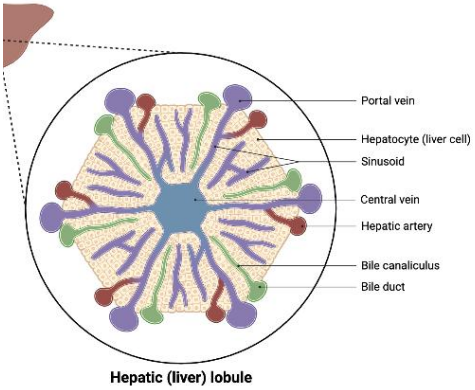
Liver introduction:

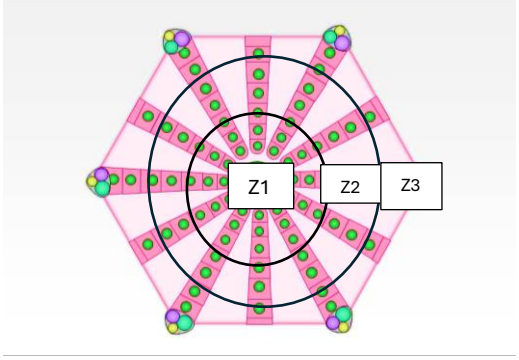
portal vein: gets the “toxic” blood to the liver to get detoxified
hepatic artery : oxygen supply to the liver
hepatic vein: takes blood away from the liver (also contains detoxified blood)



anatomy :
Hepatocytes are arranged in a **hexagonal** manner to produce a structure called **<u>lobule</u>**.
At every **corner** of the hexagon there is 3 structures **portal venule, portal arteriole, and bile ductule** (called the hepatic triad) and in the center of the hexagon there is a branch of the hepatic vein called the **central vein**.

The lobule is divided into 3 zones

1. Periportal
2. Midzone
3. Pericenter



If **ischemia** occurs, **zone one** will be the first effected since it is the **<u>furthest from the triad,</u>** and vice versa in case of inflammation.

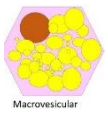
Hepatic injuries:

Inflammation:
identified by leukocytes infiltration looks like black pepper under microscope

ballooning:
expansion of the cell (either fatty change, iron deposition, or copper or all together)

Fatty changes (steatosis):
The liver will change to a yellow color due to a lot of fat in the hepatocyte *(it was mentioned before in the ballooning, but it is the most common hepatic injuries, so I mentioned it again to explain in a bit more details)*
split into two types:

1. microvascular more common with alcoholic liver disease, Reyes syndrome, and acute fatty liver of pregnancy
2. macrovascular common in nonalcoholic liver disease



Necrosis:
classified in different ways

1. Morphology
   a) Coagulative necrosis: caused by ischemia
   b) Councilman (eosinophilic and shrunken): caused by long term injury
   c) Lytic: caused by infection
2. Causes
   a) Ischemic
   b) Non ischemic
3. Location
   a) Centrilobular
   b) Midzone
   c) Periportal
   4. Scatter
   a) Focal (non-moving)
   b) Diffuse
      I. Massive (high percentage of liver failure)
      II. Sub massive

Fibrosis:

Scarring due to long term injury or repetitive injury.
different locations where(/how) it can happen

1. Portal: within the portal vein
2. Periportal: near the portal vein
3. Pericellular: fibrosis surrounding a cell
4. Pericentral: near the center
5. Bridging fibrosis:
    a) Central to central
    b) Portal to portal
    c) Central to portal

Cirrhosis:
Always means hepatic failure, forming regenerative nodule: which is fibrosis surrounding healthy cells preventing them from regenerating

Ductular prefiltration:
cells of bile duct appear in the liver

Liver failure

Liver failure has many **causes** such as:

1. Massive necrosis
    a) Fulminant viral hepatitis
    b) Toxin in huge mass (TB drugs)
2. Chronic disease
3. Dysfunction with no necrosis
    a) Reyes syndrome
    b) Acute fatty liver of pregnancy

Clinical features:

1. Jaundice (starts in the sclera)
2. Hyperammonemia
3. Fetor hepaticus (non-pleasant mouth breath)
4. Hypoalbunemia (leads to edema)
5. Coagulopathy (problem with blood clots)
6. Hyperestrogenism
    a) Hypogonadism (loss of function of the testicles)
    b) Spider nevi
    c) Palmar erythema

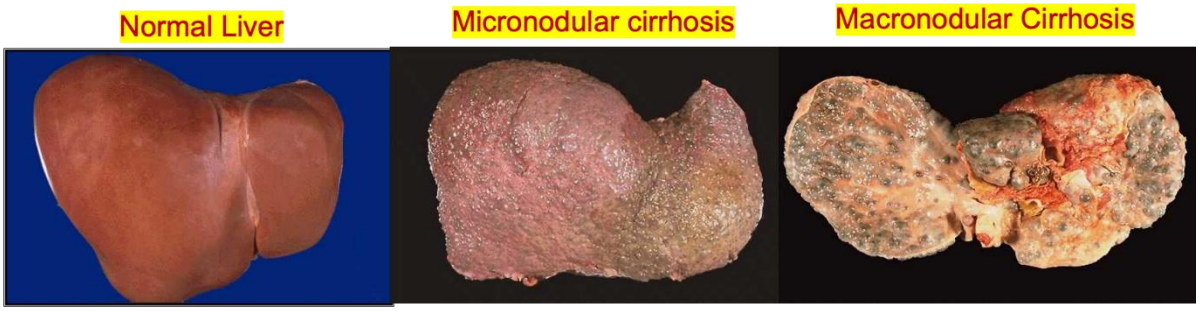
Complications:

1. Multi organ failure
2. Hepatorenal syndrome (renal injury)
3. Hepatic encephalopathy (brain injury caused by hepatic failure due to nh3)
    Clinical features of hepatic encephalopathy:
    a) Rigidity
    b) Hyperreflexia
    c) Seizure
    d) Asterixis (involutory loss of sustained muscle contraction while holding a pose)
    e) Brain edema + astrocyte reaction (fibrosis like)

Cirrhosis:

Fibrosis surrounds regenerating hepatocytes and disrupts the normal liver architecture, leading to the formation of regenerative nodules.
two types of regenerative nodules:

a) Micronodules (less than 3mm)
b) Macronodules (more than 3mm)



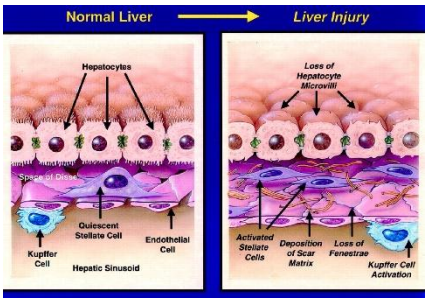
Causes of cirrhosis:

1. Alcoholic liver disease (most common cause worldwide)
2. Alpha-1 antitrypsin diff
3. Willson disease
4. Hemochromatosis
5. Biliary disease
6. Chronic viral infections
7. Cancer
8. A.I disease
9. Cryptogenic (unknown reason)

How does cirrhosis come to be:

First step is necrosis, which leads to inflammation then either regeneration occurs or fibrosis. After a lot of necrosis, the ability to regenerate is hindered so more fibrosis takes place until regenerative nodules are formed.

In space of desse there are cells called stellate cells (which store vitamin A) when they are injured, they release TGF- β which let them produce a lot of collagen fibers which lead to cirrhosis.



Complications:

1. Portal hypertension
2. Hepatic failure
3. Increases risk of hepatocellular carcinoma

Portal Hypertension:

It is classified into 3 types:

1. Prehepatic obstruction in the portal vein
   Causes
   a) Thrombosis
   b) splenomegaly
2. Intrahepatic obstruction in the liver itself
   Causes
   a) Cirrhosis
3. Posthepatic obstruction in the venous blood flow (hepatic vein)
   Causes
   a) Obstruction
   b) Right heart failure

Complication:

1. Ascites (increase of fluid in peritoneum)

A sample of the ascites should be investigated, because if there is neutrophil present the rate of death is so high and the patient should be treated fast.

Causes:

a) Portal hypertension
b) Inflammation
c) hypoalbuminemia

2. Varicose veins

In places with portosystemic shunt (where venous drainage is both systematic and portal) which causes an increase in size of the veins which may lead to them erupting

Example:

a) Esophageal varices
b) Caput medusa (anterior abdominal wall)
c) Retroperitoneal
d) Hemorrhoids (they aren't mainly caused by hypertension)

3. Splenomegaly

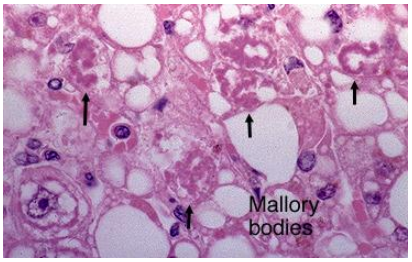
Alcoholic liver disease:

Alcohol (ethanol) gets metabolized (oxidized) in the liver using ADH to acetaldehyde causing a huge increase in NADH and ROS. High NADH means higher fat production in hepatocytes, ROS causes inflammation, acetaldehyde causing inflammation (due to immune response) when it bonds to other substances such as protein.

Stages of ALD:

1. Steatosis (more than 90% of chronic alcohol users develop Steatosis)
   Noticeable fat accumulation in hepatocyte
   This stage is reversable if alcohol consumption is stopped/reduced

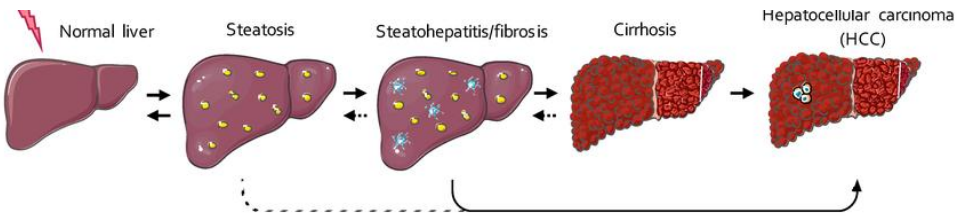
2. Steatohepatitis
   Is basically steatosis with inflammation
   Neutrophils are noticeable in histology
   Malory hyaline bodies (eosinophilic on histology) present thought to be caused by acetaldehyde bonding to keratin



3. Cirrhosis
   Discussed before

Clinical features:

1. Nonspecific (Right upper quadrant pain)
2. Higher liver enzyme level (AST is MUCH higher than ALT)



Non-Alcoholic Liver Disease:

Stages (same as ALD):

1. Steatosis
2. Steatohepatitis (NASH)
3. Cirrhosis

Riske factor Metabolic syndrome which consist of:

1. Diabetes-II
2. Hypertension
3. Obesity
4. Dyslipidemia (high ldl low hdl)

Clinical features:

1. Non-specific (like ALD)
2. High Liver Enzymes (ALT is much higher than the AST)

Tx: Lifestyle changes to reduce risk factors

DX of ADL and NAFLD:

1. Imaging
2. Biopsy

Autoimmune Hepatitis:

Causes **aren't known but** thought to be induced environmental factors and genetic factors. It is common to seen with patients **with other A.I diseases**. The chances if A.I hepatitis is **higher in females** than in males.

It is classified into two types:

1. Type one (most common)
   Two antibodies present: **ANA** & **ASMA**
   More common in older people
2. Type two
   Antibody present: ALKA
   In younger people (early teens)

Diagnosis is by exclusion

Hemochromatosis:

Increase of iron level in the body, an increase of iron level in the body causes an increase of ROS which leads to damage in the body. Absorption is highly regulated and capped at 1-2mg a day, loss is also 1-2mg a day, loss isn't regulated.

There are two causes of hemochromatosis:

1. Hereditary (Genetic)
   HFE gene mutation:
   a) C282 → Y
   b) H63 → D
2. Acquired
   a) Frequent blood transfusion
   b) Ineffective erythropoiesis (RBC don't use Fe so a lot of Fe stays int the blood)
   c) High intake + Genetic factor

Complications include:

1. Cirrhosis
2. Increases risk of hepatocellular carcinoma (hepatoma)
3. In biopsy appears:
    a) Blue in Prussian Blue dye
    b) Yellow in lipofuscin dye

4. Pancreas injury complication, like diabetes and malabsorption
5. Bronze tanning of the skin
6. Cardiomyopathy
7. Arthritis

Tx: Phlebotomy or Deferoxamine

Wilson's Disease:

Allot of Cu causes ROS production which leads to damage, displaces other iron, Binds to SH group of proteins. Unlike Fe, Cu isn't controlled by absorption it is controlled by excretion (90% through the bile 10% through urination).

Cu enters hepatocytes and protein ATP7B binds Cu to Apo-ceruloplasmin (apo) turning apo into ceruloplasmin. If mutation occurs in ATP7B gene (autosomal recessive) Cu won't be excreted leading to Wilson's disease.

Complication:

1. Cirrhosis
2. Cu accumulates in basal nuclei leading to motor problems, and neuropsychiatric symptoms (Depression)
3. Copper accumulation around cornea (kayser fleischer ring)

Dx:

1. Low level of ceruloplasmin
2. high level of Cu
3. high level of Cu in urine to compensate
4. Liver biopsy

Bronzish-Yellow color in Rhodanine /Orcein dye

Tx:

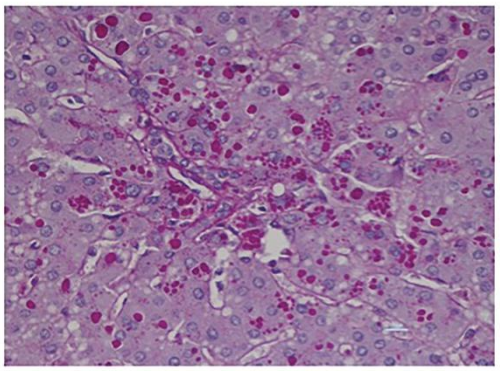
Penicillamine

α-1-antitrypsin Deficiency:

Alpha-1-antitrypsin is used to break down proteases which break down protein in case of inflammation.

Different alleles of Alpha-antitrypsin: M being the best one, Z being the worst one combination ZZ is the worst and MM is the best.

Figure 1. Z-Alpha-1 Antitrypsin Deficiency Inclusion Bodies



In A1AD damaged in A1A accumulates in the liver which is linked to mitochondrial autophagy.

Exam hint: emphysema (loss of air sacs surface area).

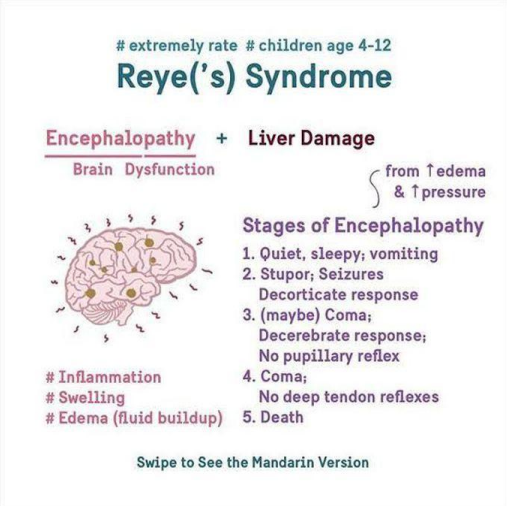
Under PAS and Diastase stain show as very eosinophilic bodies.

Reye's syndrome:

Primary patients with Reye's syndrome are kids with a viral infection who have been given Aspirin. It causes fatty changes to the liver by damaging the mitochondria. (High mortality)

Complication:

1. Fatty liver
2. Encephalopathy (can go into a coma)
3. Hepatic failure
4. Fatty changes in Muscle, Heart and the Kidney



Budd-Chiari Syndrome:

Is an occlusion in the hepatic vein. (High mortality)

Complication:

1. Portal hypertension complications (Ascites, splenomegaly, and varicose..)
2. Ischemia in the liver (leading to necrosis especially in Centrilobular)
3. Reddish liver

Causes:

1. polycythemia vera (PCV increase in RBC levels)
2. Pregnancy or post-partum
3. Oral contraceptive pills
4. Paroxysmal Nocturnal Hemoglobinuria (more thrombosis)
5. Mechanical Obstruction
6. Tumors
7. Idiopathic

Sinusoidal Obstruction Syndrome:

Other name is Veno-occlusive obstruction disease. This disease is caused by damage to endothelial of the venous membrane after Bone-marrow transplant, thought to be caused by the autoimmune suppressant specifically Cyclophosphamide.

The steps are as follows:

1. Drugs cause endothelial injury
2. Injury increases chance of Thromboembolism which blocks the blood