GI

PATHOLOGY

#2

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CLINICAL SYNDROMES

- The major clinical syndromes of liver disease are:
- 1-hepatic failure
- 2-cirrhosis
- 3-portal hypertension
- 4-cholestasis.

liver failure

- **The alterations that cause liver failure fall into 3 categories:**
- **1- Acute liver failure with massive hepatic necrosis**
- **2- Chronic liver disease**
- **3- Hepatic dysfunction without overtnecrosis.**

1-Acute liver failure.

- This is most often caused by drugs or fulminant viral hepatitis.
- Acute liver failure denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks.
- A course extending as long as 3 months is called subacute failure.

2-Chronic liver disease

- This is the most common route to hepatic failure and is the end point of relentless chronic liver damage ending in cirrhosis.

Hepatic dysfunction without overt necrosis.

- Hepatocytes may be viable but unable to perform normal metabolic function:
- 1- acute fatty liver of pregnancy (which can lead to acute liver failure a few days after onset)
- 2- tetracycline toxicity
- 3- Reye syndrome

Fulminant liver failure and encephalopathy in children with viral illness who take aspirin

Sometimes ocurrs without having morphological changes or even necrosis

Liver function test is more significant

Clinical features are similar regardless the underlying cause

1-Jaundice Yellow discoloration of the skin

2-Hypoalbuminemia → edema

Decrease in blood

3-Hyperammonemia ↑↑ level of ammoia in the Blood → impaired neural function and brain edema

4-Fetor hepaticus (musty or sweet & sour)

5-Palmar erythema

hyperestrogenemia

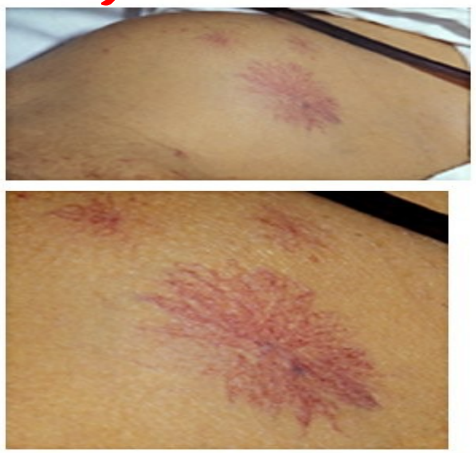
6-Spider angiomas

7-Hypogonadism & gynecomastia

*hyperestrogemia due to impaired estrogen metabolism in male with chronic liver failure → it gives rise to:

1] palmar erthyma (Due to vasodilation)

2] Spider angiomas



3] hypogonadism, gynecomastia

Consequences:

1-Multiple organ failure kidneys & lung

2-Coagulopathy → bleeding The liver is a source of these factors

def. factors II, VII, IX, X

3-Hepatic encephalopathy Because of elevated ammonia level in the blood

↓level of conseiousness

Rigidity

Hyperreflexia

EEG changes An electroencephalogram

Seizures https//:youtu.be/fZrF0-ATPvE

Asterixis

It is related to electrical activity in the brain

⊕ → means activation

4-Hepatorenal syndrome

Renal failure in patients with severe liver disease with no morpholagic or functional causes for renal failure Robbins book

↓ systemic vasodilation

⊕ of renal sympathetic NS >> vasoconstriction

↑⊕ of renin angiotensin axis

↓ glomerular filtration ↑ blood urea

Alcoholic liver disease

-Alcohol is most widely abused agent

-Excessive ethanol consumption causes more than 60% of chronic liver disease in most Western countries and accounts for 40% to 50% of deaths due to cirrhosis.-It is the 5th leading cause of death in USA due to:

1.Accident

2.Cirrhosis

Pathogenesis

- Short-term ingestion of as much as80gm of ethanol/d (8 beers or 7 ounces of 80-proof liquor) generally produces mild, reversible hepatic changes.
- • Chronic intake of 50 to 60gm/day Is considered a borderline risk for severe injury.
- women seem tobe moresusceptible to hepatic injury than are men because of low gastric metabolism of ethanol and differences in body composition. 28 -80 – 100 mg/dl i

- 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
- 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 by5-10X induction of cytochrome P-450 system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetominophen

These are not stages of the disease, the patient may present at the first time with cirrhosis however the patient who has cirrhosis usually has fatty change ...and this is helpful as you can conclude this is alcholic cirrhosis

- **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

it's present almost in all alchohics

Hepatic steatosis

REVERSIBLE initially

it begins in centrilobular hepatocyte, it can spreads to periportal and midlelobule regions.

-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

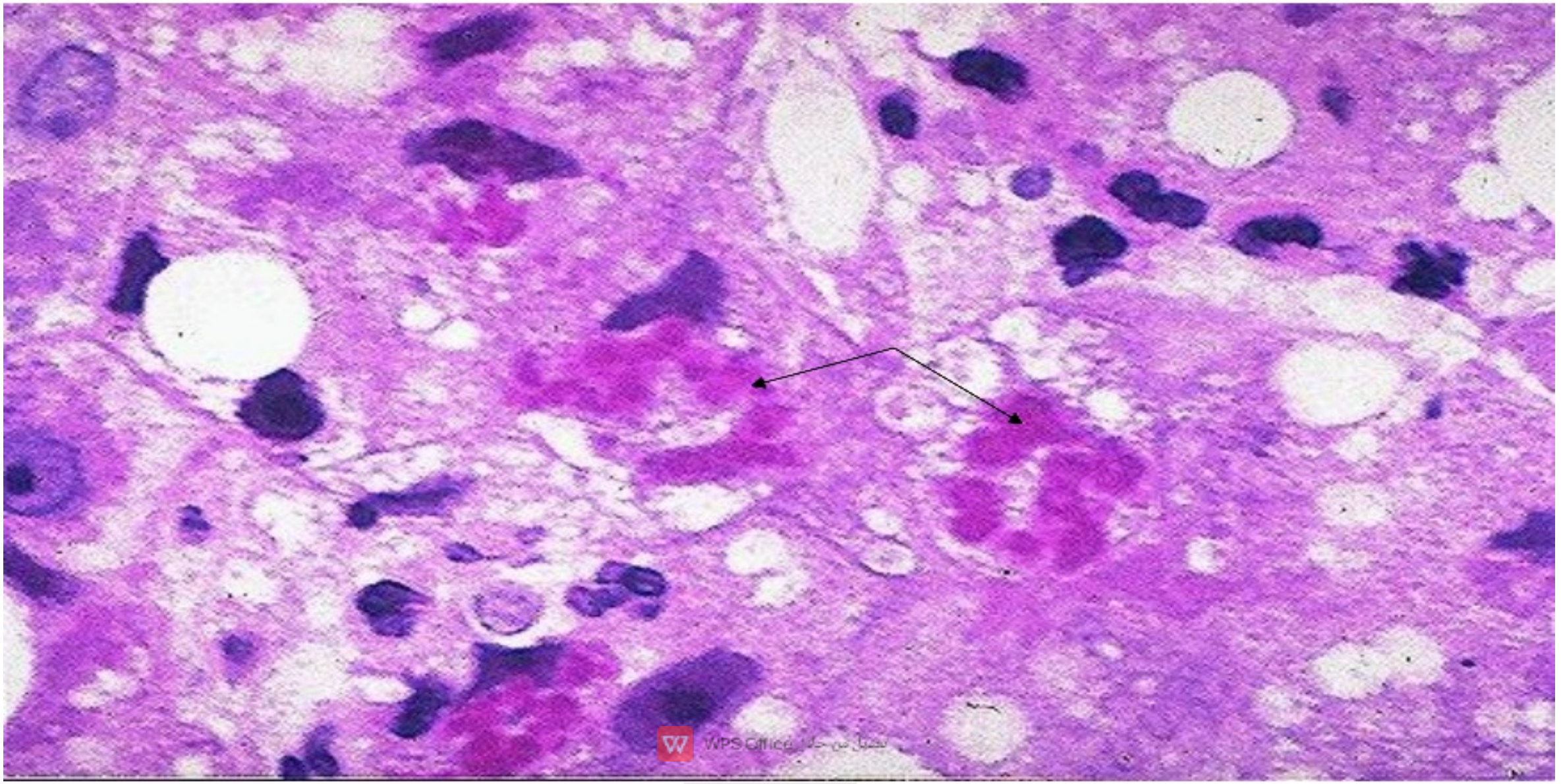
excess iron

-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

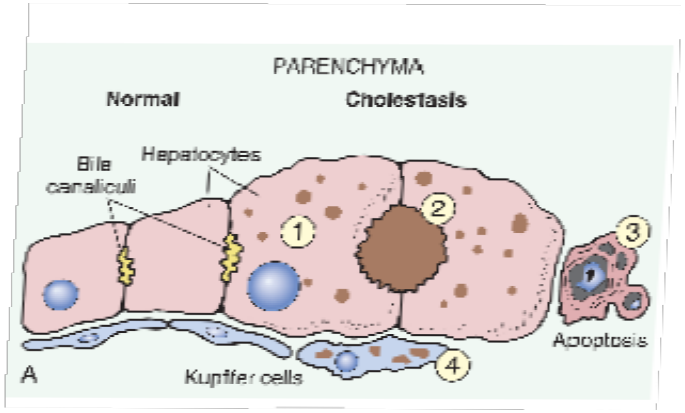
4-Fibrosis appears first in the centrilobular region

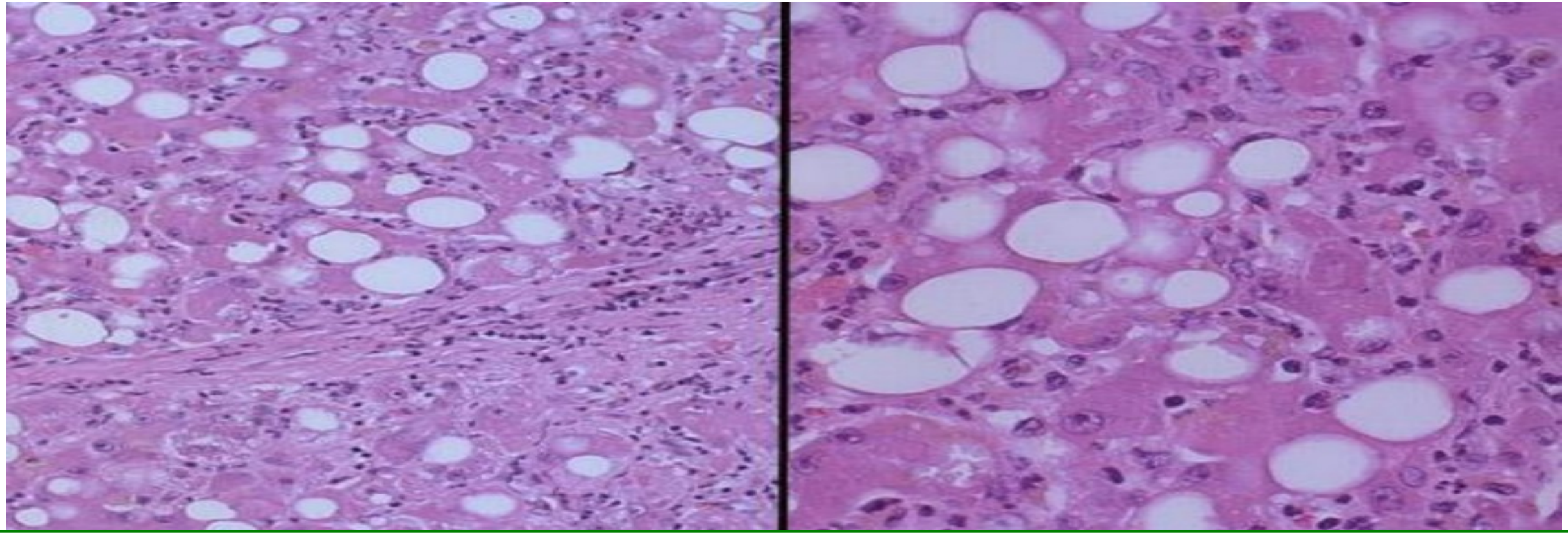
-Sinusoidal & perivenular fibrosis

-Periportal fibrosis

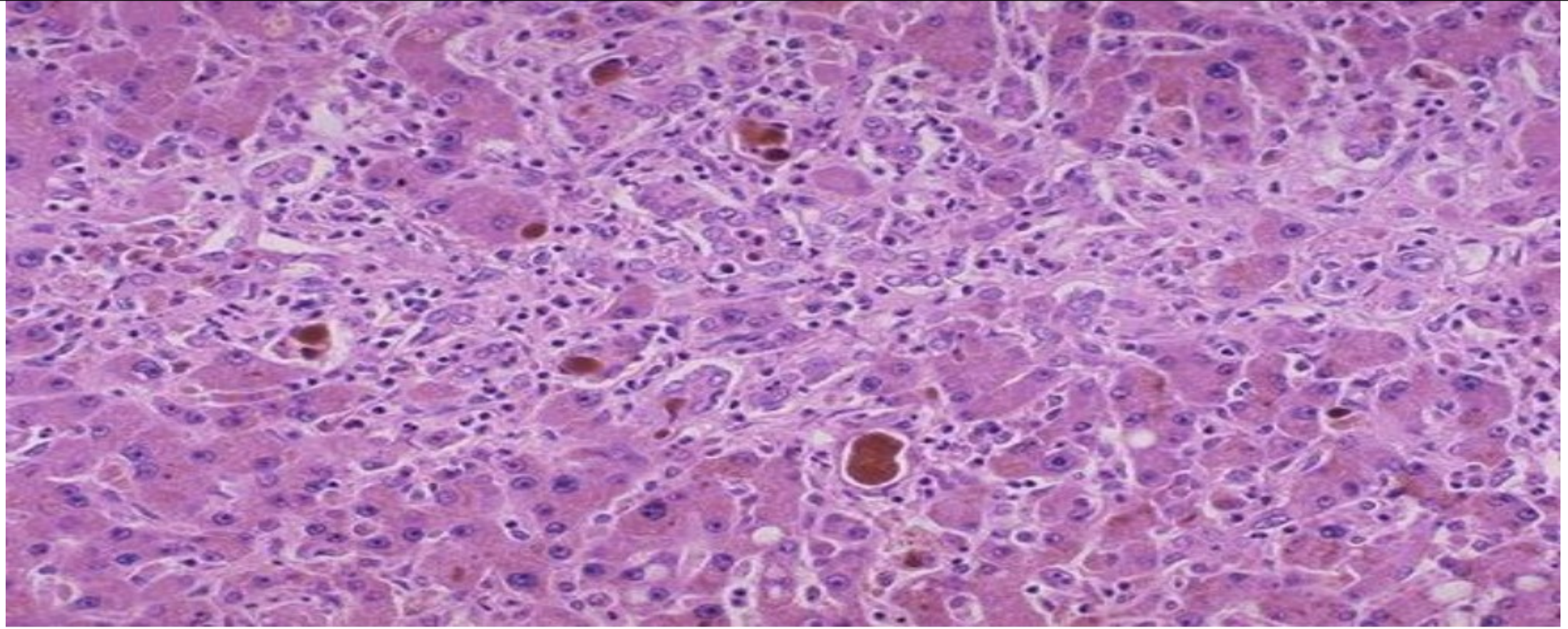
5-Cholestasis ⇝ green-brown plugs of bile

6-Mild deposition of hemosiderin in hepatocytes & kupffer cells





This is the parenchyma of the liver of an alcoholic hepatitis patient, you can see infiltration of the 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



35 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
- Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organs.t < l 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 develop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).

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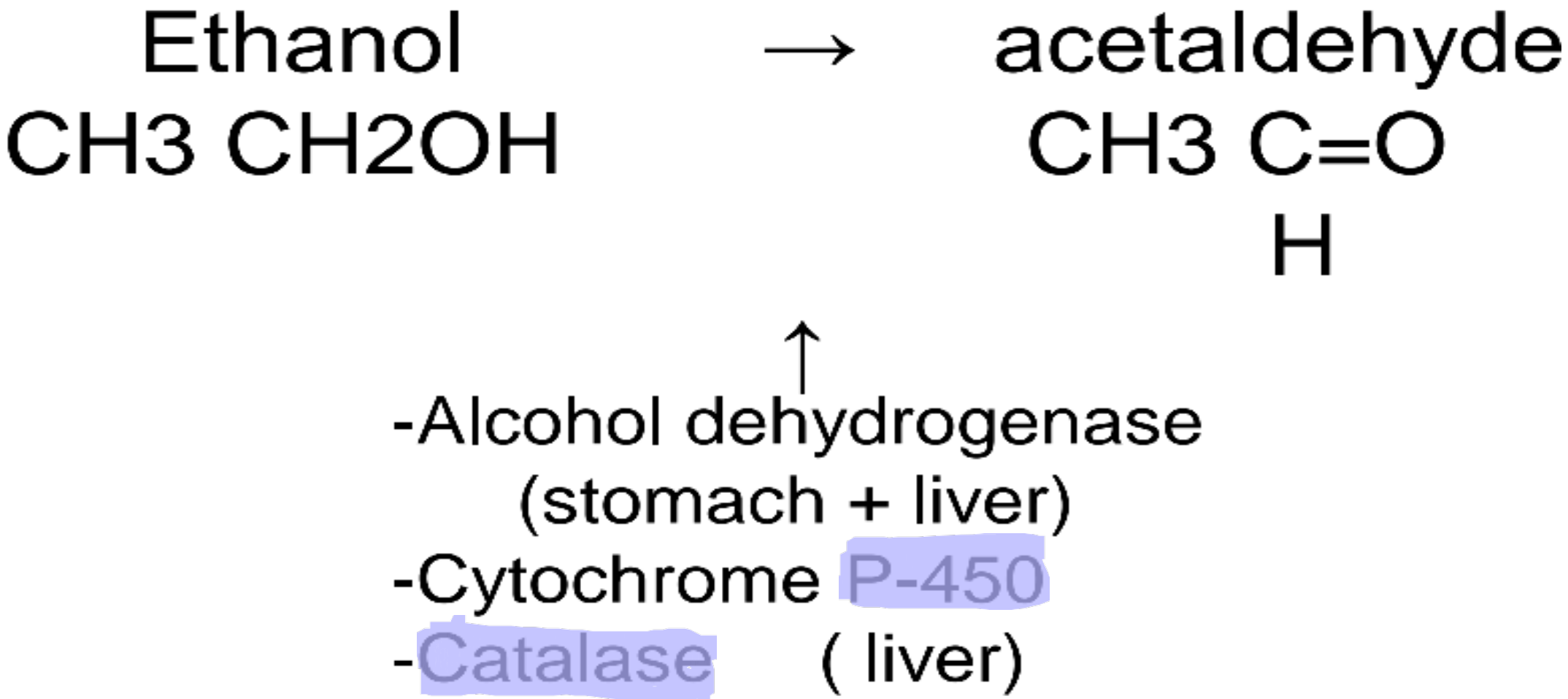
Ethanol metabolism



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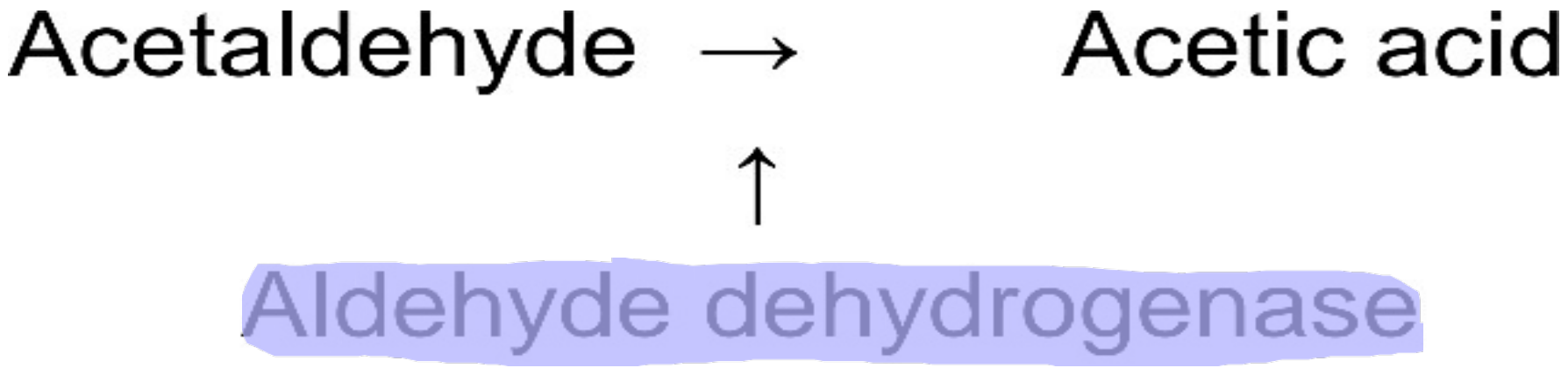

- After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level

- 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.

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 organs 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

SUMMARY

ALCOHOLIC LIVER DISEASE

- Alcoholic liver disease has three main manifestations, hepatic steatosis, alcoholic hepatitis, and cirrhosis, which may occur alone or in combination.
- Cirrhosis typically develops after more than 10 years of heavy drinking, but only occurs in a small proportion of chronic alcoholics; alcoholic cirrhosis has similar clinical signs and symptoms as cirrhosis caused by viral hepatitis.
- The multiple pathologic effects of alcohol include changes in lipid metabolism, decreased export of lipoproteins, and cell injury caused by reactive oxygen species and metabolites of alcohol.

V3

Almost 6 slides added and 4 deleted, it’s better to use the most recent version