Liver pathology 1& 2
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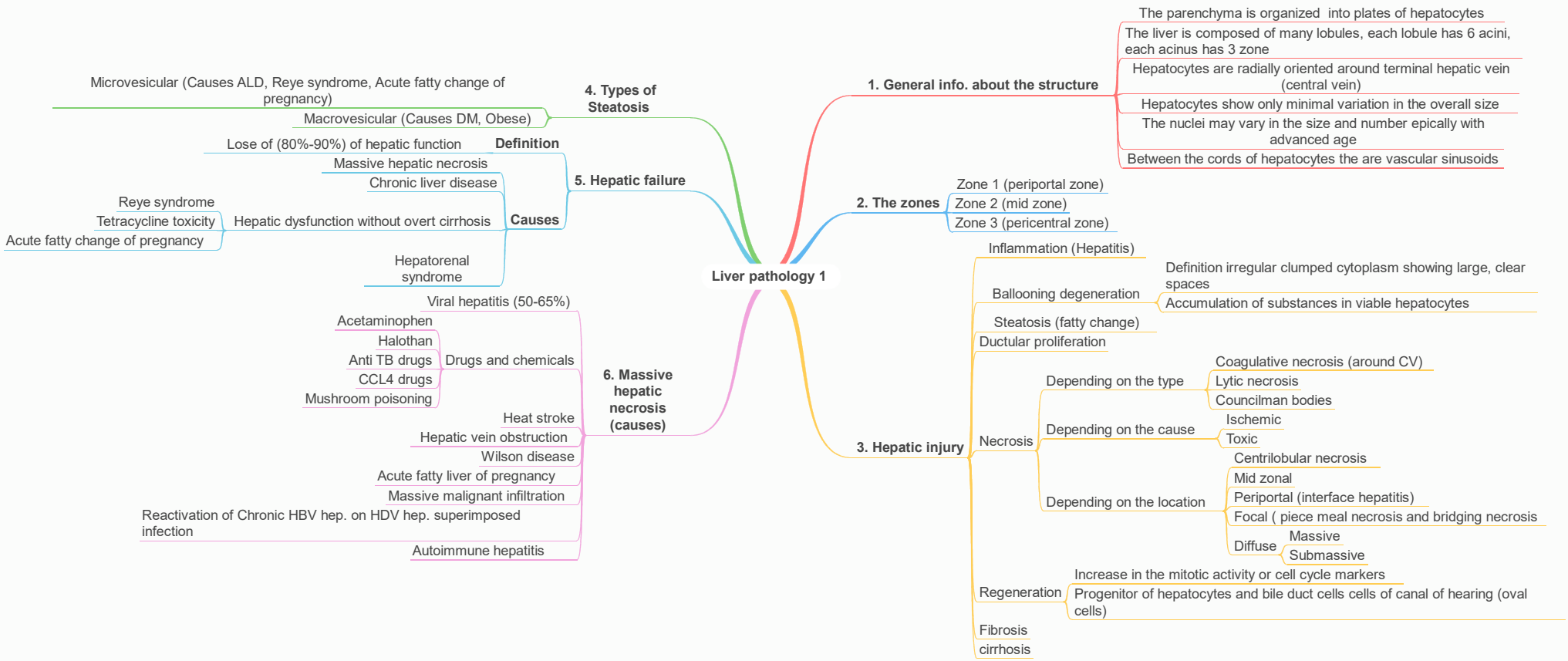


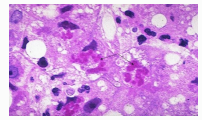
Liver pathology 2 (ALD)

1. General info.
- Alcohol is the 5th leading cause of death in USA due to
  - Accidents
  - cirrhosis
- 80-100 mg/dL is the legal definition for driving under influence of alcohol

2. Forms of ALD
- Hepatic Steatosis (90-10% of drinkers)
- Alcoholic hepatitis (1-35% of drinkers)
- Cirrhosis (14% of drinkers)

3. Steatosis
- Definition: Accumulation of fats in hepatocytes/ The liver is large (4-6 kg) yellow, greasy and soft
- 2 Forms
  - Microvesicular (moderate intake)
  - Macrovesicular (chronic intake)
- Increase in blood level of liver enzymes
- Lead to fibrosis with continued intake
- It is reversible with complete abstention of further alcohol intake
- sever dysfunction is unusual

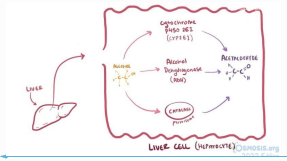
4. Hepatitis
- Characteristic findings
  - Hepatocytes swelling and necrosis, caused by
    - Accumulation of water, fat and proteins
    - chloestasis
    - Hemosidren deposition in hepatocytes and kupffer cells
  - Neutrophilic interactions
  - Fibrosis
  - Mallory hayline bodies
    - Eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed by cytokeratin intermediate filaments and other proteins



    - Charachtaristic but not pathogenomic of ALD
    - Seen in other diseases:
      - Primary biliary cirrhosis
      - Wilson disease
      - Chronic cholestatic syndrome
      - Hepatocellular carcinoma

5. Alcoholic Cirrhosis
- Firstly the liver is enlarged and yellow but over a years it become shrunken brown non fatty (<1 kg in wt.)
- It develops slowly but with presence of alcoholic hepatitis it develops rapidly
- Only 8-20 % of alcoholics develop cirrhosis
- There are a scar tissue and bile stasis
- Lead to portal hypertension
- It is irreversible

6. Alcohol metabolism
- Some facts
  - Females have lower gastric alcohol dehydrogenase activity than males so they have lower gastric metabolism of ethanol so they develop more ethanol level in blood than males when they drink the same amount
  - There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism
  - 50% of Chinese and Japanese have a lowered aldehyde dehydrogenase activity due to point mutation, which will accumulate acetaldehyde
  - Accumulation of acetaldehyde lead to facial flushing, tachycardia and hyperventilation



7. Mechanism of ethanol toxicity
- Fatty change
  - Shunting of of lipid catabolism toward lipid synthesis due to excess production of NADH over NAD+ in cytosol and mitochondria
  - Acetaldehyde adducts with tubulins and decrease the function of microtubulins that will lead to decrease the transport of lipoproteins out of the liver
  - Increase the peripheral degradation of fats so that will lead to increase the delivary of FFA to the liver
  - Decrease the oxidation of FFA in the mitochondria
- Alcohol cause regional hypoxia due to releasing of endothelial (potent vascconstriction) leading to decrease the sinusoidal perfusion
- Induction of cytochrome P-450 will enhance the metabolism of some drugs into toxic metabolites (such as acetaminophen)
- Acetaldehyde will cause lipid peroxidation and antigen alteration of hepatocytes that lead to immune attack
- Alcohol release the bacterial endotoxin into portal circulation of the gut leading to inflammation of the liver
- production of free radicals as a result of + cytochrome P-450 that lead to membrane and protein damade
- Alcohol will affect directly the microtubular and mitochondrial function and membrane fluidity
- Alteration of cytokines regulation such as TNF (the major cause of injury), IL6, IL8, IL18
- Superimposed HCV infection will accelerate the hepatic injury

Causes of death
- Hepatic failure
- Hepatorenal syndrome
- HCC in 3-6% of causes
- infections
- massive GI bleeding