

Liver

Liver

- Function:

1-Metabolic : Glucose

2-Synthetic : Albumin, clotting factors

3-Detoxification : Drugs, hormones , NH₃

4-Storage : Glycogen, TG, Fe, Cu, vit

5-Excretory : Bile

- Net wt. 1400 – 1600gm (2.5% of body wt)

- Blood supply:

Portal v : 60 – 70%

Hepatic a : 30 0 40%

- Microstructure

- Hexagonal lobules →6 acini

- Acinus is divided into 3 zones:

1-Zone 1

Periportal areas – closet to the vascular supply

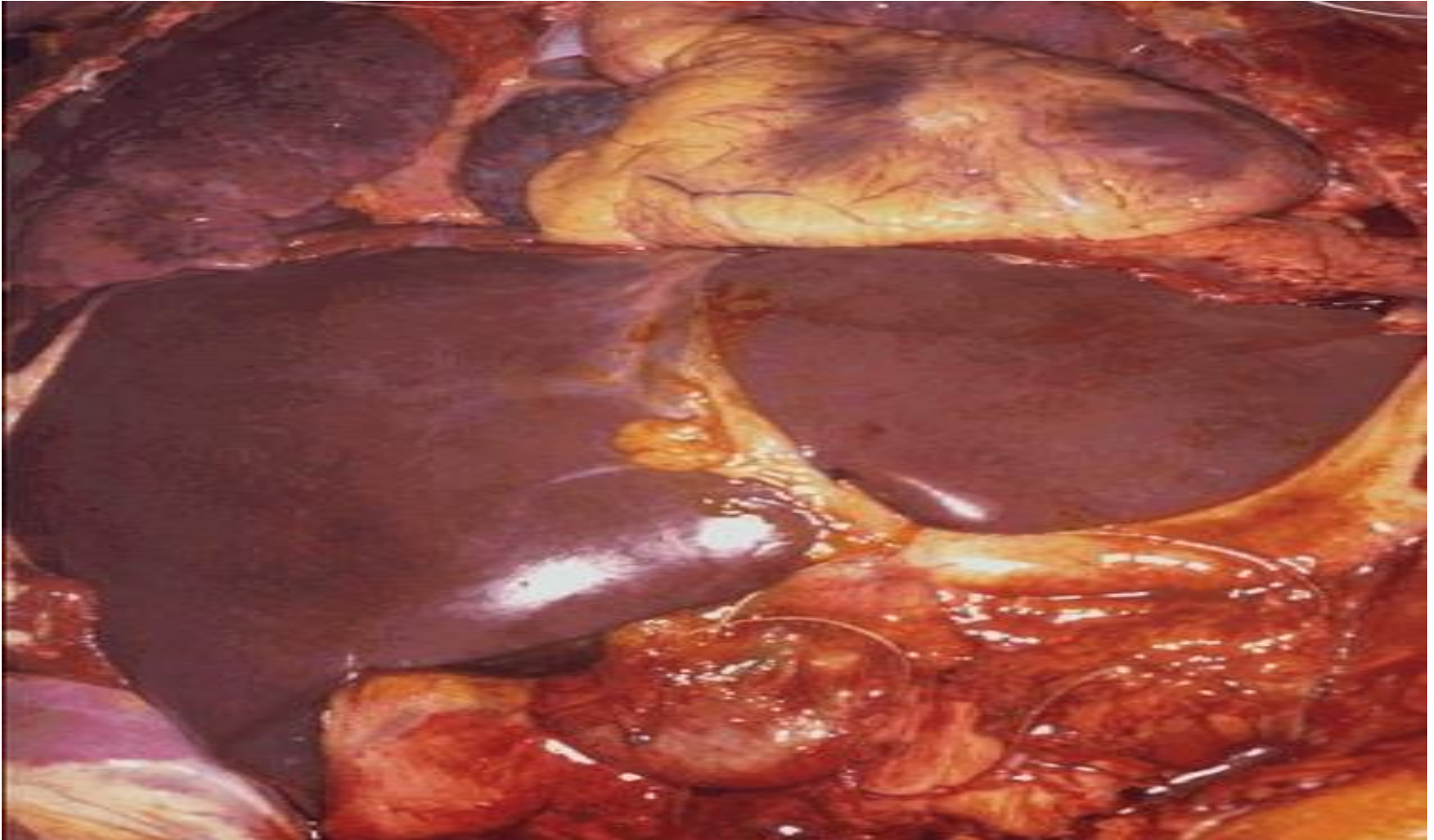
2-Zone 3

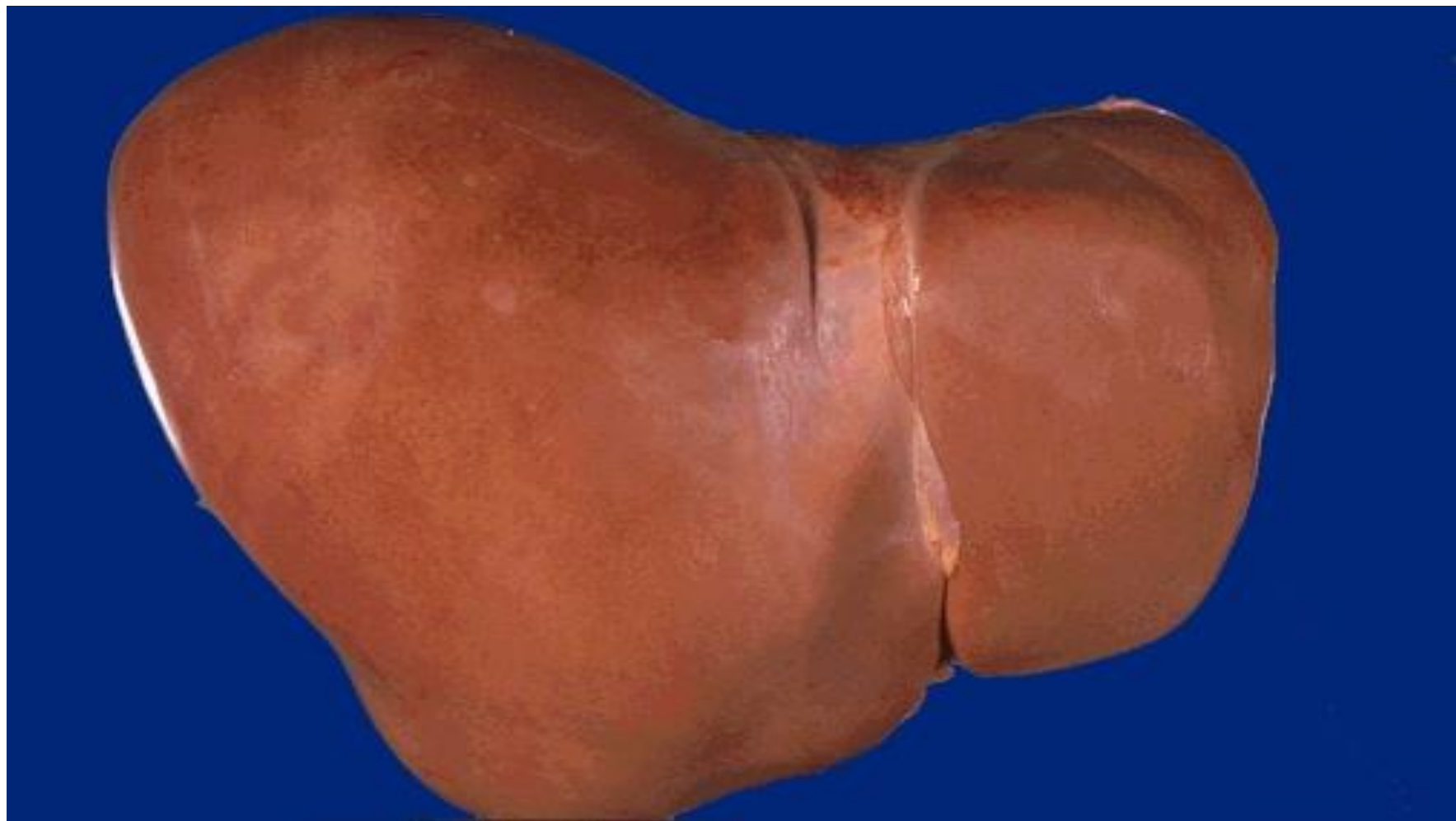
Pericentral area

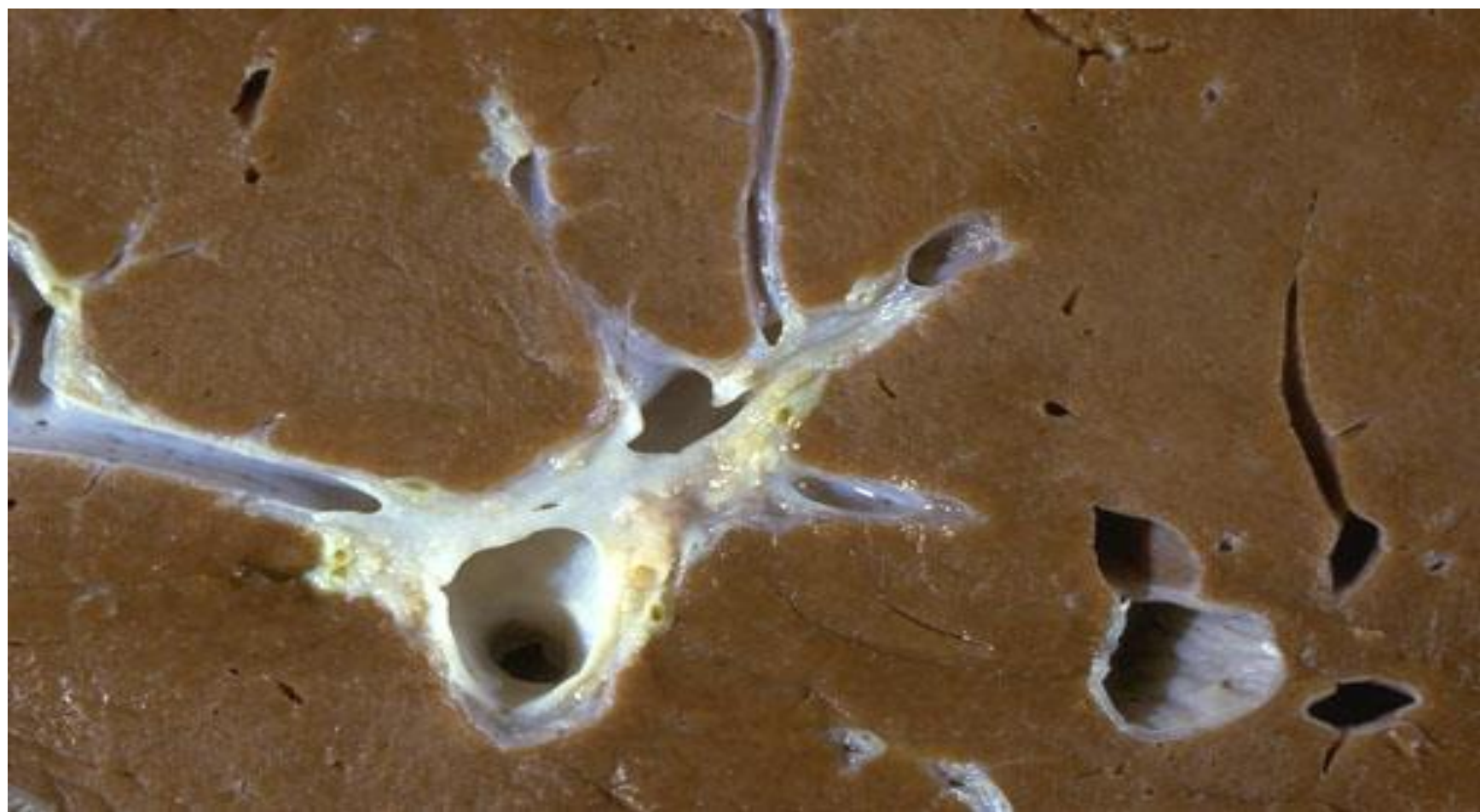
3-Zone 2

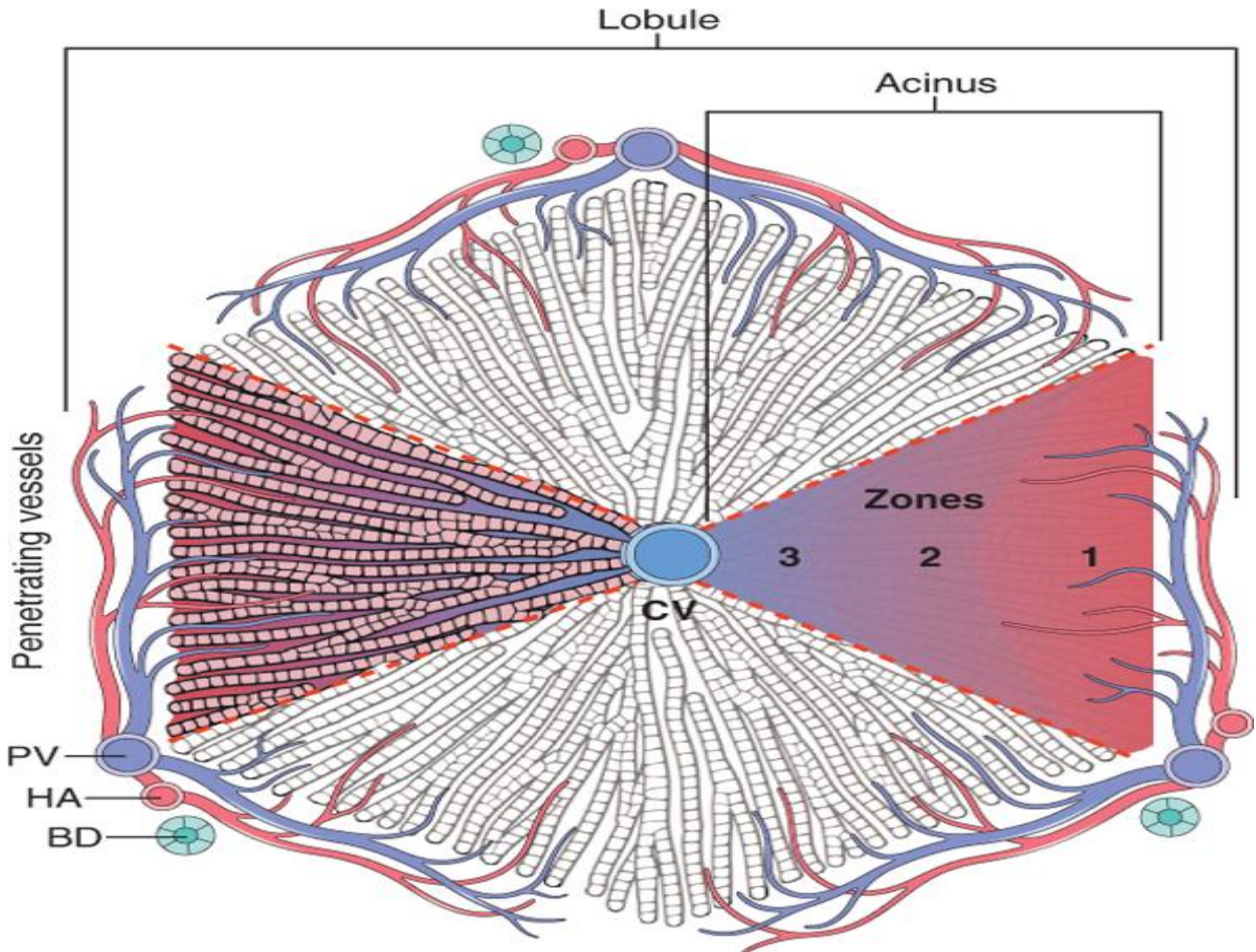
Inrmediate bet. Zone 1&2

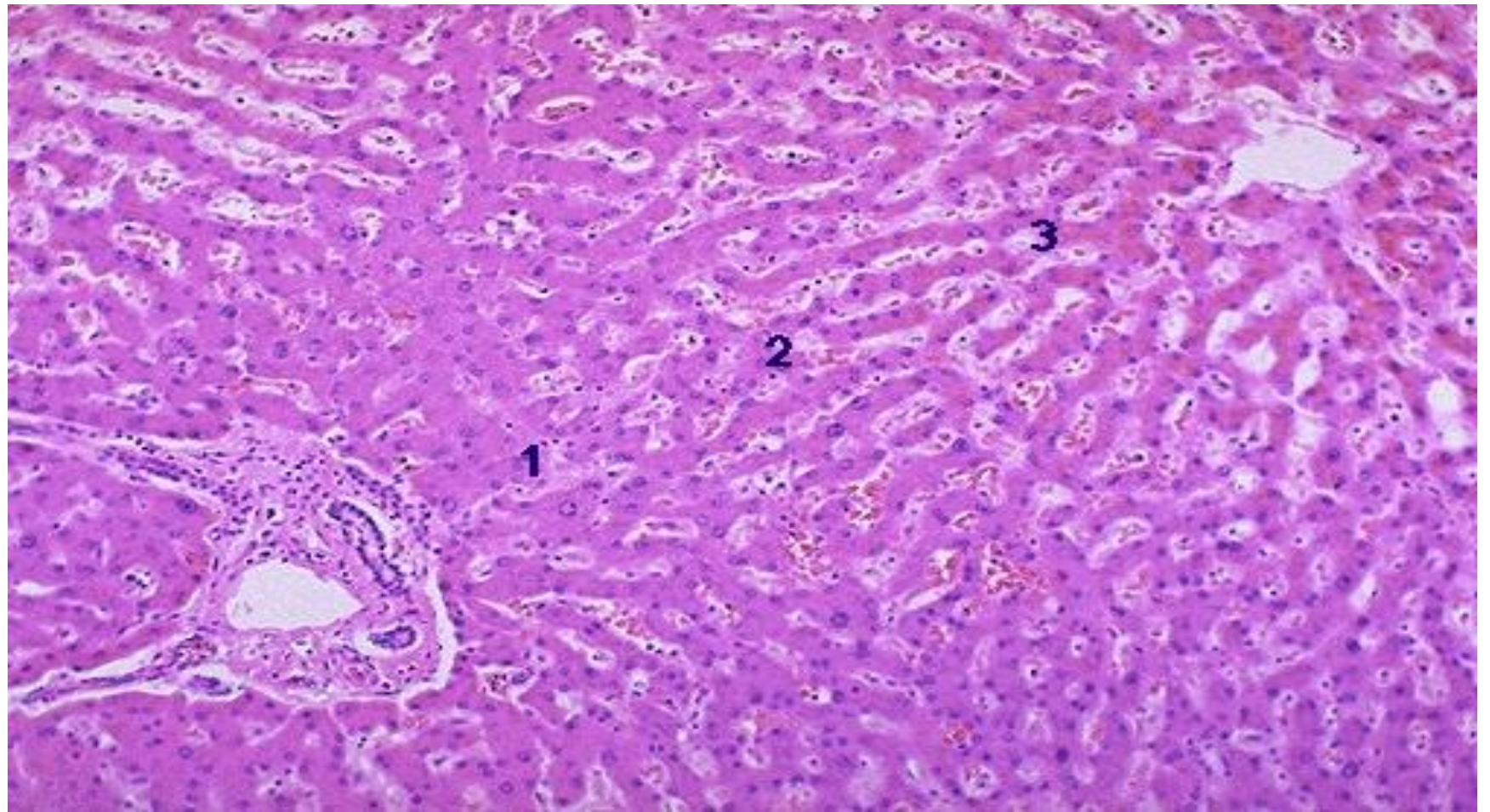
Normal Liver











The parenchyma is organized into plates of hepatocytes

Hepatocytes are radially oriented around terminal hepatic vein (central v.)

-Hepatocytes show only minimal variation in the overall size but nuclei may vary in size , number & ploidy esp. with advancing age

-Vascular sinusoids present bet. cords of hepatocytes

Hepatic injury

1-Inflammation (Hepatitis)

2-Ballooning degeneration :

- irregularly clumped cytoplasm showing large, clear spaces.

- Substances may accumulate in viable hepatocytes, including fat, iron, copper, and retained biliary material

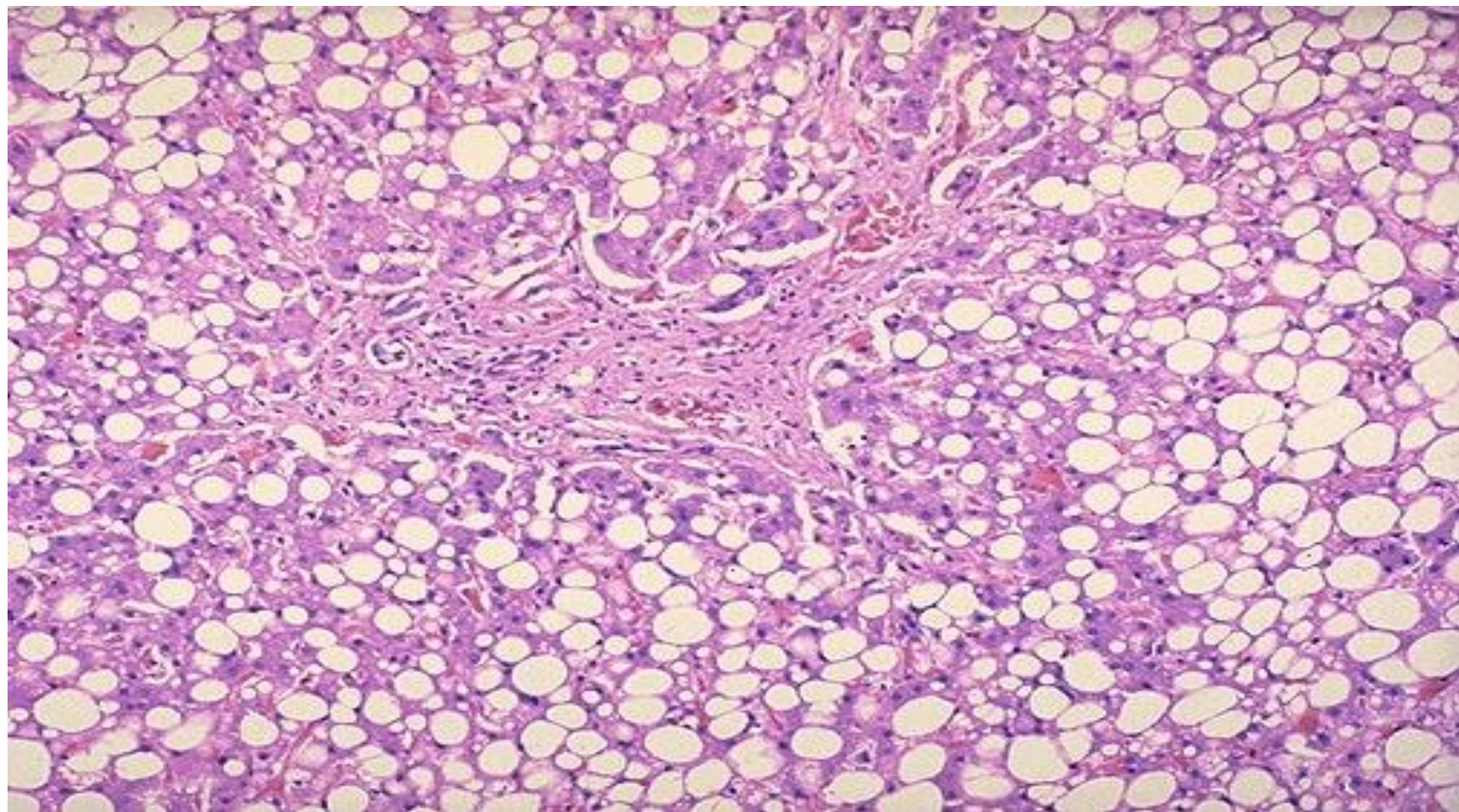
3-Steatosis (fatty change)

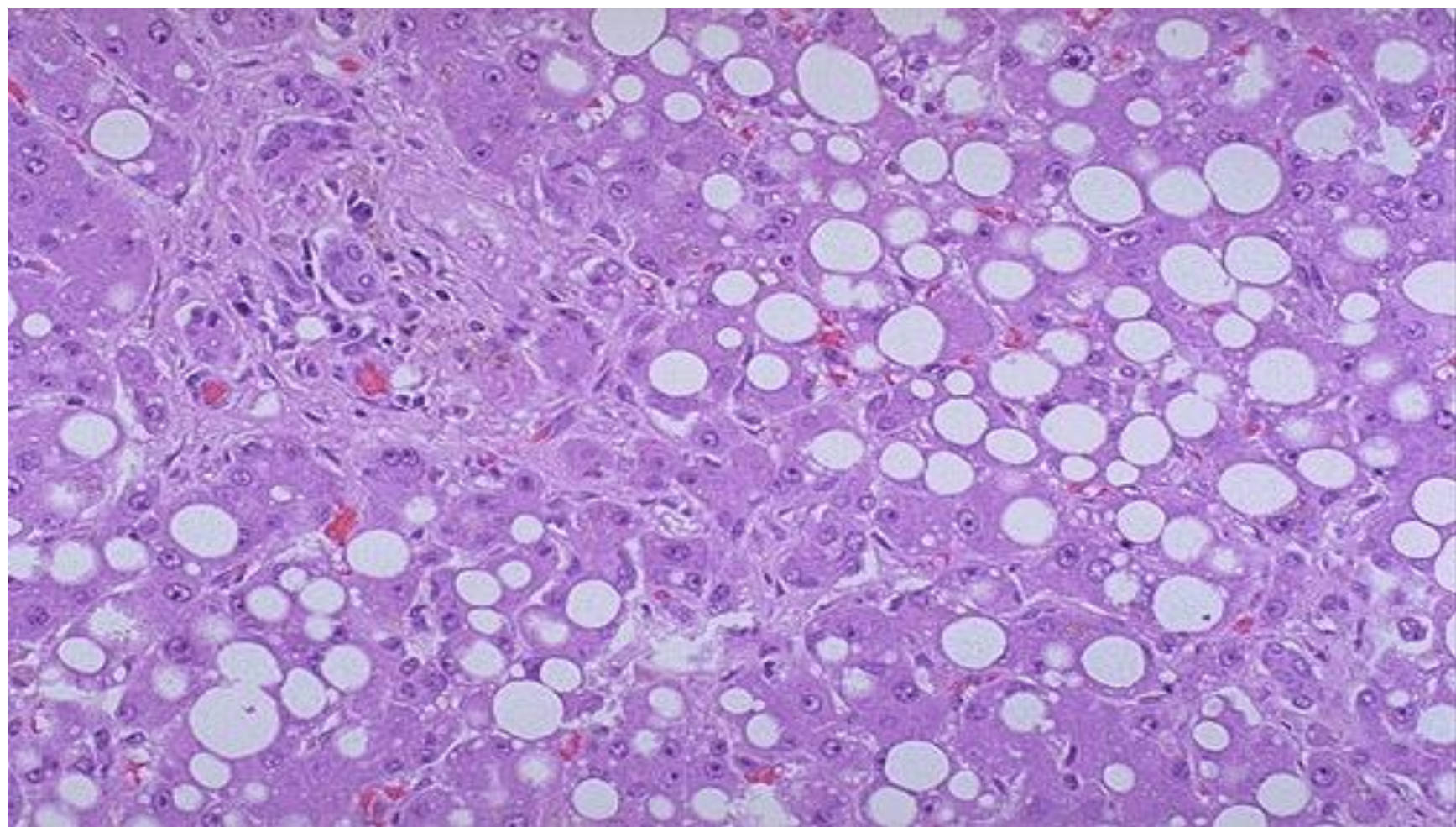
microvesicular:ALD,Reye syndrome,acute
fatty change of pregnancy

macrovesicular:DM,obese

fatty change







4-Necrosis

- Depending on the type:

Coagulative necrosis :around central v.

Councilman bodies

Lytic necrosis

Depending on the cause

Ischemic

Toxic

-depending on location

Centrilobular necrosis:

Mid zonal :

Periportal : interface hepatitis

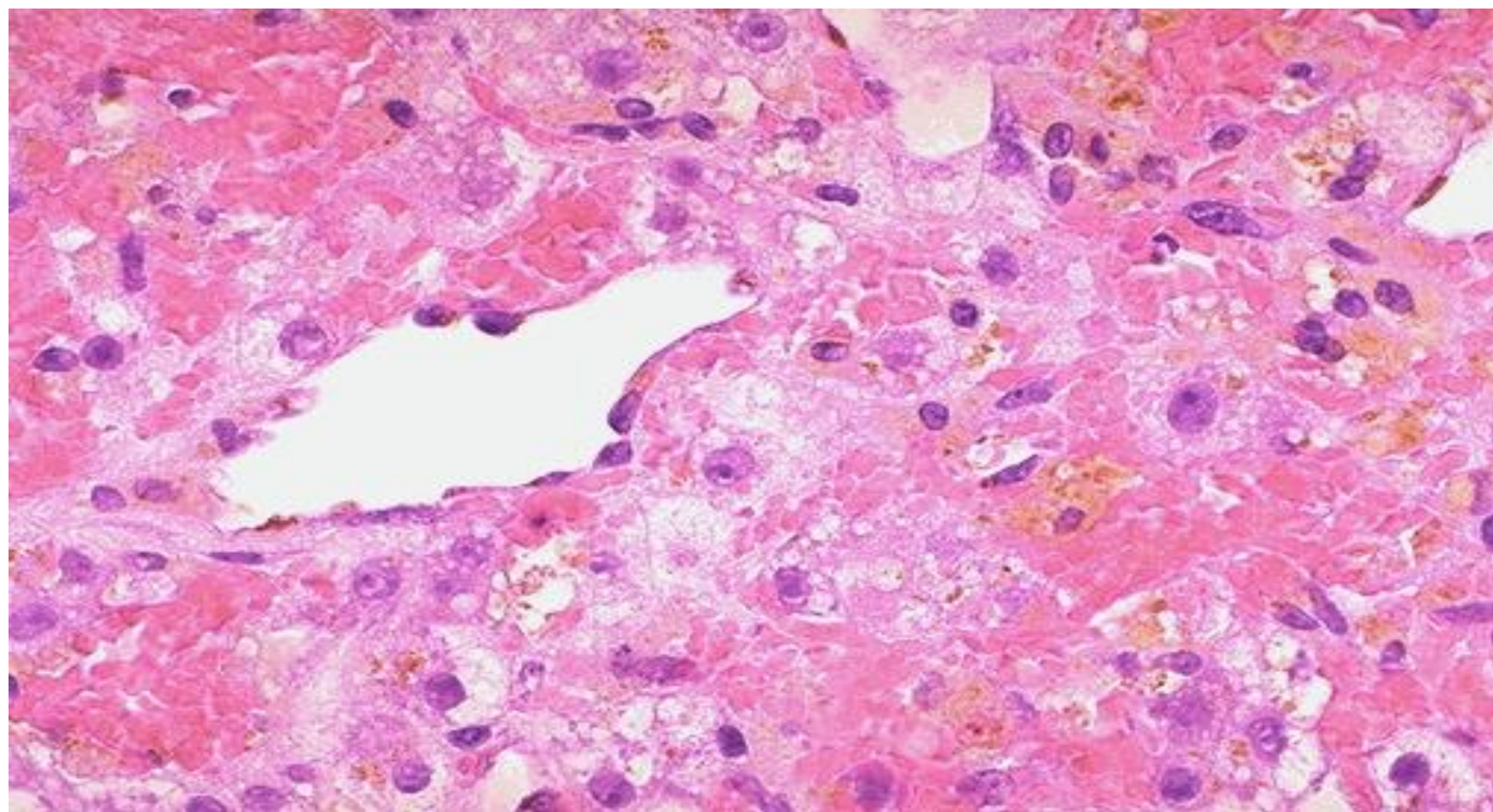
Focal:

 Piece meal necrosis

 bridging necrosis

Diffuse:

 massive & submassive necrosis



5-Regeneration

- evidenced by increased mitosis or cell cycle markers.
- the cells of the canal of Hering are the progenitor for hepatocytes & bile duct cells (oval cells).

6-Fibrosis

-*portal or periportal fibrosis*

-pericentral- around the central vein.

-*pericellular fibrosis* or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes

-*bridging fibrosis*

bridging fibrosis

7-Cirrhosis

micronodular

Macronodular

8-Ductular proliferation

Hepatic Failure

-It results when the hepatic functional capacity is almost totally lost (80 – 90%)

-Causes

1.Massive hepatic necrosis

-Fulminant viral hepatitis

-Drugs & chemicals

acetaminophen

halothane

anti TB drugs

CCL4 poisoning

Mushroom poisoning

2-Chronic liver disease

3-Hepatic dysfunction without overt cirrhosis

- Reye's syndrome
- Tetracycline toxicity
- Acute fatty liver of pregnancy

Clinical features

1-Jaundice

2-Hypoalbuminemia →edema

3-Hyperammonemia

4-Fetor hepaticus (musty or sweet & sour)

5-Palmar erythema

hyperestrogenemia

6-Spider angiomas

7-Hypogonadism & gynecomastia

Consequences:

1-Multiple organ failure kidneys & lung

2-Coagulopathy → bleeding

def. factors II, VII, IX, X

3-Hepatic encephalopathy

↓level of consciousness

Rigidity

Hyperreflexia

EEG changes

Seizures

Asterixis

4-Hepatorenal syndrome

Renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure

Massive hepatic necrosis

-Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2 -3 wks).

Subfulminant (within 3 months).

Causes:

1-Viral hepatitis 50 – 65% (B, B-D, A,C hepatitis)

2-Drugs & chemicals 20 – 30%

3-Heat stroke

4-Hepatic vein obstruction

5-Wilson disease

6-Acute fatty liver of pregnancy

7-Massive malignant infiltration

8-Reactivation of chronic HBV hepatitis on HDV superimposed infection

9-Autoimmune hepatitis

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**
-

- 27 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 & acetaminophen**

- **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

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 abstinence from further intake of alcohol

Alcoholic hepatitis

Characteristic findings :

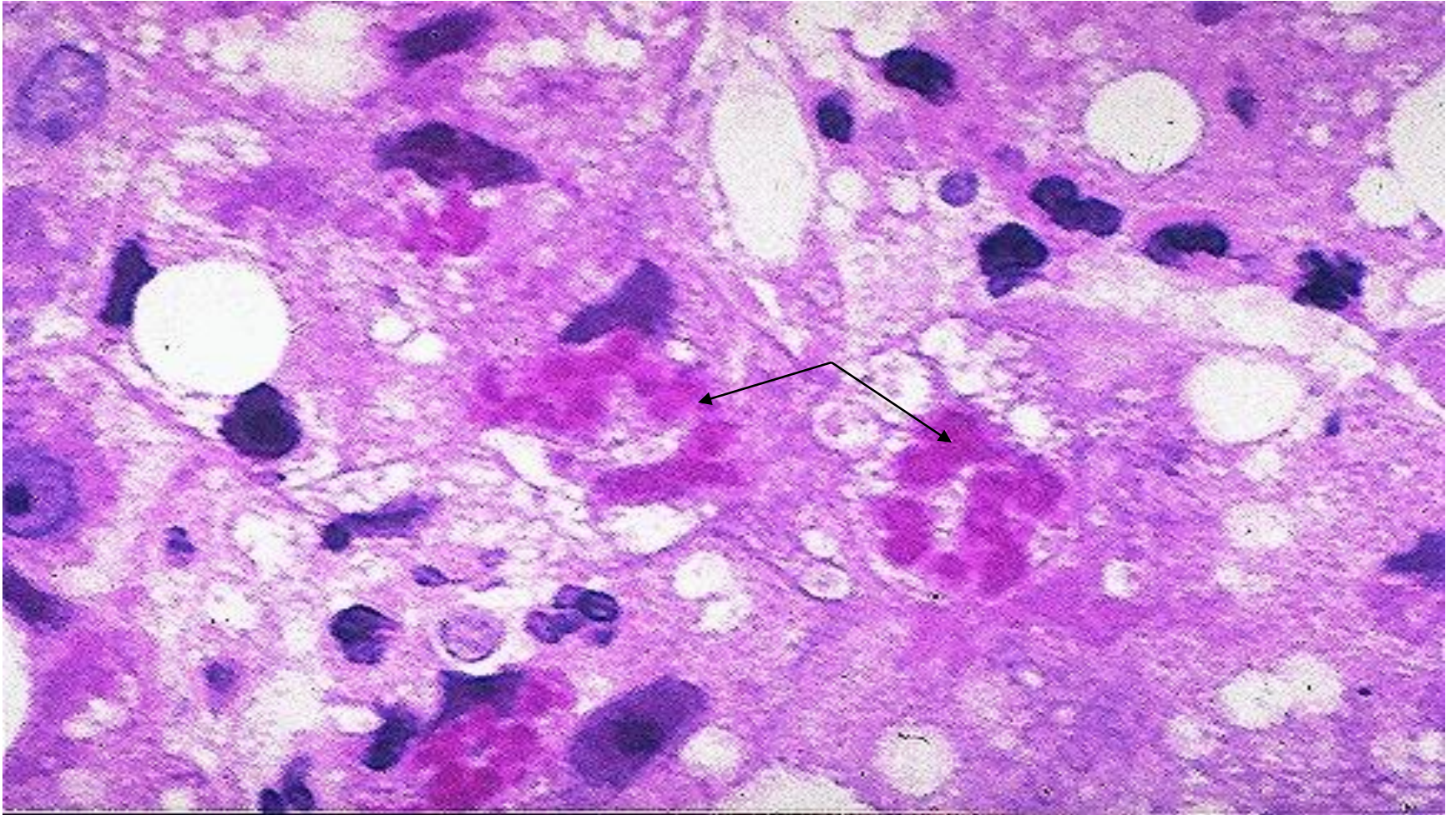
1-Hepatocyte swelling & necrosis

- Accumulation of fat & water & proteins
- Cholestasis
- Hemosidrein deposition in hepatocytes & 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

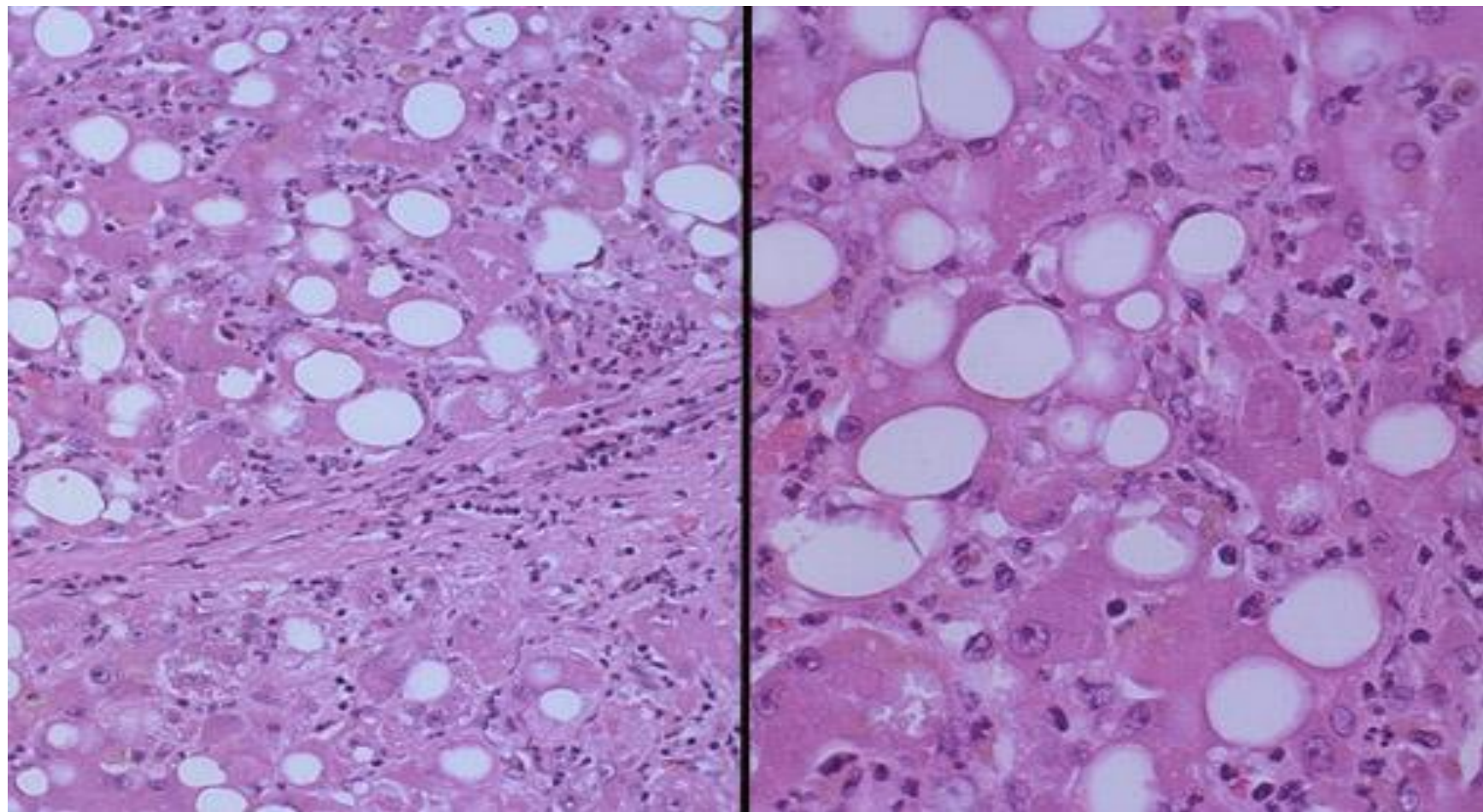
4-Fibrosis

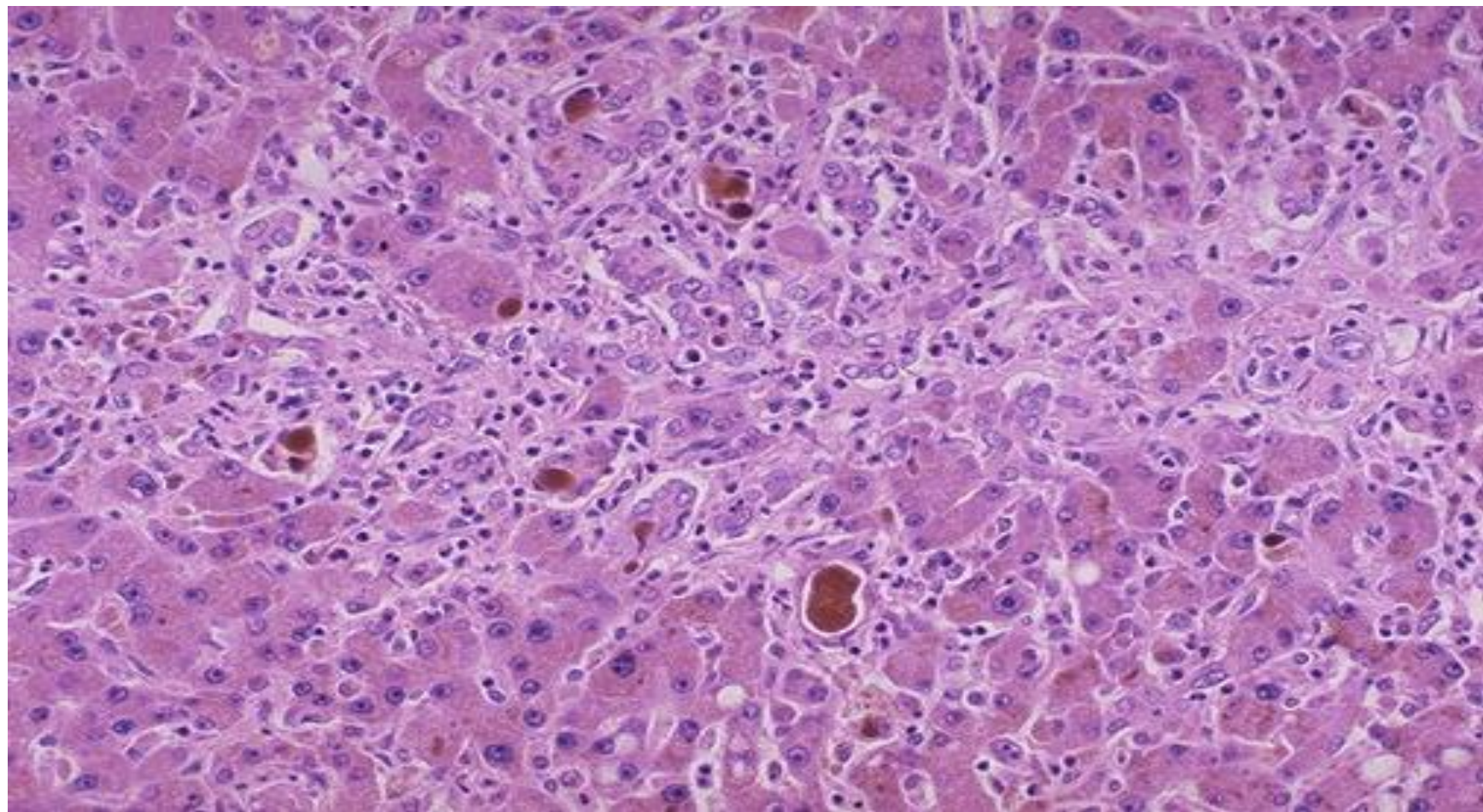
-Sinusoidal & perivenular fibrosis

-Periportal fibrosis

5-Cholestasis

6-Mild deposition of hemosiderin in
hepatocytes & kupffer cells



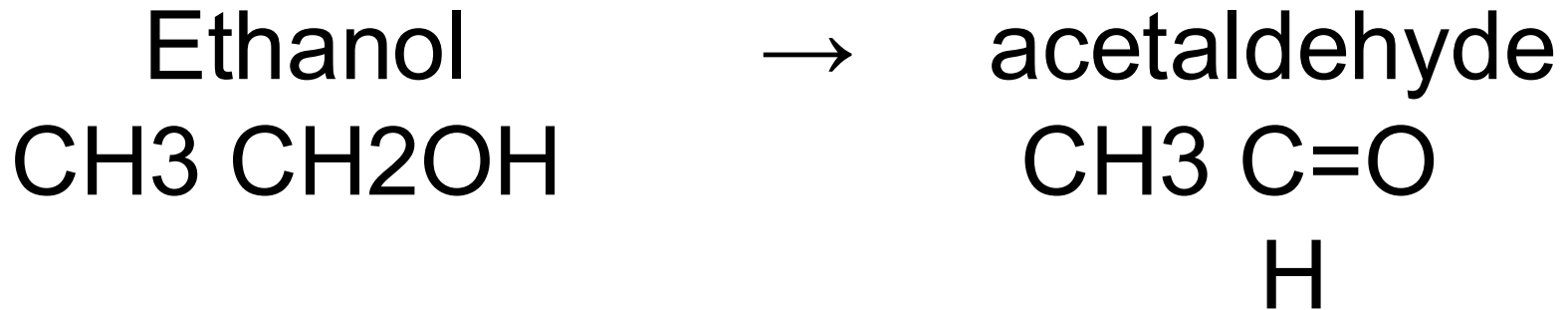


Alcoholic cirrhosis

- Usually it develops slowly
- Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < 1 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).



Ethanol metabolism



- ↑
- 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 (8beers) → 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 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- ↓ sec. 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 acetaminophen)

- 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

Cirrhosis

- **It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules .**

- **Main characteristics**

1. Bridging fibrous septae

2. Parenchymal nodules encircled by fibrotic bands

3. Diffuse architecture disruption

- **Types :**

Micronodules < 3mm in diameter

Macronodules > 3 mm in diameter

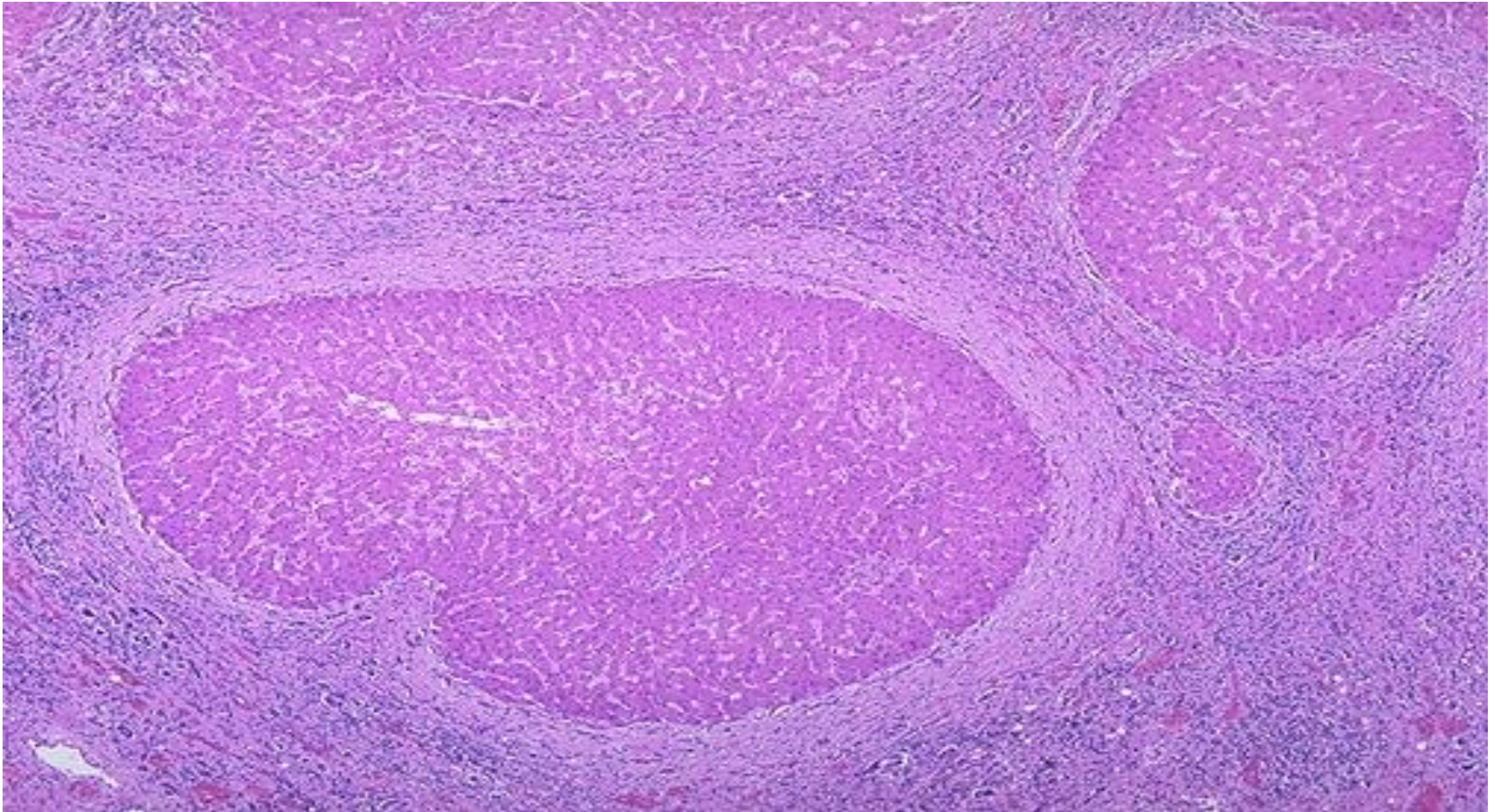
Micronodular cirrhosis



Macronodular cirrhosis



Cirrhosis



Causes of cirrhosis

- 1.Chronic alcoholism**
- 2.Chronic viral infection HBV & HCV**
- 3.Biliary disease**
- 4.Hemochromatosis**
- 5.Autoimmune hepatitis**
- 6.Wilson disease**
- 7. α -1- antitrypsin deficiency**

8. Rare causes

Galactosemia

Tyrosinosis

Glycogen storage disease III & IV

Lipid storage disease

Hereditary fructose intolerance

Drug induced e.g. methyldopa

9. Cryptogenic cirrhosis 10%

Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

- 1-Hepatocellular death
- 2-Regeneration
- 3-Progressive fibrosis
- 4-Vascular changes

Cell death should occur over a long period of time & accompanied by fibrosis

-In normal liver the ECM collagen (types I, III, V & XI) is present only in :

Liver capsule

Portal tracts

Around central vein

- delicate framework of type IV collagen & other proteins lies in space of Disse
- In cirrhosis types I & III collagen & others are deposited in the space of Disse

The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of Disse

-Perisinusoidal stellate cells act normally as storage cells for vit A & fat

upon stimulation myofibroblast- like cells



transforming growth factor β
(TGF- β)

The stimuli for the activation of stellate cells
& production of collagen are :

1-reactive oxygen species

2-Growth factors

3-cytokines TNF, IL-1, lymphotoxins

-The vascular changes include :

1-Loss of sinusoidal endothelial cell fenestration

2-development of vascular shunts as

Portal v- hepatic v

Hepatic a – portal v

→defect in liver function

-Loss of microvilli from hepatocytes →↓ transport capacity of the cells

- Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
- the movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and the plasma is markedly impaired.
- These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell.

-Clinical features of cirrhosis :

-Silent

-Anorexia, wt loss, weakness

-Complications :

1-Progressive hepatic failure

2-Portal hypertension

3-Hepatocellular carcinoma

Portal hypertension

- ↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules
- Arterial – portal anastomosis develops in the fibrous bands → increase in the blood pressure in portal venous system

- **Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension by imposing arterial pressure on the normally low-pressure portal venous system.**

Causes of portal hypertension

I. Prehepatic

- 1-Portal vein thrombosis
- 2-Massive splenomegaly

II. Post hepatic

- 1-Severe Rt.- sided heart failure
- 2-Constrictive pericarditis
- 3-Hepatic vein out flow obstruction

III. Hepatic

- 1-Cirrhosis
- 2-Schistosomiasis
- 3-Massive fatty change
- 4-Diffuse granulomatosis as sarcoidosis, TB
- 5-Disease of portal microcirculation as nodular regenerative hyperplasia

Clinical consequence of portal hypertension

1-Ascitis

2-Portosystemic shunts

3-Hepatic encephalopathy

4-Splenomegaly

Ascitis

- Collection of excess fluid in peritoneal cavity
- It becomes clinically detectable when at least 500 ml have accumulated

-Features

- 1-Serous fluid
- 2-Contains as much as 3g/ml of protein (albumin)
- 3-It has the same concentration as blood of glucose, Na⁺, & K⁺
- 4-Mesothelial cells & lymphocytes
- 5-Neutrophils = infection
- 6-RBCs = DISSEMINATED CANCER

Pathogenesis

1-Sinusoidal \uparrow Bp

2-Hypoalbuminemia

3-Leakage of hepatic lymph into the peritoneal cavity

Normal thoracic duct lymph flow is 800-1000 ml/d

in cirrhosis is 20L /d

4-Renal retention of Na^+ & water due to 2ry hyperaldosteronism

Portosystemic shunt

-Because of \uparrow portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds

-Sites:

1-Around & within the rectum (Hemorrhoids)

2-Gastroesophageal junction (varicies)

3-Retroperitoneum

4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) \rightarrow caput medusae

- Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1 bleeding

caput medusae



Esophageal varicies



Splenomegaly

- Usu. 500-1000 gms (N <300gms)
- Not necessarily correlated with other features of portal \uparrow Bp
- May result in hypersplenism

splenomegaly



cm 1 2 3 4

Hepatic encephalopathy

- It is a complication of acute & chronic hepatic failure
- Disturbance in brain function ranging from behavioural changes to marked confusion & stupor to deep coma & death
- The changes may progress over hrs. or days

Neurological signs:

Rigidity

Hyper-reflexia

Non – specific EEG

Seizures

Asterixis (non-rhythmic rapid extension flexion movements of head & extremities .

-Brain shows edema & astrocytic reaction

Pathogenesis

-Physiologic factors important in development of hepatic encephalopathy :-

1-Severe loss of hepatocellular function

2-Shunting of blood around damaged liver



Exposure of Brain to toxic metabolic products

↑ NH₃ level in blood → generalized brain edema impaired neuronal function

alteration in central nervous system AA metabolism

Drug – Induced liver disease

-Drug reactions:-

1-Predictable (intrinsic)

2-Unpredictable (idiosyncratic)

**-Predictable drug reactions depends on the dose
(dose-dependent)**

-Unpredictable drug reactions depend on :

a-The immune response of the host to the antigenic stimulus

b-The rate at which the host metabolizes the agent

-The injury m.b immediate or takes weeks to months

-Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis

Predictable drugs:

Acetaminophen

Tetracycline

Antineoplastic agents

CCL₄

Alcohol

Unpredictable drugs

Chlorpromazine

Halothane

Sulfonamides

Methyldopa

Allopurinol

-Mechanism of drug injury :

1-Direct toxic damage

e.g acetaminophen

CCl₄

mushroom toxins

2-Immune-mediated damage

-Patterns of injury

- 1-Hepatocellular necrosis
- 2-Cholestasis
- 3-Steatosis
- 4-Steatohepatitis
- 5-Fibrosis
- 6-Vascular lesions
- 7-Granuloma
- 8-Neoplasms benign & malignant

-

Drugs that may cause acute liver failure

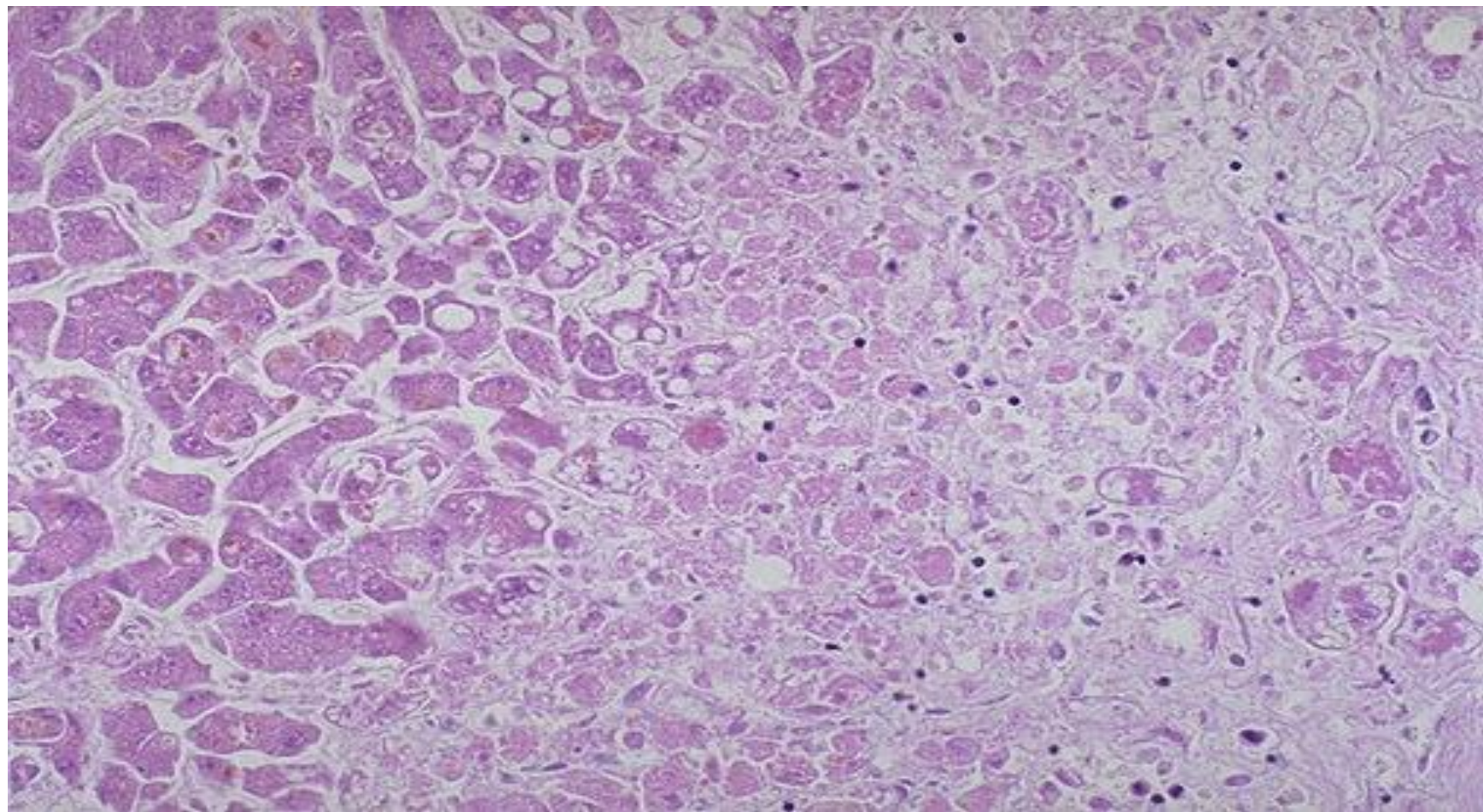
- 1-Acetaminophen most common
- 2-Halothane
- 3-Antituberculosis drugs (rifampin, isoniazid)
- 4-Antidepressant monoamine oxidase inhibitors
- 5-Toxins as CCL4 & mushroom poisoning

Morphology:

Massive necrosis → 500 – 700 gm liver

Submassive necrosis

Patchy necrosis



Fulminant hepatitis

Hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy in 2-3 wks

Subfulminant (up to 3 mon)

Causes :

1-Viral hepatitis 50 – 65%

 HBV 2x > HCV

2-Drugs & chemical 25- 50%

 e.g Isoniazid , halothane , methyldopa & acetaminophen

3-Obstruction of hepatic vein

4-Wilson's disease

5-Acute fatty change of pregnancy.

6-Massive tumor infiltration

7-Reactivation of chronic hepatitis B

8-Acute immune hepatitis

- **Morphology**

- ↓ liver size (500 – 700 gm)

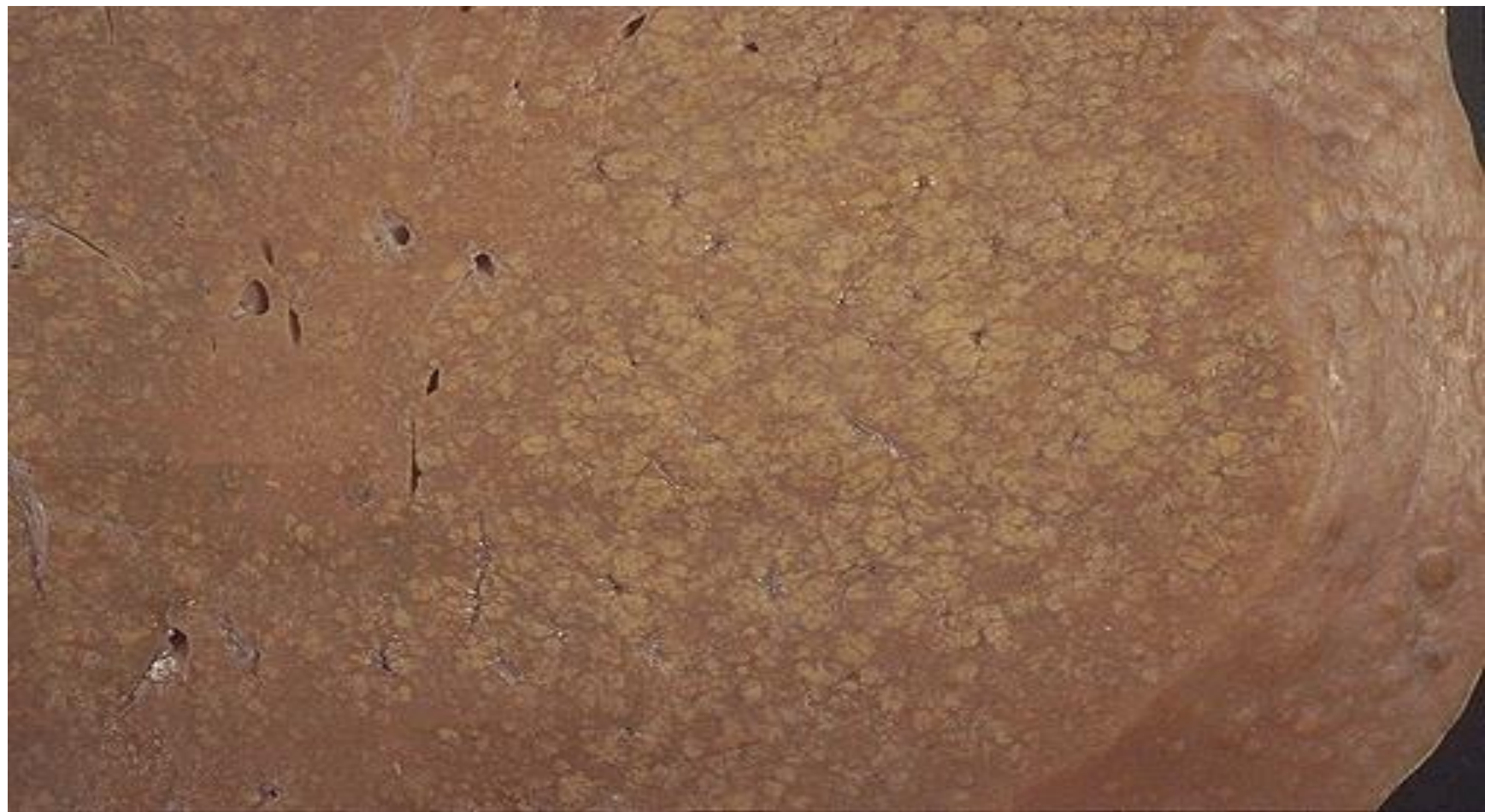
- Necrosis of hepatocytes

- Collapsed reticulin tissue

- Inflammatory infiltrate

- Regenerative activity of hepatocytes

- Fibrosis



Chronic Hepatitis

- Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease for more than 6 months with histologically documented inflammation & necrosis**
- Progressive or non progressive**
- HBV , HCV, HBV-HDV**

- **Morphology of chronic hepatitis**

-Mild to severe

1. Portal inflammation

2. Lymphoid aggregate

3. Necrosis of hepatocytes-councilman bodies

4. Bile duct damage

5. Steatosis

6. Interface hepatitis

7. Bridging necrosis & fibrosis

8. Fibrosis

9. Ground-glass appearance

10. Sanded nuclei

11. Lobular disarray

