# LECTURE 2

# Alcoholic liver disease

-Alcohol is most widely abused agent

-It is the 5th leading cause of death in USA due to :

1.Accidents

2.Cirrhosis

-80 – 100 mg/dl is the legal definition for driving under the influence of alcohol

-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

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- In occasional drinkers, bl. Level of 200 mg/dl produces coma & death & resp. failure at 300-400 mg/dl

-Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance explained by 5-10X induction of cytochrome P-450 system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetominophen

- **Forms of alcoholic liver disease**

1-Hepatic steatosis (90-100% of drinkers)

2-Alcoholic hepatitis ( 1- 35% of drinkers)

3-Cirrhosis ( 14% of drinkers)

- Steatosis & hepatitis may develop independently



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# Hepatic steatosis

-Can occur following even moderate intake of alcohol in form of microvesicular steatosis

-Chronic intake → diffuse steatosis

-Liver is large ( 4 – 6 kg) soft yellow & greasy

-Continued intake →fibrosis

-Fatty change is reversible with complete absention from further intake of alcohol

# Alcoholic hepatitis

**Characteristic findings :**

**1-Hepatocyte swelling & necrosis**

-Accumulation of fat & water & proteins

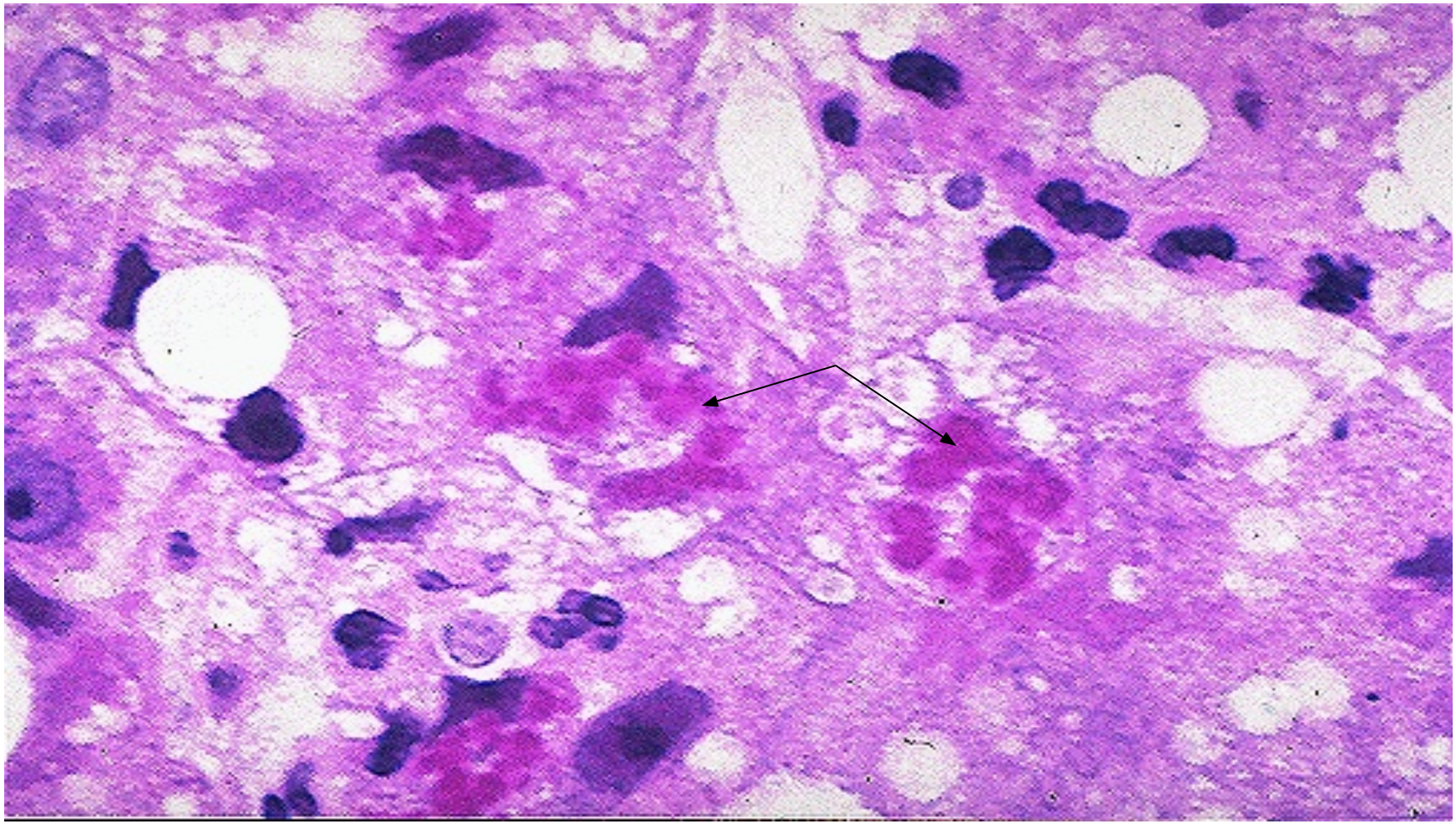
-Cholestasis

-Hemosidrein deposition in hepatocytocytes & kupffer cells

**2-Mallory-hayline bodies**

-easinoplilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin infermediate filaments & other proteins

# Mallory-hayline bodies



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

- they are also seen in :

1-Primary biliary cirrhosis

2-Wilson disease

3-Chronic cholestatic syndromes

4-Hepatocellular carcinoma

3-Neutrophilic reaction

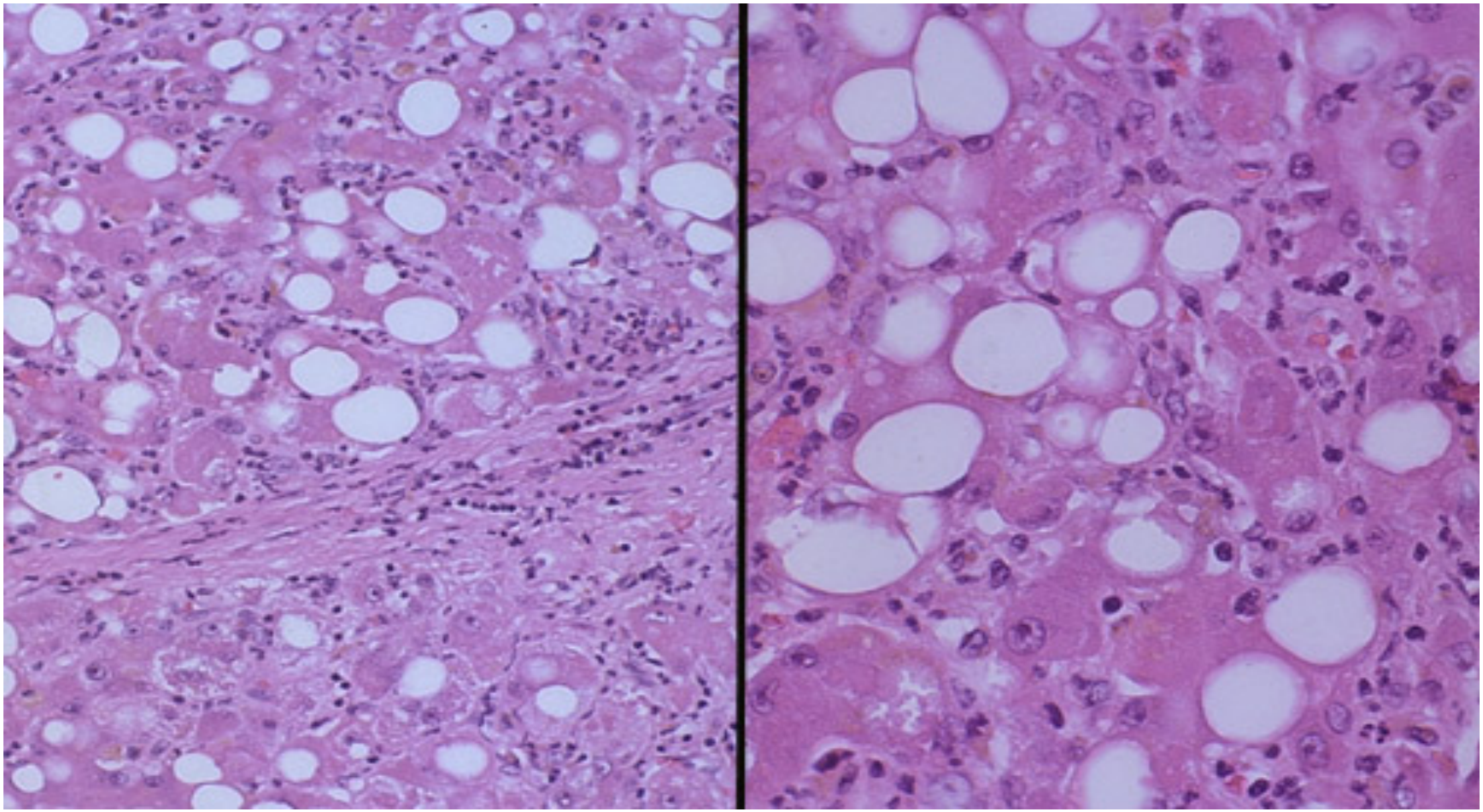
4-Fibrosis

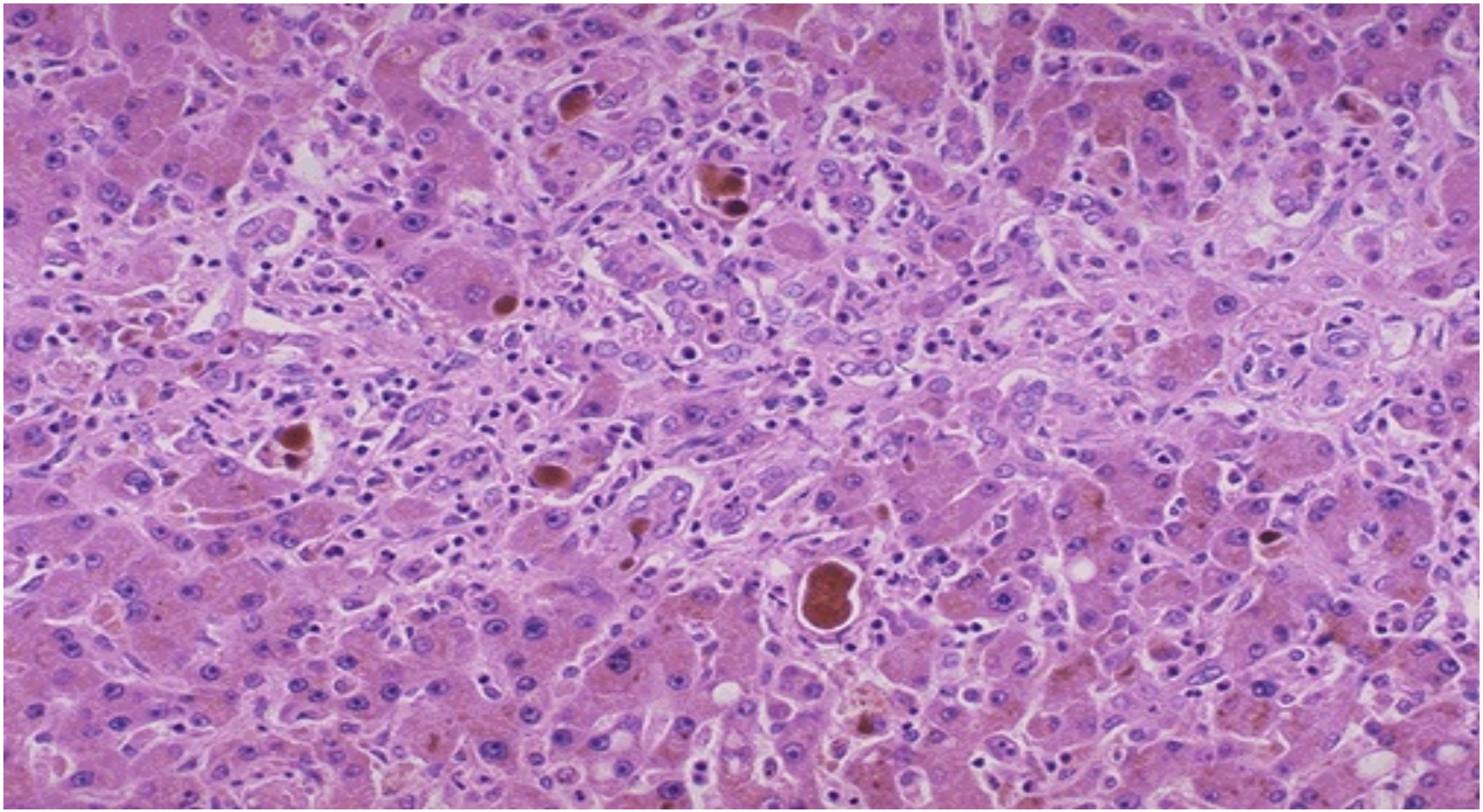
-Sinusoidal & perivenular fibrosis

-Periportal fibrosis

5-Cholestasis

6-Mild deposition of hemosiderin in hepatocytes & kupffer cells





# Alcoholic cirrhosis

-Usually it develops slowly

-Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < I kg in wt.

-Micronodular → mixed micro & macronodular

-Laennec cirrhosis = scar tissue

-Bile stasis

-Mallory bodies are only rarely evident at this stage

-Irreversible

-It can devolop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).

# Ethanol metabolism

Ethanol → acetaldehyde

CH3 CH2OH CH3 C=O

H

-Alcohol

↑

dehydrogenase

(stomach + liver)

-Cytochrome P-450

-Catalase ( liver)

-

Acetaldehyde → Acetic acid

↑

Aldehyde dehydrogenase

- 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 , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme. → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation.

# Pathogenesis of alcoholic liver disease

-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 .

-Only 8 – 20% of alcoholics develop cirrhosis

# Mechanism of ethanol toxicity

**1-Fatty change**

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

3. ↑free radicals production due to (+) of cytochrome P-450 leads to membrane & protein damage
4. Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
5. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → 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
9. Alteration of cytokine regulation

   TNF is a major effector of injury

   IL6 IL8 IL18

# Clinical features

**-Hepatic steatosis ( reversible )**

**↑ liver**

**↑ liver enz.**

**Severe hepatic dysfunction is unusual**

**-Alcoholic hepatitis**

**. 15-20 yr. of excessive drinking**

**. Non-specific symptoms, malaise, anorexia, wt. loss**

**↑ liver & spleen**

**↑ LFT**

**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**

**5-HCC in 3-6% of cases**