GIS

Pathology

| Modified slides

Written by: Ammar Sweilem

Correction: Naemah Abuhantash

Doctor: Dr.Maha Shomaf

A Recommended Short Video from osmosis:

https://l.facebook.com/l.php?u=https%3A%2F%2Fyoutu.be%2FRudR2_VVoaw&h=AT2AEGKUQo_BU7CUnHev9jZSGfV18Ld-9Q1f7A3MOc3TN6whw2ZqJBGKhuD9tXQdkQ1iG1sMd0pH5XyG7KijcH3CSiqf06IwvNtCVYNtxkhyq2q2uZnmCBFlfxe_Fy-qnPYwtFy1s6-vb9k&s=1

Alcoholic liver disease

- **Alcohol is most widely abused agent**
- **It is the 5th leading cause of death in USA due to:**
- **1. accidents** that can occur to the patient
- **2.** development of **Cirrhosis** and its complication
- **80-100mg/dl is the legal definition for driving under the influence of alcohol** and this level is associated with the development of liver injury , "**44 ml of ethanol is required to produce this level in 70kg person**"
- **Short term ingestion of 80 gms/d of ethanol is associated with fatty change in liver**

- **In occasional drinkers, blood Level of 200 mg/dl produces coma & death, and respiratory failure at 300-400 mg/dl.**

- **Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect. This is due to metabolic tolerance explained by 5- 10X induction of cytochrome P-450 system (which is responsible for the elimination of ethanol from the blood) this system includes many type of enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetaminophen.**

- **Forms of alcoholic liver disease:**

- **1. Hepatic steatosis** which is seen in almost all drinker **(90-100% of drinkers)**
- **2. Alcoholic hepatitis** which can be seen in 1/3 of drinker **(1- 35% of drinkers).**
- **3. Cirrhosis (14% of drinkers).**
- **Steatosis & hepatitis may develop independently** and should be considered as an early indication for cirrhosis development in the future

a variant form of hepatic fat accumulation whose histologic features contrast with the much more common macrovesicular steatosis

Hepatic steatosis

- **Can occur following even moderate intake of alcohol in form of microvesicular steatosis.**
- **Chronic intake** is associated with development of → **diffuse steatosis** in this case **Liver is large (hepatomegaly, 4 – 6 kg) soft yellow & greasy.**

Upon **Continuation of the intake** this can progress into development of **fibrosis** which is irreversible

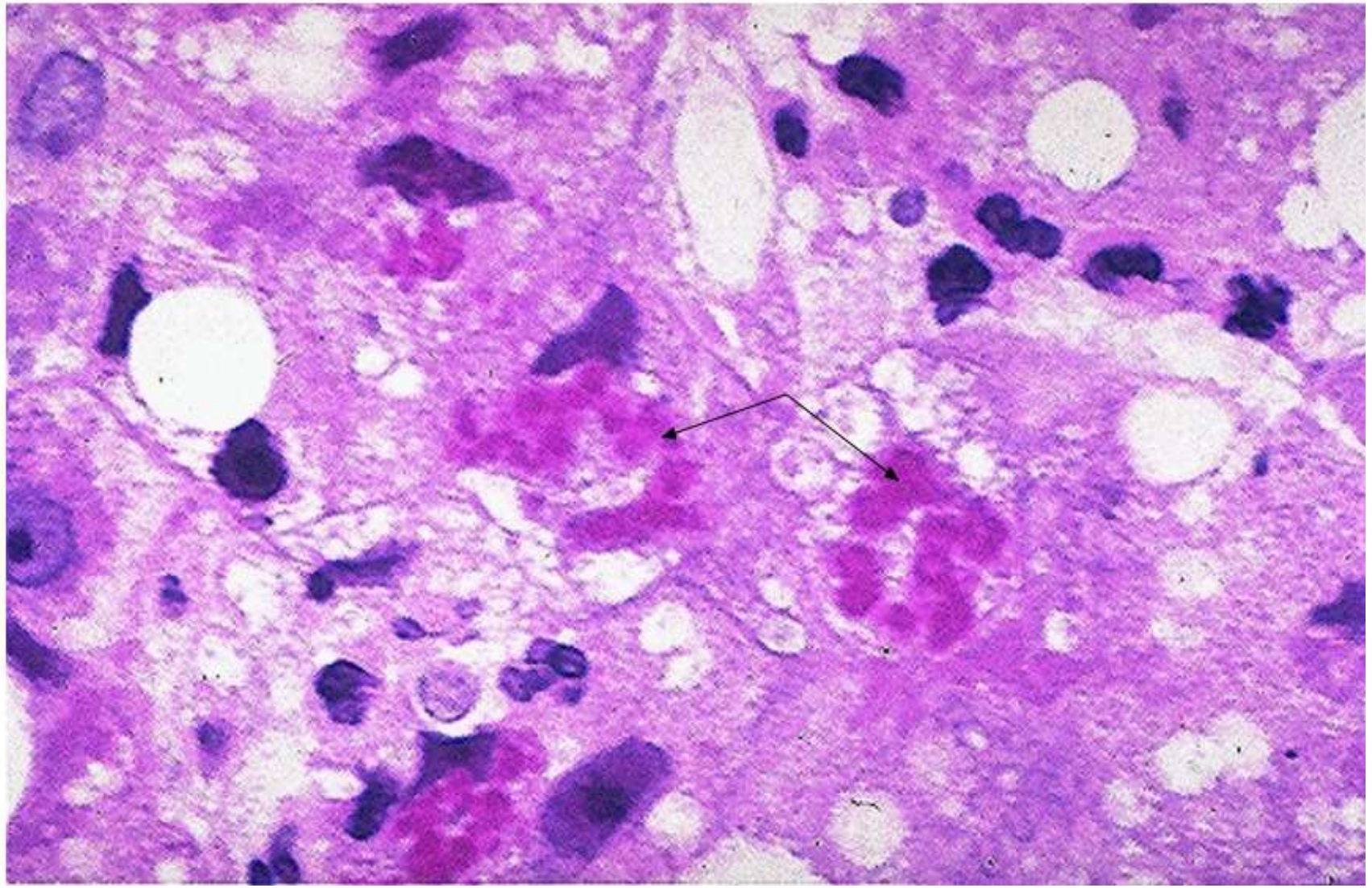
- **Fatty change is reversible with complete abstention from further intake of alcohol** (if the patient quit the intake it can resolve however if the patient continues to drink the progression into fibrosis or steatosis are inevitable)

an iron-storage complex that is composed of partially digested ferritin and lysosomes

Alcoholic hepatitis

- **Characteristic findings** in Alcoholic hepatitis there are feature that indicate more injury to the liver parenchyma such as:
- **1- Hepatocyte swelling (hepatomegaly) & necrosis:**
- **Accumulation of fat, water & proteins**
- **Cholestasis** (which is accumulation of bile salts within small bile ducts in the liver).
- **Hemosiderin deposition in hepatocytes & Kupffer cells** is increased
- **2-Mallory-hyaline bodies:**
- **Eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed** because of the collapse of the **cytokeratin intermediate filaments** within the cytoplasm hepatocytes **& other proteins** that is characteristic of Alcoholic hepatitis

Mallory-hayline bodies



This figure shows the resemblance of cytoplasmic granules in an alcoholic hepatitis patient
(Marked by the arrows)

-Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease.

<u>they are also seen in :</u>

1-Primary biliary cirrhosis

2-Wilson disease

3-Chronic cholestatic syndromes

4-Hepatocellular carcinoma

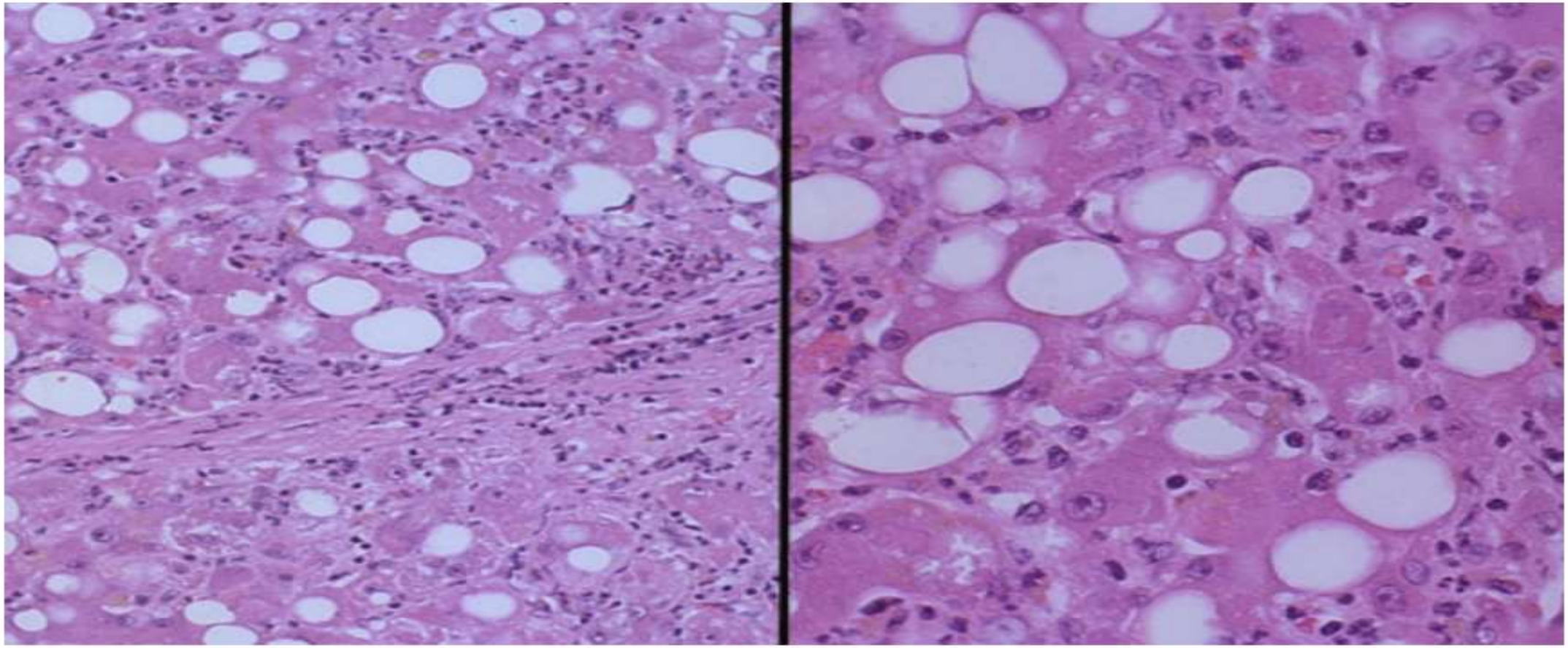
Continuation of Characteristic findings of Alcoholic hepatitis :

3-Neutrophilic reaction infiltration within the parenchyma

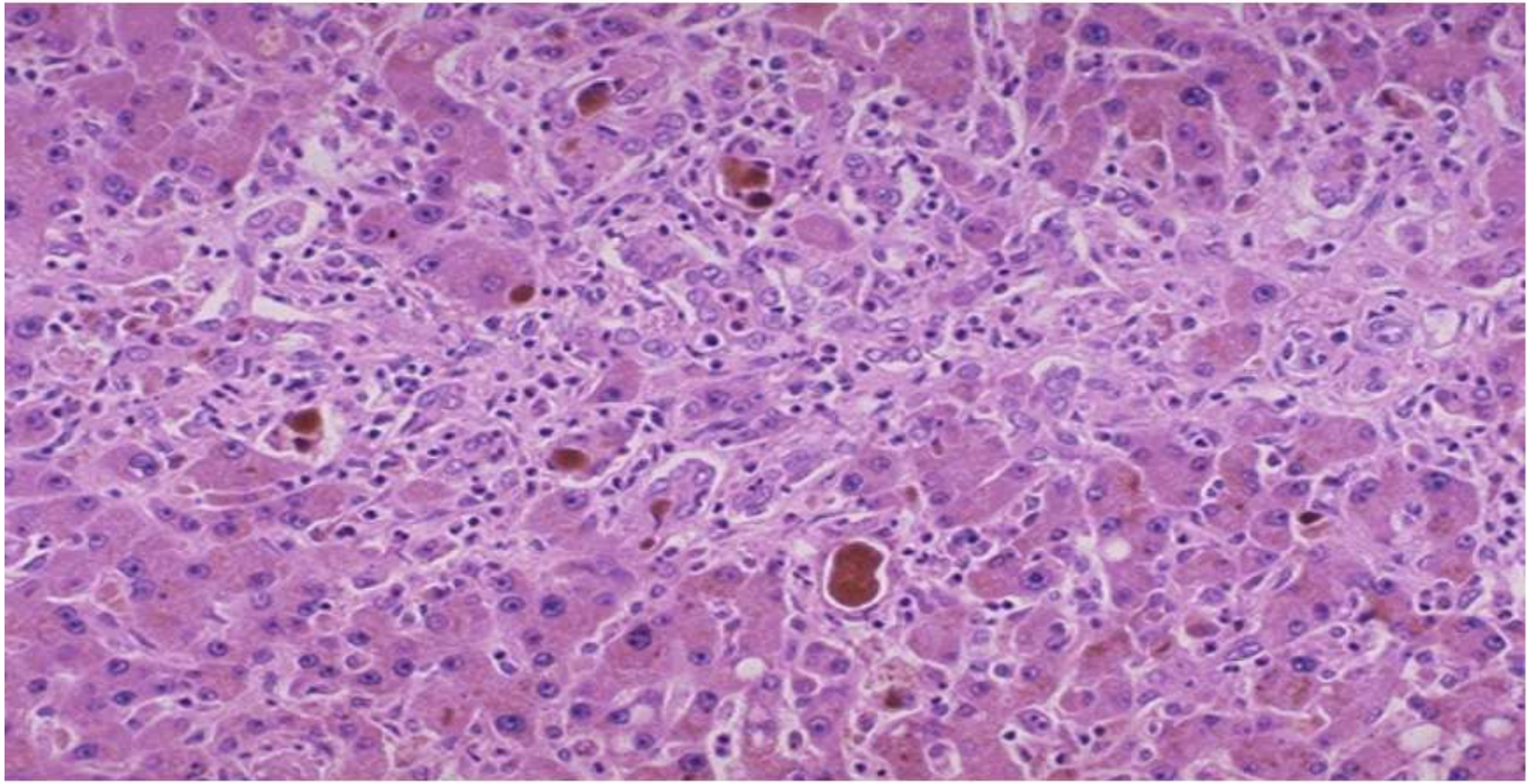
4-Fibrosis depending on the duration of ethanol intake and it can be Sinusoidal & perivenular fibrosis & Periportal fibrosis

5-Cholestasis can be seen within the endoplasm of hepatocytes and the bile duct

6-Mild deposition of hemosiderin in hepatocytes & Kupffer cells



This is the parenchyma of the liver for an alcoholic hepatitis patient, you can see infiltration parenchyma by inflammatory cell like lymphocytes; also development of fibrosis indicates that the process and the injury of the parenchyma is going on due to continuous exposure to ethanol



The dark material present within the intrahepatic duct is a feature of **Cholestasis** (accumulation of bile in the cytoplasm of hepatocytes and small bile ductule) which can be seen In alcoholic liver disease due to the injury and toxicity induced by ethanol

Alcoholic cirrhosis

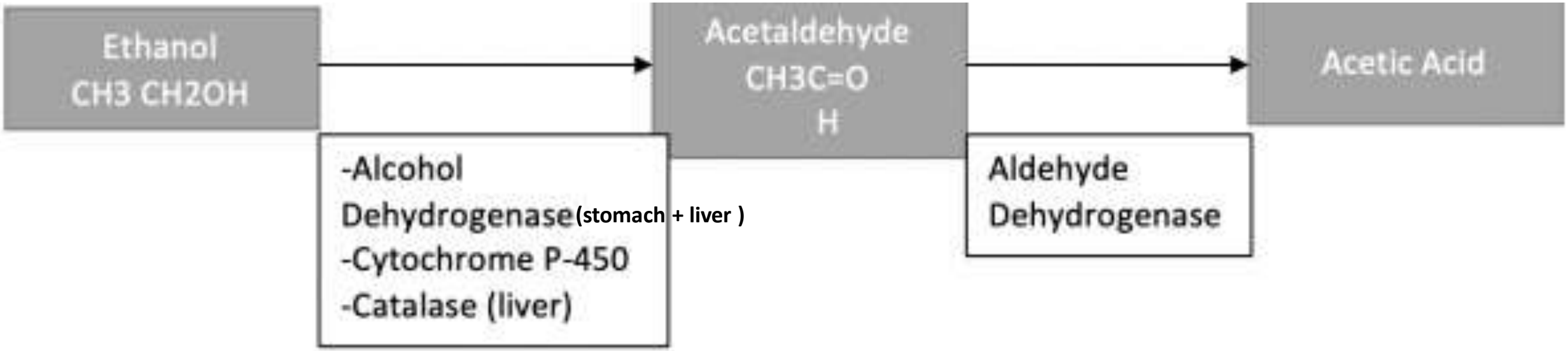
- **Usually it develops slowly** cirrhosis due to alcoholism is similar to any other cirrhosis that develops following any other disease.
- **Initially the liver is enlarged yellow** (due to associated fatty infiltration) **but over years it becomes brown shrunken non-fatty organ might be less than 1 kg in weight**
- cirrhosis is **Micronodular & it can be mixed micro & macronodular**
- When the fibrosis progress produces severe fibrosis of the liver this is called

Laennec cirrhosis = scar tissue (sever liver fibrosis)

- **Bile stasis**
- **Mallory bodies are only rarely evident at this stage**
- **Irreversible**
- **It can develop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).**

This is the gross appearance of liver with alcoholic cirrhosis the surface is transformed into nodules usually they are small nodules thats why its called microvesicular cirrhosis

Ethanol metabolism



Ethanol metabolism occurs in the liver so it's exposed to ethanol toxicity.

- After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level

- Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol.

- **less than 10% of absorbed ethanol is excreted unchanged in urine sweat & breathe**

- **There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism**
- **e.g 50% of Chinese , Vietnamese & Japanese have lowered enzyme activity due to point mutation of the enzyme. → accumulation of acetaldehyde → facial flushing, tachycardia & Hyperventilation after exposure to ethanol.**

Pathogenesis of alcoholic liver disease

Ethanol toxicity is a dose dependent that's why

- Short term ingestion of 80gm of ethanol/day (8bears) → mild reversible hepatic changes (fatty liver)
- Long term ingestion (10-20yrs) of 160gm of ethanol per day → severe hepatic injury
- 50 – 60gm/day → borderline effect
- Women are more susceptible to hepatic injury due to ↓gastric metabolism of ethanol due to Lower level of ethanol metabolism enzymes.
- Only 8 – 20% of alcoholics develop cirrhosis

FFA = free fatty acid

Mechanism of ethanol toxicity

Ethanol can interfere with all aspects of fat metabolism in the body producing excess amount of FFA in circulation that can get deposited in different organ leading to fatty change

- **1-Fatty change**

a-Shunting of lipid catabolism toward lipid bio-synthesis due to excess production of NADH over NAD in cytosol & mitochondria

b-Acetaldehyde forms adducts with tubulin & ↓ function of microtubules → ↓ in lipoprotein transport from liver

c- ↑ peripheral catabolism of fat → ↑ FFA delivery to the liver

d- ↓ secretion of lipoproteins from hepatocytes

e. ↓ oxidation of FFA by mitochondria

- **2-Induction of cytochrome P-450 enhances the metabolism of drugs to toxic**
- **metabolites (e.g acetominophen)** leading to increase the injury of the liver

- 3. ↑free radicals production due to (+) of cytochrome P-450

leads to membrane & protein damage within hepatocytes

- 4. Alcohol directly affects microtubular & mitochondrial function & membrane fluidity

- 5.Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes which can initiate → an immune attack

- 6. Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)

- 7.Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver

- 8. Alcohol → regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion leading to hypoxia

- 9. Alteration of cytokine regulation

TNF is a major effector of injury

IL6 IL8 IL18

Clinical features

- **Hepatic steatosis (reversible)**

liver enlargement

Increase of liver enzyme

Severe hepatic dysfunction is unusual

- **-Alcoholic hepatitis**

. 15-20 yr. of excessive drinking

. Non-specific symptoms, malaise, anorexia, weight loss

enlarge liver & spleen

LFT (liver function test) is abnormal with increasing of liver enzymes

Each bout of hepatitis →10-20% risk of death→ cirrhosis in 1/3 in few yrs.

- **Cirrhosis**
- Portal hypertension

- **Causes of death in alcoholic liver disease**

1-Hepatic failure

2-Massive GI bleeding

3-Infections

4-Hepatorenal syndrome and failure of other organs

5-HCC (hepatocellular carcinoma) which occurs in 3-6% of cases

GOOD LUCK….