Course Objectives

1. Recall normal liver anatomy and histology.
2. Understand basic terminology/definitions.
   - Apoptosis, cholestasis, limiting plate, interface hepatitis, micro- versus macro-vesicular steatosis, steatohepatitis, balloon cell, Mallory body, lobular hepatitis, bridging fibrosis, nodular transformation, ground glass hepatocytes, iron accumulation, PASD resistant globules, portal tract, portal hepatitis, jaundice
3. Understand the general patterns of injury, repair and fibrosis.
   - Acute versus Chronic
   - Hepatocellular, Biliary, Vascular What injury occurs in each compartment?
4. Exposure to common liver tumors. TOMORROW
   - Benign and malignant
Adult weight: 1400-1600 g

Lobes:
Right  Largest lobe
Left
Caudate
Quadrate
Blood Supply:
- Portal Vein
- Hepatic Artery
  - Along with the Common Bile Duct, they enter through the hilum
  - Branches of these structures travel within portal tracts

The vascular supply is important for anatomy, because that's how surgeons decide to resect parts of the liver. They divide up the segments of the liver:
- 1 = caudate
- 2-4 = left lobe
- 5-8 = right lobe

Blood exits through the hepatic veins and dumps into the IVC.
Portal Tract

The portal tract (made up of the three structures below) is enveloped by a small amount of fibrous tissue. The abrupt transition between the fibrous tissue and the hepatocytes is the limiting plate. This is important histologically because inflammation extending beyond that limiting plate is important to note.

**Constituents:**
- Bile duct
- Portal vein
- Hepatic artery

- Limiting plate
  - (Interface)
Microscopic Liver Anatomy

Two ways to look at the microscopic anatomy: lobule unit and acinar unit.

Lobule unit: central/terminal hepatic vein in center with cords of hepatocytes radiating out, extending to the portal triads/tracts. The blood flows from the portal tracts to the vein. Bile formed in the hepatocytes flows through the canalicular spaces back towards the portal tract.

Acinar unit: Look at one triangular portion of the lobule. The acinus is broken down based on the blood flow.
Zone 1: freshest blood, most O2-rich
Zone 3: O2-poor blood, right near central vein.

Blood

Bile

Portal Tract

BD: bile duct
HA: hepatic artery (dual supply!)
PV: portal vein
- blood: portal tract --> central vein
- bile: hepatocytes --> canaliculi
- portal tracts along periphery
- terminal hepatic vein in center
Lobular Architecture

- Hepatocytes arranged in thin plates/cords (1-2 cells thick).
- Sinusoidal spaces lined by endothelial cells and filled with blood, Kupffer cells and stellate cells.
- Bile is excreted from hepatocytes into bile canaliculi → canals of Hering → bile ducts.

If you see hepatocytes in cords that are thicker than this (1-2 cells), you start thinking about a neoplastic process.

Kupffer cells - liver macrophages
Stellate cells: pluripotent stem cells of the liver

Canals of Hering are at the limiting plate; these dump into the bile duct.
**Definitions**

**Portal hepatitis:** Inflammation of the portal tract. Can still see the demarcation where the inflammation ends and the hepatocytes begin. No interface activity like on the right - inflammation is contained with the portal tract.

Once you see spillage of the information (can’t draw a straight line between inflammatory cells and bigger hepatocytes), very irregular (projections extending out), extending beyond limiting plate - interface hepatitis.

You can have both or just portal hepatitis.
Definitions

Injury can lead to fatty metamorphosis of the hepatocytes. Heps are forming a lot of lipids that can accumulate within the cells.

Macrovesicular - large clear droplets. More common.

Microvesicular - fine, small droplets. Relatively uncommon; can sometimes see some patches. Know specifically because of how it applies to Reyes syndrome and fatty liver of pregnancy.
Definitions

Various forms of injury.
Left: balloon cells and Mallory bodies are the histological hallmark of steatohepatitis.
Right: dying hepatocyte. In the liver, don’t call them apoptotic bodies, call acidophil or councilman bodies.

Balloon Cells with Mallory Bodies

Acidophil Body (Councilman Body)
Cholestasis

Hepatocytes form bile. If something happens to either interrupt the excretion into the canalicular spaces or the flow of bile through the biliary system, you'll have backup of the bile. This can occur either within the hepatocytes (L) or within the canalicular spaces (R).
Patterns of Hepatic Injury

Dividing up injury patterns by the cell that is getting destroyed. Can have a combination of the three occurring. If the damage is severe enough, you will have regeneration. If the damage is chronic, you can develop fibrosis/cirrhosis of the liver.

• Hepatocyte Injury
  – Cell death (i.e. Apoptosis)
  – Degenerative and/or intracellular accumulations (i.e. Ballooning degeneration and steatosis)
  – Inflammation
    • Influx of acute or chronic inflammatory cells involving the portal tracts, interface and/or lobules

• Biliary Injury
  – Cholestasis  (most commonly)
    • Structural versus functional

• Vascular Abnormalities  Resulting in ischemia
  – Which can lead to hepatocyte and/or biliary injury

• Regeneration/Fibrosis
Serum Markers for Hepatic Injury

How is the liver doing in this patient? - Liver Function Tests (LFTs)
Any markers elevated= something injured.

**Hepatocyte Integrity**

*Hepatocellular enzymes*
Both specific for hepatocyte injury.

**Biliary**

*Substances secreted in bile*
Normally bilirubin is excreted; if it starts accumulating, there is something wrong with the biliary system.

*Plasma membrane enzymes*
Can also look at membrane enzymes. Serum alk phos isn't entirely specific.

**Hepatocyte Function**

*Secreted proteins (blood)*

Look at things the liver either produces (albumin) or metabolizes (ammonia).

*Hepatocyte metabolism*

Liver functions: metabolizes drugs, creates clotting factors, makes albumin, metabolizes ammonia - all crucial

**Serum aspartate aminotransferase (AST)**

**Serum alanine aminotransferase (ALT)**

**Serum bilirubin**

*Total*: unconjugated plus conjugated

*Direct*: conjugated only

**Serum alkaline phosphatase**

**Serum γ-glutamyl transpeptidase**

Serum gamma-glutamyl is quite specific for the biliary system.

**Serum albumin** ↓ in injury

**Prothrombin time**

(factors V, VII, X, prothrombin, fibrinogen) ↑ in injury

**Serum ammonia** ↑ in injury

Ammonia = bad. Too much results in psychological changes, etc. An increase means liver isn't metabolizing it.
Various forms of hepatocyte injury:

- **Infectious**
  - Viral Hepatitis
  - Others...

- **Autoimmune Hepatitis**

- **Toxic/Drug Induced Injury**
  - Alcohol

- **Metabolic Injury**
  - Non-Alcoholic Fatty Liver Disease (NAFLD)

- **Intracellular Depositions**
  - Hemochromatosis
  - Alpha-1-antitrypsin
  - Wilson Disease
  - Metabolic disease (not addressed in this talk)
Viral Hepatitis

Viruses that can affect any organ/system, not specific to liver.

• Non-Hepatotropic:
  – Epstein Barr Virus (EBV) **
    • Sinusoidal lymphocytosis
    • PTLPD
  – Cytomegalovirus (CMV)
    • Post-transplant infection
  – Herpes Simplex Virus (HSV)
    • Overwhelming infection/necrosis
  – Adenovirus
    • Mainly affects children

Viruses specific to the liver.

• Hepatotropic:
  – Hepatitis A Virus
  – Hepatitis B Virus
  – Hepatitis C Virus
  – Hepatitis D Virus
  – Hepatitis E Virus

** Complications of EBV: in liver, can cause lobular hepatitis. Sinusoidal spaces fill with lymphocytes. Post-transplant lymphoproliferative disorder - essentially a lymphoma associated with EBV. This can also occur in other immunocompromised states (HIV, chronically treated with methotrexate).
Hepatotropic Viruses

Viruses with an affinity for the liver. In general, think of hepatitis viruses as ssRNA with the exception of HBV - dsDNA. "Hep B wants to be like its brothers and sisters." Has reverse transcriptase, converts DNA to RNA. Uses RNA template for replication like the other hep viruses.

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<td>Transmission</td>
<td>• Fecal&lt;br&gt;• Oral contaminated food</td>
<td>• Parenteral&lt;br&gt;• Sexual contact&lt;br&gt;• Perinatal&lt;br&gt;• Needle stick</td>
<td>• Parenteral&lt;br&gt;• Sexual contact&lt;br&gt;• Needle stick</td>
<td>• Parenteral&lt;br&gt;• Sexual contact</td>
<td>• Water-borne</td>
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Notes:
B-D: IV drug use, sexual contact, occupational exposure (needles).
B: perinatal (through delivery).
Clinical Syndromes

- **Acute hepatitis- asymptomatic with recovery**
  - HAV and HBV infection during childhood
- **Acute hepatitis- symptomatic with recovery**
  - Uncommon for HCV
- **Chronic hepatitis**
  - Continued or relapsing disease for > 6 months
  - Hallmark of HCV
- **Fulminant hepatitis**
  - Progression to hepatic failure within 2 – 3 weeks
  - In the US, most commonly HAV and HBV (adults)
- **Carrier state**
  - Harbor replicating virus and can transmit the organism

Acute - body can clear virus by itself (typically A, sometimes B, E).

Chronic: either relapsing/remitting or continuous - HepC, sometimes B. NOT A or E.

Fulminant: patient presents acutely, and within a few weeks they need a liver transplant emergently.

Carrier: usually E. Infection, asymptomatic. Liver full of the virus, and constantly shedding.

Chronic (at least 6 months): can still have ongoing active injury (portal, interface, or lobular hepatitis) with scar tissue due to fibrosis within the liver. If it becomes more extensive, patient develops cirrhosis.
Hepatitis A

Presents acutely. Pale stools because of liver dysfunction. Does not form a chronic hepatitis; can rarely cause fulminant hepatitis.

- Can present with anorexia, nausea, and jaundice
  - Occasionally subclinical
- Typically a benign, self-limited disease.
  - Rarely causes fulminant hepatitis
- Produces an acute lobular hepatitis +/- cholestasis
- Does not progress to chronic hepatitis

Histologically: lobular hepatitis with lobule full of inflammation. Can't see nice rays/cords of hepatocytes. "Lobular disarray" due to injury and inflammation.
Hepatitis B

Can present acutely or subclinically. Hep B infection once chronic is an independent risk factor for the development of hepatocellular carcinoma.

- Often subclinical disease but can cause an acute hepatitis
  - Rarely fulminant hepatitis
- Usually resolves but can cause chronic hepatitis (5%)
  - Chronic hepatitis is associated with risk of hepatocellular carcinoma
- Can produce a “healthy” carrier state
  - Asymptomatic but infectious
  - „Ground glass“ cytoplasmic inclusion of virions (arrows)

Carrier state is unique for HBV.

Smudgy, very pink. Inclusions with a halo - "ground glass". Appearance due to HBV virion packed in the cell.

Shedding disease, very infectious.
Hepatitis C

Unlike HBV which is going down due to vaccine, HCV is still a major disease cause. Causes a much higher rate of chronic infection.

- Major cause of liver disease worldwide
- Has a higher rate of progression to chronic hepatitis than HBV (80-85%).
  - Portal, interface and lobular hepatitis
  - Progressive fibrosis - cirrhosis
  - Variable steatosis
- Various subtypes exist
  - Multiple strains and subtypes can exist within the same person

Can't draw a line of where the limiting plate is because inflammation is spreading out.
Small pic: lobular hepatitis with acidophil body.
Hepatitis D
Requires HBV to survive and cause any injury.

- AKA- “delta virus”
- In the US, it’s relatively uncommon
  - IV drug abusers
  - Hemophiliacs
- Requires HBsAg for encapsulation and thus replication (infection)
- Two pathways:
  - Acute co-infection (with HBV)
  - Super-infection
    Pre-infected with HBV, HDV causes super-infection.

Hepatitis E
Rarest of hepatotropic viruses.

- Usually causes acute self-limited hepatitis
  - Can cause fulminant hepatitis;
  - Fatal outcome particularly associated with pregnancy (mortality ~ 20%)
- Does not progress to chronic hepatitis

Immunocompromised in pregnancy. Risk of fulminant hepatitis is higher and the women don't recover as well. Infection with another Hep virus would potentially turn into a chronic hepatitis (HEV is the most fatal).
Other Infectious Diseases

• Bacterial
  – Spirochetes
    Syphilis, Borrelia.

• Fungal
  – Aspergillus
    Immunocompromised patients. Can also see Candidiasis.

• Parasitic
  – Echinococcus
  – Schistosomiasis
    Cyst with multiple layers of wall. If you have any radiographic suspicion of this, don’t stick a needle in - can develop anaphylactic shock. Resect carefully!

Echinococcus
Autoimmune Hepatitis

Can also form chronic hepatitis.

• Chronic and progressive hepatitis of unknown etiology
  – Autoimmune mediated injury
    • Several potential “triggers” – infection, drugs, herbal products
    • HLA DR3 and DR4
  – ANA and Anti-smooth muscle Ab (ASMA) (Type 1)
    • +/- anti-actin or anti-soluble liver/ liver-pancreas antigen (Type 3)
      These Type 3 antibodies are often grouped under Type 1. Conflict in literature.
  – Anti-liver kidney microsome-1 (ALKM-1) (Type 2 )
    Type 2 is least common.

• Young to middle aged women primarily effected
  – M:F  1:3; ~ 40 y/o
  – Majority develop a chronic hepatitis that can progress to cirrhosis (40%).
  – Acute fulminant hepatitis can occur (40%)

Fulminant hepatitis can often lead to transplantation.
Autoimmune Hepatitis

• **Associations:**
  – Celiac disease, SLE, RA, Sjogren syndrome, UC, etc…
    They’re all associated.

• **Morphology:**
  – Interface and lobular hepatitis with a predominant population of **plasma cells** and lymphocytes.
  – May present with zone 3 (perivenular) injury
  – Can have overlap with PSC or PBC. The presence of many **plasma cells** can help differentiate autoimmune hepatitis from other types.

• **Treatment:**
  – Immunosuppression (i.e. prednisone/ azothioprine)
  – Transplantation
    Progression to cirrhosis will eventually require transplantation.

PSC: Primary sclerosing cholangitis.
PBC: Primary biliary cirrhosis - both biliary processes, also autoimmune.
Autoimmune Hepatitis

Inflammation up here in lobular tissue too.


High power: a sea of plasma cells.
Alcohol (Toxic) Related Injury

• Excessive ethanol consumption: one of the leading causes of liver disease
  – Alcohol abuse is the 5th leading cause of death in the U.S.
  – More than 14 million Americans abuse alcohol
  – Rate is higher in males (11%) versus females (4%)

• “Alcohol abuse” definition varies
  – 140 grams (~14 “drinks”) of alcohol per week for males
    • Women are more susceptible to injury
  – Interesting new data suggests that mild to moderate intake actually protects against liver disease.
  – Increased AST:ALT (≥2:1)

AST and ALT, specific for hepatocellular integrity. If elevated, hepatocellular injury. With alcohol related injury, the ratio changes as above - this can help distinguish from other types of liver damage.
Alcohol (Toxic) Related Injury

Alcohol is absorbed unaltered. Metabolized in the liver.

3 mechanisms for conversion of EtOH, only one for metabolizing acetaldehyde. Important!
3 systems dumping acetaldehyde into 1. Rate-limiting step is conversion to acetate.

• Normal Metabolism:
  – EtOH → Acetaldehyde → Acetate
  – Oxidizing system (CytP450, ER) and Catalase (peroxisomes)
  – Acetaldehyde: nausea, reactive intermediate
  – Ethanol: affects protein synthesis, membrane integrity

- 50% of Asians have low ALDH.

• Net effects of excess intake:
  – Metabolism diverted: NADH equivalents → fat (lipid biosynthesis - steatosis)
  – Damage to protein export machinery and cellular membranes EtOH and ROS
  – Clumped intermediate filaments (Mallory bodies) Ropy hyaline seen in histology
  – Recruitment of inflammatory cells and activation of stellate cells leads to the development of fibrosis Will eventually develop steatohepatitis

ADH: alcohol dehydrogenase
ALDH: acetaldehyde dehydrogenase
Alcohol (Toxic) Related Injury

Steatosis and hepatitis are reversible if you stop drinking.

3 distinct but overlapping forms:
hepatic steatosis, alcoholic hepatitis, and alcoholic cirrhosis

10-15%
Alcohol (Toxic) Related Injury

Morphology

- Fatty liver (microvesicular and macrovesicular steatosis)
- Alcoholic hepatitis (steatohepatitis)
  - Hepatocyte swelling and necrosis
  - Mallory bodies
  - Neutrophilic reaction
  - Fibrosis (sinusoidal fibrosis pattern)
  - Alcoholic cirrhosis

Fatty liver is reversible.

Q: How long does it take the liver to heal after you stop drinking?
A: So, let's say you had a fun week, if you stop and don't totally abstain, within a few days its totally back to normal.
Non-Alcoholic Fatty Liver Disease

Very similar histologically to alcoholic fatty liver. No strong markers besides the clinical appearance of the patient - AST and ALT are only somewhat elevated.

• Strong association with the metabolic syndrome:
  – Obesity, hyperlipidemia, hypertension and insulin resistance
  – Little to no alcohol consumption

• Estimated that ~24% of the US population has NAFLD
  – With the global “obesity epidemic” (affecting adults and children), it is estimated that the prevalence of NAFLD will increase
  – Can present with mild elevations in AST and ALT

• ~10-30% eventually develop cirrhosis

• Morphologic findings range from:
  – Macrovesicular steatosis to steatohepatitis (NASH)
  – Minimal pericellular fibrosis to cirrhosis
Steatohepatitis

Same thing as seen with alcoholics.

Progression

Fibrosis (blue) pattern is rather unique. Fibrosis starts surrounding individual cells that are injured; called perisinusoidal or pericellular fibrosis. Usually starts in zone 1 around terminal hepatic vein and extends out from there.
Drug Induced Injury

- The liver is the major drug metabolizing and detoxifying organ.
- Many drugs can cause liver disease through various mechanisms:
  - The drug or one of its metabolites is directly toxic to the liver.
  - The drug reduces the immunologic or hormonal defense of the host.
  - The drug or one of its metabolites becomes a hapten to convert an intracellular protein into an immunogenic signal.

Examples that are important to know:

- Major hepatic drug reactions and some implicated agents
  - Centrilobular necrosis: acetaminophen, halothane
  - Microvesicular steatosis: tetracycline, salicylates
  - Macrovesicular steatosis: ethanol, methotrexate
  - Cholestasis (impaired bile formation): oral contraceptives
  - Granuloma formation: sulfonamides
  - Neoplasia
    - Adenoma: oral contraceptives
    - Thorotrast: Angiosarcoma and hepatocellular carcinoma
Drug Induced Injury

Acetaminophen toxicity
- Residual normal portal tract and some hepatocytes
- Dead tissue - Tylenol toxicity
- Residual central vein

Methotrexate toxicity
- Steatohepatitis
- Anisonucleosis - variability in nuclear size
Normal Iron Homeostasis

1. Diferric transferrin in the serum binds to the HFE receptor on the hepatocyte.

2. Binding of DT promotes hepcidin release.

Promotes secretion of Hepcidin

3. Hepcidin tells other cells (macrophages, duodenal enterocytes) to start storing iron.

Promotes intracellular iron storage

- Normally, iron is regulated through a negative feedback system. Once this loop is dysregulated, you get problems.

Decreased serum iron

- Inhibits iron absorption

- Iron storage signals duodenum to stop absorbing iron

> Adapated from 2006 Long Course at USCAP
Hemochromatosis

- Hemochromatosis is characterized by excessive iron accumulation in the body
  - Excess iron is deposited in parenchymal organs such as liver, pancreas, and heart
  - Iron is directly toxic to the cells of these organs and stimulates fibrosis

- Two types of hemochromatosis
  - 1. Hereditary Hemochromatosis Primary. Usually due to a defective receptor.
  - 2. Secondary Hemochromatosis (hemosiderosis)
    - Parenteral intake (blood transfusions, i.e. sickle cell disease)
    - Oral ingestion (“Bantu siderosis” or African iron overload)

Too much intake of iron can cause secondary hemochromatosis.
Normal Iron Homeostasis

**Decreased serum iron**

- Hepatocyte
- Serum Diferric Transferrin
- HFE/Transferrin Receptor complex

**Inhibits iron absorption**

Promotes secretion of Hepcidin

- Serum Hepcidin
- Duodenal Enterocyte
- Iron poor cells
- Promotes iron absorption

**Decreased intracellular iron storage**

- Macrophage

Body iron stores continuously increase

- This receptor can be knocked out. No hepcidin, no storage, no cessation of absorption in duodenum. Negative feedback loop shut off, iron concentration increases.

Adapted from 2006 Long Course at USCAP
Hereditary Hemochromatosis

- Autosomal recessive iron overload disorder
  - Mutations in **HFE gene** on chromosome 6p.
    - Cysteine-to-tyrosine mutation at position 282 (70%)
  - Prevalent inherited genetic defect: allele frequency 6%
    - Homozygosity 0.45% (1:220 persons), 11% heterozygosity (1:9 persons)
    - **Variable penetrance** Many people have the gene but don't have disease
- Affects the **liver, heart, pancreas, joint linings, endocrine glands, and skin**
  - Can lead to cirrhosis, cardiomyopathy, pancreatic destruction “bronze diabetes”, arthritis
    - "Bronze:" iron deposits in the skin give a tanned color.
  - Organ end-stage disease by fourth-to-fifth decade with **heart failure** most common cause of death; increased risk of hepatocellular carcinoma
Hereditary Hemochromatosis

Morphology

• Early changes:  
  – Iron deposition in periportal hepatocytes

• With disease progression:  
  – As iron accumulates:
    – Iron deposition in the rest of the lobule, in bile ducts, and Kupffer cells (macrophages)
    – Fibrous septa develop and then micronodular cirrhosis

• Gold standard for diagnosis is quantitative iron analysis on the liver biopsy  
  Not just histology, need to check dry weight iron in the tissue.

• Treatment:  
  – Phlebotomy  
    Works early on
  – Transplantation  
    Once patients are cirrhotic
Hereditary Hemochromatosis

Very dark pigmented inclusions in hepatocytes. Prussian blue stain on the right is specific for iron.
Alpha-1-Antitrypsin Deficiency

• Autosomal recessive disorder
  – Leads to low serum levels of a protease inhibitor- A1AT
    • A1AT is a small glycoprotein synthesized in hepatocytes’ endoplasmic reticulum (ER)
    • Mutations result in an abnormally folded A1AT protein which inhibits it from exiting the ER, produces cytoplasmic accumulation and systemic deficiency
    • Low serum levels permits uninhibited tissue destruction (e.g., pulmonary emphysema)
  – Gene located on chromosome 14 (carrier rate 10%)
### Alpha-1-Antitrypsin Deficiency

Various genotypes associated with the deficiency.

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**Disease Associations:**

- Emphysema (75%-85%)
- Hepatitis/Cirrhosis
- Panniculitis
- Anticytoplasmic neutrophilic antibody (C-ANCA) - positive vasculitis (Wegener's granulomatosis)
Alpha-1-Antitrypsin Deficiency

- Hepatic syndromes are extremely variable ranging from neonatal hepatitis, childhood cirrhosis and subclinical chronic hepatitis.

- Treatment:
  - Transplant (curative) You have removed the liver that can't excrete alpha-1-antitrypsin, new liver can.

Morphology

- Round/oval cytoplasmic globular inclusions in hepatocytes
  - PAS-diastase (PASD) histochemical stain highlights the inclusions
- Can lead to advanced fibrosis and/or non-specific changes
- Neonatal (giant cell) hepatitis
Alpha-1-Antitrypsin Deficiency

Round cytoplasmic inclusions/globules. PASD positive (see upper right)

PASD

A1AT Accumulating in hepatocytes
Wilson Disease

Normal copper metabolism:

- Absorbed by the stomach/duodenum; transported to the liver
- The liver incorporates Cu into ceruloplasmin and secretes ceruloplasmin into the serum
- “Old” ceruloplasmin returns to the liver, is degraded, and the copper is excreted into bile

Wilson Disease is an autosomal recessive disorder which creates a defective hepatocyte canalicular transporter

- ATP7B located on chromosome 13
- Cu accumulates in hepatocytes (hepatotoxic)
- Cu spills out into the circulation causing hemolysis and pathologic changes in the brain (deposits in basal ganglia) and eyes (corneal deposits, “Kayser-Fleischer rings”)

K-F rings - arc of copper deposition around periphery of the iris
Wilson Disease

• Clinical course:
  – Acute hepatic failure: childhood to young adulthood
  – Cirrhosis: adolescence to young adulthood
  – Psychosis: adolescence to young adulthood

• Treatment:
  – Chelation therapy (D-penecillamine)
    Remove copper.

• Morphology
  – Ranges from mild to severe:
    • Cu accumulation
    • Fatty change, hepatic necrosis
    • With progression, cirrhosis can develop
Biliary Injury

- Primary Biliary Cirrhosis (PBC)
- Primary Sclerosing Cholangitis (PSC)
- Obstructive Biliary Disease (Secondary SC)
- Bile Duct Paucity (not addressed in this talk)
  - Biliary Atresia
  - Alagille Syndrome
  - Drug related injury
- Hereditary Disorders
  - Crigler-Najjar
  - Gilbert Syndrome
  - Dubin-Johnson
  - Rotor Syndrome
  - Progressive Familial Intrahepatic Cholestasis (PFIC)
General Principles

• Hepatic bile serves 2 major functions
  1. Elimination of bilirubin, cholesterol, and non-water soluble wastes
  2. Bile salts promote emulsification and absorption of dietary fat in the gut

Bilirubin: breakdown product of heme

• Bile formation is a sophisticated function of hepatocytes and is therefore is one of the most readily disrupted
  Normal bile formation is one of the first things lost during hepatocellular injury

• Cholestasis = Retention of not only bilirubin but also other solutes eliminated in bile (bile salts and cholesterol)
  - Causes: a) Bile duct obstruction or b) Hepatic dysfunction (non-obstructive)
    Can be due to damage to the hepatocyte itself or to the flow of bile.

• Jaundice = Yellow discoloration of skin and sclera
  - Occurs when serum bilirubin levels get above 2 mg/dl [normal ~ 1.2 mg/dl]
    Accumulation of bile in the system.
• Bilirubin is derived from the breakdown of RBCs
• Bilirubin is bound to albumin in the serum and transported to the liver
• In the liver is undergoes conjugation and becomes water-soluble and excreted into the bile goes through glucoronidation via UGTA1
  • UGT1A1 enzyme
• Gut bacteria conjugates and degrades it into urobilinogens, which gets excreted in the feces
  Once bilirubin is conjugated and secreted into bile, it is water soluble
Primary Biliary Cirrhosis

Autoimmune disorder. Targeted destruction of bile ducts. The presence of AMA antibodies and elevation of LFTs is pathognomonic for this disorder. Don’t have to do a biopsy.

- Chronic, progressive cholestatic liver disease caused by the inflammatory destruction of intrahepatic bile ducts
  - Autoimmune disorder- **Anti-mitochondrial Ab (AMA)**, +/- ANA
    - IgM Ab to pyruvate dehydrogenase complex- E2 subunit (PDC-E2) found on the inner mitochondrial membrane
  - Elevated Alkaline Phosphatase and γ-glutamyl transpeptidase

- Middle aged women primarily effected
  - F:M 6-9:1 with a mean age 50-55

- Associations:
  - Sjögren’s syndrome, arthropathy, sicca

Remember the AMA antibodies - this is a key distinction she made between PBC and Primary Sclerosing Cholangitis (in 3 slides)
Primary Biliary Cirrhosis

Can be clinically silent until biliary cirrhosis develops. Progressive, chronic disorder.

• Clinical features:
  – Insidious, can present with pruritis, fatigue, and/or abdominal discomfort
  – Progresses over 10-20 years, ultimately developing cirrhosis

• Morphology
  – Portal inflammation with non-suppurative, granulomatous destruction of medium-sized bile ducts (“Florid duct lesion”)
  – Minimal to mild lobular hepatitis
  – May have no cholestasis until late stages of the disease
  – Cirrhosis develops in the final stage (biliary cirrhosis)
  – Can overlap with autoimmune hepatitis

Lobular hepatitis is not a prominent feature; if you see a lot of this, you should start thinking about an overlap with autoimmune hepatitis (remember: interface and lobular hepatitis).

• Treatment:
  – Symptomatic (i.e. Ursodial)
  – Liver transplantation

Pruritis (itchiness) due to cholestasis
Potentially also immunosuppression
Primary Biliary Cirrhosis

No obvious injury up here

Portal tract full of inflammation

Inflammation is infiltrating and destroying the epithelium, attacking the bile duct

Bile duct: see high power image on right
Primary Sclerosing Cholangitis

The big differential: PBC from PSC. Remember the sclerosis: choking off and fibrotically destroying the bile duct. Because of the serial areas of sclerosis, you get the appearance below.

- Fibrotic and inflammatory destruction of intra and extra-hepatic bile ducts
  - Radiology- characteristic “beading” and stricturing of the biliary tree
  - Elevated Alk Phos and GGT
    LFTs aren't really going to help you

- Slight male predominance
  - F:M ratio ~1:3
  - Age range of 20-70 years

- Associations: Inflammatory bowel disease (~70%)
  - May occur before, during, or after IBD onset (UC)

**PSC**
- no AMA antibodies
- Normal or slightly abnormal LFTs
- Typically males, wide age range
- Beaded appearance of bile duct
- Fibrotic
- Progresses to biliary cirrhosis
- Associated with IBD, cholangiocarcinoma

**PBC**
- AMA antibodies
- Elevated LFTs
- Typically middle aged females
- Inflammatory (granulomatous destruction)
- Progresses to biliary cirrhosis
- Associated with Sjogrens, arthropathy, etc. (autoimmune)
Primary Sclerosing Cholangitis

- Etiology and pathogenesis are largely unknown
  - Autoantibodies are present in <10% of patients
    Not generally considered an autoimmune disease; no autoantibodies specific for PSC

- Clinical  
  - Non-specific symptoms
  - Symptoms include fatigue, pruritis
  - Progressive clinical course which can lead to biliary cirrhosis
    - Marked increased risk for cholangiocarcinoma

- Morphology:
  - Concentric periductal “onion skin” fibrosis which leads to fibrous obliteration of the duct
  - Modest lymphocytic portal infiltrate +/- copper accumulation
  - Biliary cirrhosis
  - Can overlap with autoimmune hepatitis

- Treatment:
  - Symptomatic (Ursodiol)
  - Liver Transplantation

Due to chronic cholestasis
Primary Sclerosing Cholangitis

Injured duct

Dense fibrosis surrounding duct

Final progression: ball of fibrous tissue where the duct once was

Reticulin stain highlighting the dense fibrous network
Obstructive Biliary Disease

• Prolonged obstruction of the extrahepatic biliary tree (large duct obstruction) can result in profound liver damage
  – Most common cause is extrahepatic cholelithiasis. Gallstones

• Initial manifestations may include cholestasis, jaundice, and/or abdominal pain
  – Initial morphologic changes are reversible
  – Over time: inflammation, bile duct and hepatocellular damage, fibrosis and secondary biliary cirrhosis develop

• Subtotal obstruction may promote bacterial infection of the biliary tree (Ascending cholangitis)
Large Duct Obstruction with Ascending Cholangitis

Neutrophils in lumen of bile duct. Neutrophils come up from the gut, up through the bile duct, affecting the liver.
## Hereditary Disorders

Hereditary disorders involving the biliary system.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Defects in Bilirubin Metabolism</th>
<th>Liver Pathology</th>
<th>Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNCONJUGATED HYPERBILIRUBINEMIA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type I</td>
<td>AR</td>
<td>Absent <strong>UGT1A1</strong> activity</td>
<td>None</td>
<td>Fatal in neonatal period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzyme used to conjugate bilirubin</td>
<td>Don't biopsy</td>
<td>Buildup of unconjugated bilirubin</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type II</td>
<td>AD with variable penetrance</td>
<td>Decreased <strong>UGT1A1</strong> activity</td>
<td>None</td>
<td>Generally mild, occasional kernicterus</td>
</tr>
<tr>
<td>Gilbert syndrome</td>
<td>AR</td>
<td>Decreased <strong>UGT1A1</strong> activity</td>
<td>None</td>
<td>Innocuous (fluctuating)</td>
</tr>
<tr>
<td><strong>CONJUGATED HYPERBILIRUBINEMIA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dubin-Johnson syndrome</td>
<td>AR</td>
<td><strong>Impaired biliary excretion</strong> of bilirubin glucuronides due to mutation in canalicular multidrug resistance protein 2 (MRP2)</td>
<td>Pigmented cytoplasmic globules; ?epinephrine metabolites Not bile</td>
<td>Innocuous</td>
</tr>
<tr>
<td>Rotor syndrome</td>
<td>AR</td>
<td>Decreased hepatic uptake and storage? Decreased biliary excretion?</td>
<td>None</td>
<td>Innocuous</td>
</tr>
</tbody>
</table>
Dubin-Johnson syndrome

Intracellular pigmented accumulations

These are core biopsies of liver; DJS look green/brown - obvious color change