE B:** Tumor invades muscularis and/or serosa.
 - **STAGE C:** Metastases to regional lymph nodes.
 - **STAGE D:** Distant metastases
-

THE LIVER

LOBULAR STRUCTURE:

- **LOBULE:** Dividing up the liver into sections, with the Central Venule in the middle of the section, and three portal triads in a triangular arrangement around the outside.
 - **Sinusoids:** In the center of the lobule.
 - **Kupffer Cells:** Antigen-presenting cells lined along the sinusoids.
 - **Fenestrae:** Endothelial cells have gigantic fenestrae to allow blood-products to freely flow through the sinusoids.
 - **Space of Disse:** Lies between the capillary endothelial cell and the hepatocyte.
- **ACINUS:** Dividing up the liver into sections, with the Portal Triad in the middle of the section, and central venules around the outside. Divided into three zones:
 - **Zone 1:** The region immediately surrounding the **Portal Triad**.
 - Zone is the first to get exposed to toxins from portal blood. Zone 1 cells are most affected by toxic damage.
 - **Zone 2:** The middle region.
 - **Zone 3:** The region closest to the **Terminal Hepatic Venule**.
 - Zone 3 gets the least oxygenated blood. Zone 3 cells are most susceptible to hypoxic damage.
- **Portal Triad:**
 - Bile Duct: Low columnar epithelium
 - Hepatic Arteriole: Small muscular artery
 - Portal Venule: Vein, the largest structure (histologically) in the triad.
 - **Limiting Plate:** The hepatic cells immediately surrounding the portal triad. They form a sharp demarcation between the portal triad and the rest of the lobule.
- **COUNTERCURRENT FLOW:**
 - **BLOOD-FLOW:** Zone-1 -----> Zone-3
 - Portal Vein -----> Portal Triad -----> Portal Venule -----> Terminal Hepatic Venule -----> Central Venule -----> Central Vein -----> Hepatic Vein.
 - Hepatocytes closest to the Portal Triad receive the most oxygenated blood. They are specialized for drug detoxification, and are most susceptible to damage from drug toxicity.
 - Hepatocytes closest to the Terminal Hepatic Venule receive the least oxygenated blood. They are specialized for bile production, and are most susceptible to damage in the event of hypoxia.
 - **BILE-FLOW:** Zone-3 -----> Zone-1
 - Bile is synthesized in the hepatocytes closest to the Terminal Hepatic Venule. Those cells are more specialized for bile synthesis rather than drug detoxification.
 - Flow = Central Venule -----> Bile Canaliculus -----> Bile Duct -----> Portal Triad -----> Hepatic Duct -----> Common Bile Duct

LIVER ENZYMES:

- **Aspartate Aminotransferase (AST, SGOT):**
 - NORMAL VALUE: 2 - 35 IU / I
 - Used to measure the degree of liver-cell membrane damage.
- **Alanine Aminotransferase (ALT, SGPT):**
 - NORMAL VALUE: 0 - 45 IU/I
 - Used to estimate liver cell injury due to viral hepatitis.
- **Alkaline Phosphatase (Alk-Phos):** This enzyme is normally synthesized and secreted in the bile, to aid in intestinal digestion of phospholipids.
 - NORMAL VALUE: 30 - 130 IU / I
 - **Hepatitis:** Alk-Phos is *not elevated*. Hepatocytes are dead and not synthesizing that much enzyme.
 - **Cholestasis, Biliary Cirrhosis:** Alk-Phos is *highly elevated*. Hepatocytes can't secrete the enzyme, which not only makes it back up into the blood, but also stimulates further synthesis of it by liver cells.
- **Albumin:** It is a measure of compromised metabolism. It remains normal in all forms of hepatitis, and does not become deficient until severe cirrhosis.

BILIRUBIN METABOLISM:

- **BILIRUBIN CYCLE:**
 - Heme Breakdown: Heme -----> Biliverdin -----> Bilirubin.
 - Hepatocytes take up **indirect bilirubin**, or unconjugated bilirubin.
 - *Glucuronyl Transferase*: Hepatocytes conjugate **Bilirubin** -----> **Bilirubin Glucuronide**.
 - Bilirubin Glucuronide is transported into the **bile canaliculus** -----> secreted into intestine.
 - Intestinal bacteria convert Bilirubin Glucuronide -----> Bilirubin -----> **Urobilinogen**
 - Some of urobilinogen is reabsorbed in ileum -----> back to liver. Some it is excreted in feces, giving feces its **brown color**.
 - Urobilinogen in liver is either re-secreted (enterohepatic circulation) or enters the systemic circulation where it goes to the **urine**.
- **Indirect Bilirubin:** Unconjugated bilirubin.
 - *A high indirect bilirubin in the blood, coupled with a high total bilirubin, usually means a hemolytic jaundice.*
 - The conjugate system is saturated and the liver can't conjugate it all, so unconjugated bilirubin remains in the blood.
- **Direct Bilirubin:** Conjugated bilirubin. **Bilirubin glucuronide**.
 - *A high direct bilirubin in the blood means hepatitis, or an obstructive jaundice.* The liver was able to conjugate the bilirubin, but could not secrete it into the bile tracts.

JAUNDICE DISORDERS:

- **HEMOLYTIC JAUNDICE:** It will show a high total bilirubin and *high indirect bilirubin*.
 - **PATHOGENESIS:** It results from any process that gives us too many dead RBC's -- either hemolytic anemia or ineffective erythropoiesis.
- **CRIGLER-NAJJAR DISEASE:** Unable to conjugate bilirubin -----> **high indirect bilirubin**.
 - **PATHOGENESIS:** Absence of **UDP-Glucuronyl transferase** activity.
 - No conjugation of bilirubin -----> excessive indirect bilirubin in blood.
 - Autosomal recessive enzyme deficiency.
 - **CLINICAL:** Presents as neonatal jaundice complicated by encephalopathy (kernicterus). Death usually occurs during the first year of life.
- **GILBERT SYNDROME:** Autosomal dominant unconjugated hyperbilirubinemia of unknown pathogenesis.
 - **EPIDEMIOLOGY:** Affects 5-10% of population, more often in males. Typically occurs after puberty.
 - **CLINICAL:** Asymptomatic. Jaundice is the only symptom, and it requires no treatment.
- **DUBIN-JOHNSON SYNDROME:** Unable to transport bilirubin out of hepatocytes and into bile canaliculi -----> **high direct bilirubin**.
 - **PATHOGENESIS:** Autosomal recessive chronic or intermittent jaundice, due to defective intracellular transport of bilirubin.
 - **PATHOLOGY:** Accumulation of brown granular pigment in liver cells and Kupffer cells. It looks like hemosiderin but it is actually bilirubin.
- **NEONATAL (PHYSIOLOGIC) JAUNDICE:** Innocent jaundice of the newborn, because livers aren't always ready for bilirubin conjugation in the newborn.
 - **KERNICTERUS:** *Only in the neonate*, high concentration of indirect bilirubin in the CNS, resulting in brain damage. This is a complication of physiologic jaundice, or can occur with Neonatal Hepatitis.
- **CHOLESTASIS:** Impeded flow of bile.
 - **PATHOGENESIS:**
 - **Intrahepatic Cholestasis:** Cholestasis caused by intrinsic liver disease.
 - **Extrahepatic Cholestasis:** Cholestasis caused by extrahepatic causes, such as gallstones or pancreatic carcinoma.
 - **PATHOLOGY:** Brownish bile pigment found in dilated canaliculi.
 - **Centrilobular:** Bile plugs tend to be found in the middle of the lobule -- not around the portal tracts! Remember where bile is synthesized.
 - **Feathery Degeneration:** Triad of morphological findings in chronic cholestasis
 - Hydropic swelling of hepatocytes
 - Diffuse impregnation of bile pigment (both centrally and portally)
 - Reticulated appearance

- **Bile Lakes:** Longstanding cholestasis, leading to destroyed hepatocytes. Bile lakes replace the destroyed cells.
- CLINICAL: DIAGNOSIS is based on finding excessive amounts of things in the blood:
 - **Cholesterol:** Hypercholesterolemia.
 - **Bilirubin:** Both direct and indirect.
 - Bile Acids in blood.
 - **Alkaline Phosphatase** is usually elevated.

LIVER ABSCESS: Focal suppurative inflammation of the liver. May be **pylephlebitis** due to ascending infection that enters the liver through the portal veins, or **cholangitis**, if the infection had reached the liver through the bile ducts.

HEPATITIS:

- **HEPATITIS-A (HAV):** Enterovirus-72
 - EPIDEMIOLOGY: Prevalent in underdeveloped countries due to mode of transmission.
 - TRANSMISSION: Fecal-oral. Found in shellfish, where viral particles can become concentrated.
 - *It is not sexually transmitted*, whereas both HAV and HCV are.
 - CLINICAL: As opposed to HBV and HCV, *HAV is only acute* -- there is no persistent infection.
 - **Anicteric:** Children with HAV usually do not present with jaundice. The disease may be silent. Adults, on the other hand, usually do have jaundice.
 - Recovery: Less than 1% of people with HAV get fulminant hepatitis and die. Most people recover.
 - DIAGNOSIS:
 - 25-28 day incubation period.
 - Period of highest infectivity: then there is lots of virus in the feces -- before the patient becomes symptomatic.
 - Then, Anti-HAV IgM will appear in blood. Around the same time, AST and ALT will be high.
 - Then (5 -6 weeks later), IgM drops off and is replaced by IgG, which persists for life.
 - VACCINE: Available, and given to people traveling to endemic areas. Three doses.
 - *HAV infection confers permanent immunity.* There is only one serotype, and antibodies are protective.
 - Both passive immunity, and more recently, active immunization, is available.
- **HEPATITIS-B (HBV):** Hepadnavirus
 - STRUCTURE:
 - **Dane Particle:** The entire infectious virion, including nucleocapsid, core antigens, and surface antigens.
 - **HBV Surface Antigen (HBsAg):** 4 phenotypes, useful for epidemiology: adw, ayw, adr, ayr.
 - EPIDEMIOLOGY: Sexual, fecal-oral, or intravenous or by exposure to blood products.
 - Due to multiple serotypes (a, d, y, w, r), the same person may be infected with HBV multiple times! However, simultaneous infection with multiple strains is common.
 - High incidence seen in SE Asia and Africa, corresponding to the incidence of hepatoma.
 - DIAGNOSIS:

| Term | Abbrev | Description |
|---|----------|---|
| Hepatitis-B Surface Antigen | HBsAg | <p>Surface antigen present on viral envelope. Its presence indicates <i>acute HBV infection</i>.</p> <p>Has serotype-makers: (1) a (always found), (2) d or y, and (3) w or r.</p> |
| Antibodies to Hepatitis-B Surface Antigen | Anti-HBs | <p>Antibodies to the surface antigen are <i>not</i> detectable during acute infection even though they are being made, because there is way more antigen and it sops it all up, making it undetectable in the blood.</p> <p>Presence of Anti-HBs indicates <i>immunity to HBV</i> or <i>previous vaccination for HBV</i>.</p> |
| Hepatitis-B Core Antigen | HBcAg | Its presence indicates <i>acute HBV infection</i> , and signifies that the patient |

| | | |
|--------------------------------------|----------|---|
| | | is currently infective. |
| Antibodies to Hepatitis-B Core | Anti-HBc | Its presence indicates <i>acute or chronic HBV infection</i> . Whether it is acute or chronic depends on whether IgM is present or IgG. |
| Hepatitis B e Antigen | HBsAg | This is the hepatitis viral polymerase and is present during acute infection. It indicates that the patient is currently infective. |
| Antibodies to Hepatitis-B e Antigen. | Anti-HBe | These aren't usually tested but are present during acute or chronic infection. |
| Antibodies to Hepatitis-A | Anti-HAV | Indicates acute infection of Hepatitis-A. There is no chronic Hepatitis-A infection. |
| Antibodies to Hepatitis-C | Anti-HCV | Indicates <i>acute or chronic</i> infection of Hepatitis-C. |

- CLINICAL:
 - PROGRESSION:
 - HBsAg appears early on. Patient may have fever, malaise, jaundice, myalgia.
 - **Window phase**: Period after surface antigen disappears, but before antibody appears, during which patient may test negative for both!
 - Recovery: Anti-HBsAg antibodies are formed, indicating recovery from infection.
 - LAB:
 - Albumin would not be elevated and is not affected in the acute phase.
 - AST and ALT go sky high.
 - Both indirect and direct bilirubin will be elevated.
 - COMPLICATIONS:
 - Ag-Ab complex complications: Glomerulonephritis, arthritis, rash, vasculitis.
 - **Chronic Hepatitis** (either carrier, or chronic-active) occur in 5% of patients -----> further leads to **cirrhosis**
 - **Fulminant Hepatitis** also occurs, with rapidly progressing bad course. This has high mortality, but if patient recovers, they will not go into chronic hepatitis.
 - **Hepatocellular Carcinoma** risk is elevated, due to cirrhosis secondary to chronic hepatitis.
- **HEPATITIS-D (HDV)**: Hepatitis-B is required in order for this virus to infect. Can either be a co-infection, or it can be transmitted to a chronic HBV carrier.
 - EPIDEMIOLOGY: Prevalent in Mediterranean. In U.S., it is found mostly in IV at-risk groups: drug-users and hemophiliacs.
 - CLINICAL: Course is more severe and prognosis is poorer when Delta agent is present.
- NON-A NON-B HEPATITIS:
 - **HEPATITIS-C (HCV)**: Flavivirus
 - EPIDEMIOLOGY: Primary mode of transmission is parenteral route (blood). In the past has been associated with transfusions.
 - CLINICAL:
 - SYMPTOMS: Fever, malaise, flu-like symptoms, myalgia. Jaundice in 25%
 - AST and ALT levels may wildly fluctuate.
 - COMPLICATIONS: 50-70% progress to chronic liver disease. Many of those go on to develop cirrhosis.
 - **HEPATITIS-E (HEV)**: Calicivirus
 - EPIDEMIOLOGY: Fecal-oral, often found in contaminated water. Found primarily in other countries -- India and central Asia.
 - CLINICAL: Acute infection similar to HAV.
 - High fatality rate among pregnant women, and high perinatal fatality.
 - **HEPATITIS-G (HGV)**: Paramyxovirus
- **ACUTE VIRAL HEPATITIS**:
 - PATHOLOGY:
 - Baloon hepatocytes can be seen.
 - **Acidophilic Bodies** can be seen.

- CLINICAL:
 - **AST, ALT** will be extraordinarily high (5,000 - 10,000). If the patient has low or normal enzymes the next day, then that is bad! That means that there has been massive hepatic necrosis, and the liver cells are not producing the enzymes anymore.
- **CHRONIC HEPATITIS:** The presence of inflammation and necrosis in the liver for more than 6 months.
 - PATHOLOGY: Chronic Persistent and Chronic Active are really just ends of a continuous spectrum.
 - **CHRONIC PERSISTENT HEPATITIS:** Milder form. Lymphocytic inflammation is limited to the portal tracts. "Asymptomatic Carrier" is the extreme mild end of the spectrum.
 - The **Limiting Plate** is still visible.
 - **CHRONIC ACTIVE HEPATITIS:** More severe. Necrotizing inflammation progresses to cirrhosis.
 - The **Limiting Plate** is impinged upon -- inflammatory cells destroy the limiting plate and invade the hepatic lobules themselves.
 - This form of infiltration results in **piecemeal necrosis**.
 - CLINICAL: Hepatosplenomegaly, jaundice, hepatic encephalopathy in severe cases.
- **AUTOIMMUNE HEPATITIS:**
 - EPIDEMIOLOGY: Young and middle-aged women
 - PATHOGENESIS: Auto-immune SLE-like syndrome.
 - CLINICAL: Hypergammaglobulinemia, autoantibodies, positive LE-cell prep, are all found. Multisystem autoimmune involvement is typical (SLE-like syndromes).
 - TREATMENT = Corticosteroids. A favorable response is usually found.
- **CONFLUENT HEPATIC NECROSIS:** Fulminant hepatitis, characterized by death of a large number of liver cells, or all liver cells. It affects whole lobules at a time. Three stages of severity:
 - **Bridging Necrosis:** Bands of necrosis stretch between adjacent portal tracts, or between adjacent central veins.
 - **Submassive Confluent Necrosis:** Necrosis of entire lobules or groups of adjacent lobules.
 - **Massive Hepatic Necrosis:** Soft, mottled parenchyma. Wrinkled capsule. Liver destroyed.

FATTY LIVER:

- PATHOGENESIS: It can be caused by alcohol, Diabetes, obesity, drugs.
 - BIOCHEMISTRY: Alcohol increases lipolysis and delivery of free fatty acids to the liver. Fat metabolism in the liver decreases, while fat mobilization in the periphery increases.
 - Increased fat synthesis.
 - Decreased mitochondrial oxidation.
 - Impaired release of lipoproteins.
- PATHOLOGY: Liver becomes big, yellow, and greasy. It is fully reversible.

ALCOHOLIC LIVER DISEASE:

- PATHOGENESIS: Not all people who drink get alcoholic liver disease. There are genetic predisposing factors.
 - **Alcohol Dehydrogenase** metabolism results in toxic metabolites (formaldehyde) that can damage the liver.
 - There are also contributions from microsomal oxidases, peroxisomes, and catalases.
- CLINICAL: DIFFERENTIAL DIAGNOSIS. Other diseases that resemble alcoholic liver disease
 - Steatonecrosis of liver caused by obesity.
 - **Amiodarone** = drug for cardiac arrhythmias is hepatotoxic.
 - Jejunioileal bypass can have complications similar to alcoholic liver.
 - Wilson's Disease
- **ALCOHOLIC HEPATITIS:**
 - PATHOLOGY: Hepatic architecture remains basically intact, with isolated necrotic liver cells.
 - Necrosis of hepatocytes in the central zone.
 - **Mallory Bodies:** Hyaline inclusions are found in hepatocytes.
 - Neutrophilic infiltrate.
 - **Central Hyaline Sclerosis:** Collagen collects around the central venules. When it is extreme, it is called Central Hyaline Sclerosis, in which terminal venules are obliterated.
 - **COUNCILMAN BODIES:** Disparate dead hepatocytes. They are seen in alcoholic hepatitis and in viral hepatitis.
 - CLINICAL: Malaise, jaundice, RUQ pain

- LABS: Leukocytosis, elevated AST.
- **ALCOHOLIC CIRRHOSIS:** Micronodular cirrhosis.

CIRRHOSIS: The destruction of liver architecture. It is replaced by **fibrous septa** that contain islands of regenerating hepatocytes.

- Morphological Classification:
 - **MICRONODULAR CIRRHOSIS:**
 - **PATHOGENESIS:** Most cases of cirrhosis, resulting from alcohol, Primary Biliary Cirrhosis, Hemochromatosis, Wilson's Disease.
 - **PATHOLOGY:** Uniform, small fibrous septa, surrounding inflammatory cells and hepatocytes.
 - **MACRONODULAR CIRRHOSIS:** Also called **Post-Hepatic** or **Post-Necrotic Cirrhosis**.
 - **PATHOGENESIS:** It occurs secondary to **chronic active hepatitis**.
 - Also, the micronodular pattern can be converted to the macronodular pattern by coalescence of micronodules.
 - **PATHOLOGY:** Large, irregular lobules surrounded by fibrous septa.
 - LABS:
 - Albumin is decreased (end-stage cirrhosis)
 - **Gamma globulins** are increased
 - Post-prandial chylomicrons are deficiency (exactly when they should be elevated).
- **PRIMARY BILIARY CIRRHOSIS:** An autoimmune disease characterized by destruction of intrahepatic bile ducts and obstructive jaundice.
 - **ETIOLOGY:** Typically affects middle aged women.
 - **PATHOGENESIS:** Autoimmune; autosomal-recessive. They think that cytotoxic T-Cells attack the biliary epithelium.
 - Often associated with other autoimmune diseases, such as: Thyroiditis, rheumatoid arthritis, Sjögren Syndrome, SLE.
 - **ANTIMITOCHONDRIAL ANTIBODIES** are found in the serum of almost all patients.
 - Antinuclear Antibodies (ANA) and Anti Smooth Muscle antibodies may also be seen.
 - **PATHOLOGY:** *Non-suppurative destruction of the intrahepatic bile ducts*. Cirrhosis revolves around the portal triads. You would see **bile lakes**, just as in cholestasis. Four Stages, all of which can be present at the same time:
 - **Duct Lesion:** Non-Suppurative destruction of the bile-ductules. Mostly lymphocytic infiltrate.
 - Either no cholestasis or only central cholestasis may be present.
 - May see **non-caseating granulomas** in ductules or portal tracts.
 - **Compensatory Ductule Proliferation:** Bile ductule proliferation is seen in response.
 - **Portal Fibrosis:** Scarring leads to portal fibrosis and a paucity of bile ducts. Small bile ducts virtually disappear. Cholestasis may be severe and has moved to the periphery of the lobules.
 - Portal triads remain present but the ductules themselves are virtually obliterated.
 - **Cirrhosis:** End-stage liver. Green bile-stained gross appearance to liver.
 - **CLINICAL:** Female predominance,.
 - **DIFFERENTIAL DIAGNOSIS:** Primary Biliary Cirrhosis can be confused with other disease entities.
 - **Primary Sclerosing Cholangitis:** This is the easiest one to confuse it with. It affects bigger (more distal) segments of the bile ducts than PBC, and it has a slight male predominance.
 - Sarcoidosis: Granulomas in liver may be found.
 - Chronic Active Hepatitis: Look for destruction of bile ducts to distinguish them.
 - Drug-induced cholestasis.
 - LABS: **High Alk.Phos.** is characteristic. Bilirubin may be high or normal.
 - **SYMPTOMS:**
 - **Intense Pruritus:** Caused by retention of bile acids and bile salts.
 - **XANTHOMAS: High Cholesterol** is almost always seen, resulting in subcutaneous fatty lesions termed xanthomas.
 - **Steatorrhea** is seen due to no fat absorption, because of no bile secretion.
 - Vitamin-D deficiency (no absorption) -----> osteomalacia, osteoporosis.
 - Portal Hypertension.
 - **TREATMENT:** Methotrexate, or Liver Transplant. 5-yr survival at 65%

- **PRIMARY SCLEROSING CHOLANGITIS (SECONDARY CIRRHOSIS):**
 - **EPIDEMIOLOGY:** Slight male predominance, as opposed to PBC which is female predominant. Can occur at any age, but under 45 is typical.
 - **PATHOGENESIS:** It is usually a *partial* idiopathic destruction of the **extrahepatic** bile ducts, causing bile backup. Cause of the inflammation is unknown.
 - 40% of patients also have **ulcerative colitis**.
 - **PATHOLOGY:**
 - Onion-ring configuration around bile-ductules, followed by fibrosis.
 - **CLINICAL:** It causes obstructive jaundice and biliary cirrhosis.
 - **SYMPTOMS:** Fatigue, pruritus, jaundice, fever. Fever is more common with PSC than with PBC.
 - **DIAGNOSIS: Endoscopic Retrograde Cholangiography (ERCP):** Used for diagnosis. Inject dye into common bile duct to illuminate the biliary tree.
 - Normal = smooth ducts can be seen.
 - PSC: Rough edges are seen, along with areas of constriction followed by dilatation.
 - **PROGNOSIS:** Poor. **Cholangiocarcinoma** is a common complication.
- **SECONDARY BILIARY CIRRHOSIS (OTHER CAUSES):** Extrahepatic biliary obstruction can be caused by many things:
 - Gallstones
 - Carcinoma of the head of the pancreas
 - Cancer of the Ampulla of Vater
 - Benign strictures
 - Congenital Biliary Atresia
- **HEREDITARY HEMOCHROMATOSIS (PRIMARY IRON OVERLOAD):**
 - **PATHOGENESIS:** Idiopathic, congenital hyper-absorption of iron, and toxic accumulation of iron in liver and other organs.
 - **PATHOLOGY:**
 - Intense brown granules can be seen on trichrome stain.
 - **Prussian Blue** stain illuminates the iron.
 - The iron is usually found in the hepatocytes themselves.
 - **SYMPTOMS: CLASSICAL SYMPTOM-CLUSTER**
 - **Cirrhosis:** Iron-deposition in liver
 - **Diabetes:** Iron deposit in pancreas -----> damage to beta-cells.
 - **Skin** pigmentation
 - **Cardiac failure.**
 - **SECONDARY IRON OVERLOAD:** Iron accumulation by any other cause, such as increased dietary iron overload, thalassemia, anemias.
 - **PATHOLOGY:** Iron accumulates in **Kupffer** cells -- not the hepatocytes themselves.
- **WILSON DISEASE (Hepatolenticular Degeneration):**
 - **PATHOGENESIS:** Autosomal-recessive deficiency of **ceruloplasmin**, leading to no way to transport copper in the blood -----> copper accumulates in liver.
 - Because it has no carrier protein, you also see a reduced amount of copper secretion in the bile, leading to yet more buildup of copper in blood.
 - Copper builds up in other organs, too: Brain, cornea, renal tubules.
 - **PATHOLOGY:** Resembles chronic active hepatitis.
 - It cannot be diagnosed as Wilson's Disease based on histology alone. It looks like chronic active hepatitis.
 - **Copper Stain:** Copper will appear as brown-granules in the hepatocytes.
 - **CLINICAL:**
 - Disease affects brain as well as liver, hence "Hepatolenticular Degeneration."
 - **Kayser-Fleischer Ring:** Seen in the eyes. The deposition of copper in Descemet's Membrane. Considered pathognomonic for Wilson's Disease.
 - **TREATMENT:** It can be treated by using chelating agents to sequester the extra copper.
- **CYSTIC FIBROSIS:** Due to thick secretions in the bile, secondary biliary cirrhosis is found in 10% of patient who survive beyond 25 years.
- **alpha₁-ANTITRYPSIN DEFICIENCY:** An autosomal recessive disorder characterized by childhood cirrhosis and emphysema. AAT accumulates in liver cells in form of PAS positive globules.
 - **PATHOGENESIS:** alpha₁-Antitrypsin is normally synthesized by liver. Failure of the liver to export the alpha₁-Antitrypsin (due to the mutation) results in *build-up of the Antitrypsin in hepatocytes*, which leads to liver damage.

- **PHENOTYPES:**
 - **PI-MM:** Normal wild-type 95%
 - **PI-MZ:** Heterozygote (deficient PI) 3-5%
 - **PI-ZZ:** Homozygote (no PI) <1% . Only the double-recessive allele is associated with liver damage.
- **CLINICAL:** Can manifest in children or adults.
 - **CHILDREN:** Neonatal hepatitis, jaundice, paucity of bile ducts.
 - **ADULT:** Chronic active hepatitis, or cirrhosis.
 - **DIAGNOSE:** Measure alpha₁-Antitrypsin blood levels to make diagnosis.
- **PATHOLOGY:**
 - **PAS-positive inclusions** are seen in the cytoplasm of hepatocytes. These can be confused with Mallory Hyaline or with Councilman bodies. Use a PAS stain to differentiate them.
- **Inborn Errors of Carbohydrate Metabolism:**
 - **GLYCOGENOSIS TYPE IV (ANDERSON DISEASE):** This is the only subtype of glycogenoses that is always complicated by cirrhosis.
 - It may occur in Glycogenosis Type III (Cori Disease), but it is not inevitable.
 - **GALACTOSEMIA:** Autosomal recessive deficiency of *Galactose-1-Phosphate Uridyltransferase*, which helps in converting galactose to glucose.
 - **SYMPTOMS:** Hepatomegaly, jaundice, hypoglycemia. Cataracts, mental retardation.
 - **HEREDITARY FRUCTOSE INTOLERANCE:** Deficiency of Fructose-1-Phosphate Aldolase. In infancy, buildup of fructose can lead to hepatomegaly, jaundice -----> progressive cirrhosis.
 - **TYROSINEMIA:**

HEPATIC FAILURE: The common endpoint to many liver diseases, and the clinical manifestations of cirrhosis. Presents with the following complications:

- **JAUNDICE:** Build-up of direct and indirect bilirubin.
- **HEPATIC ENCEPHALOPATHY:**
 - **PATHOGENESIS:** Caused by failure of liver to perform detoxification functions.
 - No **urea cycle**. The liver cannot make urea -----> build-up of **ammonia**.
 - Buildup of mercaptans.
 - Buildup of tryptophan, GABA, and benzodiazepines.
 - **CLINICAL:** Confusion -----> drowsiness -----> **hepatic coma**
 - **ASTERIXIS:** Flapping tremor of the hand that occurs when asked to dorsiflex the wrist.
- **HEPATORENAL SYNDROME:** Renal failure often co-occurs. Cause unknown, but bile can be found in renal tubules.
- **COAGULOPATHY:** No synthesis of clotting factors -----> easy bleeding, easy bruising.
 - Low platelet count (**thrombocytopenia**) -----> Splenomegaly, bone-marrow depression, DIC.
- **HYPOALBUMINEMIA:** Leads to edema and ascites.
- **ENDOCRINE PROBLEMS:** Caused by decreased hormone detoxification. Estrogen builds up as a result.
 - **GYNECOMASTIA:** Feminization due to excessive estrogen. Feminine body habitus.
 - **SPIDER ANGIOMA:** Usually in upper trunk and face.
 - **PALMAR ERYTHEMA**
- **PORTAL HYPERTENSION**

PORTAL HYPERTENSION: Sustained increase in portal venous pressure, usually, but not always, due to cirrhosis.

- **INTRAHEPATIC PORTAL HYPERTENSION:** Portal hypertension caused by intrinsic liver disease.
 - **ALCOHOL** is the most common cause.
 - Worldwide, **Schistosomiasis** is a common cause of intrahepatic portal hypertension.
- **PREHEPATIC PORTAL HYPERTENSION:** Portal hypertension caused by an occlusion proximal to the portal tracts.
 - **Portal Vein Thrombosis** is most common cause.
 - Other causes: Tumors, hypercoagulability states.
- **POSTHEPATIC PORTAL HYPERTENSION:** Portal hypertension caused by an occlusion anywhere beyond the liver lobules, either in the Central Veins or in the Hepatic Vein.
 - **BUD-CHIARI SYNDROME:** Occlusion of hepatic veins and venules, resulting in post-hepatic portal hypertension.

- **PATHOGENESIS:** Often idiopathic, but it can be caused by polycythemia vera, primary and secondary liver cancers, oral contraceptives, trauma.
 - **PATHOLOGY:** Usually it is thrombosis of the larger hepatic veins that cause problems.
 - Centrizonal necrosis and fibrosis of central areas is seen, as central zone gets packed with backed-up blood.
 - **Reverse Lobulation** occurs, in which adjacent central zones join together, due to increased pressure, and are connected by fibrous septa.
 - **Hepatic Veno-Occlusive Disease:** A variant of Bud-Chiari, in which the smaller intrahepatic venules are occluded *Crotalaria* and *Senecio* plant alkaloids ("Bush Teas")
 - **COMPLICATIONS:**
 - **PORTAL-CAVAL ANASTOMOSES:** Blood is diverted to caval system due to back-up in the liver.
 - **Esophageal Varices:** Engorged veins around lower esophagus, which can rupture, causing surgical emergency.
 - **Internal Hemorrhoids:** Portal-caval anastomoses around the rectum.
 - **Caput Medusae:** Engorged umbilical veins, around the umbilicus.
 - **Splenomegaly:** Occurs due to increased blood pressure.
 - **Hypersplenism** is a decrease in the life-span of all blood-cells -----> enhanced removal of blood cells because of a hyperplastic spleen.

TOXIC LIVER INJURY:

- **ZONAL HEPATOCELLULAR NECROSIS:** *Predictable hepatotoxins* typically cause **centrilobular necrosis**.
 - Examples of predictable hepatotoxins:
 - Yellow phosphorous
 - **Phalloidin** from mushroom *Amanita Phalloides*
 - Acetaminophen
 - Carbon Tetrachloride
 - **PATHOLOGY:** Coagulative necrosis, hydropic swelling, various amounts of fat.
- **FATTY LIVER:** From drugs, it occurs in two predictable patterns.
 - **MACROVESICULAR STEATOSIS:** Large fat globules accumulate in the cytoplasm of liver cells.
 - *Nucleus is pushed to the side.*
 - **MICROVESICULAR STEATOSIS:** Smaller fat globules dispersed throughout. Usually associated with more severe liver disease. *Nucleus retains its central position.*
 - **REYE'S SYNDROME:** Example of microvesicular steatosis. Aspirin-induced toxicity after a febrile illness.
 - **SYMPTOMS:** Hepatic failure and encephalopathy.
- **INTRAHEPATIC CHOLESTASIS:** A frequent complication of idiosyncratic hepatic drug reactions.
- **ACUTE VIRAL HEPATITIS:** Morphologically, the idiosyncratic reactions of **Isoniazid**, **Halothane**, and **Methyldopa** are indistinguishable from acute viral hepatitis.

NEONATAL HEPATITIS: In the neonate, prolonged cholestasis, morphologic evidence of liver injury, and inflammation. Multiple etiologies.

- **PATHOGENESIS**
 - α_1 -Antitrypsin Deficiency: 30% of cases.
 - Infections: Viral hepatitis (HBV, HCV), TORCH Complex.
- **PATHOLOGY:**
 - **Giant-Cell** transformation of hepatocytes is characteristic. Bile pigment prominent with hepatocytes.
- **BILIARY ATRESIA:** Absence or hypoplasia of intrahepatic biliary tracts or the extrahepatic biliary ducts.
 - **PATHOGENESIS:** It either occurs *secondary to* or concurrent with neonatal hepatitis. It is thought to result from an inflammatory destructive process in the bile ductules.
- **CLINICAL:** Neonatal hepatitis usually leads to full recovery. When it occurs with biliary atresia, it often leads to biliary cirrhosis, and the prognosis is much poorer.
 - **KERNICTERUS:** Permanent brain damage in cases of pro-longed hyperbilirubinemia, in neonatal hepatitis.

BENIGN NEOPLASMS:

- **HEPATIC ADENOMA:** Benign tumors in women, occurring during reproductive years.
 - **PATHOGENESIS:** **Oral Contraceptives** are a well-known risk-factor.
 - **PATHOLOGY:** Solitary, sharply demarcated masses in liver. They are strictly benign and do not metastasize.
 - Tissue resembles normal liver tissue, except it is not arranged into lobules, and there are no portal tracts or central venules.
 - **CLINICAL:** Tumor can bleed into peritoneal cavity, in which case it is a surgical emergency.
- **FOCAL NODULAR HYPERPLASIA:** Liver mass composed of fibrous septa and hepatocytic nodules.
 - **PATHOLOGY:** Center of mass contains a scar, from which the fibrous septa radiate.
- **HEMANGIOMA:** Vascular tumor found in liver. Very common.

MALIGNANT NEOPLASMS:

- **HEPATOCELLULAR CARCINOMA:** Primary Hepatocellular Carcinoma is also known as Hepatoma.
 - **EPIDEMIOLOGY:** Uncommon in U.S. Particularly common in sub-Saharan Africa, SE Asia, and Japan.
 - **PATHOGENESIS:**
 - **Hepatitis-B, HBV** is a causative factor. The genome of HBV is integrated into liver cells, in people with HBV infection who develop cancer.
 - **Hepatitis-C, HCV** also seems to be a causative factor.
 - Secondary cirrhosis from **Hemochromatosis** or **alpha₁-Antitrypsin deficiency** is also a risk-factor.
 - **PATHOLOGY:** Soft and hemorrhagic tan masses in the liver. Multiple histologic types.
 - **CLINICAL:** Presents as a painful, enlarging mass in liver. Prognosis is dismal.
 - **Complications:** Peritoneal bleed, portal hypertension, cachexia, hepatic failure.
 - **LANS:** Increased **alpha-Fetoprotein (AFP)** will be found. Also, the hepatocellular tumors can secrete bile and mucin.
- **CHOLANGIOCARCINOMA:** Malignant tumors of biliary epithelium, either intrahepatic or extrahepatic.
 - **PATHOLOGY:** Characteristic extensive fibrosis of bile ductules.
- **METASTATIC CANCER:** *As in the lung, the most common malignant tumors in the liver are metastases* (at least in the U.S.)
 - They are also the most common cause of massive hepatomegaly.
 - **CLINICAL:** Weight loss is a common finding.

THE GALLBLADDER

CHOLELITHIASIS: Gallstones

- **CHOLESTEROL GALLSTONES:** Due to hypercholesterolemia.
 - **PATHOGENESIS:** Cholesterol is normally solubilized by a combination of bile acids and lecithin. Cholesterol stones can occur due to an excess of cholesterol or to a *deficiency of bile acids*, since bile acids solubilize the cholesterol. Either one can result in precipitation of cholesterol.
 - The **LIVER** is usually the culprit in the pathogenesis: hypercholesterolemia due to some reason, usually intrahepatic biliary obstruction or cirrhosis.
 - **7-Hydroxylase Deficiency:** Deficiency in enzyme required to make bile acids out of cholesterol --> build-up of cholesterol *and* deficiency of bile acids --> cholesterol stones.
 - **Mucinous Glycoproteins** from the liver are thought to serve as the **nidus** (seed) for the gallstone.
 - **RISK-FACTORS:**
 - **Estrogen** (oral contraceptives) results in increased secretion of cholesterol and may result in decreased production of bile salts.
 - Increased age
 - Obesity
 - Familial predisposition
 - **PATHOLOGY:** Yellow or tan. Size from 1 to 4 cm.

- EPIDEMIOLOGY: Women are more likely than men to get during reproductive years.
- **PIGMENT GALLSTONES:**
 - **BLACK PIGMENT GALLSTONES:** Due to precipitation of **bilirubin** in the bile.
 - PATHOGENESIS: Increased unconjugated bilirubin in the bile. Usually idiopathic.
 - Chronic hemolysis (hemolytic jaundice) can cause it.
 - **BROWN PIGMENT GALLSTONES:** Gallstones of calcium bilirubinate, intermixed with cholesterol and calcium soaps of fatty acids. Located more frequently in the bile ducts than in the gallbladder.
- **CLINICAL:** Gallstones often remain silent until they cause obstruction.
 - **Biliary Colic:** Waxing and waning pain due to gallstones.
 - **Acute cholecystitis** may occur.
 - **Cholelithiasis:** Gallstones passing into the common bile duct, where they cause obstruction.
 - **Acute pancreatitis:** May occur secondary to an obstructed bile duct.
 - **Mucocele:** Hydrops of the gallbladder occurring secondary to gallstones. It is a clear mucinous secreted by the gallbladder in a patient with gallstones in the cystic duct.

CHOLECYSTITIS:

- **ACUTE CHOLECYSTITIS:** Diffuse inflammation of gallbladder, usually secondary to gallbladder obstruction.
 - PATHOGENESIS: 95% associated with presence of gallstones.
 - PATHOLOGY: Moderate neutrophilic infiltrate, and focal ulcerations.
 - Widespread ulcerations is called "Gangrenous Cholecystitis."
 - **CLINICAL**
 - **COMPLICATIONS:**
 - **Perforation** -----> gallbladder contents spill, but are often contained by inflammatory adhesions.
 - **Bile Peritonitis** results if gallbladder contents escape the gallbladder region.
 - **SYMPTOMS:** Leukocytosis with left shift, fever, RUQ pain, shaking chills.
- **CHRONIC CHOLECYSTITIS:** The most common disease of the gallbladder, associated with gallstones.
 - PATHOGENESIS: Repeated attacks of acute cholecystitis, or longstanding gallstones.

GALLBLADDER CANCER:

- **CARCINOMA of the GALLBLADDER:**
 - PATHOGENESIS: Usually associated with gallstones or with chronic cholecystitis, thus it is more common in women than in men.
 - PATHOLOGY: Infiltrative, well-differentiated adenocarcinoma.
 - CLINICAL: 5-yr survival rate is less than 5%. The tumor does not become symptomatic until late stage.
 - **CARCINOMA of the BILE DUCT and AMPULLA of VATER:**
 - **CLINICAL:** You find obstructive jaundice relatively early, because of its location.
 - 5-yr survival rate is thus much better, due to it becoming symptomatic earlier.
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THE PANCREAS

CONGENITAL DISORDERS:

- **ANNULAR PANCREAS:** The duodenum is encircled by the pancreas.

PANCREATITIS:

- **ACUTE PANCREATITIS:**
 - **PATHOGENESIS:** Autodigestion of pancreatic enzymes, resulting from a number of different causes. Most common causes are alcoholism, impacted gallstones and hyperlipidemia.
 - **Obstruction:** Impacted gallstones, carcinoma of the ampulla of Vater, pancreatic carcinoma.
 - **Alcoholism:** Obscure pathogenesis, but extremely common.
 - Hyperlipidemia
 - Cholelithiasis
 - **PATHOLOGY:** *Pancreatitis is non-infectious.* It is strictly caused by autodigestion. It may, however, become secondarily infected.
 - **Fat Necrosis:** Digestion of pancreatic tissue leads to fat necrosis.
 - Two Subtypes:
 - **ACUTE EDEMATOUS PANCREATITIS:** Interstitial pancreatitis, most common and mildest form.
 - **ACUTE HEMORRHAGIC PANCREATITIS:** 5% of cases, very severe. Massive hemorrhage leads to quick death.
 - **CLINICAL:**
 - **SYMPTOMS:** Severe epigastric pain radiating to back.
 - **Hypocalcemia:** Fat Necrosis and autodigestion release fats into the blood -----> saponification of fats with calcium -----> hypocalcemia as all calcium is sequestered by fats.
 - Shock and superinfection, leading to sepsis.
 - Pulmonary and renal complications are both common and correlate with a bad prognosis.
 - **Steatorrhea** from fat malabsorption.
 - Pancreatic stones
 - Diabetes, from damage to islet cells.
 - **DIAGNOSIS:**
 - **Amylase** blood-levels go up in first 24 hrs (> 400 units)
 - **Lipase** levels will go up within 72-96 hours.
 - Enlarged pancreas by CT scan.
- **CHRONIC RELAPSING PANCREATITIS:**
 - **PATHOGENESIS:** Repeated bouts of acute interstitial pancreatitis.
 - **Alcoholism** causes chronic pancreatitis.
 - **Gallstones** can cause chronic pancreatitis.
 - **PATHOLOGY:** Irregularly distributed fibrosis with decreased acinar tissue.
 - **Calcification** of pancreatic tissue is common. Ducts become hardened and form strictures, impeding flow. Calcification is visible on X-Ray.
 - **Cysts:** True cysts can form, with junk surrounded by fibrotic tissue.
 - **PSEUDOCYST:** Large spaces in pancreas filled with blood, exudate, pancreatic juices. The junk can become infected and form an abscess.
 - It is called a "pseudocyst" because it has no lining epithelium.
 - **CLINICAL:** Varied presentation, from colicky pain, to acute epigastric pain, to malabsorption.
 - Exocrine insufficiency
 - **Steatorrhea**
 - Weight loss

CYSTIC FIBROSIS:

- **PATHOGENESIS:**
 - **CFTR (CF Transmembrane Conductance Regulator):** Faulty transporter

- **STRUCTURE:** The protein consists of two transmembrane domains, two nucleotide-binding domains and a regulatory domain, containing protein kinase A and C phosphorylation sites.
 - **DeltaF508** deletion of phenylalanine is 70% of cases and the most severe form of CF. There are other mutations that are less severe.
 - **MECH:** The DeltaF508 mutation results in defective processing of CFTR protein, which does not become fully glycosylated and is degraded before it reaches the cell surface.
- Inadequate or no excretion of Cl⁻ in glandular cells -----> little or no secretion of water -----> viscous mucous.
- **CLINICAL:** Overall life expectancy of 24-25 years.
 - **SYMPTOMS:**
 - **Chronic Pulmonary Disease** -----> **Bronchiectasis**, widening and hypertrophy of bronchioles.
 - High risk for infection by *Pseudomonas*
 - Most common source of morbidity and mortality from CF in the young adult.
 - **Pancreatic Insufficiency** -----> Malabsorption
 - **Pancreatitis** results from plugged pancreatic ducts.
 - Endocrine pancreas usually is still okay.
 - **Liver:** Plugged mucous in biliary system can result in biliary cirrhosis and jaundice.
 - **Meconium Ileus:** Obstruction of the small bowel in the newborn. Caused by failure to pass meconium in neonate. Has been attributed to failure of pancreatic secretions to digest meconium.
 - This is the most common cause of death from CF in the newborn.
- **DIAGNOSIS: Sweat test**
 - Sweat gland cell cannot reabsorb Cl⁻ due to CFTR defect, therefore sweat is hypertonic rather than normal hypotonic.
- **EPIDEMIOLOGY:** The most common lethal genetic disorder.
 - 1/2,500 get the disease.
 - 1/25 are heterozygous carriers.

EXOCRINE CANCERS of PANCREAS:

- **CYSTADENOMA:** Large, benign, cystic tumor of pancreas, either of mucinous or serous types.
 - **Mucinous Cystadenocarcinoma:** A large multiloculated tumor lined by columnar mucin-producing epithelium in 40-60 year old women. It has a better prognosis of 40-90% survival rate if resected.
 - **Serous Cystadenocarcinoma**
- **PANCREATIC CARCINOMA:** Very deadly cancer, due to its anatomic location.
 - **EPIDEMIOLOGY:** Tendency toward Native Americans, Hawaiians, New Zealanders.
 - **PATHOGENESIS:**
 - **RISK-FACTORS:** Smoking, Chemical Carcinogens, high-fat diet, Diabetes.
 - **PATHOLOGY:**
 - **Anatomic Distribution:**
 - **Head:** 60% of cancers and is more quickly diagnosed, because it causes biliary obstruction.
 - **Tail / Body:** 35%, insidious onset, late detection, and dissemination.
 - **Desmoplastic Reaction:** Formation of collagen around the tumor, due to reaction to secretory tumor cells.
 - Metastases go to liver, peritoneum, lungs, adrenals, bones.
 - **CLINICAL:**
 - **SYMPTOMS:** Weight loss, loss of appetite, gnawing epigastric pain, jaundice.
 - **PROGNOSIS:** Very grim prognosis, due to its anatomical location. Probably the worst prognosis of all cancers.
 - **Courvoisier Sign:** Obstruction of the common bile duct -----> acute painless dilatation of gallbladder, and jaundice.
 - **Trousseau Sign:** Increased risk for thromboembolism with pancreatic carcinoma. One fourth of patients will develop thromboembolism.
 - **TREATMENT: Whipple Procedure.** Surgery to remove the pancreas, duodenum, and a portion of the stomach. Operative mortality is quite high.

- **INSULINOMA**: 75% of islet cell tumors. beta-Cell Tumor.
 - **PATHOLOGY**: Usually benign.
 - **Hyperinsulinemia**.
 - Serum **proinsulin** levels are also elevated.
 - **CLINICAL: Whipple triad**:
 - Hypoglycemic attack with serum glucose at 50 mg/dl
 - Symptoms of hypoglycemia -- CNS symptoms
 - Hypoglycemic attacks relieved by glucose intake.
 - **GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)**: 15-20% of islet cell tumors. G-Cell Tumor.
 - **PATHOLOGY**: Gastric hypersecretion leading to severe Peptic Ulcer Disease.
 - 2/3 of tumors are malignant. They may occur in duodenum or pancreas, but not in stomach.
 - **GLUCAGONOMA**: 1-2% of islet cell tumors. alpha-Cell Tumor.
 - **SYMPTOMS**: Triad of symptoms
 - Necrotizing migratory erythema
 - Diabetes
 - Anemia
 - **SOMATOSTATINOMA**: 1% of islet cell tumors. delta-Cell Tumor.
 - **VIPOMA**: 1-2% of islet cell tumors. VIP-secreting tumor.
 - **Symptom Cluster**:
 - Non-insulinoma tumor
 - Profuse watery diarrhea (10-20 gallon/day)
 - Hypokalemia and achlorhydria (WDHA syndrome)
 - **PPOMA**: 1% of islet cell tumors. Pancreatic Polypeptide-secreting tumor. Elevated pancreatic polypeptide in blood, with no specific symptoms.
 - **MULTIPLE ENDOCRINE NEOPLASIA (MEN)**: Also called Multiple Endocrine Adenomatosis (MEA).
 - **PATHOGENESIS**: Autosomal dominant, with high degree of penetrance.
 - **MEN TYPE I (WERMER SYNDROME)**: Cluster of findings
 - Gastrinoma -----> **Peptic Ulcer**
 - Prolactinoma -----> **Hyperprolactinemia**
 - Adrenal Cortical Adenoma
 - **MEN TYPE II (SIPPLE SYNDROME)**: Cluster of findings
 - Bilateral Pheochromocytoma
 - No gastrinoma
 - Bilateral medullary carcinoma of the thyroid.
-

DIABETES

| | Diabetes Type I (IDDM) | Diabetes Type II (NIDDM) |
|---------------------------------|---|--|
| Mechanism | Insulin is defective or is never formed. Antibodies against pancreatic beta-cells. | Insulin resistance; down-regulation of insulin receptors; failure of pancreas to release insulin even though it being formed. |
| Survival | Insulin is absolutely required for survival. | Patient will survive without insulin |
| Synonyms | Ketosis-Prone Diabetes Juvenile-Onset Diabetes | Ketosis-Resistant Diabetes Adult-Onset Diabetes |
| Onset | Sudden, often discovered by ketoacidosis. Childhood polydipsia, polyphagia, polyuria. | Gradual, insidious. Often discovered incidentally, or when chronic complications arise. |
| Nutrition | Often thin. Failure of action of insulin. | Usually obese. |
| Ketoacidosis | Frequent | Seldom or never |
| Amyloidosis | Amyloidosis of Islets occurs | Amyloidosis does not occur. |
| Complications | Nephropathy is often cause of death Microvascular disease does not show up until 20 or more years after diagnosis. | Multiple causes of death (atherosclerosis, nephropathy). Microvascular atherosclerosis is present at time of diagnosis. |
| Epidemiology | 10% of cases. 50% concordance of disease between twins. | 90% of cases. Multifactorial inheritance. Diet with genetic predisposition. |
| Treatment (order of importance) | Insulin always required Diet Never oral hypoglycemics | Diet and exercise Oral hypoglycemics Insulin |

TYPE-I DIABETES: IDDM

- PATHOGENESIS: Few or no beta-cells, and little or no secretion of insulin.
 - Genetic predisposition. 50% concordance rate among twins.
 - **Insulinitis**: Auto-immune attack against beta-cell is one of the mechanisms by which beta-cells are destroyed and insulin is deficient. Cause of auto-immune attack is unknown.
- DIAGNOSIS:
 - In children, Classic symptoms:
 - **Polydipsia**
 - **Polyphagia**
 - **Polyuria**
 - Unequivocal elevation of plasma glucose > 200 mg/dl.

TYPE-II DIABETES: NIDDM

- PATHOGENESIS: **Multifactorial** inheritance. Diet, environment, and genetic predisposition. Twins have 90% concordance rate for disease.
 - MECH: **Insulin Resistance**, caused by gross obesity. Defined as an insulin requirement of over 200 U per day for one week.
 - Both decreased receptor affinity and decreased receptor concentration contribute to insulin resistance.
 - Normal pancreas secretes 30-50 U insulin per day.
- PATHOLOGY: **Amyloidosis** of islets is seen.
- DIAGNOSIS: Two step process to establish diagnosis.
 - **Fasting plasma glucose (FPG) > 140 mg/dl** on two occasions.
 - **Glucose Tolerance Test**: Give oral glucose 75gm. Wait 2 hours and measure plasma glucose:
 - **Failed Test**: 2 hr plasma glucose > 200 mg/dl at least twice (1/2 hr intervals) during the two hour period.
 - **Impaired Test**: 2 hr plasma glucose > 140 mg/dl, with one intervening value >200 mg/dl after oral glucose tolerance test. About 25% of patients of this condition eventually become diabetic.

COMPLICATIONS of DIABETES:

- MECHANISMS:
 - **GLYCOSYLATION** of blood proteins
 - Examples of glycosylated proteins: hemoglobin, myosin in muscle, components of the lens, collagens, myelin.
 - **Advanced glycosylation products** are formed through time. The initial glycosylations are usually reversible.
 - **Hemoglobin A1C (Hb-A1C)**: Glycosylated hemoglobin that is often measured to monitor the blood-sugar levels of diabetics.
 - **POLYOL PATHWAY**: The way to get rid of excess glucose in non-insulin-dependent tissues, such as the brain.
 - **Glucose + NADH + N⁺ -----> Sorbitol + NAD⁺ (*Aldolase Reductase*).**
 - Accumulation of Sorbitol is believed to play a role in Diabetic retinopathy, nephropathy, neuropathy, and microangiopathy.
- **ATHEROSCLEROSIS**:
 - PATHOLOGY: **Hyaline Arteriosclerosis**. Pathogenesis uncertain.
 - CLINICAL: Major cause of death in older Type-II Diabetics.
 - Silent MI is common (50%) in this group because of accompanying diabetic neuropathy.
 - Coronary bypass is less effective in this group.
- **NEUROPATHY**: Loss of touch, pain perception, and proprioception, particularly in extremities. Pathogenesis is complex.
 - **FOOT PROBLEMS**: They result from Neuropathy (they can't feel the sore), poor circulation (microvascular disease), and tendency to infection.
 - Greater than 50% of non-traumatic foot amputations occur in Diabetics.
- **RETINOPATHY**: Microvascular disease of the eye. Neovascularization, and Retinopathy with macular sparing.
- **NEPHROPATHY**:
 - INCIDENCE: It is more prevalent in Type-I Diabetes (50% of cases) than Type-II (10% of cases).
 - CLINICAL: Look for proteinuria, nephrotic syndrome and hypertension.
 - PATHOLOGY: A gradual increase in basement membrane (BM). After 10-20 years, material start to accumulate in mesangial zone -----> compromise vascular and urinary spaces.
 - **Kimmelstiel-Wilson**: Nodular glomerulosclerosis. Still the hallmark of diabetic nephropathy.
 - **Papillary Necrosis** can occur, as the renal pelvis can get infarcted due to microvascular disease (it is the least to receive blood supply in the kidney). Necrotic pelvis can be sluffed into the ureters and cause kidney stones.
- **INFECTIONS**: Diabetics have depressed immunity and are prone to infection
 - Mucormycosis
 - UTI's

KETOACIDOSIS: Lack of insulin (i.e. high Glucagon:Insulin ratio) promotes lipolysis, breakdown of proteins, and glycogenolysis.

- **Coma:** In hyperglycemia, high **sorbitol** in plasma -----> dehydration -----> coma.
 - *Coma is more often seen with hypoglycemia than with hyperglycemia.*
- **TREATMENT:**
 - **Crystalline Zinc Insulin** is the most immediate-acting insulin, which is the treatment of choice for acute ketoacidosis.
 - Ketoacidosis is treated with both HCO_3^- (to relieve the acidosis) and K^+ (to replace lost K^+ in cells).
 - In Ketoacidosis, there is plenty of K^+ in the blood, but the cells are starving for K^+ because the patient is dehydrated.
 - When you give the IV insulin, glucose goes into cells, and K^+ follows it. We therefore must replace this K^+ to avoid hypokalemia.
- **BIOCHEMICAL CAUSE:**
 - Glucagon promotes **Lipolysis** -----> lots of Acetyl-CoA in the blood.
 - Acetyl-CoA builds up in liver.
 - Glucagon promotes **Gluconeogenesis** -----> **Oxaloacetate** is diverted to work on making glucose and is *therefore unavailable for the TCA cycle.*
 - *Excess Acetyl-CoA cannot be used in TCA cycle and is hence diverted to Ketone Body production.*

HYPOGLYCEMIA:

- **SYMPTOMS:** Palpitations, sweating, tachycardia, fainting, coma.
- **TREATMENT:** IV-Glucose.
- **COMA:** Hypoglycemic coma is more common in Diabetic than ketoacidosis coma, due to over treatment with insulin.
 - Give a comatose diabetic **IV glucose**, until their blood sugar is known for sure. If you give insulin to a hypoglycemic patient, you'll probably kill them!
- **ALCOHOL** inhibits gluconeogenesis and thus can lead to hypoglycemia in Diabetics. Alcohol combined with insulin can lead to hypoglycemia.
- **SOMOGYI PHENOMENON:** *Paradoxical response to insulin*, showing hyperglycemia and ketonuria because of exaggerated physiologic response to exogenous insulin.
 - **PATHOGENESIS:** Results from the release of catecholamine, cortisol, growth hormone and glucagon.
 - Type-I Diabetics are usually the people who exhibit this.
 - **TREATMENT:** You are giving them too much insulin for them to handle. Gradually decrease the amount of insulin by 10-20%.

INSULIN:

- **SYNTHESIS:** **Proinsulin** is hydrolyzed to **Insulin + C-Peptide**
 - **PRO-INSULIN:** Consists of single-chain peptide (A and B chains and C-peptide).
 - **C-PEPTIDE:** Can be used in diagnosis of Diabetes.
 - Type-I Diabetics: It is completely absent due to no insulin synthesis.
 - Type-II Diabetics: It is normal or elevated.
- **SECRETION:** Stimulated by Glucose, Vagal stimulation, and some amino acids. Mechanism involves a K^+ channel and Ca^{+2} channel on the pancreatic beta-cell.
 - **Fasting State:** No glucose is around.
 - ATP is depleted.
 - **K^+ channels** are open.
 - The cell is in the resting, hyperpolarized state.
 - **Resting State:** Plenty of glucose is around (or vagal stimulation).
 - ATP is plentiful.
 - The K^+ channel closes.
 - The cell depolarizes.
 - **Ca^{+2} -channels** open, Ca^{+2} flows in, and insulin is secreted.
 - **Sulfonylureas:** *They promote insulin release by blocking the K^+ -channel*, such that it is always closed. Hence the cell is depolarized and insulin is released.
- **INSULIN RECEPTOR:** It's a Tyrosine Kinase.

- **STRUCTURE:** A glycoprotein of 400 kDa consisting of four glycosylated peptide chains covalently linked by disulfide bonds. The molecules are each dimers, with alpha and beta subunits.
 - **alpha-subunits** (120 kDa): Include binding sites for insulin
 - **beta-subunits** (80 kDa): Involved in initiating some of the insulin actions.
- **Receptor-Affinity:** In Scatchard plot, the negative slope of the line (K_e). Several things can decrease receptor affinity.
 - Glucocorticoid excess.
 - Insulin resistance due to anti-receptor antibodies.
 - **Lipoatrophy:** Loss of sub-cutaneous fat associated with insulin-resistant Diabetes.
- **Receptor Concentration:** In Scatchard plot, the abscissa intercepts, R_0 . Can be decreased in several conditions:
 - Obese Type-II Diabetics: 10-20% decrease in insulin receptors is seen.
 - **Acanthosis Nigricans:** Velvety wart eruption, hyperpigmentation.
- **ACTION:**
 - **GLUCOSE-TRANSPORTERS:** Insulin up-regulates the transport of **GLUT4** transporters into the membranes of target cells.
 - **LIVER:**
 - Insulin promotes glycogenesis
 - Insulin antagonizes glucagon effects of glycogenolysis, ketogenesis, and gluconeogenesis.
 - **MUSCLE:** Insulin promotes protein synthesis and glycogenesis.
 - **FAT:** Insulin promotes fat uptake and storage in adipocytes.
 - It stimulates **lipoprotein lipase** -----> free fatty acids from circulating lipoproteins.
 - Glucose transport and glycolysis generate **glycerophosphate**, which is needed as the glycerol backbone in triglyceride synthesis.
 - It inhibits intracellular lipase, preventing lipolysis in adipose tissue.