



Fundamental Liver Pathology

Part 1

APPROVED

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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

Normal Liver Anatomy



Adult weight:
1400-1600 g

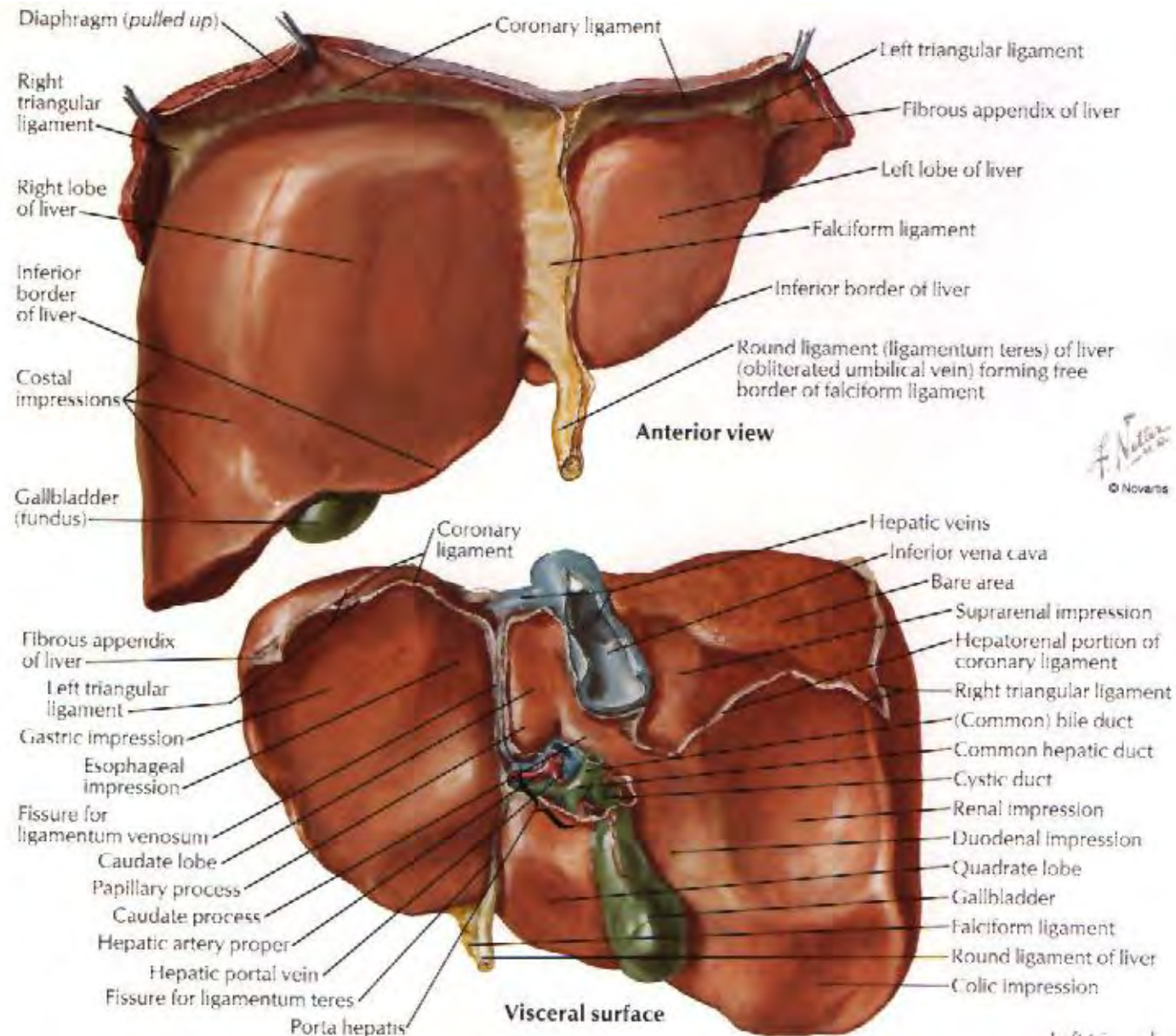
Lobes:

Right **Largest lobe**

Left

Caudate

Quadrante



Normal Liver Anatomy

Important! Dual blood supply



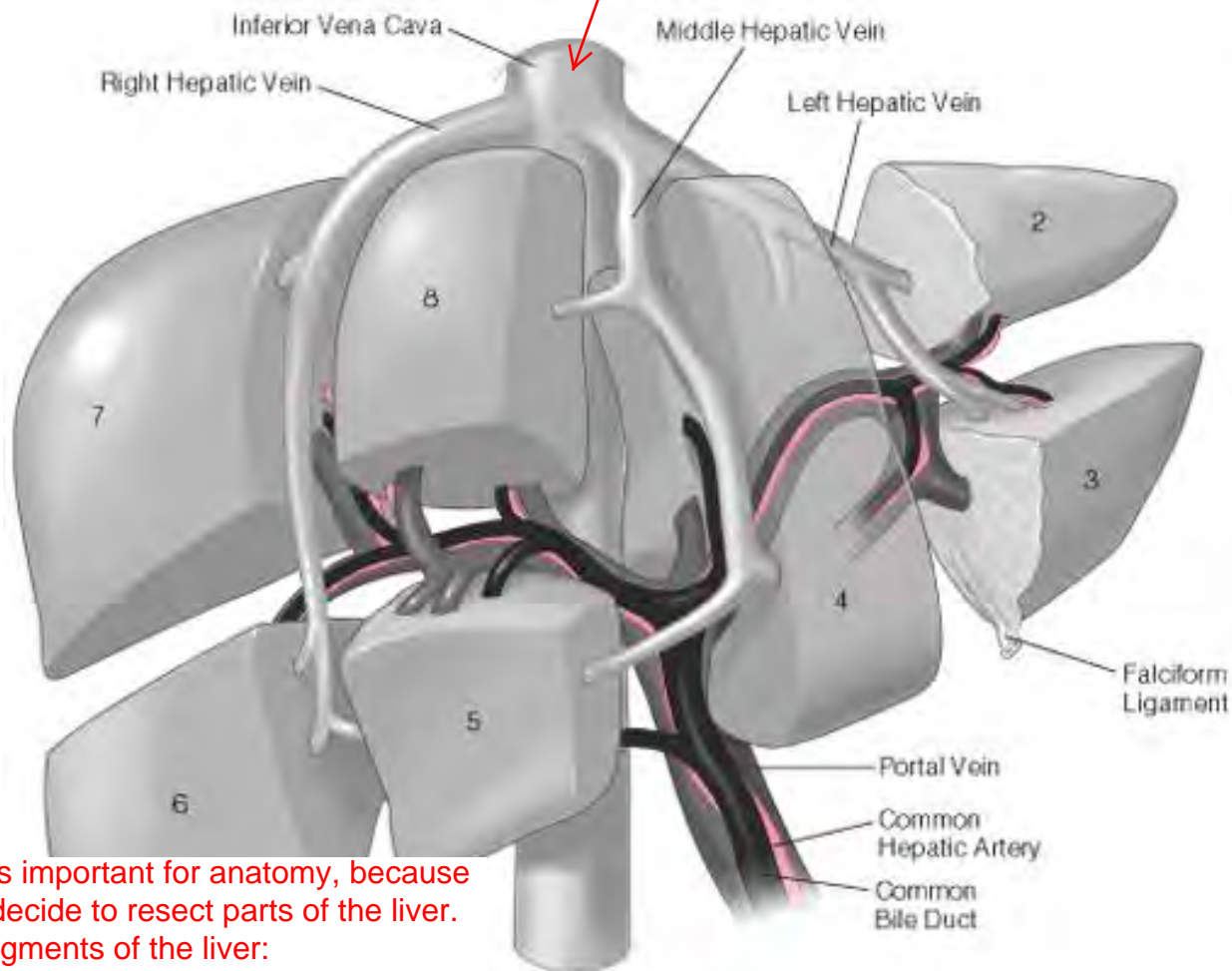
Blood Supply:

Portal Vein

Hepatic Artery

- Along with the Common Bile Duct, they enter through the hilum
- Branches of these structures travel within portal tracts

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



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

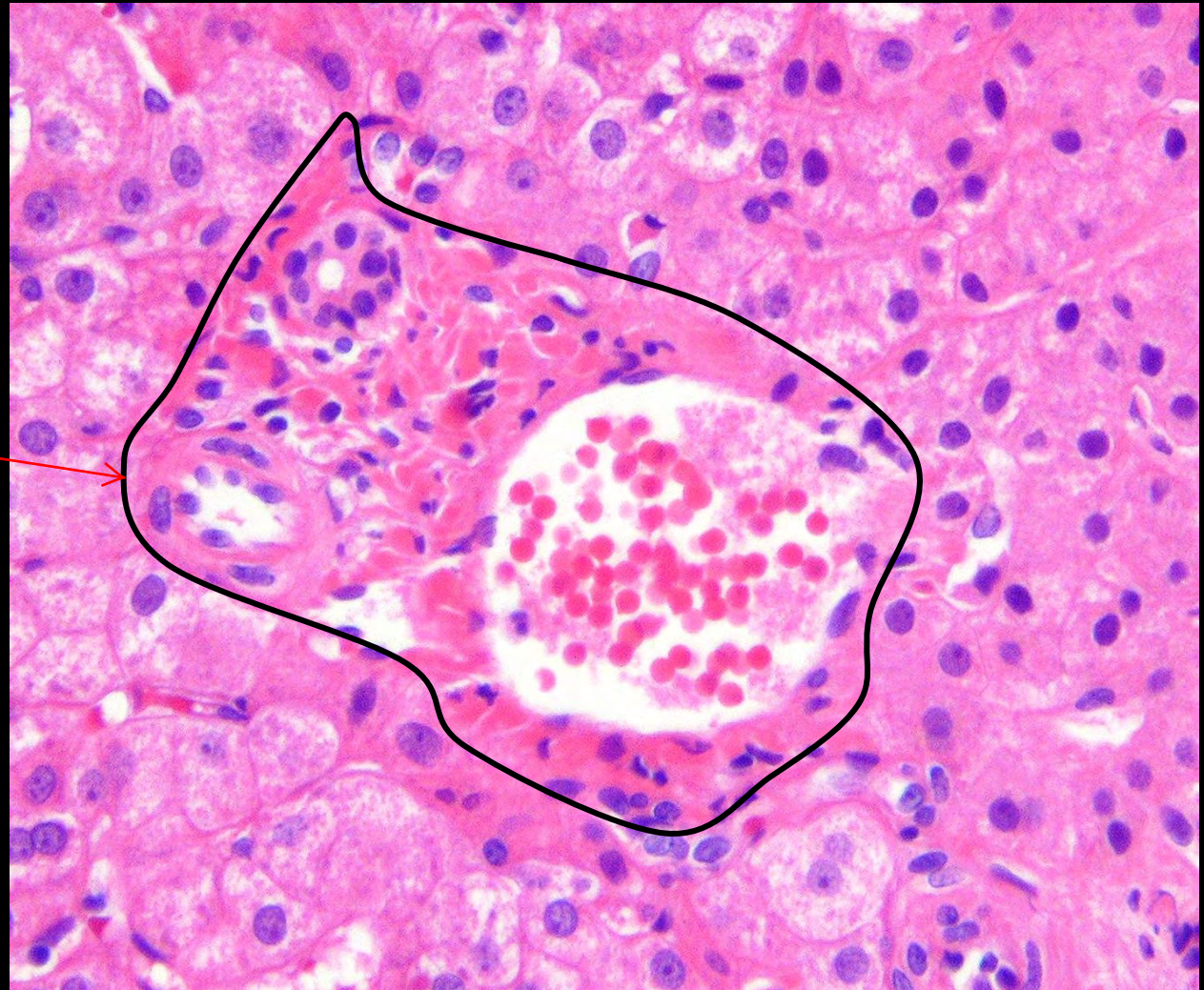


Portal Tract

The portal tract (made of up 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 b/c inflammation extending beyond that limiting plate is important to note.

Constituents:

- Bile duct
- Portal vein
- Hepatic artery
- Limiting plate
 - (Interface)

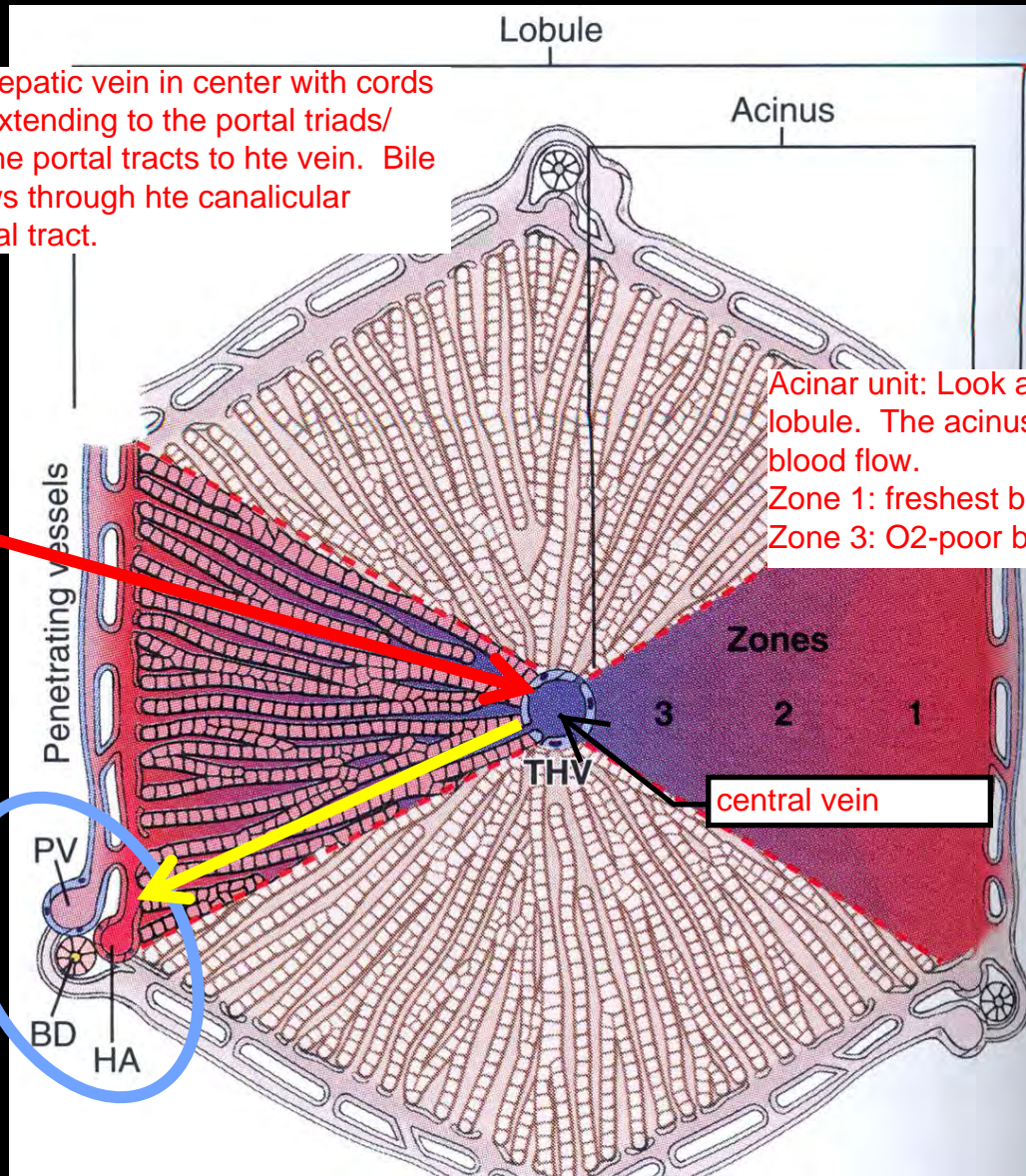




Microscopic Liver Anatomy

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

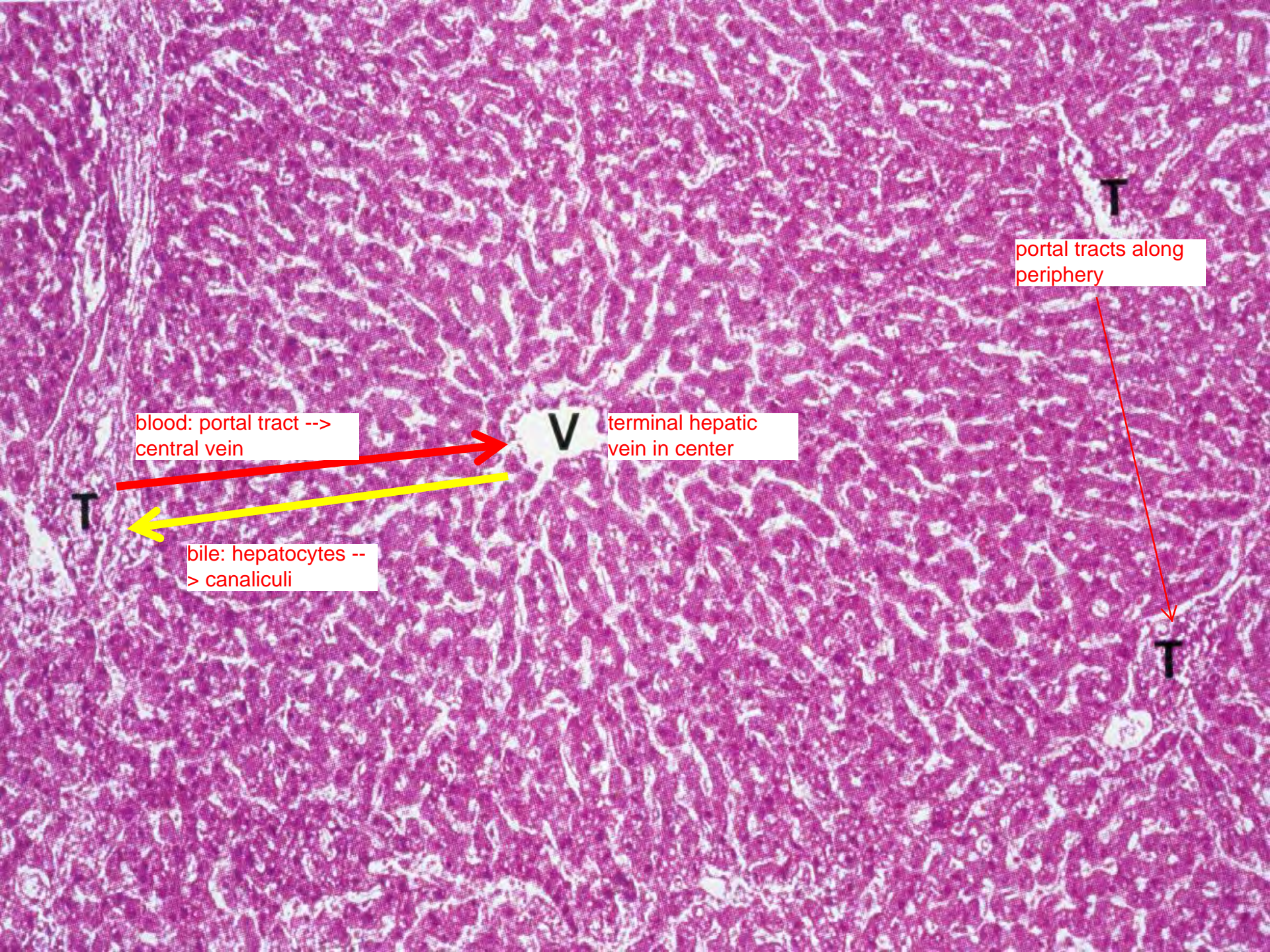
Zone 3: O₂-poor blood, right near central vein.

Blood

Bile

Portal Tract

BD: bile duct
HA: hepatic artery (dual supply!)
PV: portal vein



blood: portal tract -->
central vein

terminal hepatic
vein in center

bile: hepatocytes --
> canaliculi

portal tracts along
periphery

Lobular Architecture



- Hepatocytes arranged in thin plates/cords (1-2 cells thick).

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

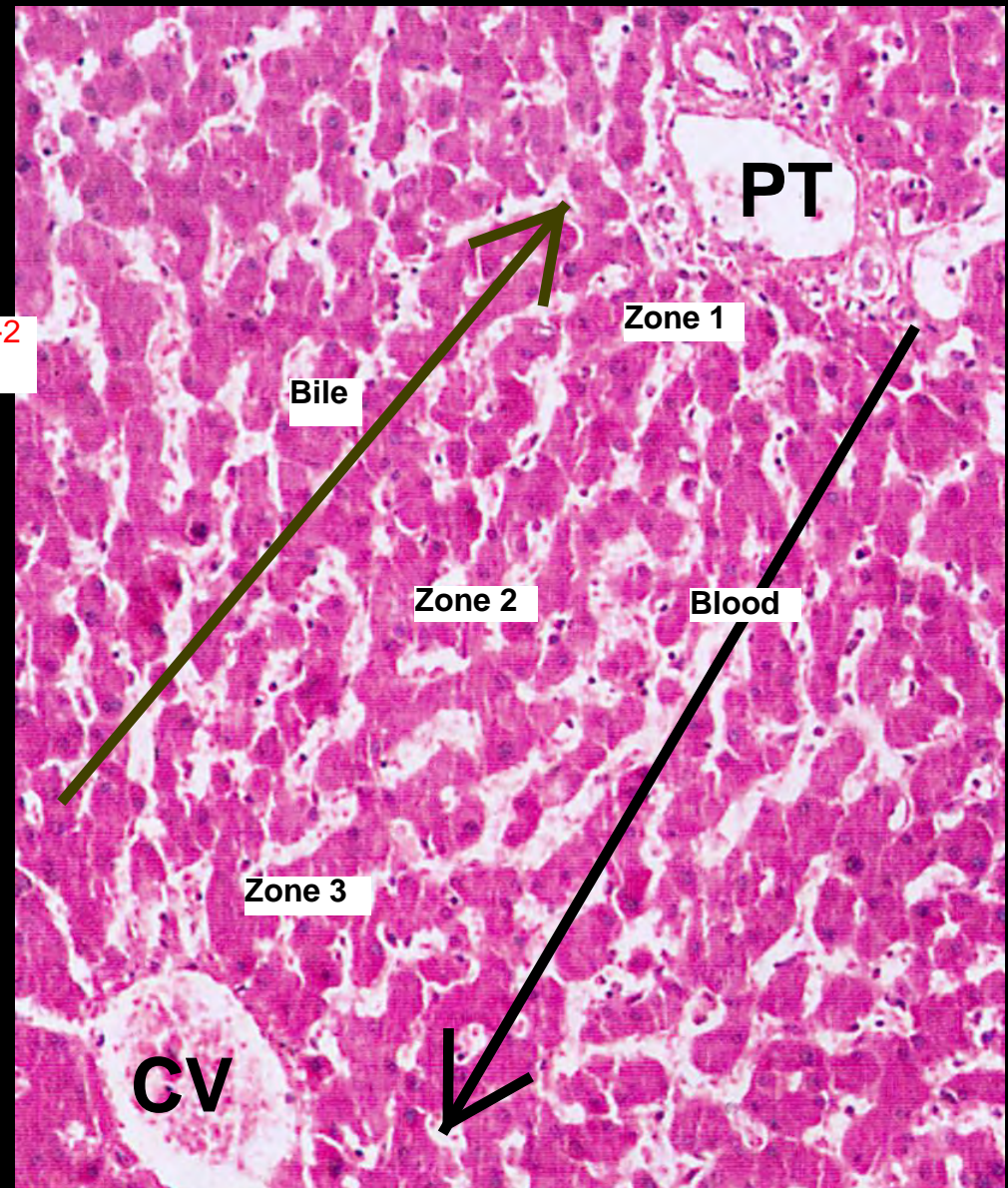
- Sinusoidal spaces lined by endothelial cells and filled with blood, Kupffer cells and stellate cells.

Kupffer cells - liver macrophages

Stellate cells: pluripotent stem cells of the liver

- Bile is excreted from hepatocytes into bile canaliculi → canals of Hering → bile ducts

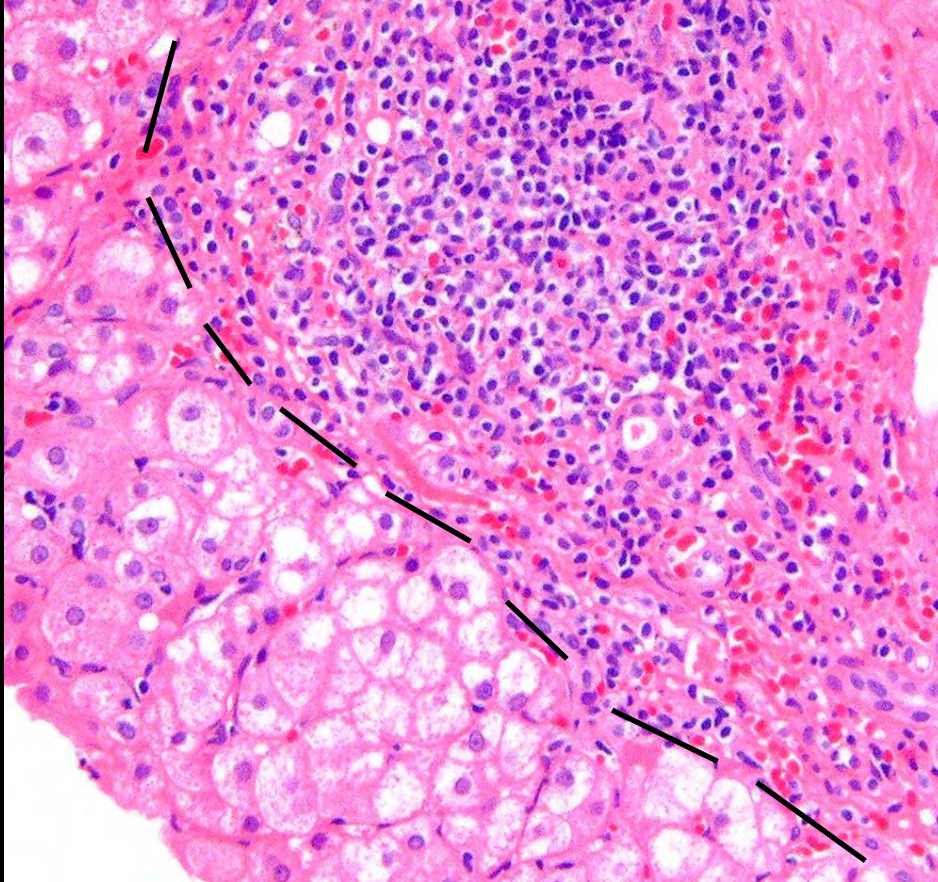
Canals of Hering are at the limiting plate; these dump into the bile duct.



Definitions

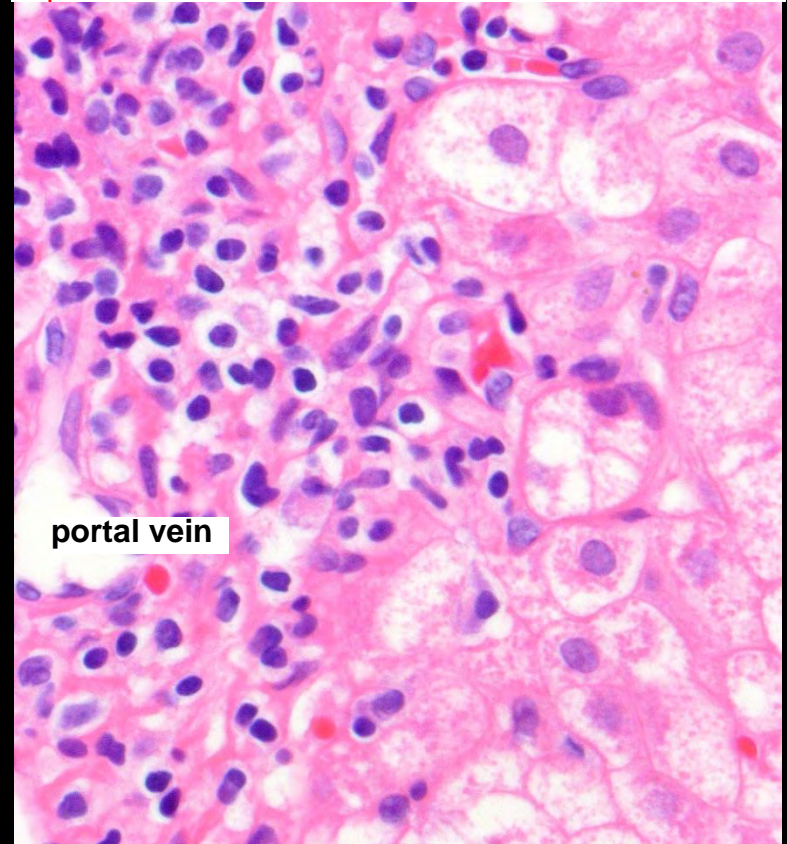


Portal hepatitis: Inflammation of the portal tract. Can still see the demarcation where the inflammation ends and the hepatocytes begin. No interface activity like on the right - inflammation is contained with the portal tract.



Portal Hepatitis

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



Interface Hepatitis

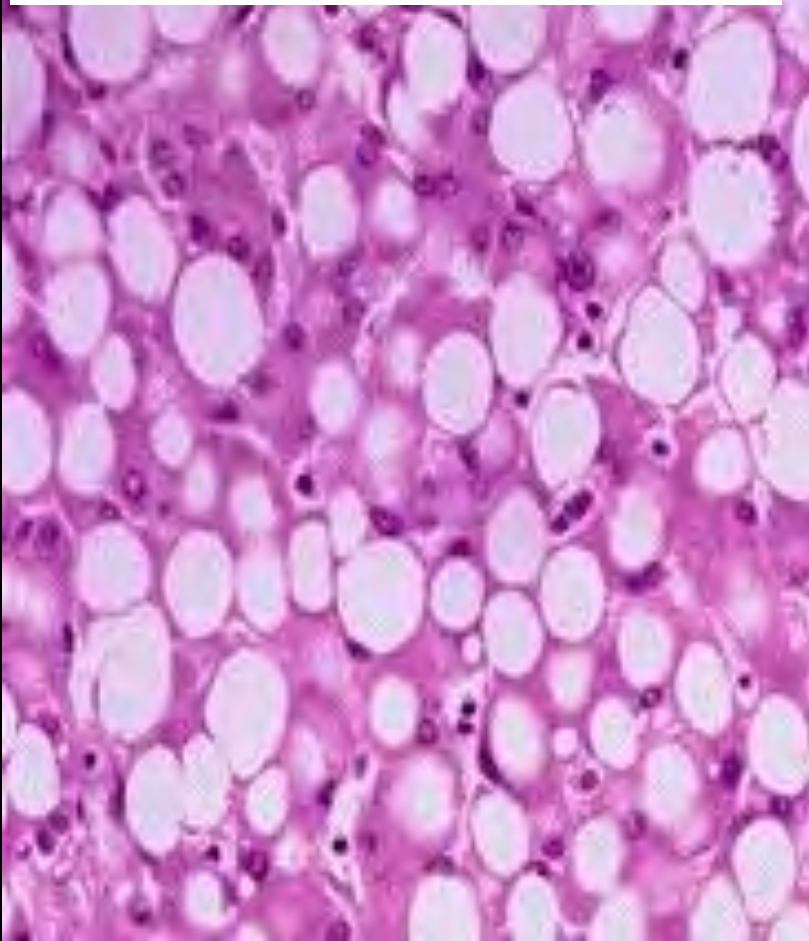
You can have both or just portal hepatitis.

Definitions



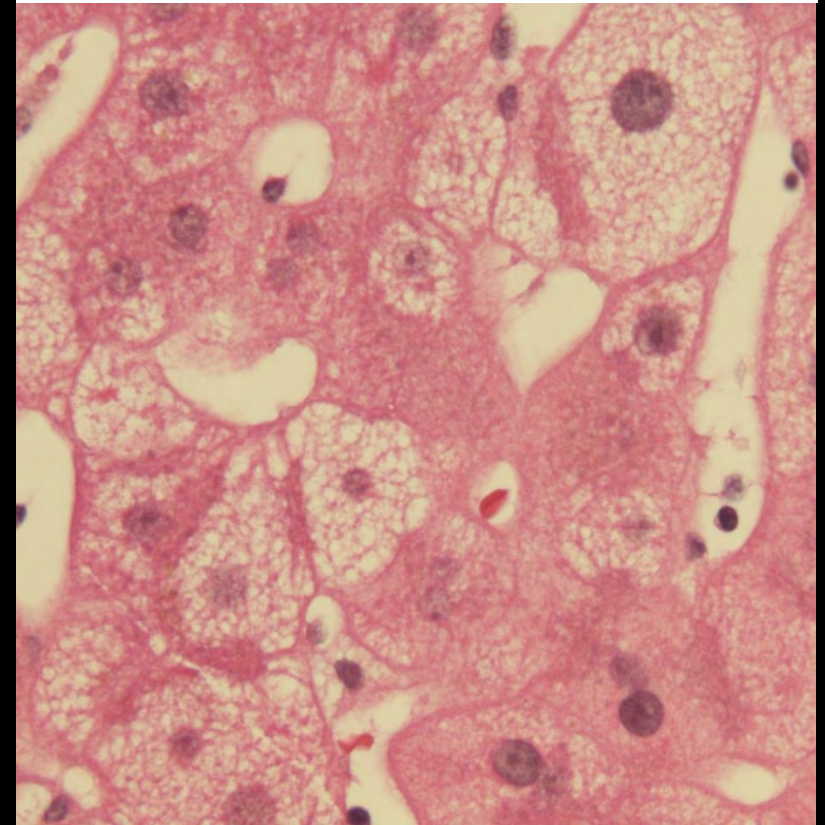
Injury can lead to fatty metamorphosis of the hepatocytes. Heps are forming a lot of lipids that can accumulate within the cells.

Macrovesicular - large clear droplets. More common.



Macrovesicular
Steatosis

Micro - 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.



Microvesicular
Steatosis

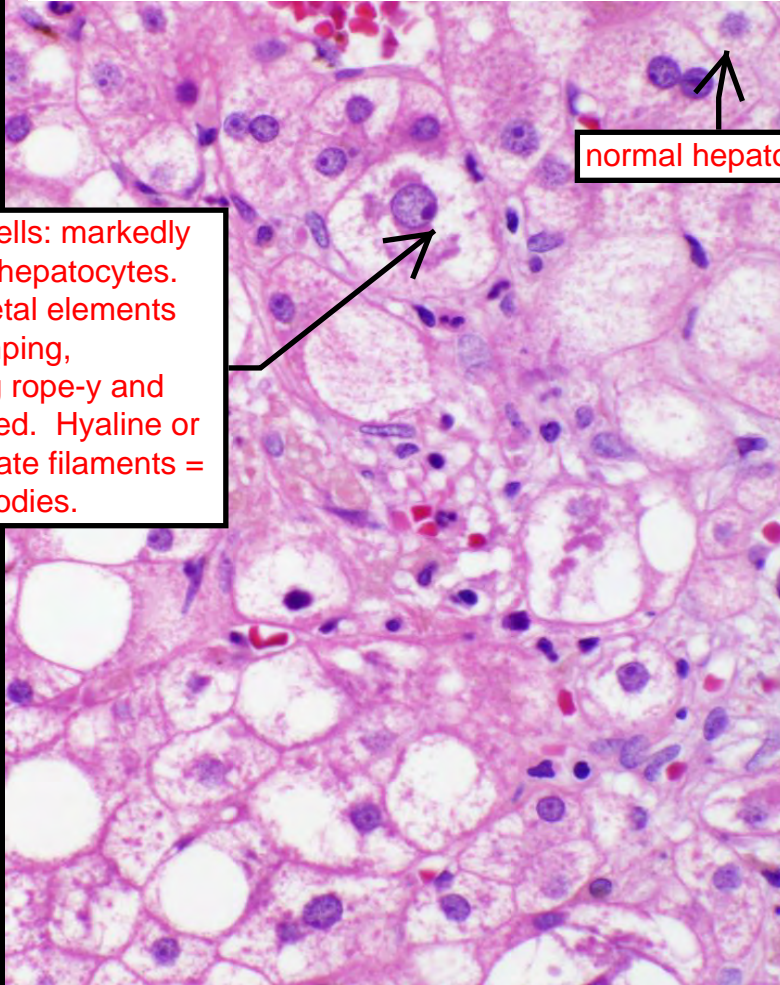
Definitions



Various forms of injury.

Left: balloon cells and Mallory bodies are the histological hallmark of steatohepatitis.

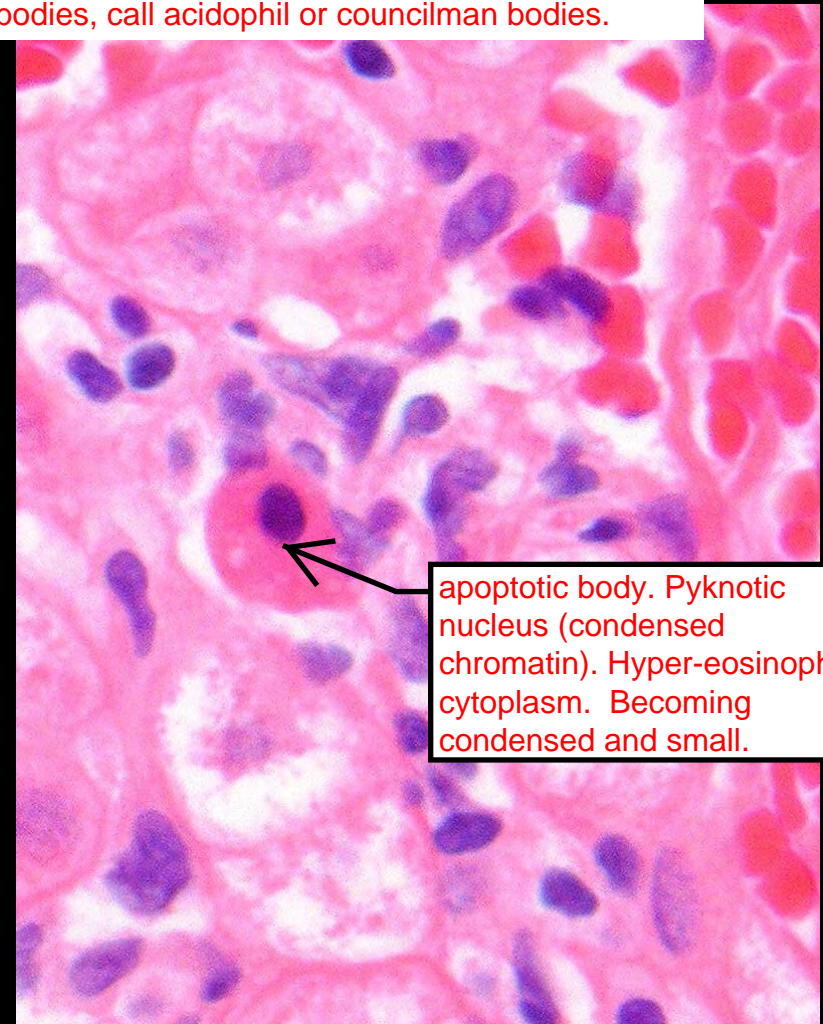
Right: dying hepatocyte. In the liver, don't call them apoptotic bodies, call acidophil or councilman bodies.



normal hepatocyte

balloon cells: markedly enlarged hepatocytes. Cytoskeletal elements start clumping, becoming rope-y and bi-quituated. Hyaline or intermediate filaments = Mallory bodies.

Balloon Cells with
Mallory Bodies



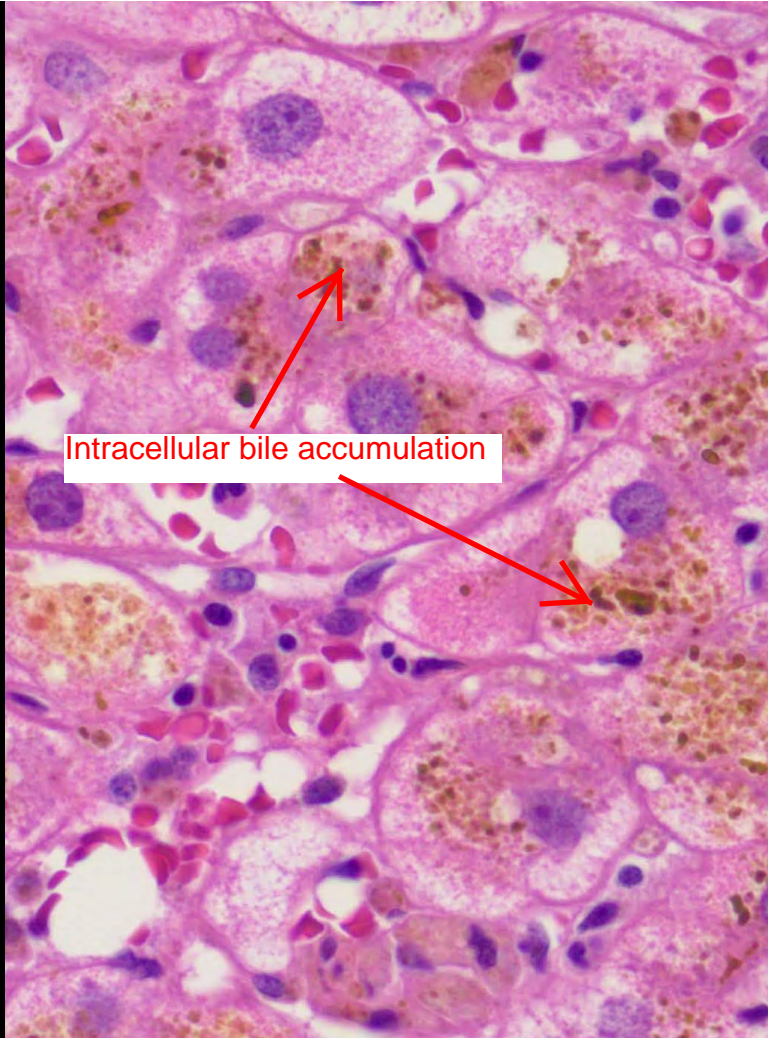
apoptotic body. Pyknotic nucleus (condensed chromatin). Hyper-eosinophilic cytoplasm. Becoming condensed and small.

Acidophil Body
(Councilman Body)

Cholestasis

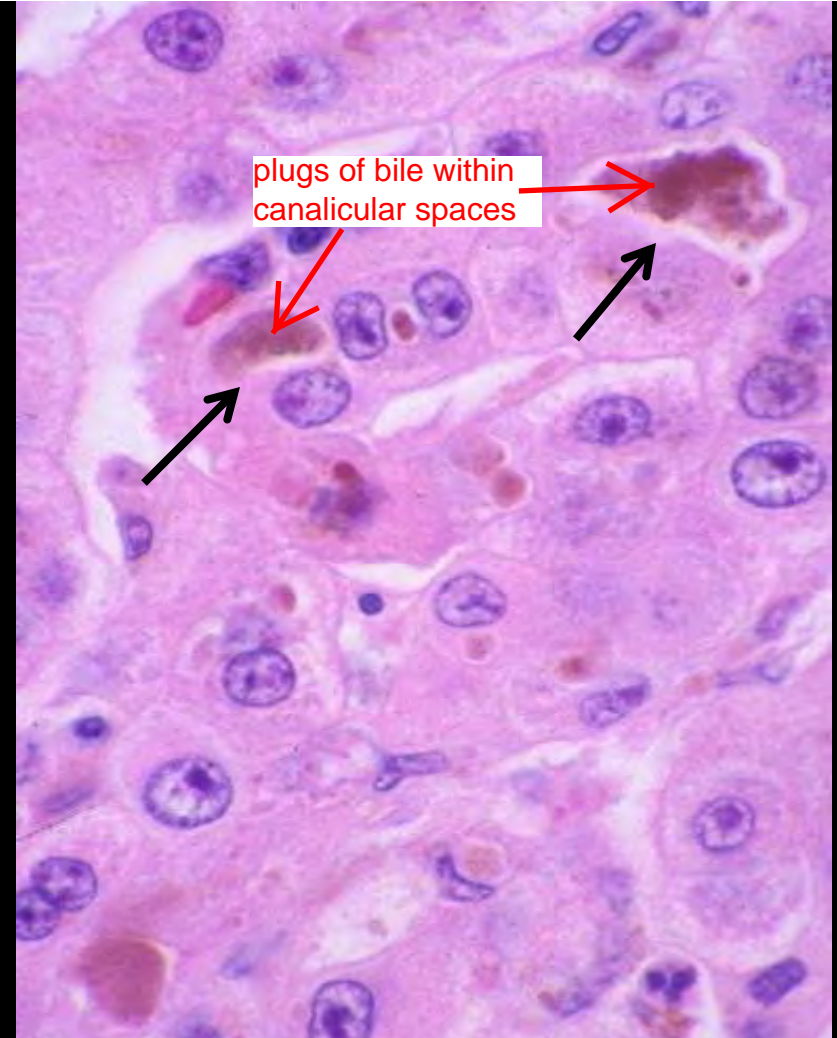


Hepatocytes form bile. If something happens to either interrupt the excretion into the canalicular spaces or the flow of bile through the biliary system, you'll have backup of the bile. This can occur either within the hepatocytes (L) or within the canalicular spaces (R).



Intracellular bile accumulation

Hepatocellular cholestasis



plugs of bile within
canicular spaces

Canicular cholestasis

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) Intracellular accumulations: fatty change, steatosis, iron accumulation
 - 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.

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

Hepatocyte Integrity

Hepatocellular enzymes

Both specific for hepatocyte injury.

Serum aspartate aminotransferase (AST)
Serum alanine aminotransferase (ALT)

Biliary

Substances secreted in bile

Normally bilirubin is excreted; if it starts accumulating, there is something wrong with the biliary system.

Serum bilirubin

Total: unconjugated plus conjugated

Direct: conjugated only

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

Serum alkaline phosphatase

Serum γ -glutamyl transpeptidase

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

Hepatocyte Function

Secreted proteins (blood)

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

Serum albumin ↓ in injury

Prothrombin time

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

Hepatocyte metabolism

Serum ammonia ↑ in injury

Ammonia = bad. Too much results in psychological changes, etc.
An increase means liver isn't metabolizing it.

Hepatocyte Injury



Various forms of hepatocyte injury:

- Infectious
 - Viral Hepatitis Most common form of injury - viral hepatitis
 - Others...
- Autoimmune Hepatitis
- Toxic/Drug Induced Injury
 - Alcohol
- Metabolic Injury
 - Non-Alcoholic Fatty Liver Disease (NAFLD) Epidemic of metabolic syndrome, obesity. This is a growing topic.
- Intracellular Depositions
 - Hemochromatosis
 - Alpha-1-antitrypsin
 - Wilson Disease
 - Metabolic disease (not addressed in this talk) Like glycogen storage disorders - not covered today

Viral Hepatitis



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

- Non-Hepatotropic:

- Epstein Barr Virus (EBV) **
 - Sinusoidal lymphocytosis
 - PTLPD
- Cytomegalovirus (CMV) Seen in immunocompromised patients. Results in hepatitis.
 - Post-transplant infection
- Herpes Simplex Virus (HSV)
 - Overwhelming infection/necrosis Fulminant, overwhelming hepatitis.
- 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.

	HAV	HBV	HCV	HDV	HEV
Agent	ssRNA	<u>dsDNA</u>	ssRNA	ssRNA	ssRNA
Transmission	<ul style="list-style-type: none">•Fecal•Oral contaminated food	<ul style="list-style-type: none">•Parenteral•Sexual contact•Perinatal•Needle stick	<ul style="list-style-type: none">•Parenteral•Sexual contact•Needle stick	<ul style="list-style-type: none">•Parenteral•Sexual contact	<ul style="list-style-type: none">•Water-borne

Notes:

B-D: IV drug use, sexual contact, occupational exposure (needles).

B: perinatal (through delivery).

Clinical Syndromes



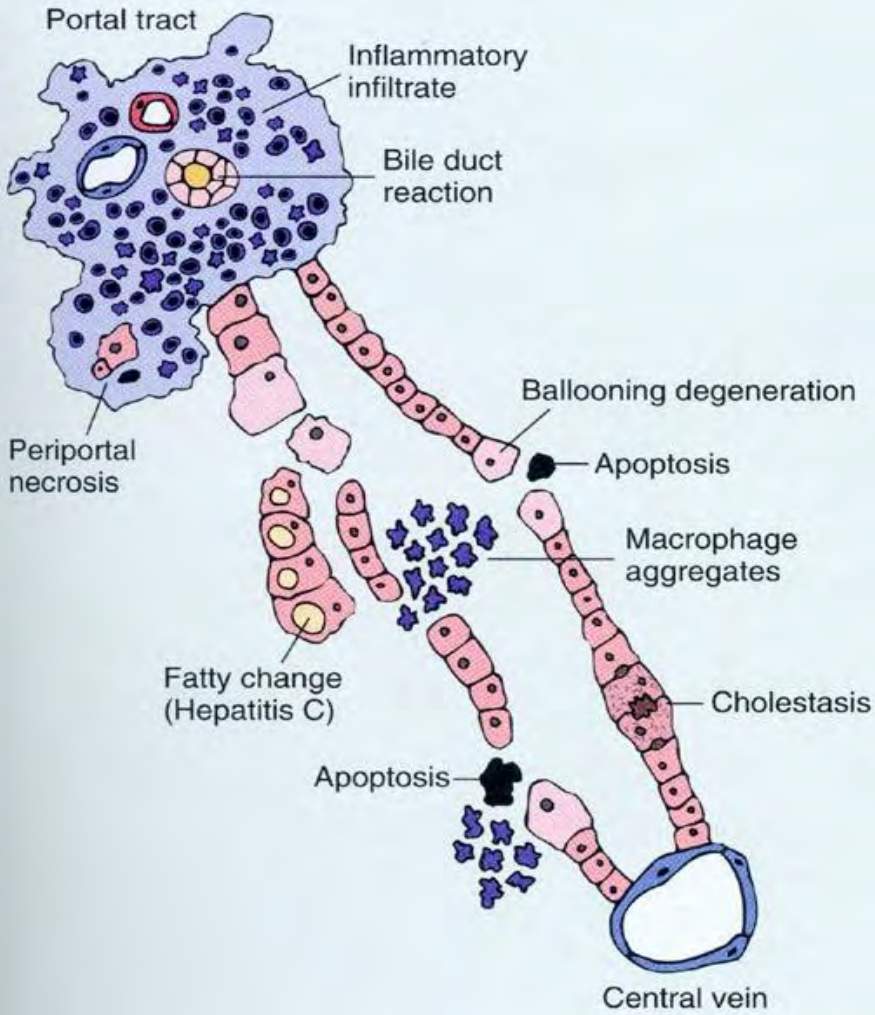
- Acute hepatitis- asymptomatic with recovery
 - HAV and HBV infection during childhood
- Acute hepatitis- symptomatic with recovery
 - Uncommon for HCV
- Chronic hepatitis Chronic: either relapsing/remitting or continuous - HepC, sometimes B. NOT A or E.
 - Continued or relapsing disease for > 6 months
 - Hallmark of HCV
- Fulminant hepatitis Fulminant: patient presents acutely, and within a few weeks they need a liver transplant emergently.
 - 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 organismCarrier: usually E. Infection, asymptomatic. Liver full of the virus, and constantly shedding.

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

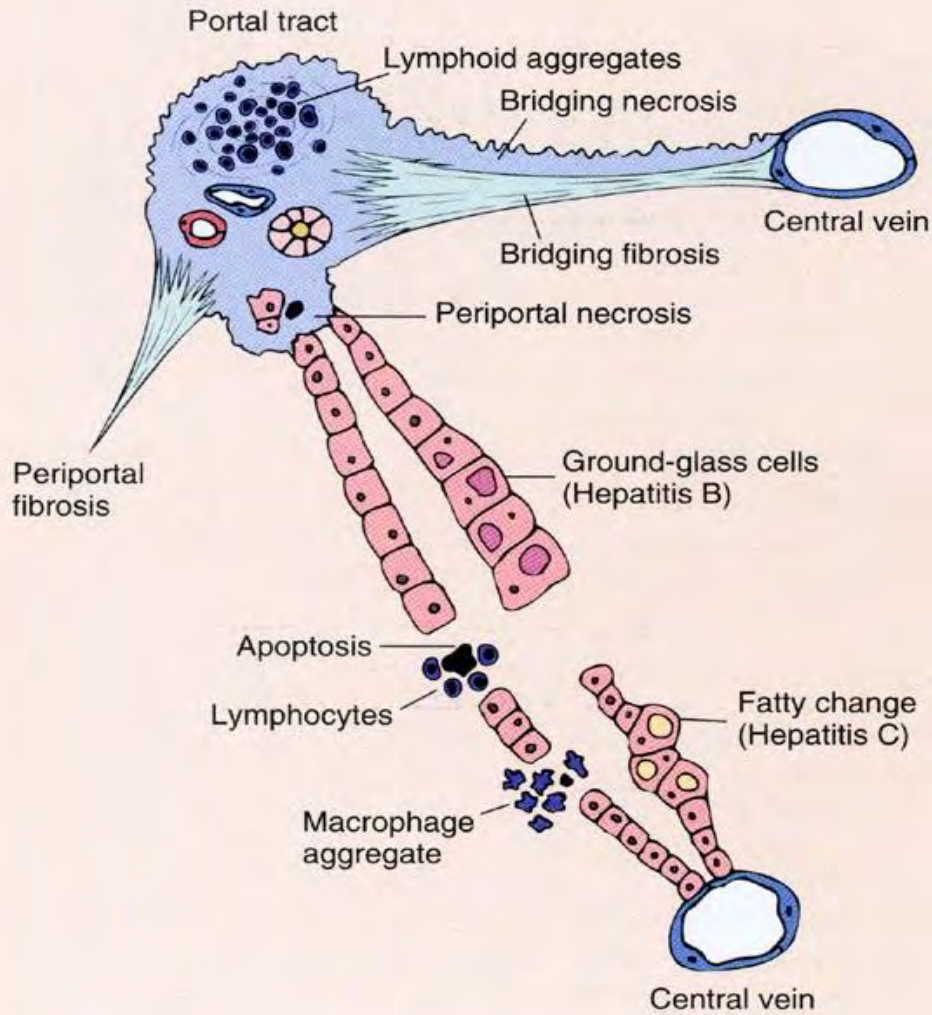
Acute: portal, or portal + interface hepatitis. Portal tract with inflammatory cells. Extends beyond limiting plate, causing hepatocellular injury. Old terminology: piecemeal necrosis. Lobular injury: inflammation and injury of the hepatocytes - Councilman bodies, balloon cells, etc.

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.

ACUTE HEPATITIS



CHRONIC HEPATITIS

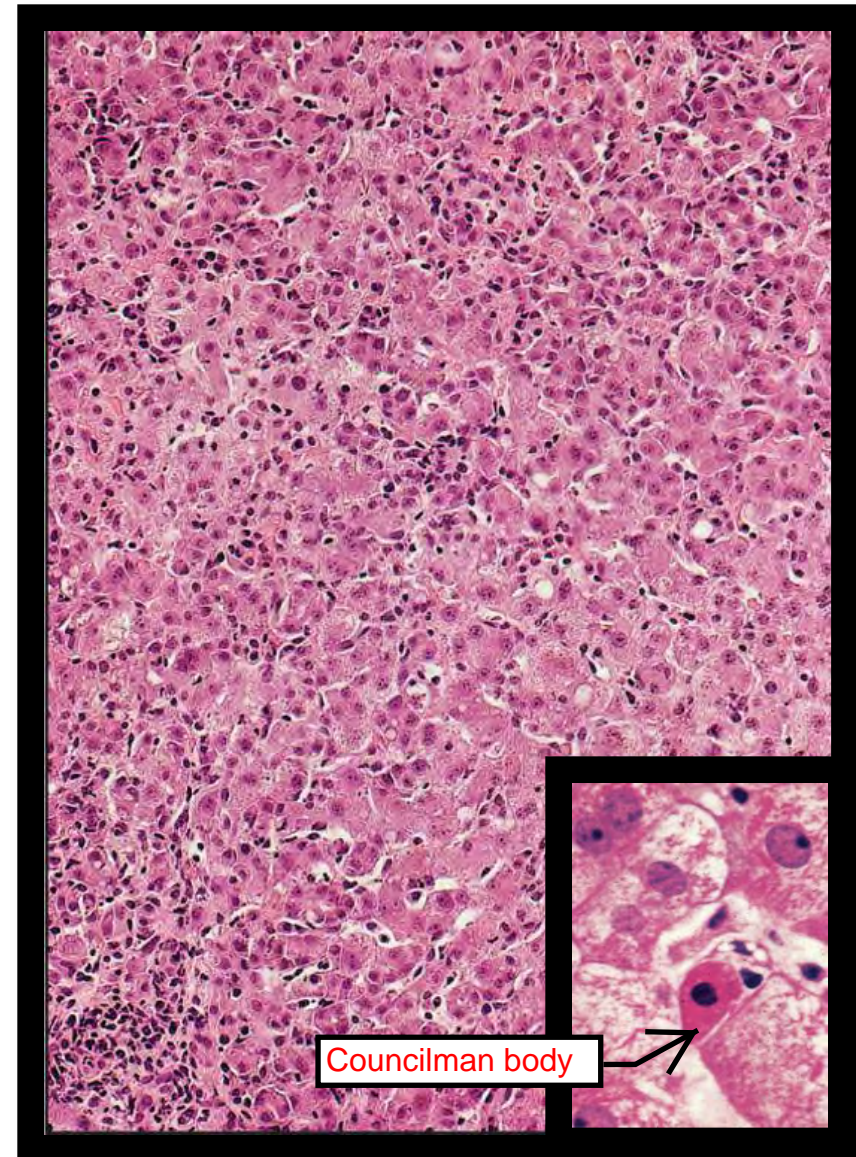


Hepatitis A

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.

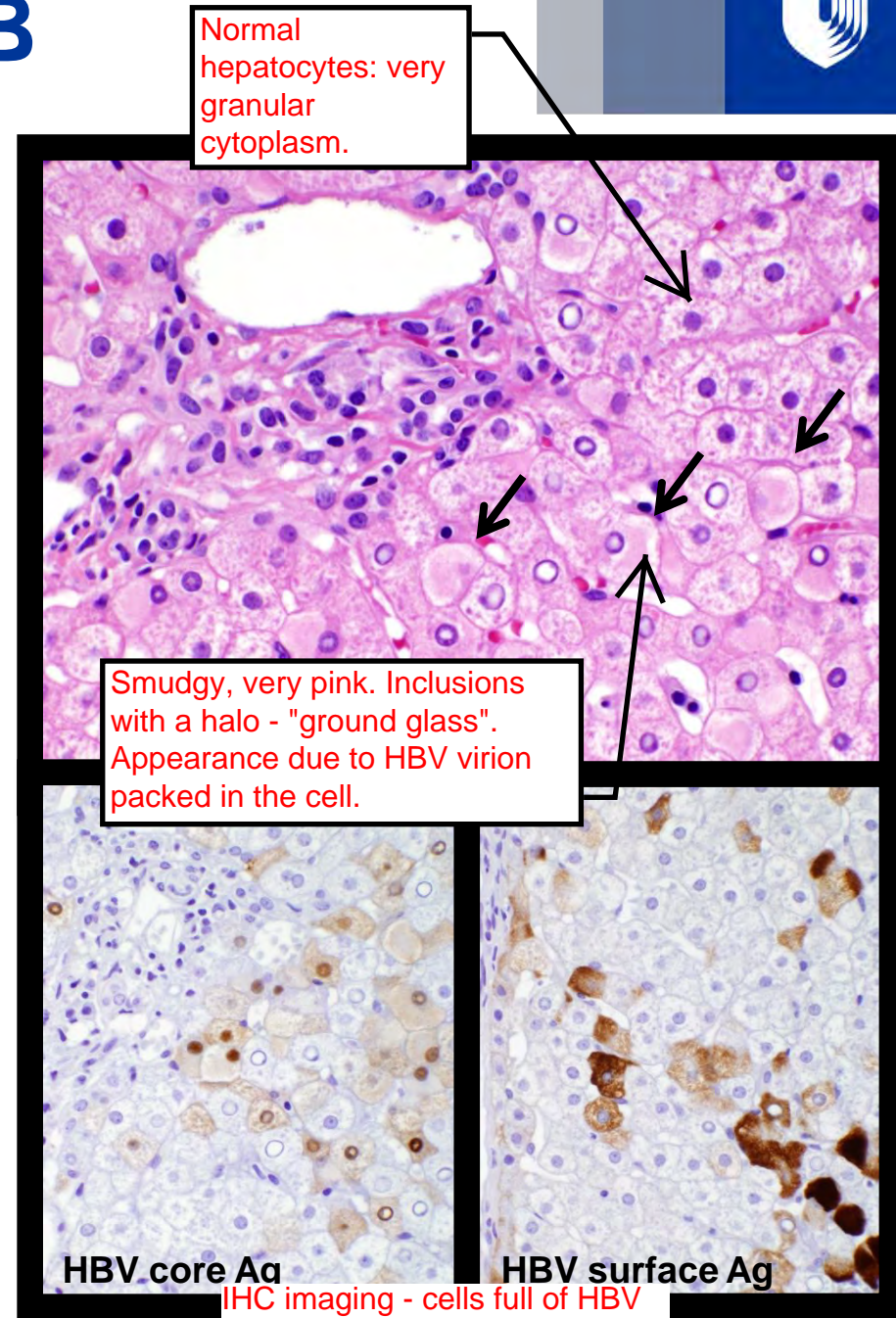


Hepatitis B

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 Carrier state is unique for HBV.
 - Asymptomatic but infectious
 - „Ground glass” cytoplasmic inclusion of virions (*arrows*)

Shedding disease, very infectious.



Hepatitis C

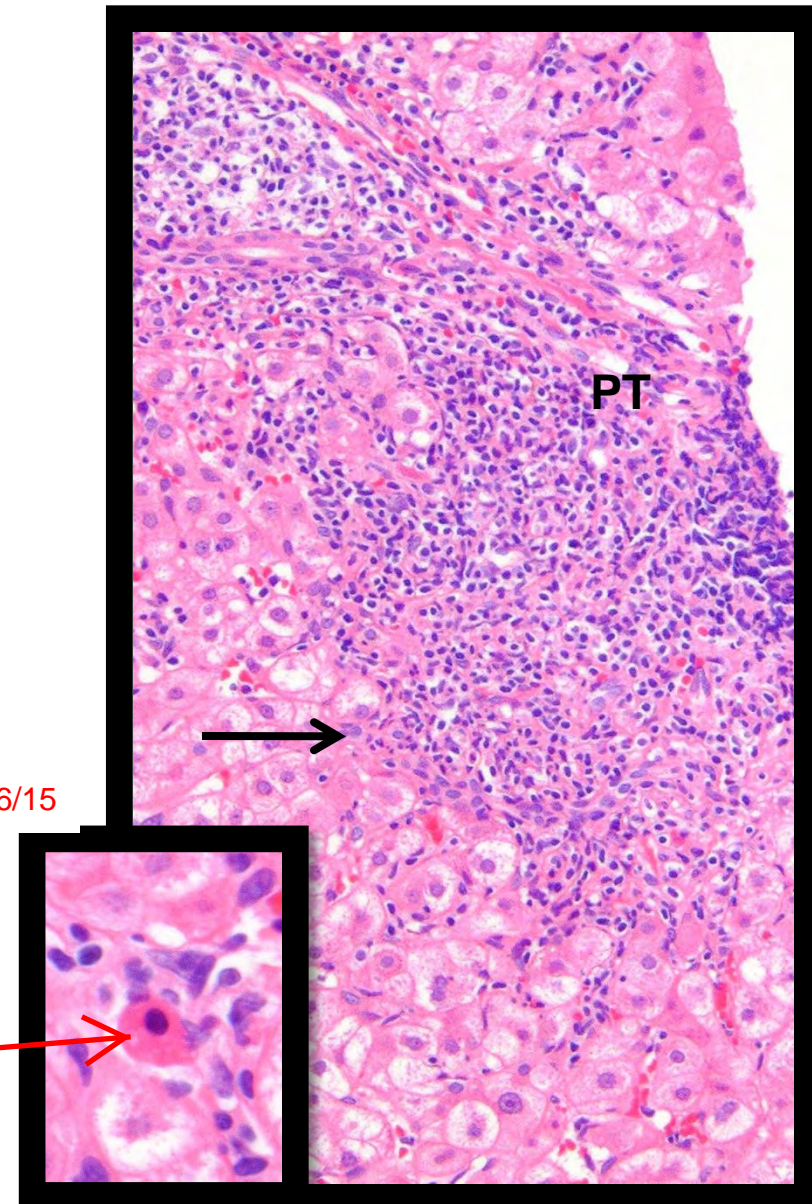


Unlike HBV which is going down due to vaccine, HCV is still a major disease cause. Causes a much higher rate of chronic infection.

- 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 We'll hear more on 6/15
 - 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



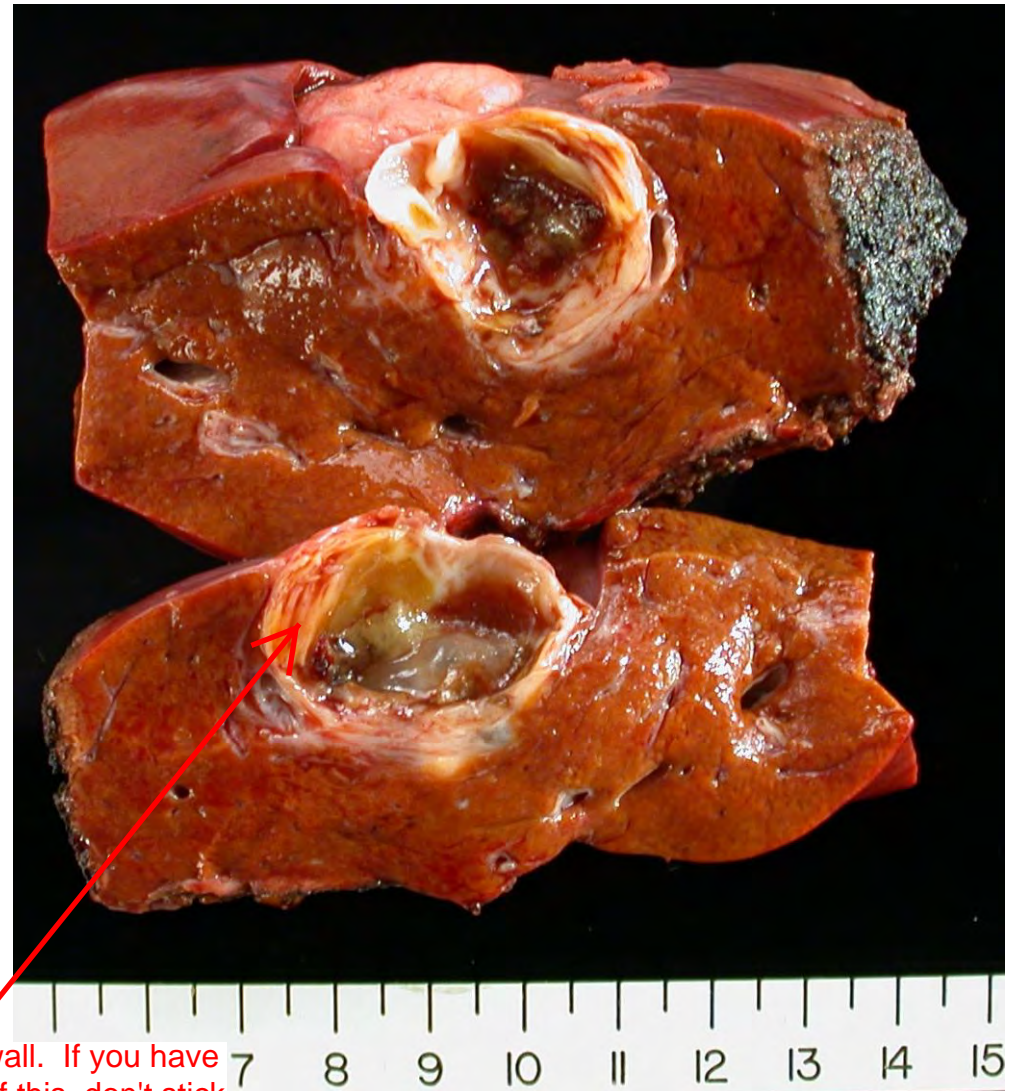
- Bacterial
 - Spirochetes

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 Exposure can elicit a reaction.
 - HLA DR3 and DR4
 - ANA and Anti-smooth muscle Ab (ASMA) (Type 1) Type 1 most common - 80% of pts
 - +/- 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.

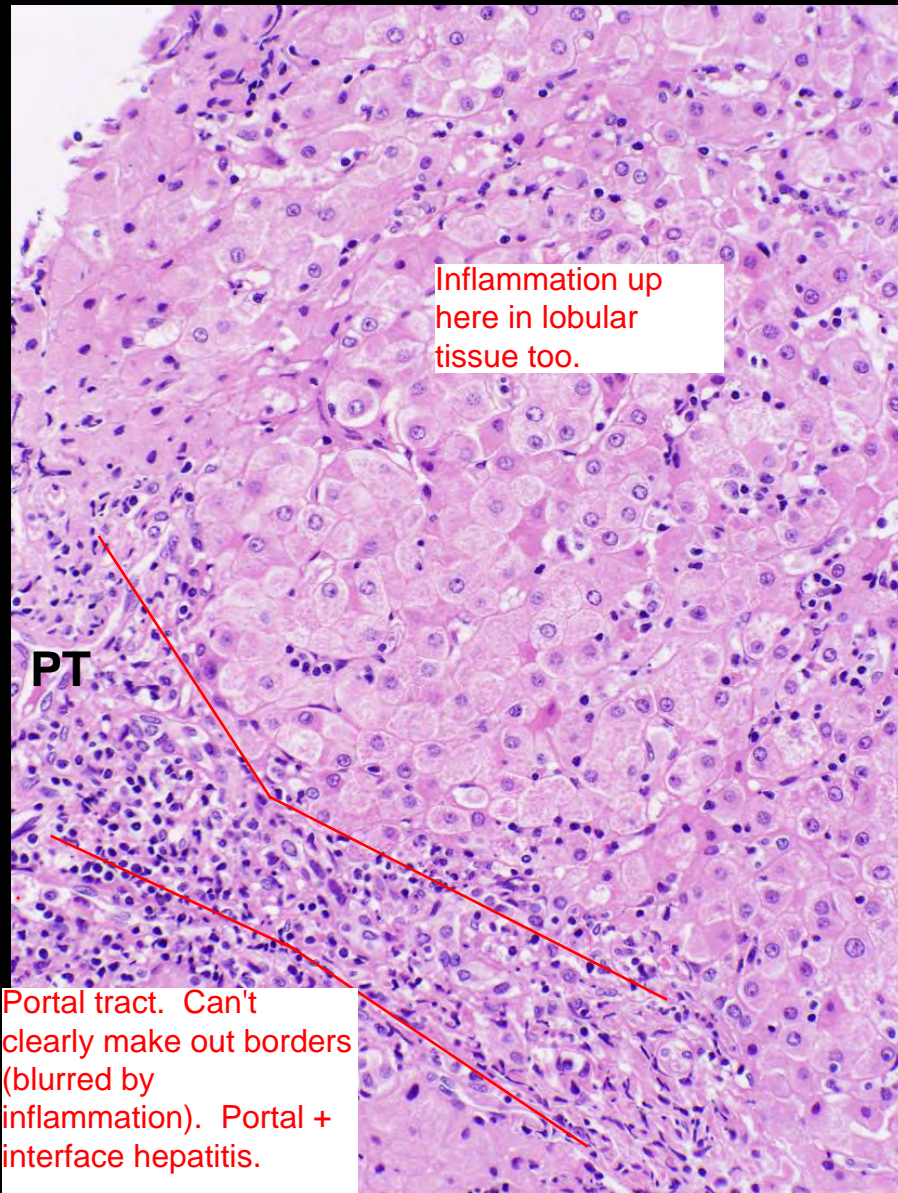
Autoimmune Hepatitis



- 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.

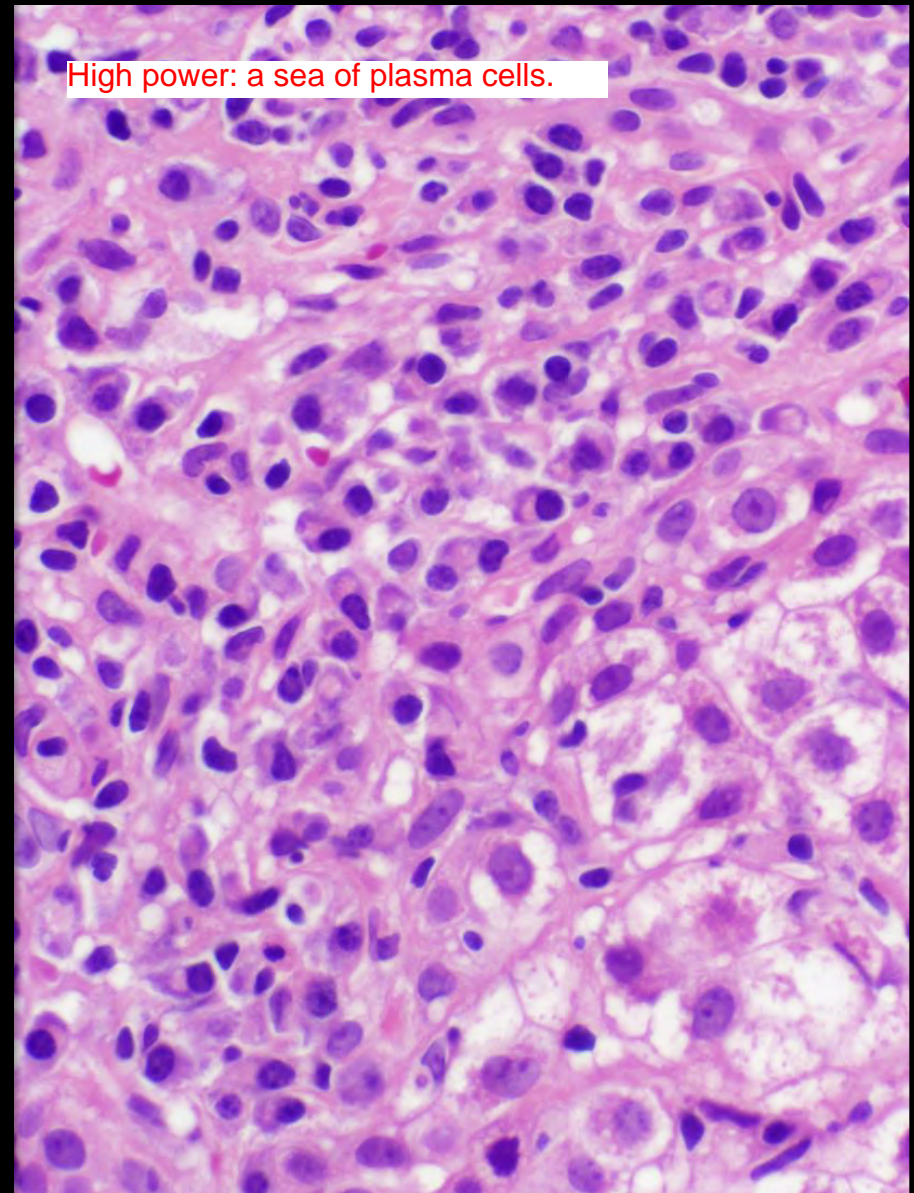
Autoimmune Hepatitis



Inflammation up here in lobular tissue too.

PT

Portal tract. Can't clearly make out borders (blurred by inflammation). Portal + interface hepatitis.



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 ($\geq 2:1$)

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 $\xrightarrow{\text{ADH}}$ Acetaldehyde $\xrightarrow{\text{ALDH}}$ Acetate these can also convert EtOH to acetaldehyde.
- Oxidizing system (CytP450, ER) and Catalase (peroxisomes)
- Acetaldehyde: nausea, reactive intermediate
- Ethanol: affects protein synthesis, membrane integrity EtOH itself is toxic.
- 50% of Asians have low ALDH.

- Net effects of excess intake:

- Metabolism diverted: NADH equivalents \rightarrow 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

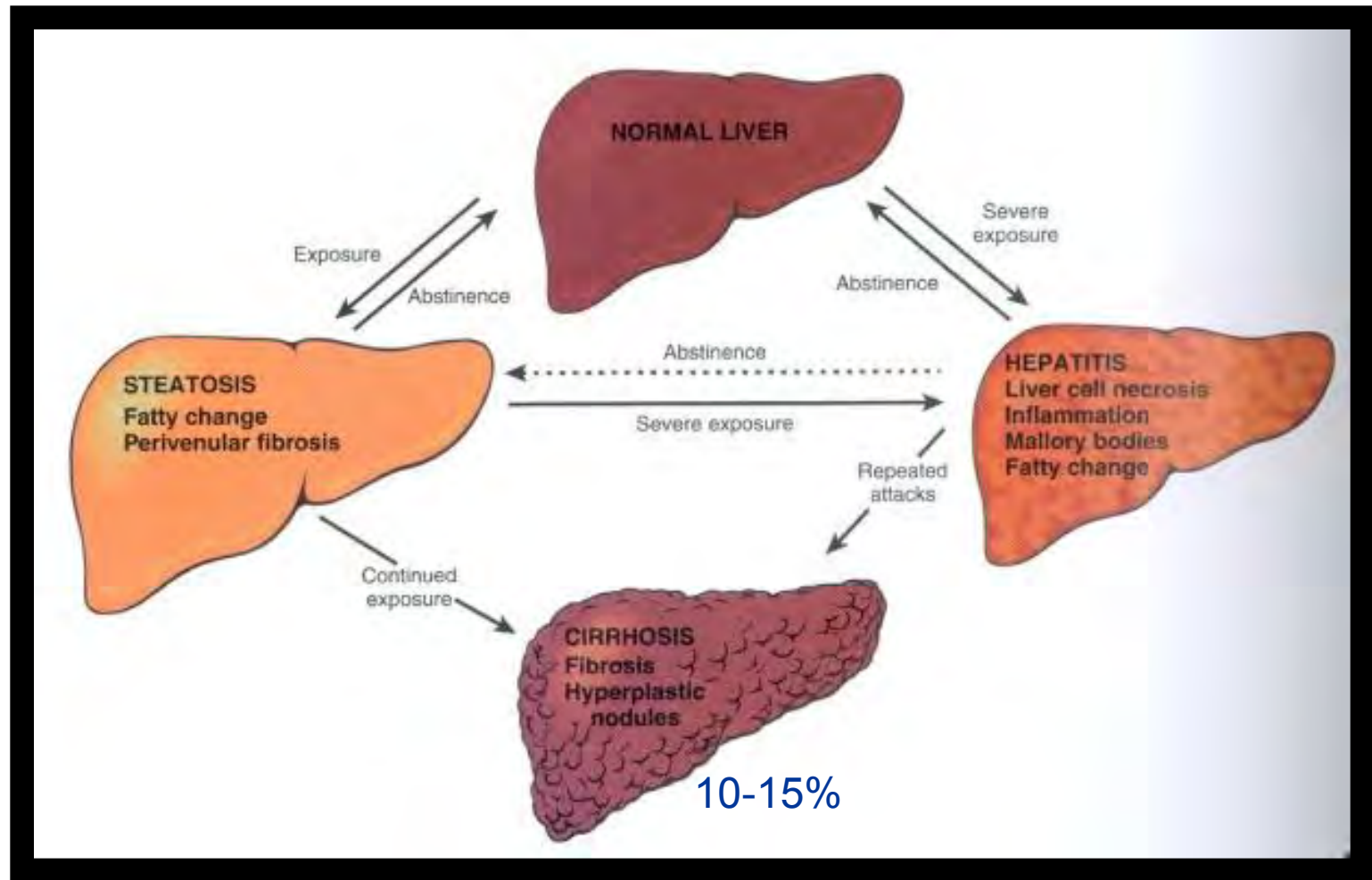
ADH: alcohol dehydrogenase

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**

Alcohol (Toxic) Related Injury



Morphology

Fatty liver is reversible.

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

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.

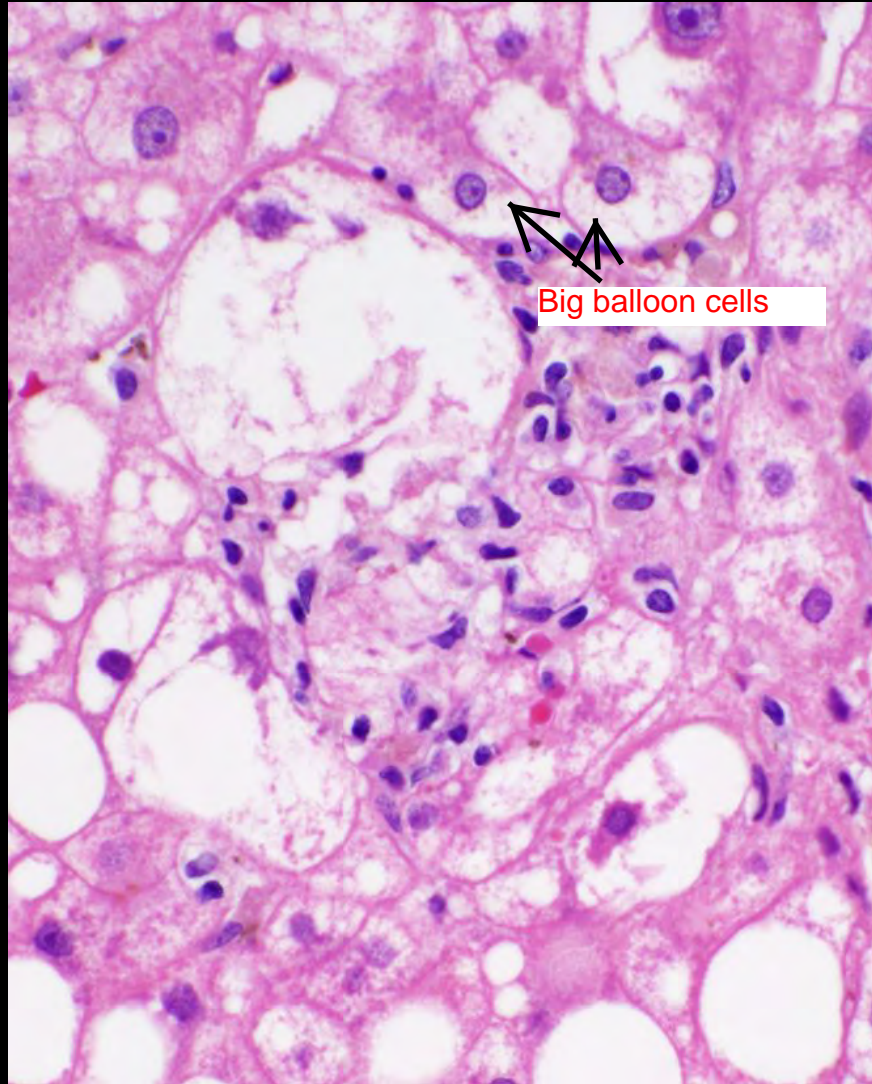
- Strong association with the metabolic syndrome:
 - Obesity, hyperlipidemia, hypertension and insulin resistance
 - Little to no alcohol consumption
- Estimated that ~24% of the US population has NAFLD
 - With the global “obesity epidemic” (affecting adults and children), it is estimated that the prevalence 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

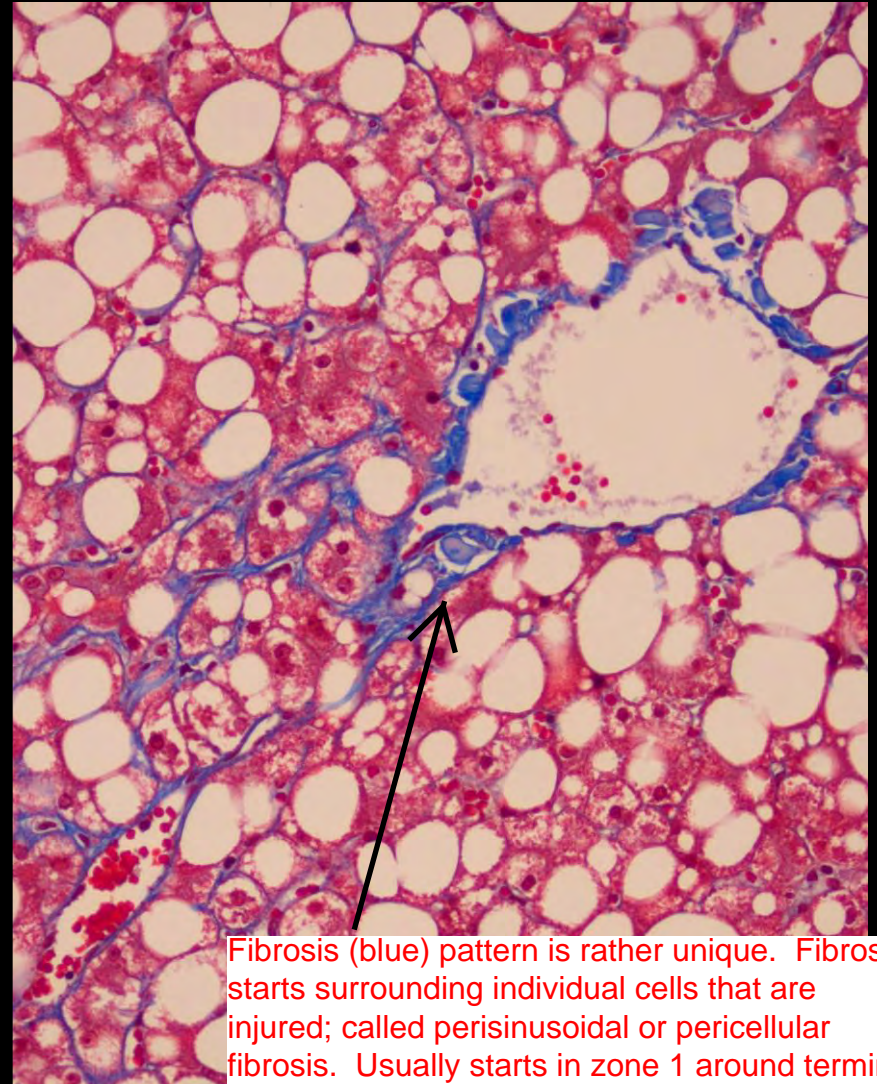


Same thing as seen
with alcoholics.

Progression 



Big balloon cells



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



Residual normal
portal tract and
some hepatocytes

Dead tissue -
Tylenol toxicity

Residual central vein

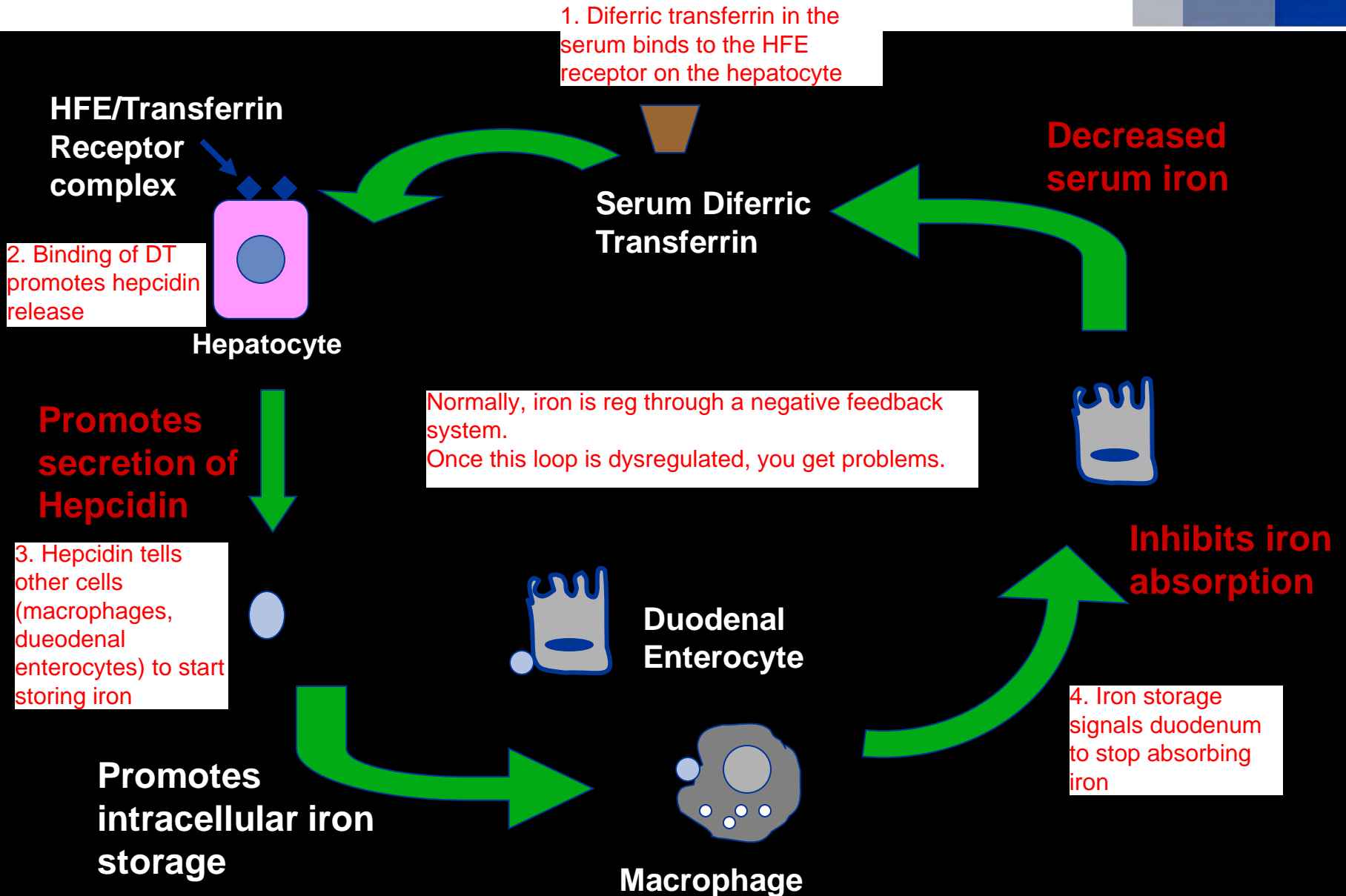
Acetaminophen toxicity

Anisonucleosis -
variability in
nuclear size

Steatohepatitis

Methotrexate toxicity

Normal Iron Homeostasis



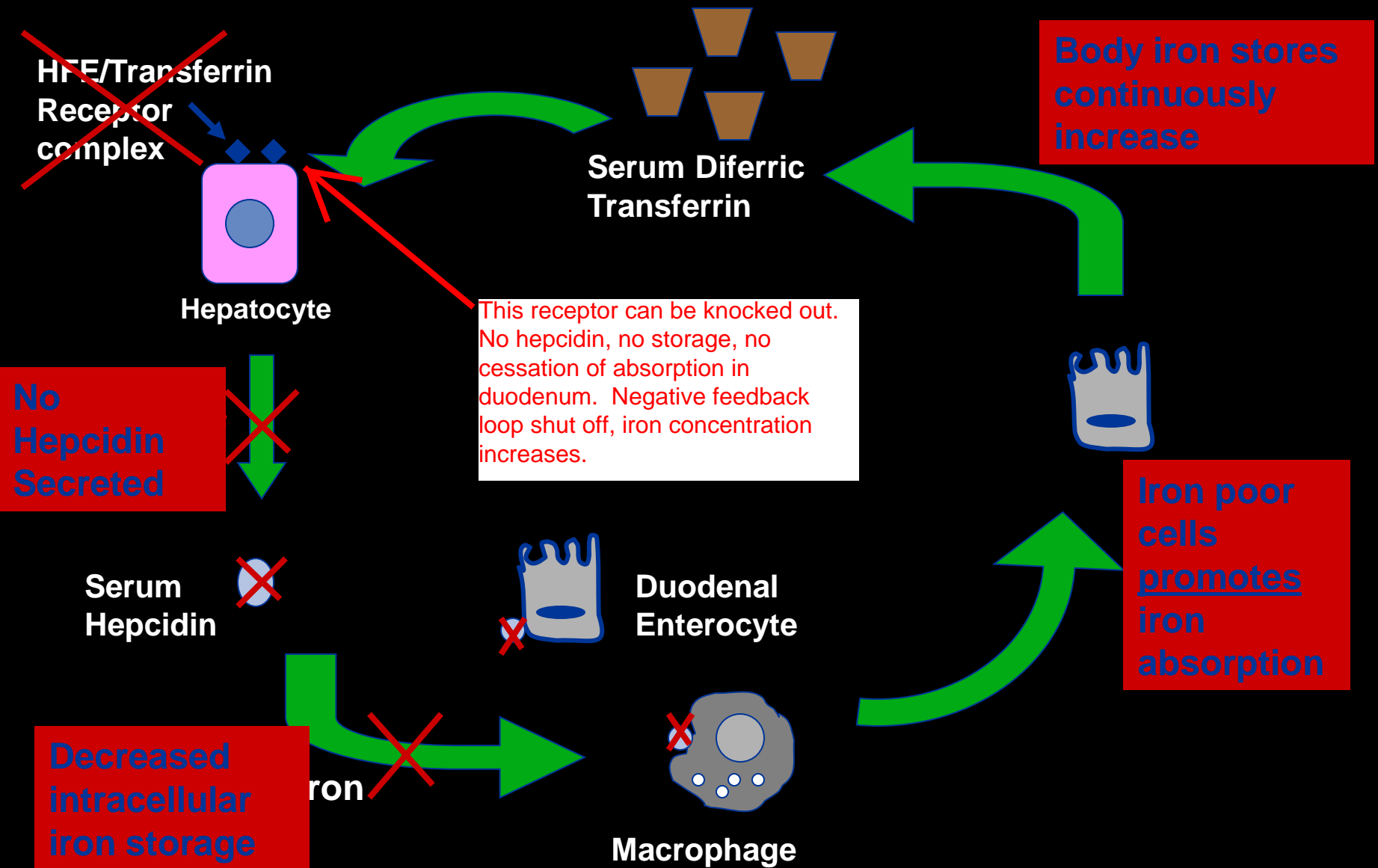
Hemochromatosis



- 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.

Ab Normal Iron Homeostasis



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

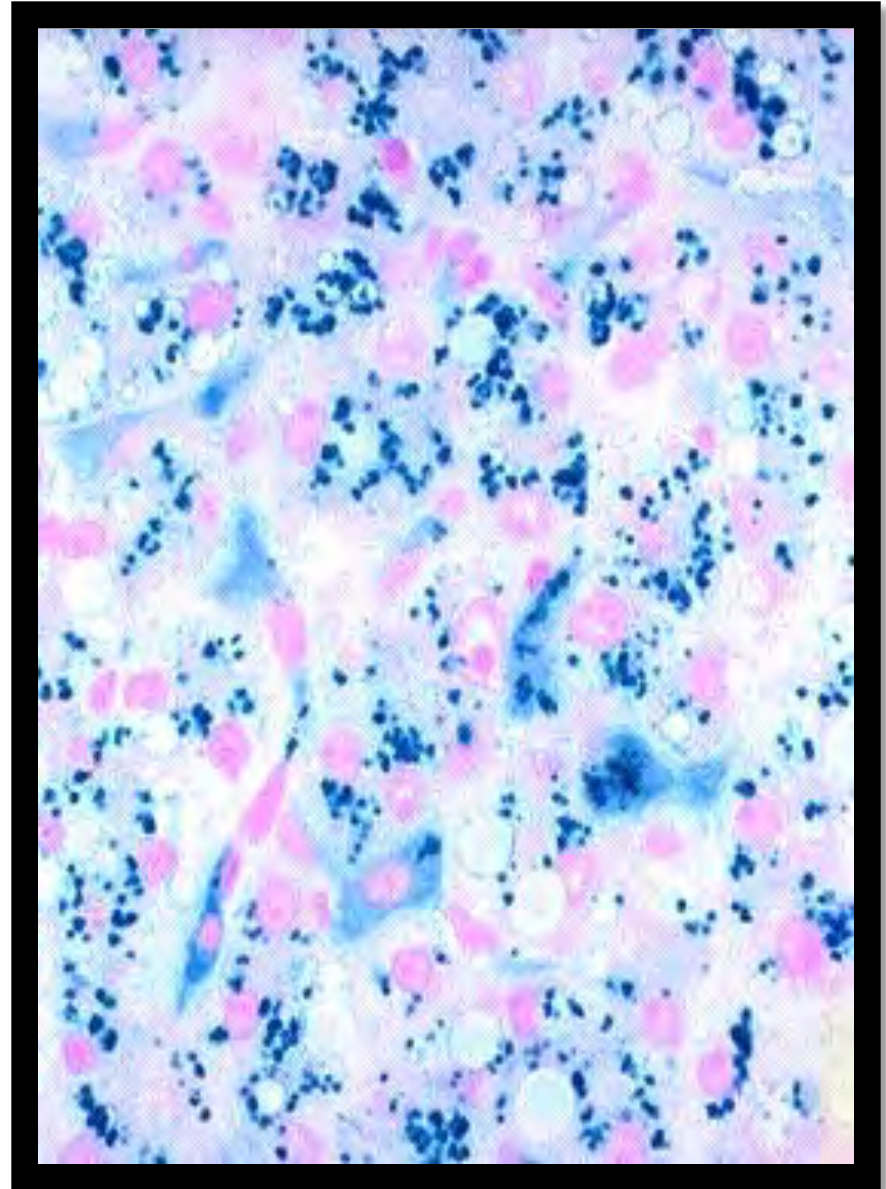
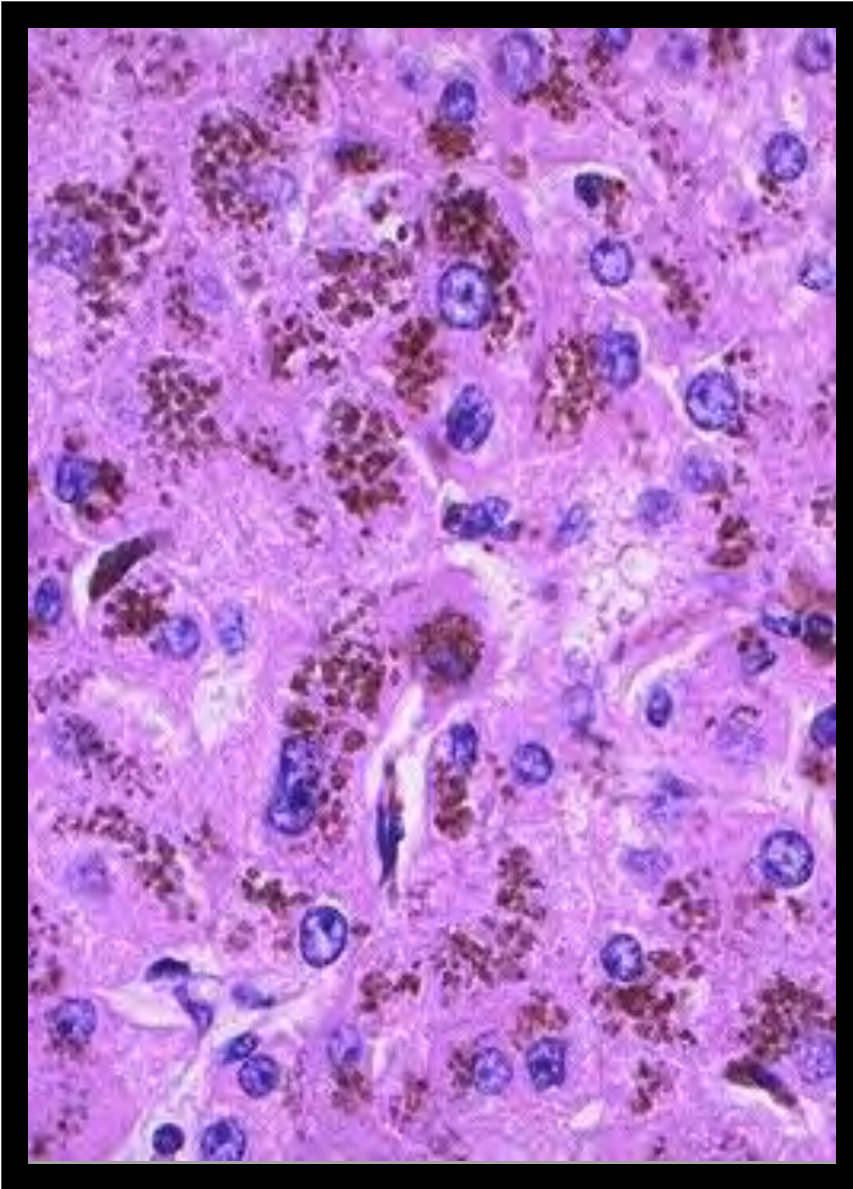


Morphology

- 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

Remember emphysema?



- 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.

Genetics

M	MM
Z	ZZ
	MZ
S	MS
	SZ

Serum A1AT Levels

100%
10%
60%
80%
40%

Disease Associations:

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

Alpha-1-Antitrypsin Deficiency

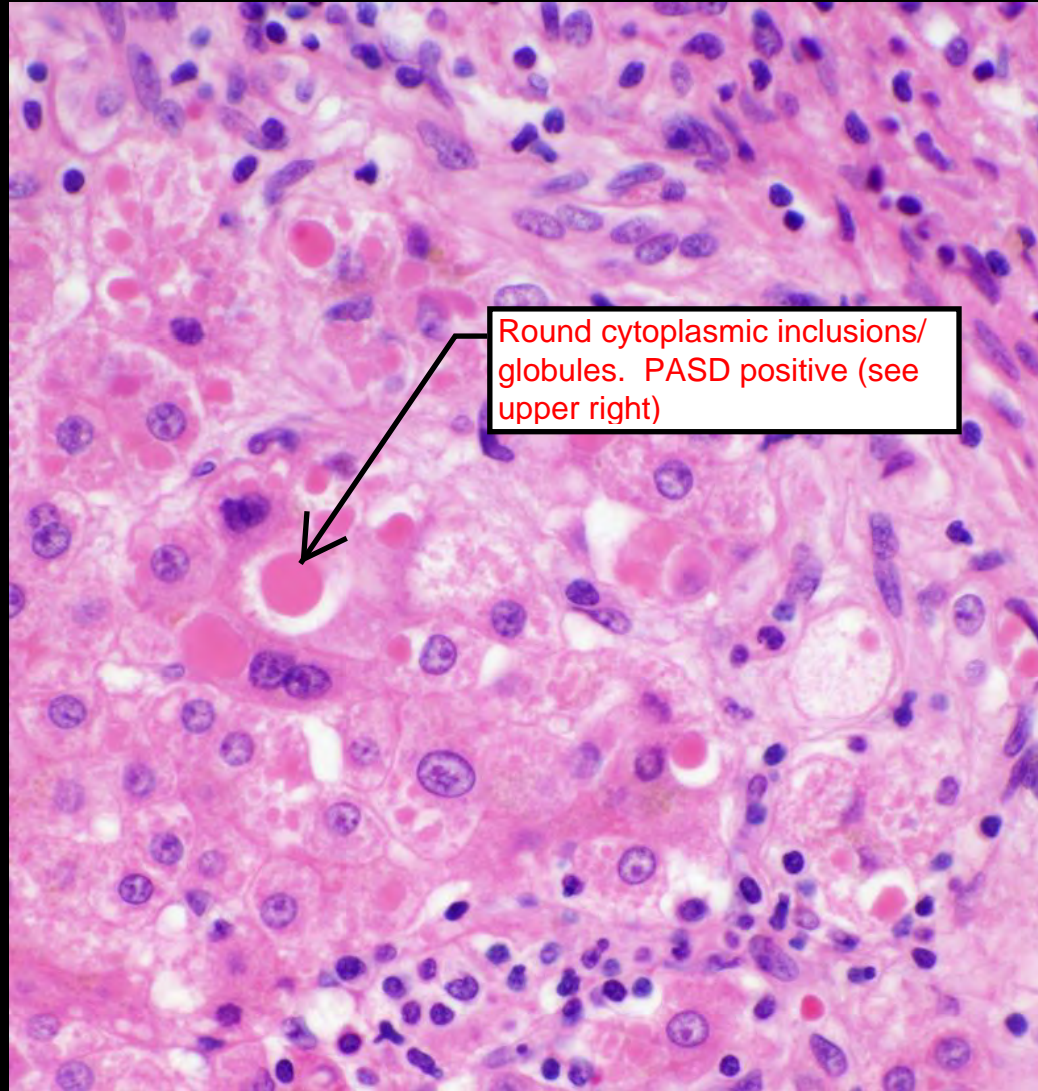


- Hepatic syndromes are extremely variable ranging from neonatal hepatitis, childhood cirrhosis and subclinical chronic hepatitis Chronic hepatitis in adults.
- Treatment:
 - Transplant (curative) You have removed the liver that can't excrete alpha-1-antitrypsin, new liver can.

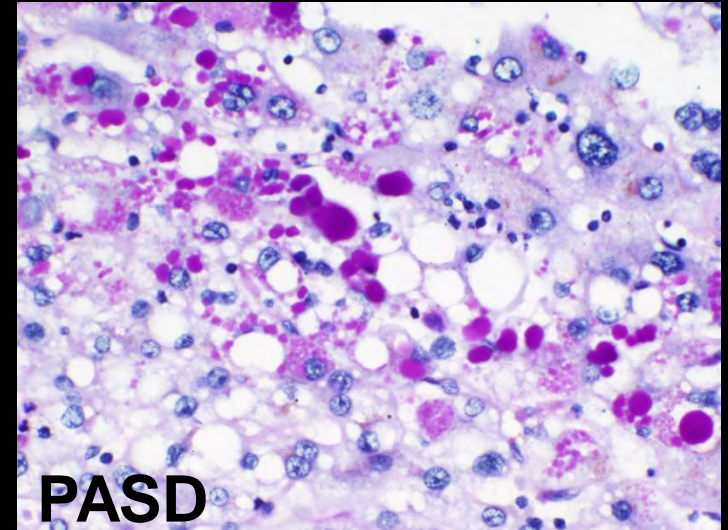
Morphology

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

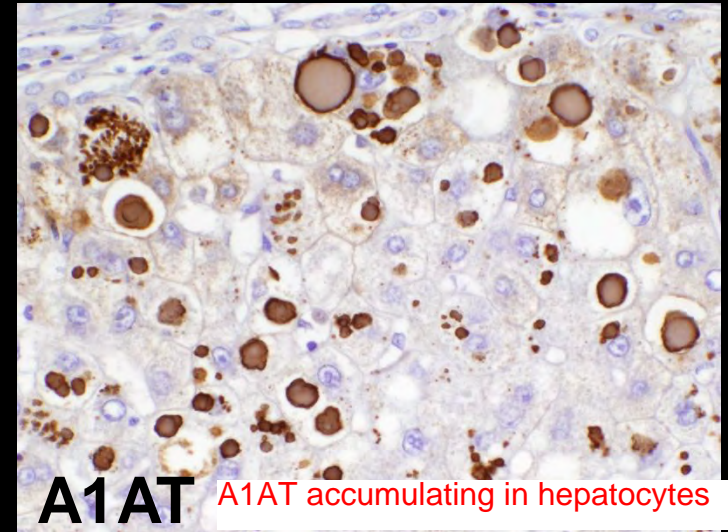
Alpha-1-Antitrypsin Deficiency



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



PASD



A1AT

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”)

Willson Disease blocks the excretion of copper in the bile (at the end of this cycle)

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-penicillamine)
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



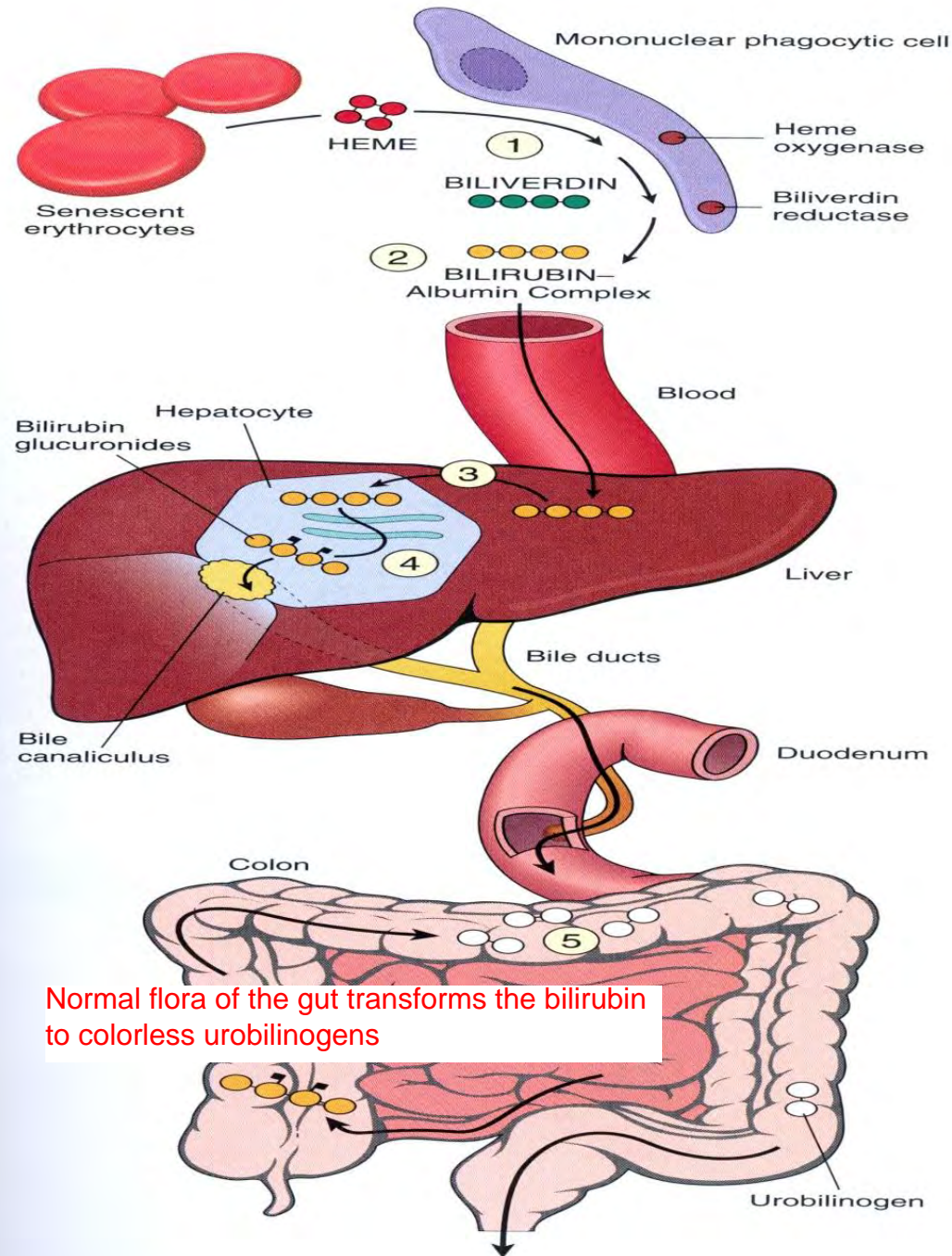
- Hepatic bile serves 2 major functions
 1. Elimination of bilirubin, cholesterol, and non-water soluble wastes
 2. Bile salts promote emulsification and absorption of dietary fat in the gut

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 it undergoes conjugation and becomes water-soluble and excreted into the bile goes through glucoronidation via UGT1A1
 - 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

Like most autoimmune disorders: middle-aged women.

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
- Treatment:
 - Symptomatic (i.e. Ursodial)
 - Liver transplantation

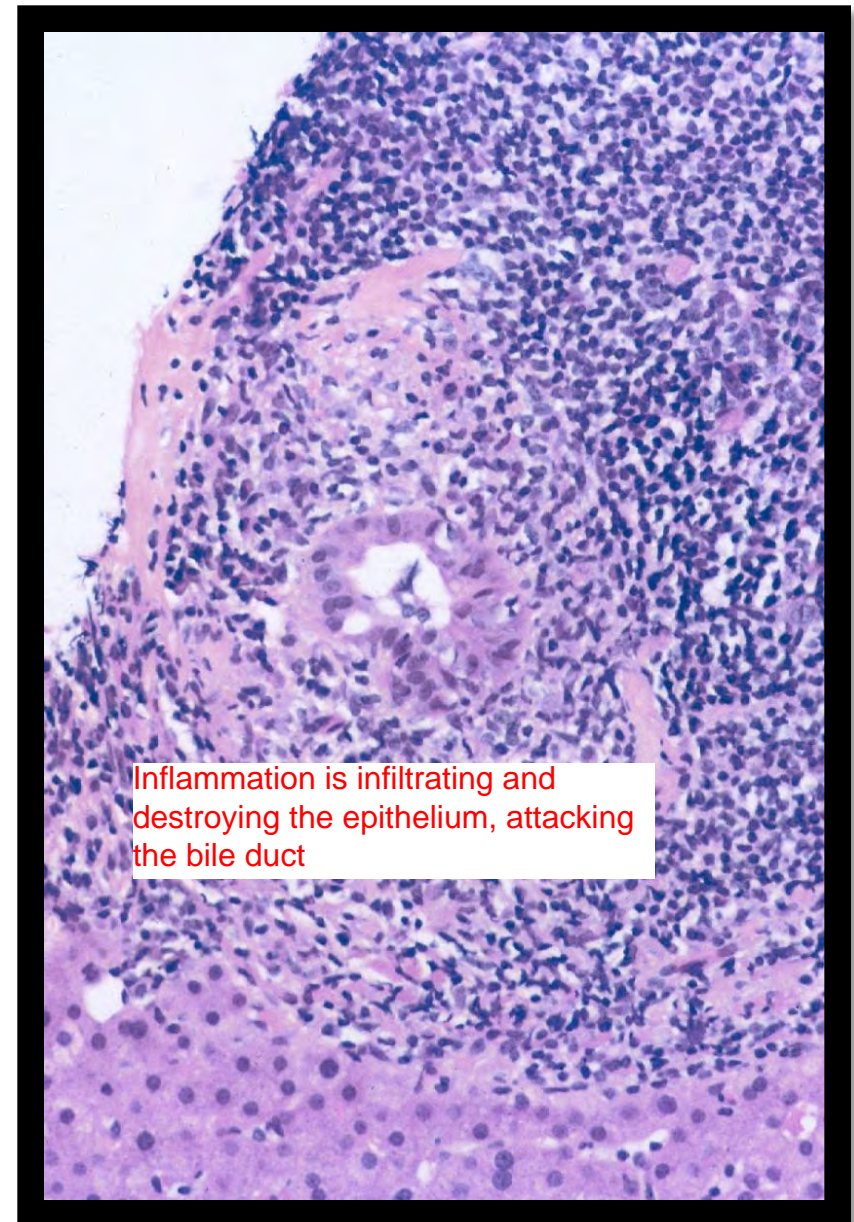
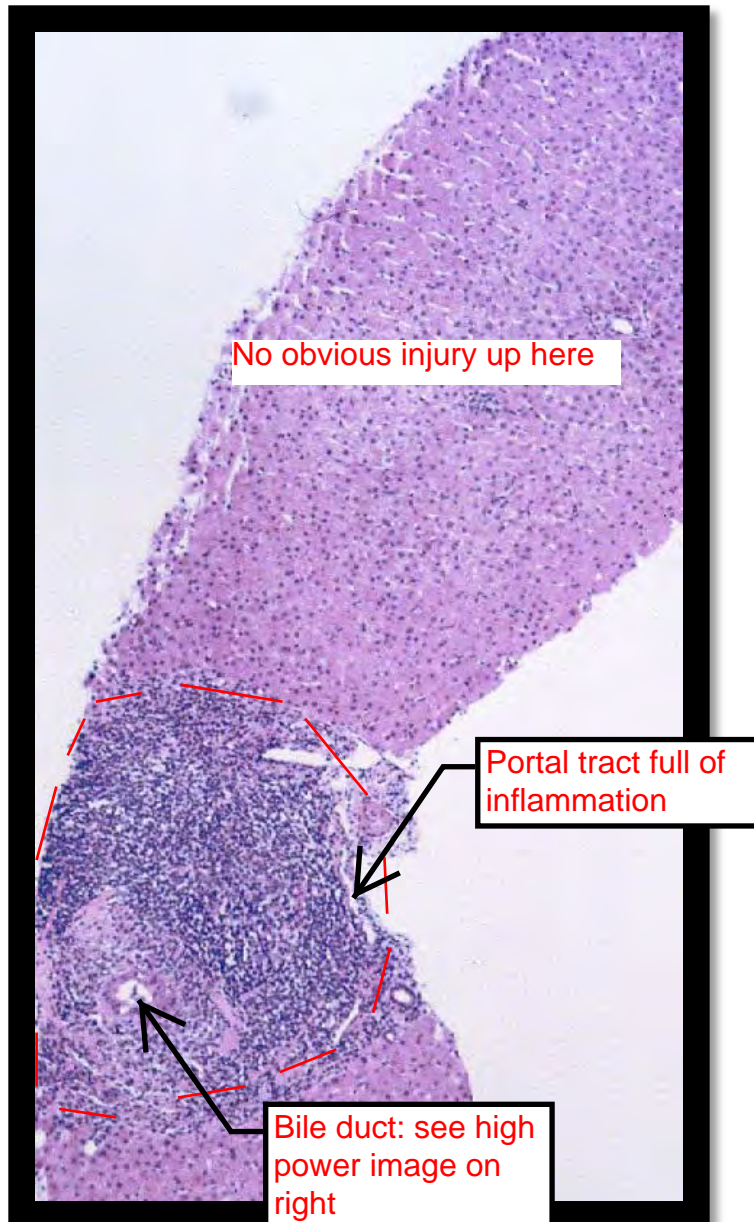
Pruritis (itchiness) due to cholestasis

Inflammation attacking the bile ducts specifically

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).

Potentially also immunosuppression

Primary Biliary Cirrhosis



Primary Sclerosing Cholangitis



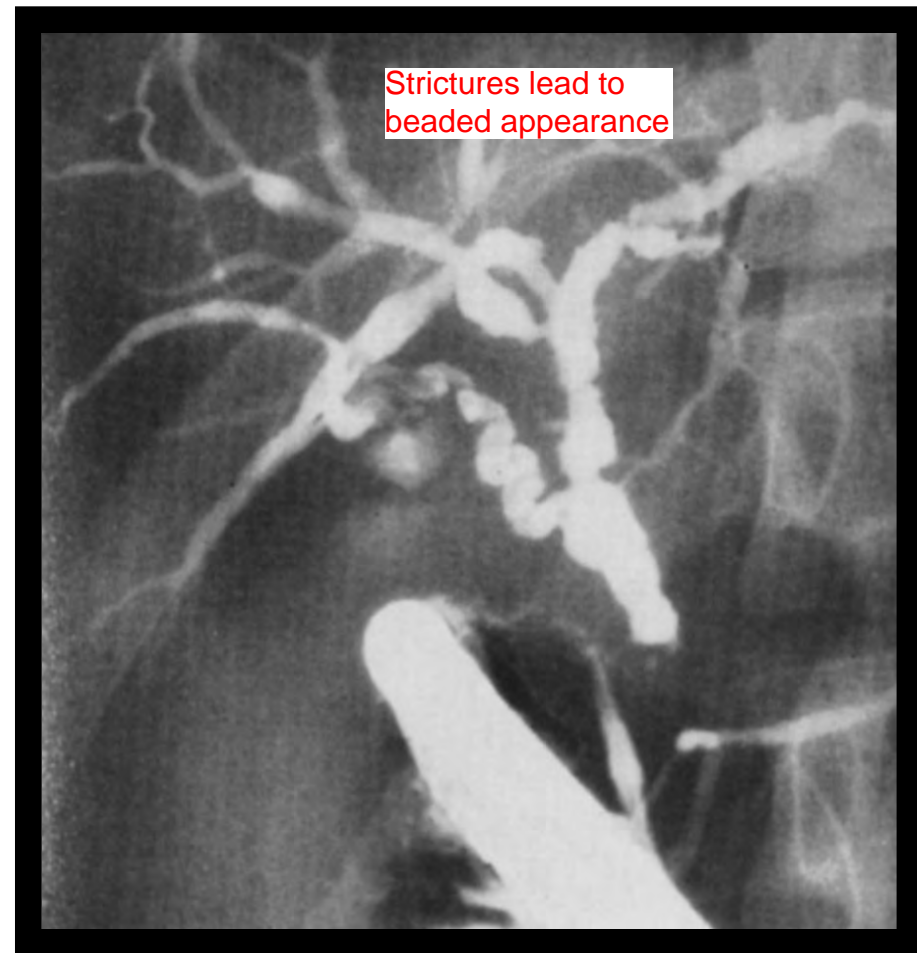
The big differential: PBC from PSC.

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
- 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)

LFTs aren't really going to help you



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)

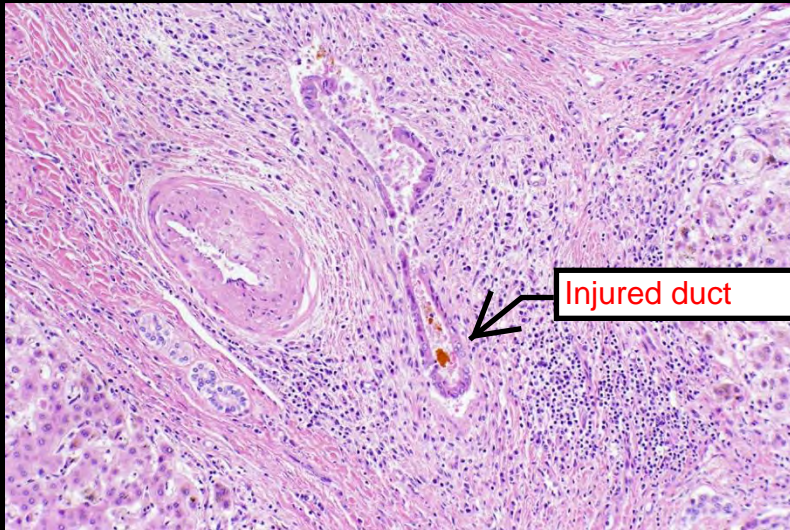
Primary Sclerosing Cholangitis



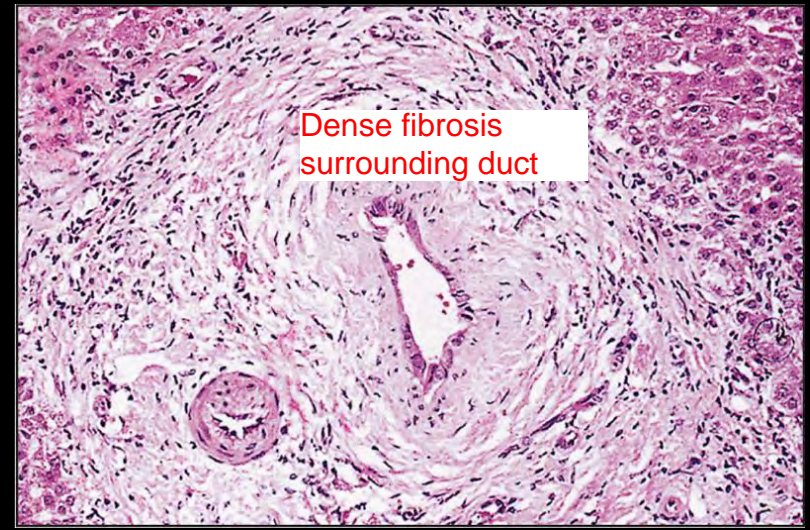
- Etiology and pathogenesis are largely unknown
 - Autoantibodies are present in <10% of patients
 - Not generally considered an autoimmune disease; no autoantibodies specific for PSC
- Clinical Non-specific symptoms
 - Symptoms include **fatigue, pruritis**
 - Progressive clinical course which can lead to **biliary cirrhosis**
 - Marked increased risk for **cholangiocarcinoma** Independent risk factor for bile duct carcinoma
- Morphology:
 - Concentric periductal **“onion skin” fibrosis** which leads to fibrous obliteration of the duct A fibrotic process, not primarily inflammatory
 - 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



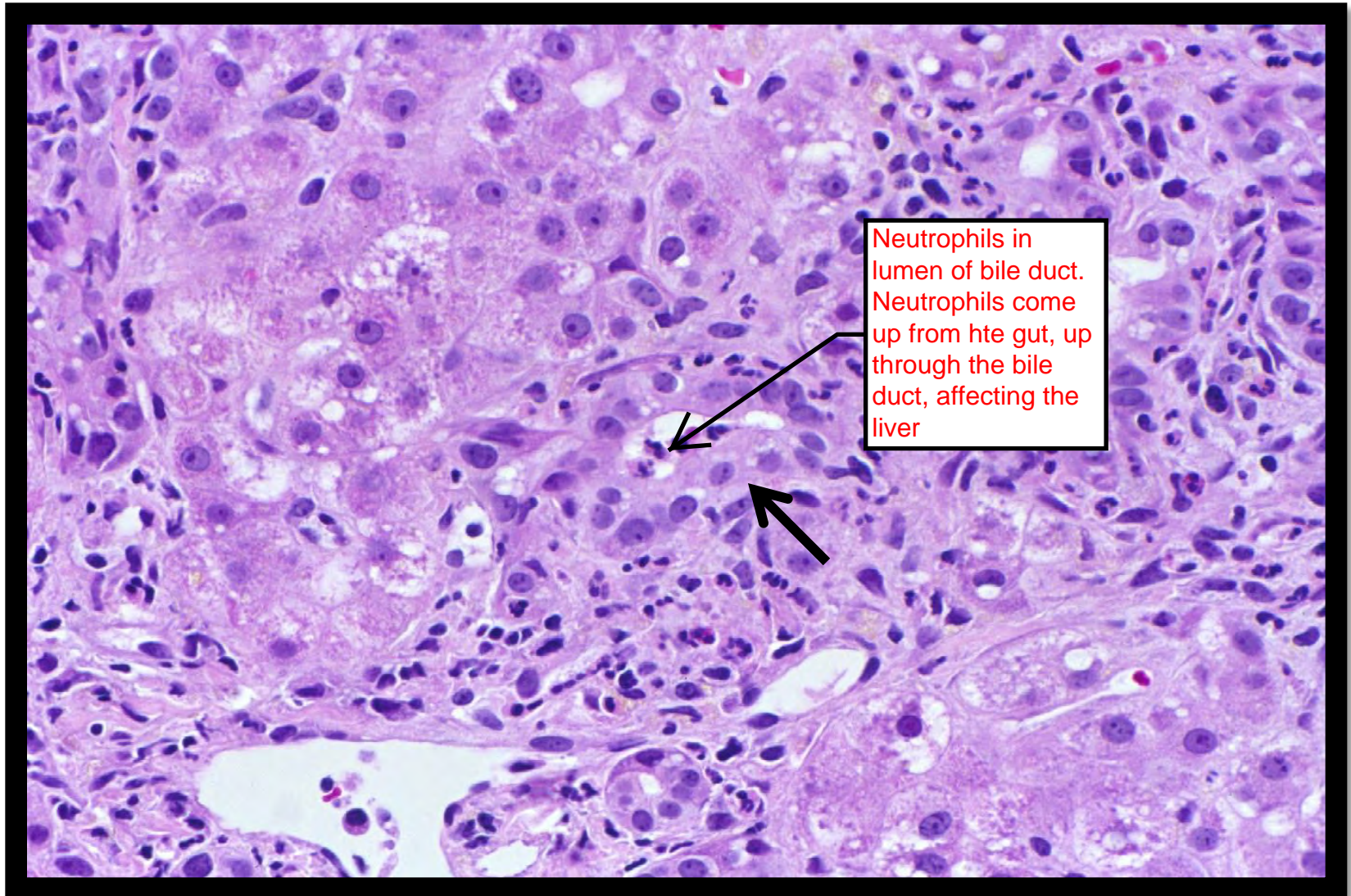
Reticulin stain highlighting the dense fibrous network

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** If the patient passes the stone.
 - 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



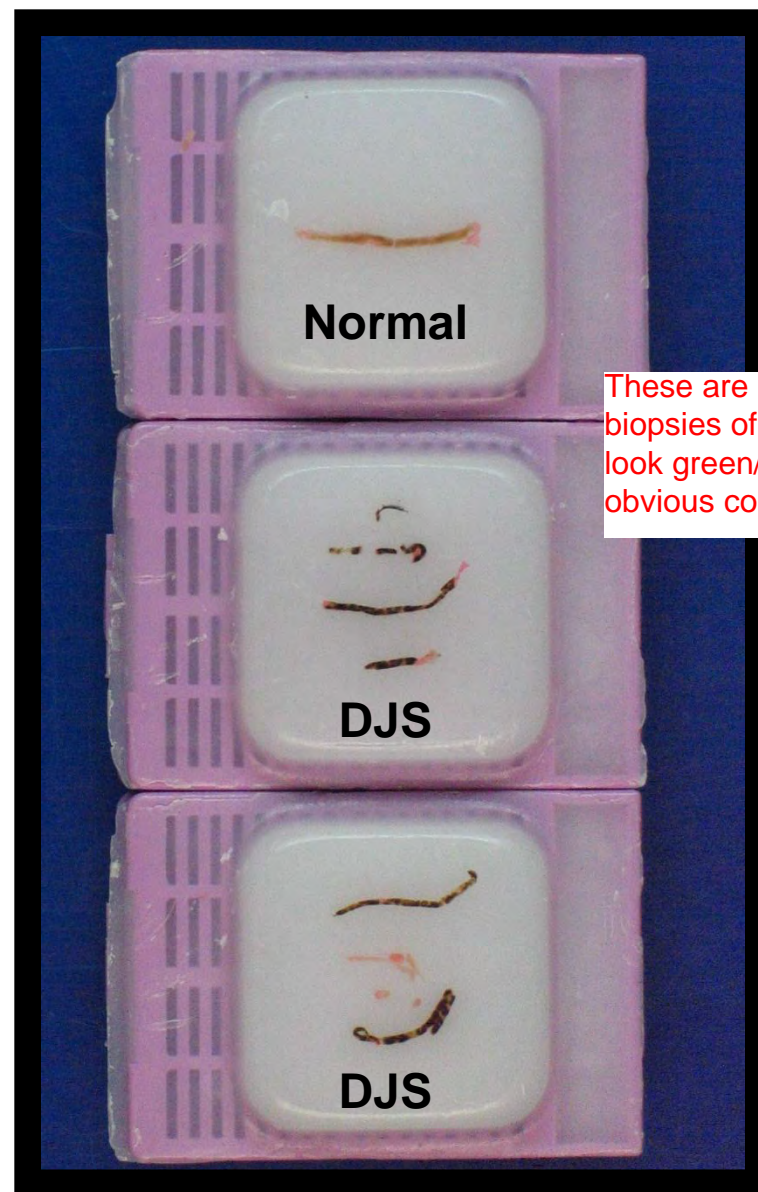
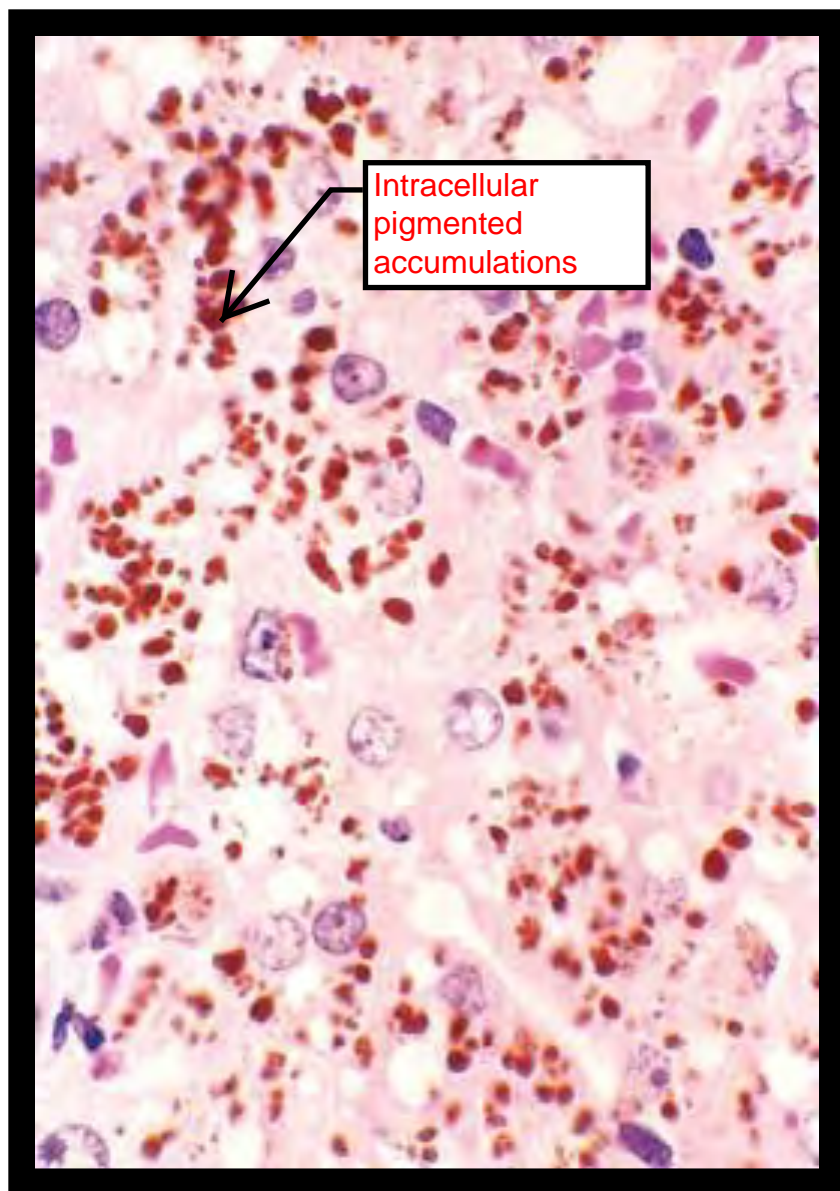
Hereditary Disorders

Hereditary disorders involving the biliary system.



Disorder	Inheritance	Defects in Bilirubin Metabolism	Liver Pathology	Clinical Course
UNCONJUGATED HYPERBILIRUBINEMIA				
Crigler-Najjar syndrome type I	AR	Absent UGT1A1 activity Enzyme used to conjugate bilirubin	None Don't biopsy	Fatal in neonatal period Buildup of unconjugated bilirubin
Crigler-Najjar syndrome type II	AD with variable penetrance	Decreased UGT1A1 activity	None	Generally mild, occasional kernicterus
Gilbert syndrome	AR	Decreased UGT1A1 activity	None	Innocuous (fluctuating)
CONJUGATED HYPERBILIRUBINEMIA				
Dubin-Johnson syndrome The only one that shows pathology! If you get a slide, it's this one.	AR	Impaired biliary excretion of bilirubin glucuronides due to mutation in canalicular multidrug resistance protein 2 (MRP2)	Pigmented cytoplasmic globules; ?epinephrine metabolites Not bile	Innocuous
Rotor syndrome	AR	Decreased hepatic uptake and storage? Decreased biliary excretion?	None	Innocuous

Dubin-Johnson syndrome



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