CONGENITAL DISEASES OF THE ESOPHAGUS

**Tracheoesophageal Fistula**
- Esophagus has both atresia (blind pouch) and fistula (connection to something else)
- Patients have the trachea and esophagus connected
  - Patients “swallow” food into their lungs = *aspiration pneumonia*
  - Coughing and Cyanosis *during feeding*
  - Amniotic fluid cannot be swallowed, causes *polyhydramnios*
- Must be surgically corrected, which is easily done.
  - Most common = atresia of upper esophagus and fistula of lower esophagus to trachea

**Esophageal Webs**
- Web-like projections of esophageal mucosa into the lumen
- Food gets stuck in webs, presenting with dysphagia and bad breath
  - Associated with
    - Plummer-Vinson Syndrome = webs, iron deficiency anemia, women, ↑ Risk for squamous cell carcinoma
    - Schacktzi Ring = webs down at the esophageal-gastric junction

**Achalasia**
- Inability to relax the Lower Esophageal Sphincter (LES)
- Presents with dysphagia or megaesophagus (can’t get food into stomach)
- Diagnosed with barium swallow revealing “bird’s beak” esophagus
- Caused by death of ganglion cells in the LES
- Treated with stenting or surgical resection

**HEMATEMESIS AND BLEEDS**

**Mallory-Weiss Tear**
- Associated with retching or prolonged vomiting = bulimics and alcoholics
- Are longitudinal tears, usually at the gastro-esophageal junction
- May cause hematemesis, but bleeding usually spontaneously heals
- Lesions may completely heal over time, if retching is discontinued

**Esophageal Varices**
- Patients with liver failure develop porto-caval shunts (Left Gastric Vein → Esophageal)
- One shunt = *esophageal veins* giving rise to distending, tortuous veins in esophagus
- Varices are prone to rupture producing massive hematemesis and melena
- Surgical emergency; these will not spontaneously stop on their own
  - Can do a balloon tamponade to temporarily stop the bleeding
Path GI – Liver – Biliary – Exocrine Pancreas

ESOPHAGITS (Big Robbins 803, Baby Robbins 412)

Esophagitis = inflammation of the esophageal mucosa. It has many causes, but here we cover the most common three: Reflux, Barrett’s, and Infectious/Chemical

Reflux Esophagitis, aka GERD, aka “Heartburn”

- Definition
  - Reflux or regurgitation of gastric contents through the LES causing caustic damage to the lower esophagus

Causes

- ↓ LES Tone allowing gastric contents to come back out the in hole
  - CNS depressants, Pregnancy, Obesity, Alcohol, and Tobacco all ↑ incidence
- Presence of a sliding hiatal hernia with subsequent dilation of LES
- Inadequate or slowing of gastric emptying with increased volume of stomach
- Action of gastric juices is critical to the development of mucosal injury

Morphology

- Dependent on severity and exposure time (two weeks versus seven years)
- Simple Hyperemia (“redness”) may be the only indicator
- Inflammatory Infiltrate = PMNs, Lymphocytes, and/or Eosinophils
- Basal Zone Hyperplasia > 20% of epithelial thickness
- Elongation of Lamina Propria Papillae

Clinical

- Common with increased age (>40) though possible in children through adulthood
- Severity of symptoms ≠ severity of disease (lots of burning without lots of changes)
- Most common complaint is “heartburn,” diffuse burning in the center of the chest
- If not treated, the burning will stop as metaplastic changes create Barrett’s Esophagus

Barrett Esophagus – this, or cancer, will undoubtedly be on your Tulane exam, Shelf, and on Step 1

Definition

- Long-term GERD results in a ‘protective’ replacement of distal esophageal squamous epithelium by a metaplastic columnar, glandular epithelium resembling the duodenum

Pathogenesis

- Long-standing acidic pH in the lower esophagus induces metaplastic differentiation of pluripotent stem cells into columnar type epithelium with goblet cells
- A protective precancerous change to defend against acidic pH

Morphology

- Gross = circumferential, red, velvety mucosa at the gastroesophageal junction
- Micro = columnar epithelium with glandular differentiation and goblet cells
  = Dysplasia is not required for diagnosis but is critical for prognosis

Clinical

- GERD lasts 20 years before Barrett’s sets in
- Patient goes from severe heartburn to no pain spontaneously (progressive or acute)
- This is precancerous with 30-40 TIMES risk for adenocarcinoma
- Treatment with PPIs can potentially reverse both dysplasia and metaplasia
Infectious and Chemical Esophagitis – the “others”

- **Types**
  - Ingestion of *mucosal irritants* = alcohol, corrosive acids/alkali (suicide), hot beverages
  - *Infection* of any kind such as fungus (candida), bacteria, or virus (Herpes, CMV)
  - Uremia from Renal Failure

- **Morphology**
  - Dependent on etiology, Baby Robbins basically says “don’t bother with specifics”
  - All share *acute inflammation, superficial necrosis/ulceration*, and eventual *granulation/fibrosis*

**TUMORS** (Big Robbins 806, Baby Robbins 413)

**Malignant Tumors – Squamous Cell Carcinoma**

**Definition**
- Dysplastic carcinoma of the squamous cells of the esophagus

**Etiology and Pathogenesis**
- Obvious impact of *various environmental factors* combined with *genetic predisposition*
- Chronic esophagitis, Alcohol, or Tobacco contribute to ↑ risk
- Most common esophageal tumor *worldwide*
  - GERD → Barrett’s → Adenocarcinoma equal to or more common in US

**Morphology**
- Similar development to other SCC, with characteristic benign transformation through *carcinoma in situ*, and presence of *keratin pearls*
- Appear as *gray-white plaques* or elevations (unnoticed except on endoscopy)
- Location of tumor may help identify
  - *Squamous Cell Carcinoma* can grow anywhere in the esophagus
  - *Adenocarcinoma* can grow only in lower third
  - If it is in proximal esophagus, then it must be SCC

**Clinical**
- Insidious onset with *without early symptoms* (early detection only with endoscopy)
- *Dysphagia* is late, ominous sign, usually indicated by a *change from solid to liquid foods*
- Early detection = positive prognosis with resection
- Late detection = poor prognosis from tumor invasion
- Hemorrhage and Weight Loss (tumor steals nutrients and causes malnutrition from stenosis) are also possible.
**Malignant Tumors – Adenocarcinoma**

**Definition**
- True metaplasia of the esophagus to gastric mucosa with subsequent dysplasia; when Barrett’s turns to cancer

**Etiology and Prevention**
- Most common esophageal tumor in the US
- Essentially this is caused by Barrett’s Esophagus
- Helicobacter may contribute, but the only way to get glandular tissue in the esophagus is metaplasia or local spread of gastric carcinoma

**Morphology**
- Located in the distal esophagus
- They are flat, mucin producing glandular tissue resembling the duodenum/stomach
- Degree of anaplasia varies even in locations adjacent to obvious lesions

**Clinical**
- Presents with dysphagia, hemorrhage, and ulceration, just like SCC
- Prognosis is very poor once they reach this stage
- They have an obvious clinical course
  - 10 years of “heartburn” without treatment for GERD
  - 2-5 years of Barrett’s without treatment for GERD
  - 1-5 years of adenocarcinoma leading to their death
- Proton Pump Inhibitor Therapy prior to adenocarcinoma formation is curative and reversed metaplasia/dysplasia back to esophageal mucosa

**Progression of GERD to Carcinoma**

1. Squamous epithelium
2. Esophagitis
3. Barrett’s esophagus
4. Dysplasia
5. Adenocarcinoma

**Heartburn, Acid Reflux, GERD**
- Proton Pump Inhibitors are preventative of disease. Get an endoscopy to track changes.

**Barrett’s Esophagus**
- The burn begins to spontaneously disappear over the course of years. You “feel better” but your esophageal epithelium has undergone metaplasia.
- Proton Pump Inhibitors are curative. They reverse the metaplasia and hold off dysplasia. Get endoscopy for diagnosis and to track changes.

**Adenocarcinoma**
- You are screwed. At this point its too late, as these are nasty invaders and have a very poor prognosis, even with resection.

**Metaplasia has given way to dysplasia. You’ve got cancer.**

**Cancerous growth shows no signs or symptoms until you can’t eat (dysphagia) or a fistula is made to your lungs (aspiration pneumonia). You die within 5 years (20% 5 year survival)**
Path GI – Liver – Biliary – Exocrine Pancreas

STOMACH START

CONGENITAL STOMACH (Big Robbins 812, Baby Robbins 415)

- **Pancreatic Heterotopia** = islands of pancreas found within mucosa or the muscle
- **Diaphragmatic hernia**
  - Congenital Defect in the diaphragm, allowing intestines into mediastinum
  - ↓ lung development (pulmonary hypoplasia) if severe
- **Pyloric Stenosis**
  - Occurs in males more than females
  - Patient will present with nonbiliary projectile vomiting after eating
  - Look for **olive-like mass** in the vignette
    - There is an overgrowth of muscle, causing a physical obstruction
    - Myotomy is curative, removing the excess muscle
- **Menetrier’s Disease**
  - This is a **protein losing enteropathy** that is not congenital but doesn’t fit anywhere else
    - If patient presents with edema or ascites, but has normal kidneys and liver, look for this disease as an option choice
  - There will be **significantly enlarged rugal folds** caused by a proliferation of **mucous** cells
    - ↑ Mucous = ↓ Parietal Cell = ↓ Acidic Content = ↓ Digestion = Malabsorption
    - ↑ Mucous = ↓ Chief Cells = ↓ Pepsinogen = ↓ Digestion = Malabsorption
    - ↑ Mucous cell = ↑ Proliferation = ↑ risk for Cancer
- **Zollinger Ellison**
  - A **gastrin-secreting tumor** of the **pancreas**, causing an **increased rugal fold size**
    - Gastrin is the growth stimulator and acid secretion stimulator for the parietal cells (differentiating from Menetrier’s Disease)
    - ↑ Acidic Content leads to **refractory gastric** and **duodenal ulcers**
    - Gastrin is elevated in the blood at all times, and does not suffer acid content feedback as the G cells do in the antrum
  - If you see a patient with a duodenal ulcer (gnawing epigastric pain relieved by food) and H. Pylori is not an option, pick Zollinger-Ellison

GASTRITIS (Big Robbins 812, Baby Robbins 416)

**Definition**

- Histologic definition meaning **inflammation within the gastric mucosa**
- Can be for many reasons, and be **acute** (right now) or **chronic**
- Gastritis can present as an erosion (superficial lesion) or ulceration (deep lesion)
**Acute Gastritis** = “Gastritis without H. Pylori”

- Associated with many causes (NSAIDs, ASA, EtOH, Smoking, NG Tubes, Uremia, Chemotherapy)
- Must be a **failure of mucosal defense**
  - ↑Parietal Cell mass = ↑**acid production**, caused by ↑Gastrin or ↑Sensitivity to Gastrin
  - Regurgitation of duodenal contents = **detergent damage**
  - Ischemia = **mucosal layer necrosis** = no protective mucous
  - NSAIDs = ↓Cox = ↓**prostaglandins**

- Presence of **neutrophils** defines **acute inflammation**
  - There may be **erosion** of mucosal layer
  - There may be **ulceration** of mucosal layer (see acute ulceration)
  - There may be **hemorrhage** into gastric lumen (hemorrhagic gastritis)

- Presentation can vary from **asymptomatic** to epigastric pain, nausea, vomiting, up to **massive hematemesis and melena** (which is life threatening)

**Acute Gastric Ulceration** = “Stress Ulcers” or “Super Acute Gastritis”

- **Small** (<1.0 cm), **focal**, often **multiple** erosions or ulcers of varying depth
- Represent erosive gastritis following a significant stressor (burns, shock, sepsis, head trauma)
  - Splanchnic vasoconstriction (cellular hypoxia) and academia (low pH) injures cells
  - NSAIDs, when abundant, can significantly impair mucosal defenses
- Heal in days to weeks if **underlying cause is fixed** and patients don’t die first
- Found in intensive care patients. If from ↑ICP = Cushings, if from Trauma = Curling’s

---

Gross view of punctuate erosions in an otherwise unremarkable mucosa

![Image](image1.png)

**normal mucosa (arrowheads) hemorrhagic mucosal disruption (arrow)**

Multiple tiny stress ulcers, highlighted by the dark pigment (digested blood) on an otherwise normal mucosa

![Image](image2.png)
**Chronic Gastritis** = “Gastritis caused by H. Pylori”

- **Definition**
  - **Chronic Mucosal Inflammation** that may lead to mucosal atrophy, intestinal metaplasia, dysplasia, and even carcinoma usually without erosion

- **Pathogenesis**
  - **Type A: Autoimmune gastritis**, Fundic Type
    - Antibodies target and kill the Parietal Cells and eliminate Intrinsic Factor
    - Autoantibodies directed against H/K-ATPase, Gastrin Receptor, Intrinsic Factor
    - Leads to chronic inflammation, ↓Acid (infection), and Pernicious Anemia
  - **Type B: H. Pylori Infection**, Antral Type
    - It is flagellated and motile allowing it to swim through mucous layer
    - Possesses urease, cutting up urea and secreting a buffer against lumen acid
    - Yields a positive urease-breath test in a patient who is infected
    - Cytotoxin CagA causes direct Cytotoxicity
    - Induces inflammation via cytokines

- **Morphology**
  - There is a chronic inflammatory infiltrate (plasma cells/leukocytes) admixed with active inflammation (neutrophils) which may predominate
  - Lymphoid aggregates, some with germinal centers, in the mucosa
  - Regenerative Change of surface and neck cells causes an ↑Nuclear: Cytoplasmic ratios with hyperchromatic nuclei; difficult to distinguish from dysplasia
  - Intestinal Metaplasia (gastric mucosa → columnar + goblet cells of duodenum)
  - Atrophy refers to the loss of gastric glands (↓Acid, ↓IF, ↓Cl)
  - Dysplasia is precancerous change
    - Atrophy causes ↑ of Gastrin Producing cells (↓inhibitory stimulus = ↑secretion of Gastrin) which leads to overstimulation of ECF cells
    - Metaplasia already activated erroneous gene production
    - Regenerative changes rev up reproduction = ↑ risk of transformation

- **Clinical**
  - Sx are persistent acute gastritis with the same range
  - Serum Gastrin is usually normal or slightly elevated, lumen is hypochloridic
  - Autoimmune shows circulating antibodies
  - H. Pylori can be seen on biopsy
Peptic Ulcers

**Definition**
- Histologically defined breach of the mucosa that **extends through the muscularis mucosae to at least the submucosa**

**Pathogenesis**
- Chronic, often solitary lesions occurring the GI tract exposed to acid/peptic juices
  - Duodenum (~75%), Gastric (~20%), Gastroesophageal Junction (~5%)
- Caused by **imbalance between GI defenses and acid/pepsin**
  - NSAIDS = ↓ prostaglandins, ASA is a direct irritant
  - Cigarette Smoking = impairs mucosal blood flow and healing
  - EtOH has no causal role, but a strong correlation
  - Rapid Gastric Emptying = ↑ acid exposure to duodenum
  - Delayed Gastric Emptying = ↑ peptic exposure to stomach
  - H pylori = urease, CagA/VacA (Cytotoxic), proinflammatory = ↑ chronic gastritis

**Morphology**
- Round to oval, sharply “punched out” defect with **straight walls**
- The base is smooth, and can sometimes **penetrate the wall of the stomach**
- Puckered mucosa, like a ‘volcanic crater’
- Are usually **singular and large**

**Clinical**
- Produce **epigastric gnawing, burning, or aching**; may present like **cardiac-like chest pain**
- Peptic Ulcer Types
  - Duodenal Ulcers = Pain is **relieved with alkali and food, 100% H. Pylori**
  - Gastric Ulcers = Pain is **increased with alkali and food, 75% H. Pylori**
- Without tx, healing takes 15 years
- With tx (H+ Pump Blockers/Omeprazole and H. Pylori Antibiotics) ulcers heal in weeks
- This was an entire slide, so we say it again: “**Ulcers = Infection, Antibiotics are the Cure**”

TUMORS (Big Robbins 821, Baby Robbins 420)

**Benign Tumors**

**Definition**
- Any growth that projects above the level of the mucosa surrounding

**Morphology**
- Gastric polyps are uncommon, more common in the colon, especially as you age
- Hyperplastic Polyps are the most common (90%) and may be **sessile** (without stalk) or **pedunculated** (with stalk), are usually singular, and are **nonneoplastic**
- Gastric Adenomas (10%) are true neoplasms with **dysplastic epithelium**

**Clinical**
- All increase with age and have a significantly increased risk with **chronic gastritis**
- May contain **carcinoma centers** and must be biopsied for diagnosis
**Gastric Adenocarcinoma**

- **Definition**
  - Most common malignant neoplasm of the stomach

- **Pathogenesis**
  - Largely unknown, though linked to all risk factors of chronic gastritis, in particular:
    - Smoking, EtOH, *H. Pylori*, Autoimmune Gastritis
    - Smoked Fish (Japan) with high amounts of Nitrosamines can do it to
  - There is a natural progression from acute gastritis → chronic gastritis → intestinal metaplasia → dysplasia → carcinoma that is accelerated particularly by smoking and *H. Pylori* infections

**Morphology**

- Antrum/Pylorus (50%); Lesser curvature (35%); Greater Curvature (12%); Cardia (25%)
- **Early Gastric Carcinoma** is confined to submucosal/mucosa;
- **Advanced Gastric Carcinoma** extends through and beyond the submucosa and has metastasized
  - Usually advanced at the time of diagnosis
- There are two subtypes
  - **Intestinal** = gland-forming columnar epithelium found within the stomach; a product of intestinal metaplasia from *H. Pylori* infections, well differentiated
  - **Diffuse** = Poorly differentiated, strongly infiltrative, signet ring on histology and linitis plastica on gross, not linked to *H. Pylori* infections

- **Clinical**
  - Typically an insidious onset tumor, early satiety and vomiting are late signs
  - Outcome dependent on depth of invasion: Early = 95%, Advanced = 15% 5 year-survival
  - Metastatic Site
    - **Virchow’s Node** is a pariumbilical lymph node pathognomonic for metastasis
    - **Krukenburg Tumor** is where the gastric adenocarcinoma goes to the ovaria

**Lymphoma**

- Rare form of Gastric Carcinoma, referred to as a MALTom
- Associated with *H. Pylori*; in fact, you should “pick MALTomas over Gastrinomas for *H. Pylori*
- Antibiotic treatment yields remission and recovery

**Gastrointestinal Stromal Tumor = “GIST”**

- Rare, solid tumor gastric submucosal
- Caused by an overactivation of tyrosine kinase activity
- Relevant because they can be treated by Gleevac/Imatinib (tyrosine kinase inhibitor for CML)

**Metastasis**

- Few tumors metastasize to the stomach;
- Most common is a lymphoma (obviously other than MALToma)
MALABSORPTION SYNDROMES (Big Robbins 842, Baby Robbins 428)

**Celiac Sprue**

- **Definition**
  - Immune disease to wheat gluten leading to destruction of intestinal epithelia

- **Pathogenesis**
  - Sensitivity to gliadin, so-called wheat gluten found in rye, oat, and barley
  - Linked to a DQ2 HLA haplotype, suggestive of genetic risk
  - T-cell mediated malabsorption disorder

- **Morphology**
  - More proximal intestine is affected more than the distal portions
  - There are flat atrophic villi (death) with elongated crypts (regeneration)
  - Lymphocytes litter the mucosal epithelium

- **Clinical**
  - Patients present with massive diarrhea, flatulence, weight loss, and fatigue
  - Patients are infancy up until mid adulthood
  - Link to the skin blistering disease, Dermatitis Herpatiformis
  - Withdrawal of gluten from the diet is curative without sequella

**Tropical Sprue**

- Malabsorptive diarrhea caused by infection of unknown organism, suspected E Coli
- Responds well to B12, Folate, and antibiotics
- Usually involves the distal small intestine
- There is atrophic villi, resembling celiac disease, but is not an autoimmune disease

**Whipple Disease**

- Rare systemic disorder caused by infection by Tropheryma Whippeli affecting intestine, joints and CNS

- **Pathogenesis**
  - Unknown, organism is an actinomycete that lives in macrophages
  - Risk increases in the Caribbean, “Caribbean Rural Farmer’s Disease”

- **Morphology**
  - Small intestinal mucosa laden with distend macrophages in the lamina propria
    - PAS positive for undigested/incomplete lysosomes
    - Organisms can be seen on EM
  - These macrophages are found in joints, brain, and heart
  - Inflammation is low to absent – there is no inflammatory reaction, villi are intact

- **Clinical**
  - Responds well to long-term antibiotics
  - Typically males (10:1) over females, and usually rural
  - Diarrhea, Malabsorption, and Arthralgia tip you off, obstruction of GI or Biliary Tract
Lactase Deficiency

- Commonly called lactose intolerant, there is a congenital or acquired deficiency of lactase
  o Lactase is the enterocyte apical enzyme that degrades lactose
  o Lactose is found in milk and milk products
- Congenital Form is usually the absence of the enzyme, presenting with frothy, massive stools in infants, shortly after each feeding
- Acquired Form shows a steady decline in almost all patients, American blacks at highest risk, presenting with foul flatulence and diarrhea
- Lactase enzyme (Lactaid, for example) taken when dairy is consumed alleviates symptoms

Abetalipoproteinemia → not talked about in Tulane’s Pathology Course

- Autosomal recessive disorder corresponding to the absence of lipoprotein B
  o Lipoprotein B is required for the fat/cholesterol to get out of epithelial cells into blood
- Causes a buildup of cholesterol and lipid within enterocytes, leading to lipid vacuolization
- Altered RBC membranes (from lack of cholesterol and lipid) cause burr cells
- Without the ability to get fat, the patient is hypocholesteremic, hypolipidemic, and have low levels of VLDL and Chylomicrons
- Can present with liver or neurologic disorders

IDIOPATHIC INFLAMMATORY BOWEL (Big Robbins 846, Baby Robbins 431)

Two diseases, Crohn’s Disease and Ulcerative Colitis, with a poorly understood pathogenesis, result in inflammation of the bowel. To what the body is reacting to is still uncertain, so morphology is the focus.

Crohn’s Disease

- Definition
  o Inflammatory disorder of the bowel that may affect multiple segments with unaffected regions in between, so called skip lesions

Morphology

- Gross
  o Skip Lesions; regions of affected bowel with normal appearing mucosa between
  o Rubbery, thick mucosal surface leading to fibrosis and stricture
  o May affect any region of GI tract, from mouth to anus
- Micro
  o Mucosal Inflammation and ulceration with intraepithelial neutrophils
  o Chronic Mucosal Damage = villus blunting, atrophy, metaplasia
  o Transmural Inflammation with lymphoid aggregates (giving rise to thickening)
  o Noncaseating Granulomas even in uninvolved segments

Clinical

- Intermittent attacks of diarrhea, fever, abdominal pain, anorexia, and weight loss
- Occurs in whites more than blacks, jews more than other whites
- With terminal ileal involvement B12 deficiency, pernicious anemia, and malabsorption of bile salts lead to corresponding symptoms
Ulcerative Colitis

- **Definition**
  - Inflammatory bowel disease localized to the colon, forming ulcerative lesions in a continuous fashion and without granulomas

Morphology

- There are no skip lesions, and involves the rectum extending in a retrograde fashion
- Psuedopolyps may be abundant, granulomas are absent, crypt abscesses present
- Thin floppy wall because the inflammation is limited to the mucosa

Clinical Findings

- Intermittent attacks of bloody mucoid diarrhea and abdominal pain
- There is, for some reason, a link to primary Sclerosing cholangitis (see liver, below)
- Increased risk of carcinoma with chronic inflammation

TUMORS (Big Robbins 856, Baby Robbins 436)

Tumors of the Small Intestine

- Basically, they don’t happen
- When they do, either adenomas (benign) or carcinomas (malignant) develop
- If symptomatic, they cause obstruction and bleeding

Benign Colon Neoplasms = Adenomatous Polyps = Colonic Adenomas

- Benign, precancerous lesions of the luminal wall

Morphologies

- Pedunculated Vs Sessile
  - **Pedunculated** polyps have a stalk
    - ↓ risk for cancer
  - **Sessile** polyps are flat and have no stalk
    - ↑ risk for cancer
- Tubular Vs Villous
  - **Tubular** looks like normal colon, with tubules throughout the polyp
    - ↓ risk for cancer
  - **Villous** have finger-like projections all over the polyp
    - ↑ risk for cancer
- Tubulovillous have combinations of both

Presentation

- May present with occult blood in stool
- Warrant a colonoscopy, sampling of polyps (removal) and histologic sectioning
- The presentation is more based on what caused them: a single polyp common with aging or 1000 polyps from FAP.
Benign Neoplasms – Polyposis Syndromes

- Familial Adenomatous Polyposis (FAP) ⇐ this one is the one to know
  - Autosomal Dominant mutation of the APC gene
  - Colon is covered in polyps, 100s-1000s of polyps in the colon
  - High chance of dysplasia → cancer
  - Prophylactic colectomy suggested
  - Has variants, as follows
    - Gardner
      - FAP variant with benign osteomas of the jaw, fibromatosis of the liver, benign epithelial inclusion cysts of the skin
    - Turcots
      - Rare, autosomal recessive version of FAP
      - 1000s of polyps in the colon + independent brain tumor (medulloblastoma, usually)
    - Hereditary Nonpolyposis Colorectal Cancer (HNPCC) aka “Lynch Syndrome”
      - Autosomal Recessive mutation of the DNA mismatch repair gene
      - These people get colon cancer, but not the polyps
    - Peutz-Jeghers
      - Hyperpigmented lesions on the lips and oral mucosa
      - Endoscopy shows benign hamartomous polyps in the small intestine
      - Look elsewhere for tumors, such as the lungs or skin

Colon Adenocarcinoma

- Pathogenesis
  - Multiple gene mutations and any polyposis syndrome can lead to colon cancer
    - p53, k-ras oncogene, DCC gene, APC (in FAP), DNA mismatch (HNPCC)
- Morphology
  - Left Sided Tumors
    - Present with alternating diarrhea and constipation with blood in stool
    - Have a napkin ring narrowing, called apple-core narrowing on barium enema
    - Tumor is circumferential around lumen, causing a stricture
    - Presentation is symptomatic earlier than right sided tumors, and are less fatal
  - Right Sided Tumors
    - Present with occult blood in the stool only
      - Feces is loose enough that luminal structures do not cause obstruction
      - These are asymptomatic until late, where they have already metastasized
- Clinical Course
  - Heme Occult Blood warrants a scope, scope finds a tumor or polyp
  - Resection is curative, unless the tumor has metastasized (first liver, then everywhere)

Carcinoid Tumors

- Secrete serotonin causing a Carcinoid syndrome = flushing, cramping, diarrhea, vomiting
- If from GI, must metastasize to liver before they become symptomatic (liver degrades 5HT)
- If from Lungs or Adrenal, metastasis is not needed
- Look for Serotonin Metabolites (5-HIAA) in the urine (5HT→5-HIAA)
Path GI – Liver – Biliary – Exocrine Pancreas

CONGENITAL AND ANTAMOIC DISEASES OF THE COLON (No Robbins Page, throwing them together)

**Volvulus**
- **Twisting** of the bowel about itself
- Can cause **obstruction** of the bowel
- Twisting of blood vessels can lead to **ischemia and infarction** which then result in perforation, **peritonitis** and death

**Intussusception**
- **Telescoping** of the bowel into itself
- Can cause **obstruction** of the bowel from luminal narrowing
- Intussuscepted segment has pinched blood vessels, leading to **ischemia and infarction** which then result in perforation, **peritonitis** and death
- Commonly seen in kids (enlarged peyer’s patches get snagged) but can be seen in adults (usually a cancer or a polyp)

**Meckel’s Diverticulum**
- Most common congenital abnormality of the colon and intestines
- Is within 2 feet from the ileocecal valve and is 2cm in size in 2% of the population, and of that, 2% will become cancerous
- Generally an **asymptomatic blind outpouching** of the intestinal wall, though they may contain pancreatic or gastric heterotopias (ectopic sites) which can bleed
  - Remnant of the Vitelline Duct and is a True Diverticulum
- Is **asymptomatic until it bleeds**; most common cause of GI bleeding in children

**Herschbrung’s Disease** = **Congenital Megacolon**
- **Congenital**
- Caused by the **failure of neural crest cells to migrate** to the distal colon
  - Histologic diagnosis is dependent on absence of ganglia within both meisner’s and auberbach’s plexus
- **Affected Segment is normal, Unaffected Segment is massively dilated**
  - Unaffected segment pushes stool through GI tract, and gets backed up at the affected segment, which dilates to accumulate the backed up stool
  - There will be aperistalsis (because of the absence of the enteric nervous system ganglia) from where the affected region starts, to the end of the colon
- Baby presents **without passage of meconium** and with a **megacolon**
- Megacolon itself may be toxic or from Chagas disease, but **baby + megacolon** = **Herschbrung’s disease**
- Surgical resection of the affected segment is required.
PATH GI – LIVER – BILIARY – EXOCRINE PANCREAS

GENERALIZED FEATURES OF HEPATIC DISEASE (Big Robbins 879, Baby Robbins 446)

**Generalities**

- ↑ Blood flow, ↑ Metabolic Activity, and first pass from GI ↑ vulnerability to metabolic, toxic, microbial, and neoplastic insults
- Liver has the **immense capacity to regenerate** and a **large functional reserve** so disease goes unnoticed until it is both severe and chronic
- Most often there is an **insidious onset** with hepatic failure occurring in weeks to years
- Most common insults are **Hep C** (50%), **Alcohol** (24%), and **Other Hep Viruses** (4%)

**Patterns Of Injury**

- **Degeneration and Intracellular Accumulation**
  - Toxic/Immunologic insult induces **cellular swelling**
  - Severe damage causes **ballooning degeneration** with clumps of organelles
  - When fat accumulates within cells it is called **steatosis**
- **Necrosis and Apoptosis**
  - Any significant injury can cause necrosis
  - **Ischemic Coagulative Necrosis** leaves behind “mummified” hepatocytes
  - **Lytic Necrosis**, a product of ballooning degeneration, leaves behind cellular debris
  - Frequently exhibits **zonal distribution** as in **Centrilobular necrosis** (around portal vein)
  - **Submassive** (entire lobule) or **massive** (most of the liver) **necrosis** is often accompanied by frank, acute, hepatic failure
- **Inflammation**
  - Aka, **hepatitis**, it is any inflammation of the liver
  - Kupfer cells (the macrophages) and Lymphocytes live in the liver
  - **Granulomas** may form to foreign bodies, organisms, or drugs
- **Regeneration**
  - Amazing **capacity to regenerate** from living hepatocyte proliferation (no stem cells)
  - Occurs in all but most fulminant diseases and chronic conditions
- **Fibrosis**
  - When it doesn’t regenerate, it scars
  - **Fibrosis is generally irreversible** (see cirrhosis for exception)
  - Divides liver into functional regenerating nodules surrounded by fibrosis = **cirrhosis**

**Liver Failure**

- **Definition**
  - Despite the incredible functional reserve, when 80-90% of hepatic function is lost, hepatic failure ensues
- **Causes**
  - **Massive Hepatic Necrosis** often drug induced (acetaminophen, Rifampin) leading to hepatic insufficiency; Hep C does **not** cause this rapid destruction
Path GI – Liver – Biliary – Exocrine Pancreas

- Chronic Liver Disease is most common route to hepatic failure and is a product of relentless Hepatitis infections resulting in cirrhosis (usually Hep C)
- Hepatic Dysfunction without Necrosis occurs where viable hepatocytes fail to do their job, as in Reye Syndrome

- Clinical Features
  - Jaundice – liver processes bilirubin, which now accumulates, turning the sclera of the eye and pigmentation of the skin yellow, may conjugated or unconjugated
  - Hypoalbuminemia - ↓Albumen (made by the liver) ↑Edema from ↓Oncotic Pressure
  - Hyperammonemia - ↑NH₃ from impaired uric acid cycle leads to cerebral dysfunction / hepatic encephalitis
  - Fetor Hepatitis – musky odor, “sweet and sour” scent to the body
  - Coagulopathy - ↓Clotting factors made by liver leads to bleeding
  - Hepatic Encephalopathy
    - ↑NH₃ leads to general edema and ↓neurotransmission in the CNS
    - Fluctuating neurologic signs include rigidity, hyporeflexia, and asterixis
    - May lead to altered mental status, coma, or death
    - Changes are not permanent and may be reversed with ↓NH₃
  - Hepatorenal Syndrome
    - Renal Failure as a multifactorial result of liver failure
    - ↑BUN, ↑Cr, ↓GFR, with a ↓Urinary Sodium, ↓Protein, and the ability to concentrate urine (differential from acute tubular necrosis)
    - Often accompanies a significant hepatic stressor (infection, GI bleed, surgery)

Cirrhosis

- Definition and Characteristics
  - An end-stage chronic liver disease marked by:
    - Bridging Fibrous Septae = lots of fibrosis linked together between portal veins
    - Parenchymal Nodules = islands of proliferating hepatocytes trapped in fibrosis
    - Global Disruption of hepatic architecture with vascular reorganization

- Etiology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Liver Disease</td>
<td>60-70%</td>
</tr>
<tr>
<td>Viral Hepatic Syndrome</td>
<td>10%</td>
</tr>
<tr>
<td>Some Rare Disorders</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cryptogenic, “We don’t know”</td>
<td>15%</td>
</tr>
</tbody>
</table>

Once present, the original cause may be morphologically indistinguishable. A good source is micronodular (usually EtOH) versus macronodular (usually Hepatitis)

- Pathogenesis
  - Stellate Cells (Ito Cells) exist within the space of disse and normally store Vitamin A
  - Stellate cells receive a pro-inflammatory signal from Kupfer cells, causing them to switch from Vitamin A / Fat-Like cells to fibroblast-like cells
  - Collagen Deposition acts as scar tissue, but irregularly bridges septae together
    - This process, once thought irreversible, may be reversible after all
    - Hepatocytes possess metalloproteinases required to degrade (slowly) collagen
  - Vascular Reorganization creates channels around fibrotic septae that may bypass hepatic cords (and escape filtration) or lead to portal-systemic shunts
Path GI – Liver – Biliary – Exocrine Pancreas

- Clinical
  - Cirrhosis may be clinically silent for years until it presents with
    - Anorexia
    - Osteoporosis
    - Hepatic Failure
    - Hepatocellular Carcinoma
    - Weight loss
    - Weakness
    - Portal Hypertension (below)
  - Portal Hypertension
    - Definition
      - Resistance to blood flow through the liver causing a “back up” of GI organ blood flow and a requirement of collateral circulation
    - Causes
      - Prehepatic = stenosis, compression, or thrombosis of portal vein
      - Posthepatic = right sided heart failure and the “nutmeg liver”
      - Intrahepatic = most dominant cause in general is cirrhosis. Schistosomiasis is possible and is prevalent around the world; cirrhosis wins by a long shot in US.
    - Consequences
      - Ascites
      - Excess collection of fluid in peritoneum, “fluid on the belly”
      - ↑ Venous Hydrostatic pressure prevents resorption of fluid on the venous side, exacerbated by the ↑ venous capillary pressure from Hypoalbuminemia
      - Lymphatic drainage insufficient to carry fluid away
      - Portosystemic Shunts
        - Normally unused channels linking GI/portal to systemic circulation
        - Esophageal Varices most dangerous (risk of hemorrhage)
        - Hemorrhoids are painful, found in anus/rectum
        - Caput Medusa is dilation of veins on the abdomen
      - Congestive Splenomegaly = big, wet, red, palpable spleen
      - Hepatic Encephalopathy = discussed above

Jaundice

Jaundice is caused by hyperbilirubinemia, and is often associated with cholestasis and increased bile salts. We discuss bilirubin pathology first in “Jaundice” then discuss bile salt pathology in “Cholestasis”

- Bilirubin Physiology
  - Bilirubin is the end produce of heme degradation (RBC lysis)
  - Extrahepatic bilirubin binds to albumin
  - Hepatocellular uptake occurs and bilirubin gets conjugated via UGT1
  - Conjugated bilirubin is water soluble, transported into bile, and excreted into GI tract
  - Bacteria deconjugate bilirubin into colorless urobilinogen and pigments lost in stool
  - Bilirubin represents only a small part of bile; the rest is Bile Acids

- Lab Values
  - Elevated Bilirubin in the serum
  - Elevated AST/ALT indicates hepatocellular injury (probably necrosis)
  - Differentiate from Alk Phos which points to biliary pathology
- **Bilirubin Pathology**
  - Jaundice occurs when there is more bilirubin being formed than being lost; the defect may be in production (systemic), conjugation (liver), or excretion (biliary)
    - Excessive Production, as in hemolysis (↑Unconjugated Bilirubin)
    - ↓Secretion and/or ↓ Bile Flow (↑Conjugated Bilirubin)
    - Reduced Hepatocyte Uptake (↑ Unconjugated Bilirubin)
    - Impaired Conjugation (↑Unconjugated Bilirubin)
  - Has a pigment, so when elevated, deposits in all tissues, giving rise to **yellow skin (jaundice)** and **yellow sclera (icterus)**
  - **Unconjugated Bilirubin** is lipid-soluble, highly toxic, not excretable through the urine, and, when it accumulates in the brain, causes **kernicterus** (which is bad)
  - **Conjugated Bilirubin** is water-soluble, nontoxic, and excretable in the urine if levels rise, producing a **dark colored urine**.

- **Specific Bilirubin Diseases**
  - **Neonatal Jaundice**
    - Neonatal conjugation mechanisms are nonfunctional until ~2weeks
    - **Mild unconjugated hyperbilirubinemia** is normal, and should resolve quickly
  - **Erythroblastosis Fetalis**
    - Caused by Rh- moms giving birth to Rh+ babies
    - Massive hemolysis = ↑unconjugated bilirubin in baby
    - No conjugation function = substantial ↑bilirubin = kernicterus
  - **Crigler-Najjar Type 1**
    - Complete Absence of the UGT Protein that conjugates bilirubin
    - Fatal without a transplant in 18 months from kernicterus
    - Feces will be pale (no pigmentation)
    - ↑unconjugated bilirubin, Autosomal Recessive
  - **Crigler-Najjar Type 2**
    - Less severe, nonfatal, **mutation of UGT protein** that conjugates bilirubin
    - Patients develop normally, and may have periodic bouts of jaundice
    - ↑Unconjugated bilirubin, Autosomal Recessive
  - **Gilbert**
    - Mutation of **TATA Box** of the **UGT gene** causing ↓ Uptake and ↓ Conjugation
    - No clinical consequence except for periodic jaundice following stressor
    - ↑ Unconjugated Bilirubin, Autosomal Recessive
  - **Dubin-Johnson** Most Commonly Tested on Board’s of all these diseases
    - Absence of MRP2, transporter that secretes conjugated bilirubin into bile
    - Normal life expectancy with periodic jaundice, **dark pigmented liver**
    - Bilirubin is conjugated, but not excreted; ↑Conjugated Bilirubin
  - **Rotor**
    - Asymptomatic mutation in multiple transporters for uptake and secretion
    - Same as Dubin-Johnson, without the dark pigmentation
    - ↑Conjugated Bilirubin, Autosomal Recessive
Path GI – Liver – Biliary – Exocrine Pancreas

**Cholestasis**

- **Definition**
  - Literally, “stoppage of the biliary tree” meaning that the flow through the bile ducts is slowed or stopped

- **Bile Acid Physiology**
  - Primary bile acids are Cholic Acid and Chenodeoxycholic Acid which get secreted with lipids called lecithins
  - Bile salts **solubilize cholesterol and fats** in the GI tract
  - Bile salts are **made from cholesterol**, are secreted into bile, excreted into GI tract, and are **mostly reabsorbed** through enterohepatic circulation
  - Bile salts lost in stool represents the **only egress for cholesterol** from the body

- **Bile Acid Pathology**
  - **Extrahepatic Cholestasis** = Anything that blocks the lumen (gallstones, tumor) will obstruct flow; is amendable to surgery
  - **Intrahepatic Cholestasis** = Anything that fails to produce bile from the liver (MRP2 Gene in Dubin-Johnson) will decrease flow; **not** amendable to surgery
  - If something blocks the flow of bile acids out of the liver, likely there will be a back up of bilirubin as well, so jaundice is likely to be seen

- **Morphology**
  - Bile accumulates in the liver, when inside the hepatocytes = **feathery degeneration**
  - Obstruction causes dilation of upstream tree and bile lakes within the liver
  - Unrelieved obstruction will causes fibrosis

- **Clinical**
  - Jaundice (obstruction to bilirubin egress)
  - Pruritis (serum bile acids ↑ and deposit into the skin)
  - Xanthomas (cholesterol deposits in skin)
  - ↑ Serum Alkaline Phosphatase (local biliary destruction from stagnant bile salts)

### GENERAL FEATURES AND SYNDROMES

<table>
<thead>
<tr>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Failure</td>
<td>Liver has large functional reservoir, requires loss of 80-90% of functional liver. Caused by massive necrosis or long-term progressive fibrosis/cirrhosis. Results in hepatic encephalopathy (↑NH₃), Hepatorenal syndrome, hypoalbuminemia, and delay in clotting times (↑PTT from ↓clotting factors)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Defined as bridging fibrosis forming islands of regenerating hepatocytes (nodular). Caused by long-term chronic inflammation (EtOH, HepB, Rare Genetic, Cryptogenic) Ito cells (vitamin A storing fat cells) turn into myofibroblasts, and lay down collagen. Presents with Liver Failure, Portal Hypertension, Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Portal Hypertension</td>
<td>Obstruction of blood flow through the liver from pathologic changes. Porto-caval shunts are formed (hemorrhoids, esophageal varices, caput medusa). Liver becomes underperfused for nutrients and cannot detoxify blood as well</td>
</tr>
<tr>
<td>Jaundice and Cholestasis</td>
<td>Skin turns yellow (jaundice) and sclera of eye turns yellow (icterus). Caused by backup of bile (intrahepatic or Extrahepatic), bilirubin causes yellow color. Bile Salts also back up = damage to biliary tress, xanthomas, and pruritis</td>
</tr>
</tbody>
</table>
INFECTION DISORDERS (Big Robbins 890, Baby Robbins 452)

**Hep A**
- **Benign, self-limiting, febrile jaundice** transmitted through the *fecal-oral route*
- It does not produce *chronic disease* nor carrier states
- It is a small ssRNA picornavirus with anicosahedral capsid
- Transmitted *fecal-oral* in the water supply with human waste, food preparers that don’t wash their hands, or *shellfish* that concentrate the virus found in contaminated water
- Patient sheds virus for 2-3 weeks before and 1 week after onset of jaundice
- IgM ↑ with disease onset marking *acute disease*, peaks as fecal shedding stops, and IgG antibodies persist, perhaps for life, making the vaccine highly effective

**Hep B** Long-winded, complicated, but you have to know it all, very Board Relevant

- **Viral Info, Structure, and Gene Products**
  - HBV is a 42nm, spherical, double-layered “**Dane Particle**” and is an *incomplete ds DNA*  
  - A **Core Protein** (Hep B Core Antigen, HBCag) stays in infected hepatocytes  
  - A **Pre Core Protein** (Hep B “e” Antigen, HBeAg) is target for release into blood  
  - A **Surface Envelope Glycoprotein** (Hep B Surface Antigen, HBsAg) is produced in mass quantities in the hepatocytes, causing “ground glass appearance”  
  - A **DNA polymerase** with *reverse transcriptase* capability (DNA viral replication occurs through a RNA intermediate)  
  - **Protein X** (HBx) necessary for viral replication & implicated in *hepatocellular carcinoma*

- **Infection and Pathogenesis**
  - Hep B does not cause hepatocyte injury; it is the *immune response* (CD 8 Cytotoxic T Cells) to *infected hepatocytes* that causes hepatocyte injury  
    - The stronger the immune response the worse the **acute hepatitis** but the lower the risk for **chronic carrier state**  
      - ↑ Risk of carrier state for Neonates, Immunocompromised  
  - Hep B is hearty, and is transmitted through *semen, saliva, urine, sweat, blood, lactation*  
    - ↑ risk for IV Drug Users, Accidental Needle stick, homosexual males  
    - **Vertical Transmission** from mom to baby during birth is possible  
  - Hep B has a **prolonged incubation** (6-24 weeks), ↑ risk of unknown viral spread  
  - Infection has 4 possibilities  
    - **Acute Hepatitis With Resolution** = nasty jaundice and terrible symptoms, but the virus is cleared, and there is no chronic state (most common, 95%)  
    - **Chronic Hepatitis** = there is a weak immune response, mild hepatitis, but a persistent carrier state that lasts forever (4%)  
    - **Fulminant Hepatitis + Massive Necrosis** = fairly rare for Hep B, not good (<1%)  
    - **Hep D** = Hep D must have coinfection with Hep B to get into a hepatocyte  
      - Once infected, Hep B **integrates into host DNA** and undergoes replications  
      - HepX protein + chronic inflammation/hepatocyte turnover can lead to both **cirrhosis** or **Hepatocellular carcinoma**
Clinicopathologic Syndromes

- **Acute Asymptomatic Infection with Recovery**
  - You get infected, you don’t know it, but you find out later on serology exam
  - Common in Hep A or Hep B in kids (they don’t get Jaundiced)
  - This is what we want when we give the vaccine

- **Acute Symptomatic Infection with Recovery**
  - Any Hep virus can present this way, almost always Hep A, usually Hep B, rarely Hep C
  - **Incubation Phase** = ↑ circulating antigens and antibodies
  - **Preicteric** = before the jaundice, people get nausea, vomiting, fever, chills, headache, arthralgia and rash (the last two from immune deposition)
  - **Icteric** = the jaundice. Other symptoms get better, but they turn yellow and their urine gets dark, a product of **conjugated bilirubin** (no risk for kernicterus)
  - **Convalescence** = take that viruses!
- **Chronic Hepatitis**
  - Symptomatic, Serologic, or Biochemical evidence of persistent infection
  - ↑ Risk with T Cell Compromised in Hep B, it is the General Rule for Hep C, and barely ever occurs in Hep A, if at all
  - Carriers, whether symptomatic or not, can shed virus and infect others
  - Etiology determines progress to cirrhosis (Hep C does it a lot, Hep B not so much)

- **Fulminant Hepatitis**
  - Hepatic Insufficiency progresses from onset to hepatic encephalopathy in 2-3 weeks
  - Viral Fulminate hepatitis accounts for 12% of all fulminate cases, with Hep B and Hep C accounting for ~100% of viral cases
  - Drugs/Toxins (50%) and “miscellaneous” make up the difference

**Morphology of Hepatitis**

**Acute**
- Hepatocytes show diffuse swelling called ballooning degeneration
- Cholestasis is an inconsistent finding, often caused by bile or pigment plugs
- Necrosis can be seen with cytolysis preceding macrophage aggregates
- Apoptosis, mediated by T cells, cause shrunken, highly eosinophilic nuclei
- Inflammatory Cells can be seen within the lumen and may spill into parenchyma causing necrosis, termed interface hepatitis

**Chronic**
- Steatosis = fatty change within the hepatocytes
- Ground Glass Cells = even larger, more “ballooned” than ballooning degeneration
- Interface Hepatitis + Bridging necrosis are harbingers of liver failure
- Fibrous deposition replaces the necrosis and is the marker of irreversible damage
  - Periportal Fibrosis stats it off, then regions of fibrosis begin to connect, called bridging fibrosis, until there are small islands of regenerating hepatocytes surrounded by fibrosis (cirrhosis)

**Fulminate**
- Widespread necrosis in variable patterns dependent on etiology (red, mushy, shrunken)
- Massive influx of PMNs, followed by lymphocytes, with eventual regeneration/fibrosis
- Hepatocyte-driven recovery may be near complete if the patient lives long enough (4 weeks) with preservation of parenchymal architecture.

Diagrammatic representation of the changes in chronic hepatitis. Use this to “get” what is meant by the different terminology in both chronic and acute. For a more clear picture of both, see images 18-17 in Big Robbins
**Morphology of Hepatitis**

**Acute Hepatitis.** There is a loss of lobular architecture. There are many mitoses as hepatocytes divide to initiate repair. Architecture will be restored. This is non-specific injury.

**Lymphoid Aggregates.** The portal triad has significant leukocytic infiltrate that has spilled over into the parenchyma. A lymphoid aggregate has formed, indicative of Hep C.

**Ground Glass Appearance.** The hepatocytes are enlarged, some are without nuclei, and have a pink fill. Also on this slide are the **sandy nuclei.** This is indicative of Hep B.

**Steatosis.** The large vacuoles (white spaces) are present within hepatocytes. The cells are filled with fat. Indicative of fatty change (EtOH, Hep C).

**Bile Duct Involvement.** There is a lymphocytic infiltrate surrounding the bile duct, which has an abnormal shape (amorphous from circular). Indicative of Hep C.

**Interface Hepatitis.** The lymphocytes from a portal triad (you can see the bile duct) butt up against the limiting plate of hepatocytes. There is necrosis of the hepatocytes on the rim, but no lymphocytes within parenchyma.

**Grade 1 Periportal Fibrosis.** Inflammatory cells come out of the portal tracts, but does not spill into the parenchyma; there is only interface hepatitis with interface necrosis.

**Grade 2 Septal Fibrosis.** The fibrosis spills into the parenchyma, but irregularly, and near the portal tracts.

**Grade 3 Bridging Fibrosis.** Fibrosis from different portal tracts begin to connect with small tracts of fibrosis.

**Grade 4 Nodules represent grade 4.** Purple islands of regenerating hepatocytes surrounded by fibrosis indicated Grade 4 hepatitis, cirrhosis.
AUTOIMMUNE HEPATITIS (Big Robbins 903, Baby 458)

Autoimmune Hepatitis

- **Female Predominance** with *bimodal age presentation* (adolescence and perimenopausal)
- **Absence of viral serologic markers** though there is symptomology of hepatic injury and the presence of IgM
- Autoantibodies to ANA (antinuclear) and SMA (smooth muscle) present in blood
- May be asymptomatic, but **clinical illness is common at presentation** though fulminate is rare
  - Weight loss, pruritis, myalgia, rash; typical hepatitis and autoimmune symptoms
  - Jaundice may be present (20%-30%)
- Autoimmune destruction of hepatocytes may be indistinguishable from cholangitis
- **Responds well to immunotherapy**

DRUG INDUCED LIVER DISEASE (Big Robbins 903, Baby 458)

**Generalities**

- Drugs may injure liver by **direct toxicity, conversion to a toxin, hapten → immunologic rxn**
- Drug-induced chronic hepatitis is **indistinguishable from chronic viral hepatitis**; serologic markers are required for diagnosis and differential
- May present with **hepatocyte necrosis, hepatitis, cholestasis, fibrosis** or it could be **insidious**
- Usually, **removal of the toxin leads to recovery**

Here’s a sample, **don’t memorize this**, but do take a look at it

<table>
<thead>
<tr>
<th>Hepatocellular Damage</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvesicular fatty change</td>
<td>• Tetracycline, salicylates, yellow phosphorus, ethanol</td>
</tr>
<tr>
<td>Macrovesicular fatty change</td>
<td>• Ethanol, methotrexate, amiodarone</td>
</tr>
<tr>
<td>Centrilobular necrosis</td>
<td>• Bromobenzene, CCl₄, acetaminophen, halothane, rifampin</td>
</tr>
<tr>
<td>Hepatitis, acute and chronic</td>
<td>• Methyldopa, isoniazid, nitrofurantoin, phenytoin, oxyphenisatin</td>
</tr>
<tr>
<td>Fibrosis-cirrhosis</td>
<td>• Ethanol, methotrexate, amiodarone, most drugs that cause chronic hepatitis</td>
</tr>
<tr>
<td>Granuloma formation</td>
<td>• Sulfonamides, methyldopa, quinidine, phenylbutazone, hydralazine, allopurinol</td>
</tr>
<tr>
<td>Cholestasis (with or without hepatocellular injury)</td>
<td>• Chlorpromazine, anabolic steroids, erythromycin estolate, oral contraceptives, organic arsenicals</td>
</tr>
</tbody>
</table>

**Alcoholic Liver Disease**

- **Morphologies**
  - **Hepatic Steatosis**
    - Consumption of alcohol causes 3 major changes that ↑ liver fat content
      - Shifting away from catabolism, switching to lipid synthesis (make fat)
      - Impaired formation and secretion of lipoproteins (fat can’t leave)
      - ↑ Peripheral Catabolism of fat (more fat comes back to liver)
    - Liver becomes **yellow, large, soft and greasy**
    - Microscopic = **macrovesicular nodules** (chronic) or **microvascular** (acute)
    - Abstinence = Recovery

---

**Zoomed in view of steatosis, large vacuoles within parenchyma**
Alcoholic Hepatitis

- Characterized by 4 changes:
  - **Hepatocyte Swelling and Necrosis** = direct hepatocyte toxicity results in ballooning degeneration
  - **Mallory Bodies** = eosinophilic inclusions of dying hepatocytes are characteristic of, but not unique to alcohol
  - **Neutrophilic Rxn** = Alcohol + its metabolite, Acetaldehyde, induce changes in hepatocellular proteins leading to an immunologic rxn. Lymphocytes enter the portal tracts and spill into parenchyma
  - **Fibrosis** = activation of stellate cells, particularly sinusoidal perivenular fibrosis; periportal may predominate. Fibrosis progresses to cirrhosis.

- Liver is mottled red, stained with bile, & possess **nODULES AND FIBROSIS** (portends coming cirrhosis)
- Abstinence = Recovery

Alcoholic Cirrhosis

- Final and irreversible change of continued fibrosis
- Presents with a **micronodular liver** (opposed to Hep Virus)
- **Regenerating Hepatocytes** trapped by **bridging fibrosis**
- Grossly, the liver is **shrunken, brown, nonfatty, and nodular**

Pathogenesis

- **EtOH** = calories, displacing vitamins (B12)
- Induction of P450 = ↑Toxic metabolites of normally safe drugs
- **EtOH and Acetaldehyde** are **directly toxic and immunogenic** to mitochondria and cytoskeletons of hepatocytes

Clinical Features

- **Hepatic Steatosis**
  - Usually asymptomatic, may have ↑bilirubin and ↑Alk Phos
  - Withdrawal is curative
  - Takes time and is insidious if there is any evidence of disease at all

- **Alcoholic Hepatitis**
  - Is **acute and symptomatic**, especially following a bout of heavy drinking
    - May be minimal, fulminate, or somewhere in between
    - Mimics other acute hepatitis (anorexia, malaise, jaundice, ↑AST/ALT)
  - Outlook is unpredictable, though **repeated bouts tends towards cirrhosis**

- **Alcoholic Cirrhosis**
  - Same as other forms of cirrhosis
    - Portal HTN, Hepatic Encephalopathy, Ascites, Hepatic Failure, etc.
  - Variable Progression to hepatic failure and death, worse with stressor

- Death results from liver failure, hemorrhage, or coma, all diseases **secondary** to the cirrhosis.
Nonalcoholic Fatty Liver (NAFL) and NonAlcoholic SteatoHepatitis (NASH)

- Morphology of alcoholic fatty liver without the history of drinking
- Linked to obesity, dyslipidemia, insulin resistance, and type 2 diabetes
  - If the patient is fat and unhealthy, their liver gets fatty and unhealthy
- Steatohepatitis = ballooning degeneration, PMNs + Steatosis, Mallory Bodies, Sinusoidal fibrosis
  - If the vignette screams ALCOHOLIC HEPATITIS, but the patient doesn’t drink, pick this
- Cirrhosis may occur, though often asymptomatic except for ↑AST+ Neutrophilic Leukocytosis

Hemachromatosis

- Definition
  - Excessive accumulation of body iron which gets deposited into parenchymal organs
- Pathogenesis
  - Primary Hemachromatosis
    - Normal Iron – 2-6g body Iron, disease is 20-50g body iron, 1/3 in the liver
    - There is no way to get iron out of the body once it gets in
    - There is loss of dietary iron regulation leading to accumulation of iron
      - Mutation in the HFE gene coding for a Cystine→Tyrosine @ 282; C282Y
      - Codes the “we have enough iron” signal
      - With homozygous loss, crypt cell programming = “get more iron”
    - Iron is directly toxic to host tissues, yet the mechanism is reversible
      - Removal of iron = healing
    - Disease is autosomal recessive
  - Secondary Hemosiderosis
    - Hemolytic Anemia with ineffective erythropoiesis causes ↑iron released (from hemolysis) and ↑dietary intake (to make more RBCs)
    - Transfusions containing iron double what is taken in by the diet
- Morphology
  - Iron deposition in organs (in order): liver, pancreas, myocardium, pituitary, thyroid, skin
  - Cirrhosis of the liver and fibrosis of the pancreas
  - Liver is larger, dense, and chocolate brown before fibrosis; shrunken, nodular, and black after fibrosis.
- Clinical
  - Typical triad = micronodular cirrhosis (liver), frank diabetes (pancreatic fibrosis) and bronze skin (↑melanin production)
  - Cardiac Dysfunction, Hepatomegaly, abdominal pain, and gynecomastia are possible
  - Always screen siblings of diagnosed patient
  - Chronic Phlebotomy (blood-letting) is the only therapy available
Wilson’s Disease

- Definition
  - Autosomal recessive disorder with accumulation of copper in the liver, brain, and eye

Pathogenesis
  - **Autosomal Recessive** mutation of a **copper-ATPase** called ATP7B on chromosome 13
    - Excess copper cannot be excreted from hepatocytes into bile for elimination
  - Multiple mutations have been found, patients are usually **compound heterozygotes**
    (missing piece A on one chromosome and missing piece B on the other)
  - Copper-handling capacity of ceruloplasmin is exceeded at ~5 years of age where acute illness results from **copper spilling into the bloodstream** and **depositing in organs**

Morphology
  - Steatosis, Acute Hepatitis, and Chronic Hepatitis have no unique characteristics
  - **Steatosis and Mallory Bodies** (usually suggestive of EtOH) may be present in Wilson’s
  - Copper content > 250ug /g dry weight liver is required for diagnosis
  - Copper deposits in organs
    - Basal Ganglia Deposits = atrophy of basal ganglia, especially putamen
    - Kayser-Fleischer Rings = corneal deposits, “rings” in the cornea

Clinical
  - First presentation is in the first two decades of life (usually around 20)
  - ↓serum ceruloplasmin, ↑hepatic copper, ↑urine copper (serum Cu is useless)
  - Psychosis or parkinsonism is possible (basal ganglia)
  - Hemolysis from Cu in blood reveals Schistiocytes
  - Transplantation and copper chelation are therapies

α1-Antitrypsin Deficiency

- Definition
  - Autosomal Codominant disorder leading to the misfolding of the protease inhibitor α1-antitrypsin (α1-AT) which causes emphysema and hepatic disease

Pathogenesis
  - α1-AT is a 394 aa **protease inhibitor(Pi)** with multiple polymorphisms
    - PiM is the normal functioning protein
    - PiZ creates diseases states
    - Homo PiMM better than Hetero PiMZ better than Homo PiZZ
  - PiZZ causes **misfolding** and **entrapment within the ER**, ↓circulating levels of α1-AT

Morphology
  - Round-to-oval PAS-positive cytoplasmic inclusions in hepatocytes = pathognomonic
  - Neonatal hepatitis, childhood fibrosis, or any stage of hepatitis at any age can be seen

Clinical
  - Neonatal Hepatitis and Cholestatic Jaundice (10-20% of newborns with deficiency)
  - ↑Risk for cirrhosis, HCC, and emphysema
  - Avoid smoking (emphysema), get a liver transplant (cirrhosis, HCC, and Pi)
INTRAHEPATIC BILIARY TRACT DISEASE (Big Robbins 913, Baby Robbins 464)

Secondary Biliary Cirrhosis
- When an initial inciting even of the biliary tree induces fibrosis and cirrhosis of the liver
- Caused by obstruction (cholelithiasis, tumors, strictures) or by biliary atresia
- Produces first cholestasis, which can then lead to periportal fibrosis, cirrhosis, and cholangitis
- Ascending infection, if present, causes intense inflammatory infiltrate
- Jaundice+ icterus may be present

Primary Biliary Cirrhosis  Women, Granulomas, AMA antibodies
- Chronic, progressive, often fatal Cholestatic disease
- Primary feature is nonsuppurative inflammatory destruction of medium-sized bile ducts
- Autoimmune (E2 subunit of the pyruvate Dehydrogenase complex)
- Disease of middle aged women (though onset of injury is much younger)
- There is a massive leukocytic infiltrate (lymphocytes, macrophages, plasma cells) in portal tracts, giving rise to destruction and fibrosis
  - Up-stream = dilation, ductular proliferation, and necrosis
  - Granulomas may form around bile tracts
  - Over decades bridging fibrosis gives rise to cirrhosis
- Initial stages may show green, bile-stained liver, late stages are indistinguishable from other causes of cirrhosis
- Insidious Onset, with cirrhosis, portal HTN, and hepatic encephalopathy found in 4th/5th decades
- Death results from ruptured varices, encephalopathy, or infection
- Labs show ↑Alk Phos, ↑Antimitochondrial Antibodies, ↑Cholesterol

Primary Sclerosing Cholangitis  Men, Ulcerative Colitis, No antibodies
- Unknown pathogenesis of a fibrosing cholangitis of bile ducts with a lymphocytic infiltrate, progressive atrophy of bile duct epithelium, and obliteration of the lumen
- There is concentric periductal fibrosis (“onion skinning”) followed by luminal absence
- With disease progression, cholestasis gives rise to cirrhosis and common complications of cirrhosis leading to death (varices, encephalopathy)
- ↑Alk Phos may be only indicator and there are no autoantibodies
- Strong association with ulcerative colitis (from GI)
Path GI – Liver – Biliary – Exocrine Pancreas

We did not cover CIRCULATORY DISORDERS (917/464) PREGNANCY (920/466) or ORGAN TRANSPLANTATION (921/467) so those subjects will not be covered here in this guide.

NODULES AND TUMORS (Big Robbins 922, Baby 468)

**Nodular Hyperplasias**

**Focal Nodular Hyperplasia**
- Spontaneous mass lesion found in **young to middle aged females** (more than males)
- It is **well-demarcated** but **poorly encapsulated** nodule, and is **paler** than normal liver
- Has a **central stellate fibrosis** with surrounding normal parenchyma

**Nodular Regenerative Hyperplasia** *(not discussed in class)*
- **Diffuse Nodular Transformation** of the liver *without fibrosis*
- Associated with **Vasculitides** and solid organ transplants *(especially kidney)*
- May lead to **portal hypertension**

**Benign Neoplasms**

**Cavernous Hemangioma, aka “Hemangioma”**
- **Most Common** benign lesion of the liver
- Consists of **well-circumscribed** lesions of **endothelial-lined vascular channels**
- Appear as deep red, soft nodules beneath the capsular surface
- These are **not metastatic tumors** and do not require biopsy

**Liver cell Adenoma**
- Benign neoplasms **arising from hepatocytes**
- Occurs in **women using the pill/pregnant**; go away once she stops pill/baby
- May be mistaken for HCC or may rupture/bleed during pregnancy *(an emergency)*
- Usually **well demarcated** but **poorly encapsulated** tumors with few bile tracts but many arteries and veins; it looks like normal liver without the vessels

**Malignant Neoplasms**

- **Metastasis**
  - Like the lungs, the liver has a **high blood flow** and so is **vulnerable to metastasis**
  - The most common sites of origin are the **colon, lung, and breast**

**Hepatoblastoma**
- Most **common tumor of childhood**, fatal in one year if not resected
- **Epithelial Type** = fetal or embryonal cells forming a semblance of liver
- **Mixed Epithelial + Mesenchymal** = poorly differentiated mass of mesenchyme
- An elevated **α-fetoprotein** *(AFP)* in a child is a good tip off

**Angiosarcoma**
- Resemble angiosarcomas occurring anywhere
- Are associated with **carcinogenic exposure** *(vinyl chloride, arsenic)* when in the liver
- Extremely **poor prognosis** with death occurring in <1 year
Path GI – Liver – Biliary – Exocrine Pancreas

**Cholangiosarcoma**
- Tumor of both or either the Intrahepatic or Extrahepatic biliary tree
- Rare in the US, common in Asia
  - Thorotrast, an obsolete contrast dye for biliary radiography caused it
  - Chronic Inflammation from Primary Sclerosing Cholangitis (US), Ulcerative Cholangitis (US), or Opisthorcis Sinensis Infection (liver fluke, Asia)
- Carry a dismal prognosis far worse than HCC
- Diagnosis is usually late, and presents with bile obstruction and jaundice
- Surgery is the only treatment option, though is usually palliative
- There is no bile production in the tumor, and it resembles ducts of the bile tract
- Serum CEA and Serum CA19-9 are markers for disease

**Hepatocellular Carcinoma** – it’s a malignant tumor, but really important, so it gets its own heading

**Pathogenesis**
- Chronic Inflammation forces hepatocytes into a cycle of necrosis and regeneration;
  - ↑ mitotic activity for regeneration = ↑ risk of transformation
- Hep B is the most prevalent cause worldwide presenting with or without cirrhosis
  - Most prevalent in Asia, where Hep B infections are abundant
  - Hep B integrates into host DNA, and Hep X protein facilitates transformation
  - Hep D coinfection exacerbates HCC

**Morphology**
- Imaging Studies of URQ mass + ↑AFP = pathognomonic (biopsy is not required)
- HCC is usually paler than the normal liver surrounding it
- Propensity for growth into vascular channels
- In well-differentiated HCC hepatocytes retain some semblance of hepatic architecture
- In poorly-differentiated HCC there are Pleomorphic giant cells, ↑ anaplasia, and cyttoplasmic inclusions that resemble Mallory bodies

**Clinical**
- Difficult to spot as patient symptoms are nondescript or masked by cirrhosis
- Hepatitis Sx (anorexia, malaise, ABD pain, weight loss) and Liver Failure Sx (hemorrhoids, esophageal varices) can be variably found
- Elevated Levels of α-fetoprotein (AFP) is a strong indication, esp. with symptoms
- While they do invade vasculature (and may grow out from the liver into the IVC or portal vein) these tumors rarely metastasize outside the liver
- Surgery is the only treatment option: resection and transplant often result in reinfection (with HepB) or in recurrence of tumor

**Fibrolamellar HCC**
- Occur in young people with normal livers and carry a good prognosis
- Mentioned in lecture, doesn’t show up in review books/Kaplan
Path GI – Liver – Biliary – Exocrine Pancreas

DISEASES OF THE GALLBLADER (Big Robbins 928, Baby Robbins 471)

Cholelithiasis = Gallstones (cholesterol or pigment formed WITHIN the gallbladder)

- **Cholesterol Stones**
  - Etiology = “**Forty, Fat, and Fertile**

<table>
<thead>
<tr>
<th>Native Americans</th>
<th>White &gt; Black</th>
<th>↑Estrogen (the pill and being female)</th>
<th>↑Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesteremia</td>
<td>Inborn errors of metabolism that ↓bile salt secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder Stasis (Pregnancy)</td>
<td>Obesity and rapid weight loss</td>
<td>Developed Countries (eat more)</td>
<td></td>
</tr>
</tbody>
</table>

  - Pathogenesis
    - Normally, cholesterol is solubilized by bile salts and lecithin
    - **When supersaturated**, cholesterol nucleates into crystals, forming stones
    - 4 Simultaneous defects are required
      1. Bile is supersaturated with cholesterol (for whatever reason)
      2. Gallbladder hypomotility allows congregation and nucleation
      3. **Cholesterol Nucleation** is accelerated (calcium salts, change in [protein])
      4. **Mucous Hypersecretion** traps the crystals, allowing them to form stones

**Morphology**
- Pure Cholesterol Stone (rare) appear pale yellow and are radio-lucent
- Most stones are composed of cholesterol, pigment, calcium carbonate, etc., though only 10-20% become radio-opaque

- **Pigment Stones**
  - Etiology =

<table>
<thead>
<tr>
<th>Asian &gt; Western</th>
<th>Rural &gt; Urban</th>
<th>Cystic Fibrosis (Pancreatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Hemolytic Syndromes (↑ production of bilirubin)</td>
<td>Biliary Tract Infection</td>
<td>Ileal Disease (resection or bypass)</td>
</tr>
</tbody>
</table>

  - Pathogenesis
    - Insoluble calcium salts + unconjugated bilirubin and other inorganic salts
    - Unconjugated bilirubin in the gallbladder requires conjugated bilirubin to be deconjugated within the lumen which occurs to a very small extent naturally
    - Intense Hemolysis will ↑concentration of unconjugated bilirubin (black)
    - Biliary infection by E.Coli, Ascaris, or Liver Flukes are more likely (brown)

**Morphology**
- Black Stones come from a sterile gallbladder and are often radio-opaque (75%)
- Brown Stones come from an infected gallbladder and are usually radio-lucent

- **Clinical** (same for both types)
  - May be asymptomatic for decades
  - Symptoms are Upper Right Quadrant, Colicky Abdominal Pain (aka Cholecystitis)
  - Obstruction may result, ↑risk of infection or obstruction preventing the elimination of bilirubin or bile salts, termed gallstone ileus
  - Depending on location of stone, it can cause biliary tract obstruction (distal biliary tree), acute pancreatitis (sphincter of oddi), or cholecystitis (neck of the gallbladder)
**Cholecystitis** (Big Robbins 931, Baby Robbins 472)

- **Definition**
  - Inflammation of the gall bladder for any reason that may be acute or chronic

**Acute Cholecystitis**

- **Pathogenesis**
  - May be *calculous* (aka, involves gallstones)
    - Most common complication of cholelithiasis, precipitated 90% by duct occlusion
    - Obstruction = ↓Flow = Stagnant lethicin = aberrant enzyme activity and the generation of toxic lysolethicin = destruction of mucosal layer and direct detergent action on wall of gallbladder
  - May be *acalculous* (aka, something other than obstruction and gallstones)
    - Resulting from ischemia (cystic artery is an end artery without collaterals)
    - ↓Blood Flow / Shock / Hypoperfusion
    - Bacterial Contamination, Mass Effect of a Tumor

**Morphology**

- Is the same for calculous vs. acalculous (except for the presence of stones, of course)
- Gallbladder is *enlarged, tense*, and *red* (engorged) or *blotchy* (hemorrhage)
- Serosa is layered with fibrin
- Lumen may contain *fibrin, pus*, or *hemorrhage*
  - If organ is transformed green-black, it is called *gangrenous cholecystitis*

**Clinical**

- **Upper Right Quadrant Pain**, Low Grade Fever, Nausea + Vomiting, Tachycardia
- Abdominal Tenderness with positive Murphy’s Sign, free of jaundice (usually)
  - Deep palpation of gallbladder will terminate inspiration (because of pain)
- May be an immediate medical emergency or may resolve without intervention
- Most (90%) calculous cholecystitis will recur
- Potential complications include perforation/peritonitis, superinfection/cholangitis and fistula formation to the duodenum

**Chronic Cholecystitis**

- **Pathogenesis**
  - May be the result of frequent acute attacks or may occur without antecedent symptom
  - Same population, risk factors, and generation as acute

**Morphology**

- Walls are thickened, fibrosis is often apparent, called *porcelain gallbladder*
- Lumen may or may not have gallstones (but it often does)
- Lipid-Laden macrophages (cholesterosis) is common
- Mucosal outpouchings into the lumen are called *Rakitansky-Aschoff Sinuses*

**Clinical**

- **Same as Acute Cholecystitis**
DISEASES OF THE GALLBLADER (Big Robbins 933, Baby Robbins 473)

**Choledeolithiasis**

- Presence of stones within the bile duct or tree (opposed to inside the gallbladder proper)
- U.S. = cholesterol stones from gallbladder; Asia = pigment stones formed in biliary tree
- Causes symptoms of obstruction

**Cholangitis / Ascending Cholangitis**

- **Bacterial Infection** of the bile ducts, often caused by choledeolithiasis
- Usually a result of **ascending infection** from the sphincter of Oddi
- Commonly caused by gram negative aerobes = *E. Coli, Klebsiella, Clostridium, Bacteroides*
- Fever, shaking chills, abdominal pain, jaundice, intermittent obstructive symptoms

**Biliary Atresia**

- **Complete Obstruction of biliary lumen within first 3 months of life** accounting for 1/3 of infantile cholestasis
- Caused by a “multihit” process that induces **fetal form** (biliary tree never develops) or the more common **perinatal form** (destroyed @ birth)
- There is **fibrosis** and **stricture** of common bile ducts
- If below the liver, it is amenable to surgery
- Patients grow, eat, and poop normally at first, then begin to get **acholic stools** as the disease progresses; **death is within two years of birth**

TUMORS OF THE GALLBLADDER (Big Robbins 934, Baby Robbins 474)

**Carcinoma of the Gallbladder**

- **Pathogenesis**
  - Occurs more commonly in females in the 7th decade of life
  - Often found with **chronic gallstones** (US) or **Pyogenic/parasitic infections** (Asia)
    - **Chronic Inflammation** from any cause thought to ↑Risk
  - Even with resection, 5-year survival is <1%
- **Morphology**
  - Two Types
    - **Infiltrating** = more common, diffusely grows around and into the gallbladder, may ulcerate, causing fistula into the GI tract
    - **Exophytic** = grows into the lumen and invades deeply. “Cauliflower stalk” in the lumen may be hemorrhagic, necrotic, or ulcerative
  - Most are **adenocarcinoma** with a select few having squamous cell characteristics
- **Clinical**
  - By the time these are found they have already metastasized / seeded locally
  - Symptoms are insidious and **indistinguishable from cholelithiasis**
  - Lucky patients find these on incidental gallstone removal
Path GI – Liver – Biliary – Exocrine Pancreas

**Carcinoma of Extrahepatic Bile Ducts**
- Rare, insidious tumors presenting similar to late stage pancreatic tumors (**painless jaundice**)
- ↑Risk with **primary Sclerosing cholangitis** and cystic liver disease
- River flukes (**clinorchis senensis**) in Asia greatly ↑risk
- Partial or complete obstruction of bile ducts rapidly produces jaundice; these are usually found **early**, as **small, grey, firm** masses of the biliary wall
- There is often abundant fibrous stroma
- These are **identical to intrahepatic bile duct cancer**, called Cholangiosarcoma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Failure</td>
<td>Consequence of long term inflammation (cirrhosis) or fulminant necrosis Results in ↓Clotting Factors = ↑PTT, ↓Albumin = Ascites, Portal hypertension (see below), ↑Estrogen = Gynecomastia, ↑Ammonia = hepatic encephalopathy, Hepatorenal syndrome, fetor hepatitis</td>
</tr>
</tbody>
</table>
| Cirrhosis                              | Islands of **Regenerating Parenchyma** amongst **Broad Bands of Fibrosis** Is **end-stage** fibrotic disease of multiple origins **Nodular** (micro=alcohol, macro = virus), shrunken, discolored appearance on gross |}

<table>
<thead>
<tr>
<th>Major Diseases of the Liver</th>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Failure</td>
<td>Hepatic Failure</td>
<td>Consequence of long term inflammation (cirrhosis) or fulminant necrosis Results in ↓Clotting Factors = ↑PTT, ↓Albumin = Ascites, Portal hypertension (see below), ↑Estrogen = Gynecomastia, ↑Ammonia = hepatic encephalopathy, Hepatorenal syndrome, fetor hepatitis</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Islands of <strong>Regenerating Parenchyma</strong> amongst <strong>Broad Bands of Fibrosis</strong> Is <strong>end-stage</strong> fibrotic disease of multiple origins <strong>Nodular</strong> (micro=alcohol, macro = virus), shrunken, discolored appearance on gross</td>
<td></td>
</tr>
<tr>
<td>Portal Hypertension</td>
<td>Consequence of impaired blood flow through liver which can be prehepatic (hypoperfusion), Posthepatic (portal vein thrombosis), or Intrahepatic (cirrhosis) Produces <strong>Portosystemic shunts</strong> = Esophageal Varices, Hemorrhoids, Caput Medusa Causes splenomegaly and increases hydrostatic pressure producing ascites</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Defined as <strong>turning the skin yellow</strong>, may also involve the eyes (<strong>scleral icterus</strong>) Consequence of <strong>elevated bilirubin</strong>; determine if unconjugated or conjugated! Caused by pre- post- or Intrahepatic mechanisms; ↑hemolysis (delivery), ↓conjugation (genetic defects), ↓bile flow (obstruction)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic Liver Disease</td>
<td>Progressive disease caused by <strong>chronic or severe acute alcohol consumption</strong>. Progresses from <strong>steatosis</strong> (lipid vacuolization) through fibrosis to cirrhosis Look for <strong>Mallory bodies</strong>, <strong>Ballooning Degeneration</strong> and a <strong>Neutrophilic reaction</strong> Unless fibrotic, changes are reversible with abstinence from alcohol</td>
<td></td>
</tr>
<tr>
<td>Nonalcoholic Fatty Liver</td>
<td><strong>Steatosis</strong> in the absence of alcohol consumption Occurring in obese diabetics with derangements in fat utilization “Fat People get Fat Livers”</td>
<td></td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Autosomal recessive <strong>C282Y mutation</strong> which disables the ‘we’ve enough iron’ signal Default of enterocytes is to <strong>bring in more iron</strong> which <strong>cannot be eliminated</strong> Iron deposits in the liver (brown liver), pancreas (diabetes) and the skin (bronzing) Treatment is phlebotomy or liver transplant</td>
<td></td>
</tr>
<tr>
<td>Wilson’s</td>
<td>Autosomal Recessive Disorder involving <strong>copper extruding protein</strong> Liver cannot excrete copper from body, ceruloplasmin is overwhelmed as blood [Cu] rises Deposits in the liver, the brain (basal ganglia) and eye (Kayser-Fleisher rings) Will find ↑<strong>Hepatic Cu</strong>, ↑<strong>Urine Cu</strong>, ↓<strong>Serum Ceruloplasmin</strong> (Serum Cu is useless)</td>
<td></td>
</tr>
<tr>
<td>α1- Anti-Trypsin Deficiency</td>
<td>Autosomal Recessive disorder involving the <strong>misfolding of α1-AT</strong> <strong>Intracellular PAS-Positive Eosinophilic Granules</strong> in Hepatocytes = pathognomonic PiMM (homozygous) is normal PiZZ (homozygous) is worst PiMZ (heterozygous) mid Increased risk of emphysema (don’t smoke) and cirrhosis (don’t drink)</td>
<td></td>
</tr>
<tr>
<td>Primary Sclerosing Cholangitis</td>
<td>Segmental Concentric Inflammation of the biliary tree with an unknown cause Associated with <strong>Ulcereative Colitis</strong>, increases risk for <strong>Carcinoma of Bile Ducts</strong></td>
<td></td>
</tr>
<tr>
<td>Autoimmune Liver Disease</td>
<td>Disease of females with <strong>ANA</strong> and <strong>SMA</strong> autoantibodies in blood Responds well to steroids</td>
<td></td>
</tr>
<tr>
<td>Drug-Induced</td>
<td>“Drugs can cause liver failure”</td>
<td></td>
</tr>
</tbody>
</table>
### TYPES OF BILIRUBIN DISEASES → JAUNDICE

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroblastosis Fetalis (↑ Hemolysis)</td>
<td>Rh⁺ mom has a second Rh⁻ baby, mom’s antibodies destroy baby’s RBCs Hemolysis releases bilirubin, baby’s liver isn’t ready for it, baby = jaundice Increased bilirubin = jaundice; model for any hemolytic anemia</td>
</tr>
<tr>
<td>Neonatal Jaundice</td>
<td>Neonates require 2 weeks to achieve conjugation capacity Neonatal Jaundice and mild hyperbilirubinemia is ok; physiologic</td>
</tr>
<tr>
<td>Crigler-Najjar 1</td>
<td>Autosomal Recessive, ↑ Unconjugated, Fatal without Transplant Absent UTG conjugation protein</td>
</tr>
<tr>
<td>Gilbert</td>
<td>Autosomal Recessive, ↑ Unconjugated, Normal Life with sporadic asymptomatic jaundice Mutated Promoter (TATA) for UTG conjugation protein, reduced expression</td>
</tr>
<tr>
<td>Dubin-Johnson</td>
<td>Autosomal Recessive, ↑ Conjugated, Normal Life and a Black Liver Mutated bile Cannalicular transport protein; most commonly tested USMLE</td>
</tr>
<tr>
<td>Rotor</td>
<td>The exact same thing as Dubin-Johnson (↑ Conjugated), except the liver isn’t black</td>
</tr>
<tr>
<td>Biliary Tract Obstruction (PSC, Stones, Cancer)</td>
<td>Bilirubin gets into liver, conjugated, can be transported but ↓ Flow = ↓ Excretion ↑ Conjugated Bilirubin = clay-colored stools, dark urine, no kernicterus</td>
</tr>
</tbody>
</table>

### COMPARISON OF BILIRUBIN TYPES

<table>
<thead>
<tr>
<th>Conjugated</th>
<th>Unconjugated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Soluble, cannot penetrate BBB, excreted in Urine Does not cause kernicterus Turns urine a dark brown, skin/eyes jaundice</td>
<td>Water Insoluble, Can penetrate BBB, not excreted in Urine Causes Kernicterus, is fatal No change in urine, but skin/eyes are jaundiced</td>
</tr>
</tbody>
</table>

### INFECTIOUS HEPATITIS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hep A</td>
<td>Fecal-Oral Route for transmission Causes Only Acute Hepatitis RNA virus, vaccine available</td>
</tr>
<tr>
<td>Hep B</td>
<td>IV Drugs and Sexual Contact for transmission (adults) or vertical transmission (children) Causes Mostly Acute but may cause Chronic Hepatitis (immunocompromised = chronic) Incomplete DNA virus, produces HBsAg, HBeAg, HBcAg, HepX protein, vaccine available Serology: HBsAg-IgG = Immunity, HBsAg-IgM = Acute/Active, HBCAg-IgG + HBsAg = chronic If chronic, ↑ risk for Hepatocellular Carcinoma (Hep X) and small ↑ risk for cirrhosis</td>
</tr>
<tr>
<td>Hep C</td>
<td>IV Drugs and Sexual Contact for transmission (adults) or post transfusion (anemic) Causes Mostly Chronic but may cause Acute Hepatitis; RNA virus transmitted through blood Usually progresses to cirrhosis, small ↑ risk for HCC</td>
</tr>
<tr>
<td>Hep D</td>
<td>IV Drugs and Sexual Contact for transmission Cannot infect hepatocytes on its own, requires Hep B coinfection Worsening Hep B infection (hepatitis and HCC) or produces fulminant hepatitis (superinfection)</td>
</tr>
<tr>
<td>Bacterial, Fungal, Parasite</td>
<td>Form abscesses, usually acquired outside of US Common pyogenic infections = same for cholangitis = GI flora (E. Coli, Klebsiella, etc) Amebiasis (entamoeba histolytica) and Schistosomiasis common parasites</td>
</tr>
<tr>
<td>Schistosoma</td>
<td>Causes ↑ Portal Hypertension, other species may cause bladder cancer</td>
</tr>
<tr>
<td>Clinorchis Senensis</td>
<td>↑ Risk of Cholangiosarcoma, causes biliary obstruction</td>
</tr>
</tbody>
</table>
### DISEASES OF THE GALLBLADDER

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
</table>
| Cholesterol Cholelithiasis    | **Cholesterol Stones** are yellow or green, formed from cholesterol calcium salts  

  ↑Risk with **Obesity, Pregnancy, Oral Contraception, Female**, Native American  

  May cause biliary obstruction, cholangitis, jaundice                                                                                               |
| Pigment Cholelithiasis        | **Pigment Stones** are black and made from unconjugated bilirubin  

  ↑Risk with **Hemolytic Anemia, Liver Flukes**  

  May cause jaundice, cholangitis, biliary obstruction                                                                                              |
| Cholestasis                   | Stasis of the biliary tree may be caused by **intrahepatic mechanisms** (Gilbert’s MRP2) which is not amendable to surgery, or by **extrahepatic mechanisms** (obstruction, cancer, stones, infection) is amendable to surgery |
| Cholangitis                   | **Bacterial Infection** most commonly coming from the GI tract and ascending  

  Common organisms = E. coli, Klebsiella, and Bacteroides                                                                                         |
| Biliary Atresia              | Biliary ducts do not form, patient cannot eliminated bile or cholesterol  

  Amendable to surgery if outside the liver                                                                                                        |
| Primary biliary cirrhosis     | **Autoimmune** disease affecting the gallbladder causing **lymphocytic granulomas**  

  **Female preponderance** with the presence of **Antimitochondrial Antibodies** (AMA)  

  Patient presents with **Xanthomas, Pruritis, and Jaundice/Icterus**                                                                           |

### TUMORS OF THE LIVER AND GALLBLADDER

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
</table>
| Focal Nodular Hyperplasia     | Benign nodular growth that is **non-neoplastic**  

  Has a **paler color** and a **central fibrotic scar**                                                                                             |
| Cavernous Hemangioma          | **Benign neoplastic growth** of vascular tissue related to CCl₄ Exposure  

  Is seen as **darker red, mushier** spots on the liver                                                                                            |
| Liver cell Adenoma            | **Benign Neoplastic growth** of hepatocytes associated with **high estrogen**  

  Females who are **pregnant** or on **oral contraceptives** are at ↑ risk  

  Cessation of estrogen source = ↓ size and growth of neoplasm                                                                                   |
| Metastasis                    | **Most common tumor of the liver**, common sites are from GI/Colon, Breast, Skin  

  High blood flow (portal vein and hepatic artery) predispose for metastasis  

  Present as **multiple diffuse small lesions** in the liver                                                                                     |
| Hepatoblastoma                | **Tumor of childhood**, consisting of fetal (epithelial) or mesenchymal (mixed) tissue  

  Large nodular growth that is **the same color** as the liver and has **central scar**  

  Indicated by an **elevated AFP in a kid** (AFP in adult = HCC)                                                                               |
| Angiosarcoma of Liver         | **Terrible Prognosis** tumor similar to angiosarcomas anywhere  

  ↑Risk with exposure to **Vinyl Chloride**                                                                                                       |
| Hepatocellular Carcinoma (HCC)| **Highest yield tumor** for the GI section  

  Caused by **chronic inflammatory diseases** (cirrhosis, Hep B infections) and are common in **Asia** (Hep B) or in **US alcoholics** (cirrhosis)  

  Loves to **invade blood vessels** though it **rarely metastasizes** outside the liver  

  Indicated by **adult liver mass** with an **elevated Alpha-Feto-Protein (AFP)**  

  Transplant may not be curative (reinfection with Hep B)                                                                                      |
| Fibrolamellar HCC             | Variant of Hepatocellular Carcinoma that occurs in **younger adults** and has a **favorable prognosis**  

  Extremely low yield (have not encountered it outside of class)                                                                               |
| Carcinoma of the Gallbladder  | Cause by **chronic inflammatory disease** of the gallbladder (Clonorchis or Cholecystitis)  

  Bears a **terrible prognosis** with metastasis and seeding found at diagnosis  

  Indicated by a **palpable, painless gallbladder**                                                                                              |
| Carcinoma of the Bile Ducts and Cholangiosarcoma | If Intrahepatic, carcinoma of the bile duct gets a special name = Cholangiosarcoma  

  Carries a **dismal prognosis** (<5% 1-year survival) presenting with a **painless jaundice**  

  In fact, painless jaundice is almost pathognomonic for carcinoma (bile duct or pancreas)                                                             |
### LABORATORY MARKERS OF LIVER FUNCTION

<table>
<thead>
<tr>
<th>Enzyme or Marker</th>
<th>With Injury or Dysfunction...</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatocyte Injury</strong></td>
<td></td>
<td><em>↑</em> All three are markers for injury, enzymes contained within hepatocytes. With Hepatocellular necrosis or apoptosis, enzymes are released, so serum levels increase, a marker for injury.</td>
</tr>
<tr>
<td>Aspartate AminoTransferase (AST)</td>
<td>↑</td>
<td><em>↑</em> Unconjugated, risk for kernicterus; lipid-soluble unconjugated can penetrate BB, cannot be excreted renally and is neurotoxic.</td>
</tr>
<tr>
<td>Alanine AminoTransferase (ALT)</td>
<td>↑</td>
<td><em>↑</em> Conjugated, most likely secretion mutation or biliary obstruction. Conjugated Bilirubin nontoxic and excreted in urine</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (LDH)</td>
<td>↑</td>
<td><em>↑</em> Bile acids are made in the liver, secreted, and recirculated through enterohepatic circulation. Increased levels means biliary obstruction. Causes pruritis, bile lakes in liver will be seen</td>
</tr>
<tr>
<td>Serum Bilirubin</td>
<td></td>
<td><em>↑</em> Contained in biliary cells, released during cholestasis, as bile acids destroy lining of biliary walls, marker of biliary damage</td>
</tr>
<tr>
<td><strong>Biliary Function</strong></td>
<td></td>
<td><em>↑</em> The liver makes albumin. If the liver isn’t working, it won’t make albumin. This increases risk for ascites and edema</td>
</tr>
<tr>
<td>Albumin</td>
<td>↓</td>
<td><em>↑</em> Liver makes clotting factors. If the liver isn’t working, it won’t make the clotting factors, so you won’t clot, and clotting time increases</td>
</tr>
<tr>
<td>Prothrombin Time (PT and aPTT)</td>
<td></td>
<td><em>↑</em> The liver process amino acids (urea cycle). If the liver isn’t working, it builds up ammonia, which can cause hepatic encephalopathy</td>
</tr>
<tr>
<td><strong>Hepatocyte Function</strong></td>
<td></td>
<td><em>↑</em> In the liver, the liver makes albumin, therefore the blood levels increase. If the liver isn’t working, it won’t make albumin. This increases risk for ascites and edema</td>
</tr>
<tr>
<td>Ammonia</td>
<td></td>
<td><em>↑</em> Alcohol causes increases in the liver, which will be released through the enterohepatic circulation. Increased levels means biliary obstruction. Causes pruritis, bile lakes in liver will be seen</td>
</tr>
</tbody>
</table>

### PANCREAS TUTORIAL SESSION (wasn’t reading, but know these exist)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agenesis</td>
<td>No pancreas forms Incompatible with life</td>
</tr>
<tr>
<td>Pancreas Divisum</td>
<td>Two tubes form to deliver exocrine juices. In this case the smaller one carries most of the juices, while the larger one (ampula of Vater) carries little of the juice</td>
</tr>
<tr>
<td>Annular Pancreas</td>
<td>A band-like ring of pancreas forms around the 2nd part of the duodenum, Presents later in childhood life with vomiting upon eating</td>
</tr>
<tr>
<td>Ectopic Pancreas</td>
<td>Pancreas grows where it shouldn’t, always near to its starting point Stomach, Duodenum, jejenum, Meckel’s Diverticula, ileum</td>
</tr>
<tr>
<td>Acute Pancreatitis</td>
<td>Reversible lesions of inflammation, fat necrosis and saponification caused by Alcohol Caused also by obstruction of pancreatic duct (Clinorchis Sinensis or Gallstone at Sphincter of Oddi) Protected enzymes get stuck and activate in pancreas = autodigestion, Represents a medical emergency Increased serum amylase and increased serum lipase with sharp epigastric pain radiating to the back Allow pancreas to “rest” after an acute episode = total dietary restriction</td>
</tr>
<tr>
<td>Chronic Pancreatitis</td>
<td>In repeated acute pancreatitis, alcoholism most common, or the formation of concretions in exocrine ducts Results in fibrosis and shrinkage of the pancreas with loss of function Presents with abdominal pain, mild fever, mild elevations of amylase, and malabsorption (A, D, E, and K)</td>
</tr>
<tr>
<td>Zollinger-Ellison Syndrome</td>
<td>Gastrin secreting tumor of the pancreas Causes upregulation of acid secretion in the stomach Presents with ulcers intractable to H. pylori treatment</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Insulin secreting tumor of the pancreas, Hypoglycemia, coma, and death can result Causes release of insulin (test for C-peptide to confirm endogenous production) It’s the only Islet tumor we learned about, you don’t have to know about other Islet Tumors</td>
</tr>
</tbody>
</table>
### TUMORS OF THE GI TRACT

<table>
<thead>
<tr>
<th>Disease</th>
<th>Location</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s</td>
<td>Esophagus</td>
<td>Protective <em>metaplasia</em> to columnar epithelium with goblet cells in response to GERD is precancerous, inducing <em>dysplasia</em> and eventual <em>adenocarcinoma</em> (30-40x risk) Treatment with <em>PPIs</em> may reverse dysplasia and metaplasia prior to carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Esophagus</td>
<td>Leading esophageal tumor in the United States</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dysphagia</strong> to solid food then liquids, bleeding, and weight Loss (same as squamous cell) Usually follows Barrett’s Esophagus, found in the <strong>lower third of esophagus</strong></td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>Esophagus</td>
<td>Leading esophageal tumor world wide</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dysphagia</strong> to solid food then liquids, bleeding, and weight Loss (same as adenocarcinoma) Resembles other squamous cell carcinomas, may be keratinized, <strong>upper third of esophagus</strong></td>
</tr>
<tr>
<td>Gastric Carcinoma</td>
<td>Stomach</td>
<td>Most common sites are <strong>Antrum (50%)</strong>, <strong>Lesser Curvature (40%)</strong> = H. Pylori Infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asymptomatic until severe, gross shows <em>initis plastica</em> (thickening of mucosal layer) <em>Intestinal Type</em> shows intestinal <em>metaplasia</em> and is associated with H. Pylori</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Diffuse Type</strong> shows signet cell rings and is <strong>poorly differentiated</strong> <strong>Krukenburg’s Tumor</strong> to the ovaries, <strong>Virchow’s Node</strong> near the clavicle</td>
</tr>
<tr>
<td>MALtomas</td>
<td>Stomach</td>
<td>Non-Hodgkin’s lymphoma of the stomach, most H. Pylori associated cancer Will regress with antibiotics if caused by H. Pylori</td>
</tr>
<tr>
<td>Stromal Tumors</td>
<td>Stomach</td>
<td>Rare tumor of the interconnective tissue of the stomach (the Stroma) Caused by an <em>overactivity of Tyrosine Kinase</em>, treated with Gleevec/Imatinib</td>
</tr>
<tr>
<td>Adenomatous Polyps</td>
<td>Colon</td>
<td>Benign growths that may become cancerous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Are either sessile (without a stalk, malignant) or pedunculated (with a stalk, benign)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Are either villous (finger-like projections, malignant) or tubular (normal colon, benign)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occult blood in stool leads to a scope, polyps are found and harvested</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td>Colon</td>
<td><strong>Autosomal Dominant</strong> mutation of the <em>APC gene</em> causing 100s-1000s of polyps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entire Colon is full of polyps, ↑ chances that one will become <em>dysplastic</em> (cancerous)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommended <em>prophylactic colectomy</em>, usually diagnosed in teens / twenties</td>
</tr>
<tr>
<td>Gardner</td>
<td>Colon</td>
<td>An FAP variant with osteomas of the jaw, fibromatosis of the abdomen and benign epithelial inclusion cysts in the skin (very low yield)</td>
</tr>
<tr>
<td>Turcot</td>
<td>Colon</td>
<td>Rare variant of FAP that is autosomal recessive; TURcots = TURban = Brain 1000s of polyps PLUS <em>independent brain tumors</em> (usually medulloblastoma)</td>
</tr>
<tr>
<td>HNCPP</td>
<td>Colon</td>
<td><strong>Autosomal Recessive Mutation of the DNA Mismatch Repair Genes</strong> These patients have no polyps but get colon cancer anyway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Risk for ovarian and endometrial tumors</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>Colon</td>
<td>Patient usually presents with Dark Spots on the lips (Hyperpigmented lesions) Endoscopy reveals hamartomous (benign) polyps of the small intestine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Look for cancers somewhere else other than the GI tract (lung, skin, liver)</td>
</tr>
<tr>
<td>Colonic Adenocarcinoma</td>
<td>Colon</td>
<td>#3 Cancer in America, #3 Cancer Killer in America, caused by one of many mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Right Sided Tumors</strong> are more dangerous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Stool is soft, so there is no obstructive presentation to the Exophytic lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Only clue is heme occult blood in stool (GUIAC test) prompted by anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Left Sided Tumors</strong> are more noticeable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Causes a napkin ring stricture, presenting with obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Bowel habits show alternating constipation and diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Barium enema shows an “apple-core” lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Heme occult blood is also positive (GUIAC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Both</strong> tend to metastasize to the liver</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>Colon</td>
<td>May occur in the Lung and Adrenal gland (which are immediately symptomatic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Those arising in the colon must first metastasize to the liver to become symptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First pass liver effect neutralizes serotonin; once metastasized, liver does not clear Causes cramping, flushing, diarrhea, and fibrosis of the heart valves (right if colon)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Look for 5-HIAA in the urine, a metabolite of serotonin (5-HT)</td>
</tr>
</tbody>
</table>
Path GI – Liver – Biliary – Exocrine Pancreas

### DISEASES OF THE ESOPHAGUS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistula</td>
<td>Connection between any two ‘tubes’ usually occurring with <strong>atresia</strong> and between the esophagus and trachea. Presents with <strong>aspiration pneumonia</strong> and <strong>polyhydramnios</strong>; Amenable to surgery</td>
</tr>
<tr>
<td>Atresia</td>
<td>Esophagus ends in a <strong>blind pouch</strong>. Common proximal atresia with distal fistula to the trachea</td>
</tr>
<tr>
<td>Webs</td>
<td>Projections of mucosal epithelium into the lumen of the esophagus; can trap food = malodorous breath When associated with <strong>iron deficiency anemia</strong> it is called <strong>Plummer-Vinson Syndrome</strong> and ↑Risk for SCC</td>
</tr>
<tr>
<td>Achalasia</td>
<td><strong>Failure</strong> of the <strong>LES to relax</strong>, preventing food from entering the stomach, Stent or resection is curative Presents with <strong>dysphagia</strong> that is usually <strong>not progressive</strong> and <strong>without weight loss</strong></td>
</tr>
<tr>
<td>Stricture</td>
<td>GERD, failure of neural crest migration, other insult (Lye Ingestion, Esophageal Chagas, Toxins) → damage; Repair leads to <strong>intraluminal fibrosis</strong> and narrowing of the lumen Presents with <strong>progressive dysphagia without weight loss</strong> (absence of weight loss differentiates from cancer)</td>
</tr>
<tr>
<td>Mallory Weiss</td>
<td>Associated with <strong>severe retching</strong> found commonly in <strong>alcoholics</strong> and <strong>bulimics</strong> Are <strong>longitudinal tears</strong> of the mucosa usually found at the gastro-esophageal junction Cause a <strong>mild upper GI bleed</strong> that will heal spontaneously with cessation of retching; non life threatening</td>
</tr>
<tr>
<td>Mallory Weiss</td>
<td>Associated with <strong>liver failure</strong> and subsequent <strong>portal hypertension</strong> (cirrhosis, Schistosomiasis) Porto-caval shunts formed through anus (hemorrhoids), abdomen (caput medusa) and esophagus (varices) Are <strong>tortuous distended veins</strong> of the esophagus that are <strong>prone to rupture</strong> (especially with vomiting) Produces a <strong>life-threatening upper GI bleed</strong> with <strong>hematemesis</strong> and <strong>melena</strong>. Surgical intervention required</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastro-esophageal Reflux Disease caused by <strong>low tone of the LES</strong> allowing stomach contents to reflux Enhanced by consumption of <strong>fat</strong> (slows gastric emptying), <strong>chocolate/alcohol/smoking</strong> (relaxes sphincter) Causes a <strong>burning pain</strong> in the <strong>epigastric region</strong> as stomach acid <strong>damages esophagus</strong> Produces a <strong>basal zone hyperplasia</strong> (↑germ cell activity to replace damaged tissue) or <strong>simple hyperemia</strong> Lasts for 10-20 years if untreated, metaplastic Barrett’s Esophagus or stricture sets in</td>
</tr>
<tr>
<td>Barrett’s Esophagus</td>
<td>A product of long standing, untreated GERD; it is a <strong>premalignant condition</strong> Results in a <strong>metaplastic change to columnar epithelium with goblet cells</strong> Appears <strong>velvety salmon-colored</strong> epithelium on endoscopy Burning of GERD progressively disappears without treatment (protective, precancerous change)</td>
</tr>
</tbody>
</table>

### DISEASES OF THE STOMACH

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragmatic Hernia</td>
<td>Congenital weakening the in diaphragm that allows for the stomach and intestines to protrude This can cause <strong>pulmonary hypoplasia</strong> if the herniation is significant (usually on the <strong>left posterior</strong>)</td>
</tr>
<tr>
<td>Hiatal Hernia</td>
<td>May be congenital or acquired <strong>Sliding Hiatal Hernia</strong> is where the Fundic stomach goes up through the hole where the esophagus is This ↑risk for GERD, almost no risk for incarceration or strangulation <strong>Paraesophageal Hiatal Hernia</strong> is where another part of the stomach goes through the diaphragm This ↑risk for Incarceration or strangulation of stomach, little risk for GERD</td>
</tr>
<tr>
<td>Pyloric Stenosis</td>
<td>A <strong>congenital</strong> stenosis or blockage of the pyloric valve in an infant, <strong>myotomy</strong> is curative Presents with <strong>nonbiliary projectile vomiting</strong> after eating and a palpable <strong>olive-like mass</strong> abdomen</td>
</tr>
<tr>
<td>Menetrier’s Disease</td>
<td>Disease of <strong>middle aged men</strong> that causes an <strong>increased thickness</strong> of the mucosa by proliferating neck cells, replacing chief and parietal, causing ↓<strong>acid secretion</strong> but with an increased risk for <strong>gastric carcinoma</strong> It is a <strong>protein losing enteropathy</strong>, which means edema and ascites NOT related to the liver</td>
</tr>
<tr>
<td>Zollinger-Ellison</td>
<td>A <strong>Gastrin secreting pancreatic tumor</strong>; Gastrin activates proliferation of and secretion from parietal cells ↑Risk for GERD and Peptic Ulcer (from ↑ acid) and thickening of mucosa/carcinoma</td>
</tr>
<tr>
<td>Acute Gastritis</td>
<td>Acute (Neutrophilic) <strong>inflammation</strong> of the <strong>gastric mucosa</strong>, a result of the <strong>failure of mucosal barrier</strong> (NSAIDs, Ischemia, Duodenal Regurgitation) or <strong>increase in acid secretion</strong> (Zollinger-Ellison) May present with <strong>erosion</strong> (confined to mucosal epithelium), <strong>ulceration</strong> (deeper layers), or <strong>hemorrhage</strong></td>
</tr>
</tbody>
</table>
### Path GI – Liver – Biliary – Exocrine Pancreas

<table>
<thead>
<tr>
<th>Disease</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volvulus</td>
<td>Looping of the bowel around itself leading to both obstruction and infarction of bowel (elderly)</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Telescoping of the bowel into itself leading to both obstruction and infarction of bowel (infants)</td>
</tr>
<tr>
<td>Incarcerated Hernia</td>
<td>A hernia is a loop of bowel penetrating a muscular wall. When the bowel goes through, the muscle may contract, trapping the bowel outside.</td>
</tr>
<tr>
<td>Herschbrung’s Disease</td>
<td>A congenital disorder whereby neural crest cells fail to migrate and the colon lacks autonomic ganglia. The affected site looks normal, has no peristalsis, and continues to the anus as totally aperistaltic. The unaffected site looks dilated, plenty of peristalsis, this part is the “megacolon”. Presentation is a neonate without muconium passage, megacolon, and may vomit feces.</td>
</tr>
<tr>
<td>Celiac Sprue</td>
<td>An IgA Immune Disease to wheat gluten, more specifically, to gliadin in wheat products (Anti-Gliadin). Causes mucosal atrophy, malabsorption, failure to thrive, foul smelling steatorrhea. Associated with Dermatitis Herpetiformis, avoid gluten products and patient will live a normal life.</td>
</tr>
<tr>
<td>Tropical Sprue</td>
<td>Similar mucosal atrophy and malabsorption as in Celiac Sprue, but with an unknown etiology. Suspected to be an infection (E. Coli?) that responds to antibiotics and vitamins.</td>
</tr>
<tr>
<td>Whipple’s Disease</td>
<td>Rare disease of male rural workers of the Caribbean caused by infection by Tropheryma Whippelli. Presents with diarrhea, and malabsorption with abundant distended macrophages (survives inside macrophages) in mucosa of small intestine with complete villi, that responds to long-term antibiotics.</td>
</tr>
<tr>
<td>Chron’s Disease</td>
<td>Bimodal age (10-30 and 50-70), affecting white females usually targeting terminal ileum. May occur anywhere along the GI tract, but occurs with skipped lesions and fistula formation. There are Noncaseating granulomas with transmural inflammation and hardly any risk of cancer.</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>Occurring in the 20s and 30s of white females that targets the colon, which is continuous from rectum. There are no skipped regions, no granulomas, the inflammation is limited to mucosa/submucosa. There is an elevated risk of colon carcinoma. Both Crohn’s and UC present with bloody mucoid diarrhea.</td>
</tr>
<tr>
<td>Ischemic Bowel Disease</td>
<td>Reduced blood flow to the bowel for any reason causes ischemia termed mesenteric angina. Regions at risk are the splenic flexure and other watershed areas. Affects the elderly or severe trauma victims presenting with hemorrhagic necrosis and 50% survival.</td>
</tr>
<tr>
<td>Meckel’s Diverticulum</td>
<td>Congenital Defect of the small bowel commonly encountered in children, a remnant of vitelline duct. Usually asymptomatic, Meckel’s may contain gastric or pancreatic mucosa, which may bleed (bright red). Found in 2% of the population, and 2% of those will become cancerous.</td>
</tr>
<tr>
<td>Colonic Diverticulosis</td>
<td>Acquired defect of the large bowel commonly encountered in elderly adults with low-fiber diets. Pouches form from increased luminal pressure (constipation); pouches are asymptomatic. Feces gets stuck in them, leading to infection (diverticulitis) which may perforate (peritonitis). May mimic cancer with alternating diarrhea and constipation or bloody diarrhea.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISEASES OF THE COLON AND SMALL INTESTINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td>Chronic Gastritis</td>
</tr>
<tr>
<td>Ulcers in General</td>
</tr>
<tr>
<td>Gastric Ulcers</td>
</tr>
<tr>
<td>Duodenal Ulcers</td>
</tr>
</tbody>
</table>
# Path GI – Liver – Biliary – Exocrine Pancreas

## TYPES OF DIARRHEA

<table>
<thead>
<tr>
<th>Secretory</th>
<th>Invasive</th>
<th>Osmotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for Fecal Leukocytes</td>
<td>Positive for Fecal Leukocytes</td>
<td>Negative for Fecal Leukocytes</td>
</tr>
<tr>
<td>cAMP stimulating toxins</td>
<td>Bloody, Mucinous Stool</td>
<td>Lactase Deficiency</td>
</tr>
<tr>
<td>E.Coli (ETEC), Cholera</td>
<td>Shigella, Salmonella, EHEC E.Coli</td>
<td>Laxatives</td>
</tr>
<tr>
<td>High Volume Diarrhea</td>
<td>Low Volume Diarrhea</td>
<td>High Volume Diarrhea</td>
</tr>
</tbody>
</table>

## BUGS CAUSING GI INFECTIONS

<table>
<thead>
<tr>
<th>Bug</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIRUS</strong></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Most common childhood of diarrhea, transmitted via the Fecal-oral route</td>
</tr>
<tr>
<td>Norwalk Virus</td>
<td>Walking Diarrhea that ruins cruise ship vacations</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>HIV immunocompromised only, Giant Cell with inclusions</td>
</tr>
<tr>
<td><strong>BACTERIA</strong></td>
<td></td>
</tr>
<tr>
<td>Staph Aureus</td>
<td>Rapid Onset (1-6 hrs) = Diarrhea and Vomiting by preformed toxin, Gram Positive, Potato Salad</td>
</tr>
<tr>
<td>Bacillus Cereus</td>
<td>Reheated rice (buffet line), Preformed Toxin, Gram Positive</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Invasive disease, 3% become chronic carriers in biliary tract, spread by poultry, flagellated</td>
</tr>
<tr>
<td>Clostridium Difficile</td>
<td>Causes Psudomembranous Colitis after wide spectrum antibiotic, treat with Vancomycin</td>
</tr>
<tr>
<td>EHEC – E. Coli</td>
<td>Shiga-Like Toxin, same as Shigella, but can also cause Hemolytic Uremic Syndrome, 0157:H7</td>
</tr>
<tr>
<td>Shigella</td>
<td>Shiga-Toxin = Cleavage of 60s subunit = bloody dysentery, non-systemic infection</td>
</tr>
<tr>
<td>Campylobacter Jejuni</td>
<td>Bloody Diarrhea, especially in HIV/AIDS associated with Guillain Barre</td>
</tr>
<tr>
<td>ETEC – E.Coli</td>
<td>Traveler’s Diarrhea (Mexico), same as cholera Toxin, watery diarrhea</td>
</tr>
<tr>
<td>Yersinia Enterocolitica</td>
<td>Granulomatous Microabscesses, this is not Yersinia Pestis (the plague)</td>
</tr>
<tr>
<td>Vibro Cholera</td>
<td>Cholera-Toxin = ADP-Ribosylation Gα, = Turns on a pump that extrudes chloride into the lumen</td>
</tr>
<tr>
<td></td>
<td>Massive amounts of watery diarrhea, treatment = parenteral fluid/electrolytes</td>
</tr>
<tr>
<td><strong>PROTOZOA</strong></td>
<td></td>
</tr>
<tr>
<td>Enteromeaba</td>
<td>Flask-Shaped Ulcerations, can ascend and cause Liver/Gallbladder problems</td>
</tr>
<tr>
<td>Histolytica</td>
<td>Has multiple nuclei, diagnosed by seeing protozoa with RBCs inside it</td>
</tr>
<tr>
<td>Giardia Lamblia</td>
<td>Immunocompromised patients or drinking water from a stream, flagellated protozoa</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>Most common cause of diarrhea in AIDS</td>
</tr>
<tr>
<td><strong>HELMNITHS</strong></td>
<td></td>
</tr>
<tr>
<td>Ascaris Lumbricoides</td>
<td>Bowel obstruction in adult phase</td>
</tr>
<tr>
<td>Diphyllobothrium Latum</td>
<td>Causes B12 Deficiency after ingestion of raw freshwater fish</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>Abdominal Pain and Diarrhea, Larvae in Soil penetrate skin, coughed up in lungs</td>
</tr>
<tr>
<td>Enterobius</td>
<td>Eat food contaminated with eggs = pin worm</td>
</tr>
<tr>
<td>Vermicularis</td>
<td>causes anal pruritis and eggs come out at night (scotch tape test)</td>
</tr>
</tbody>
</table>

Micro is its own course so a brief survey of organisms should do you well. Questions can be picky, but you should be able to narrow it down to 2-3 choices pretty easily. There is an excellent (and more thorough) table in Goljan, page 346 edition 2.