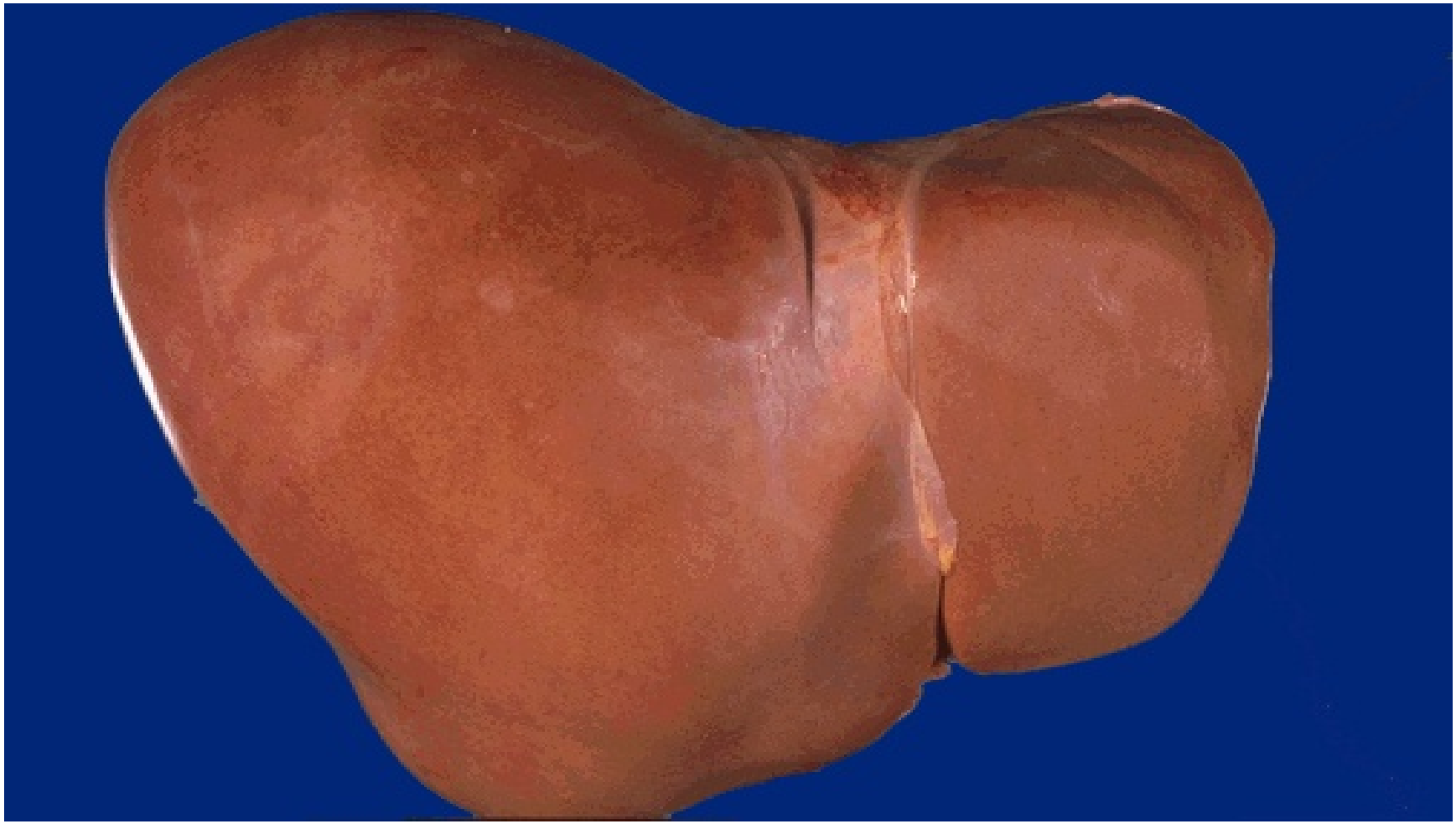
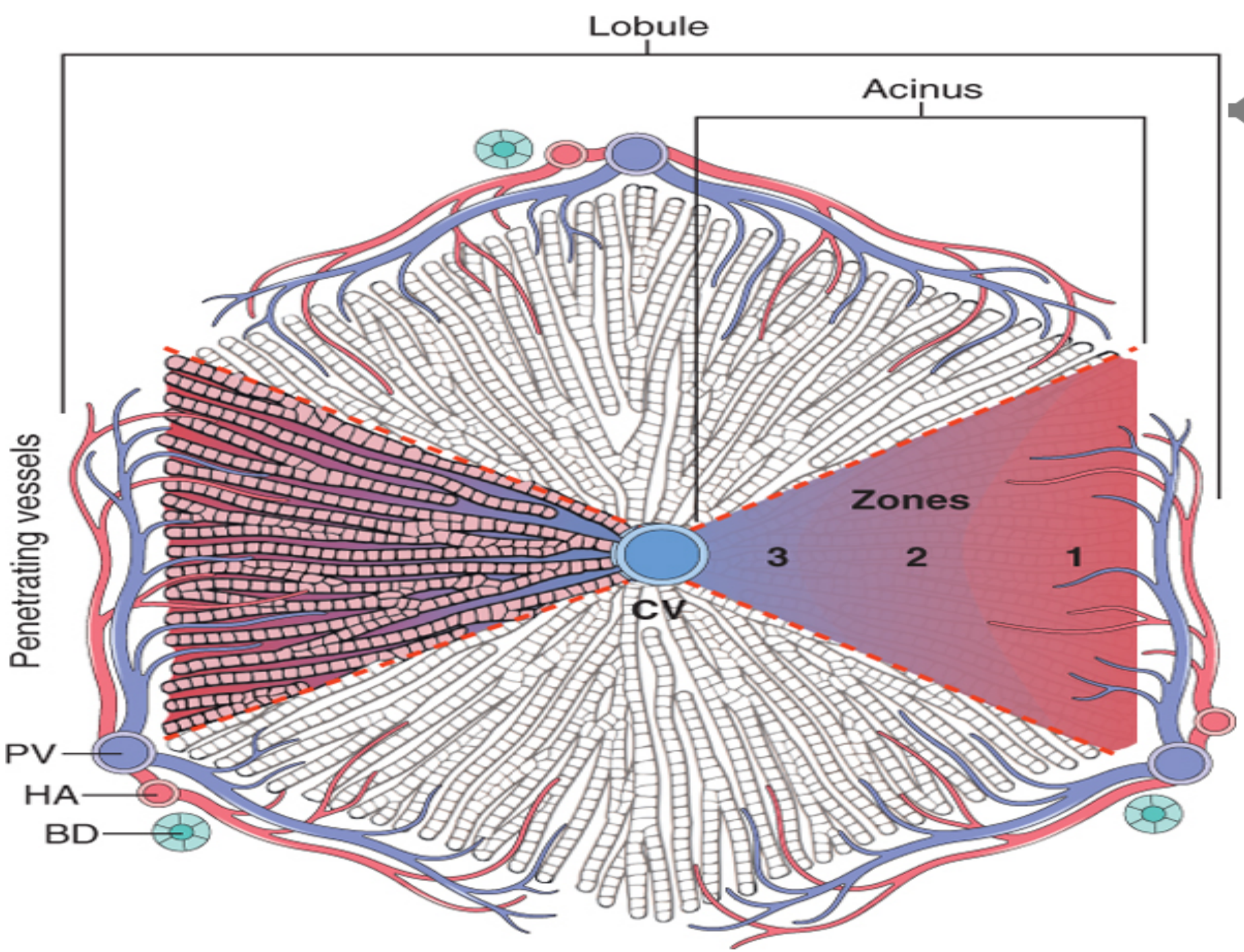
LECTURE 1

Liver





The parenbchyma is organized into plates of hepatocytes

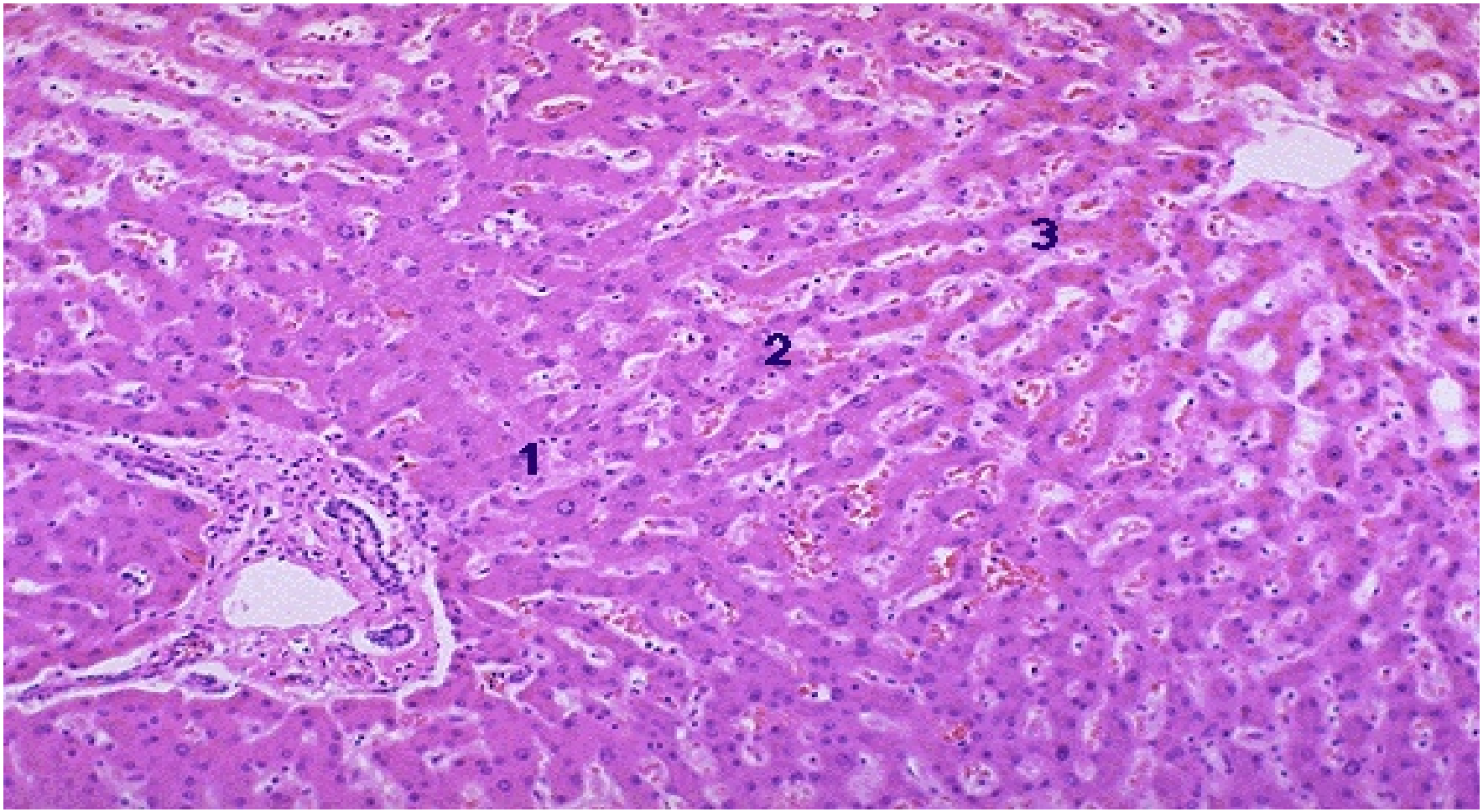
Hepatocytes are radially oriented around terminal hepatic vein (central v.)

-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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2
3

Hepatic Injury

1-Inflammation (Hepatitis)

2-Ballooning degeneration :

-irregularly clumped cytoplasm showing large, clear spaces.

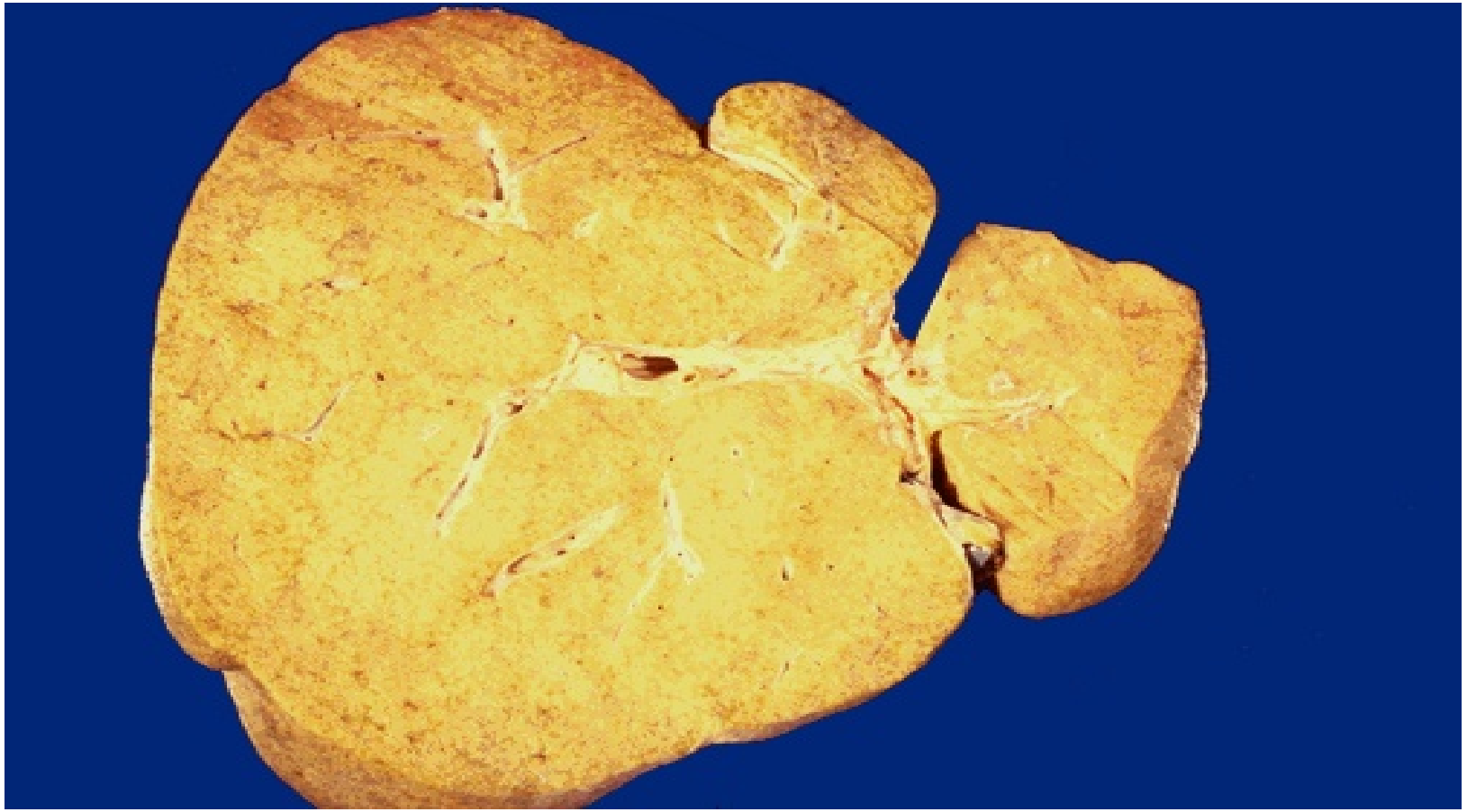
-Substances may accumulate in viable hepatocytes, including fat, iron, copper, and retained biliary material

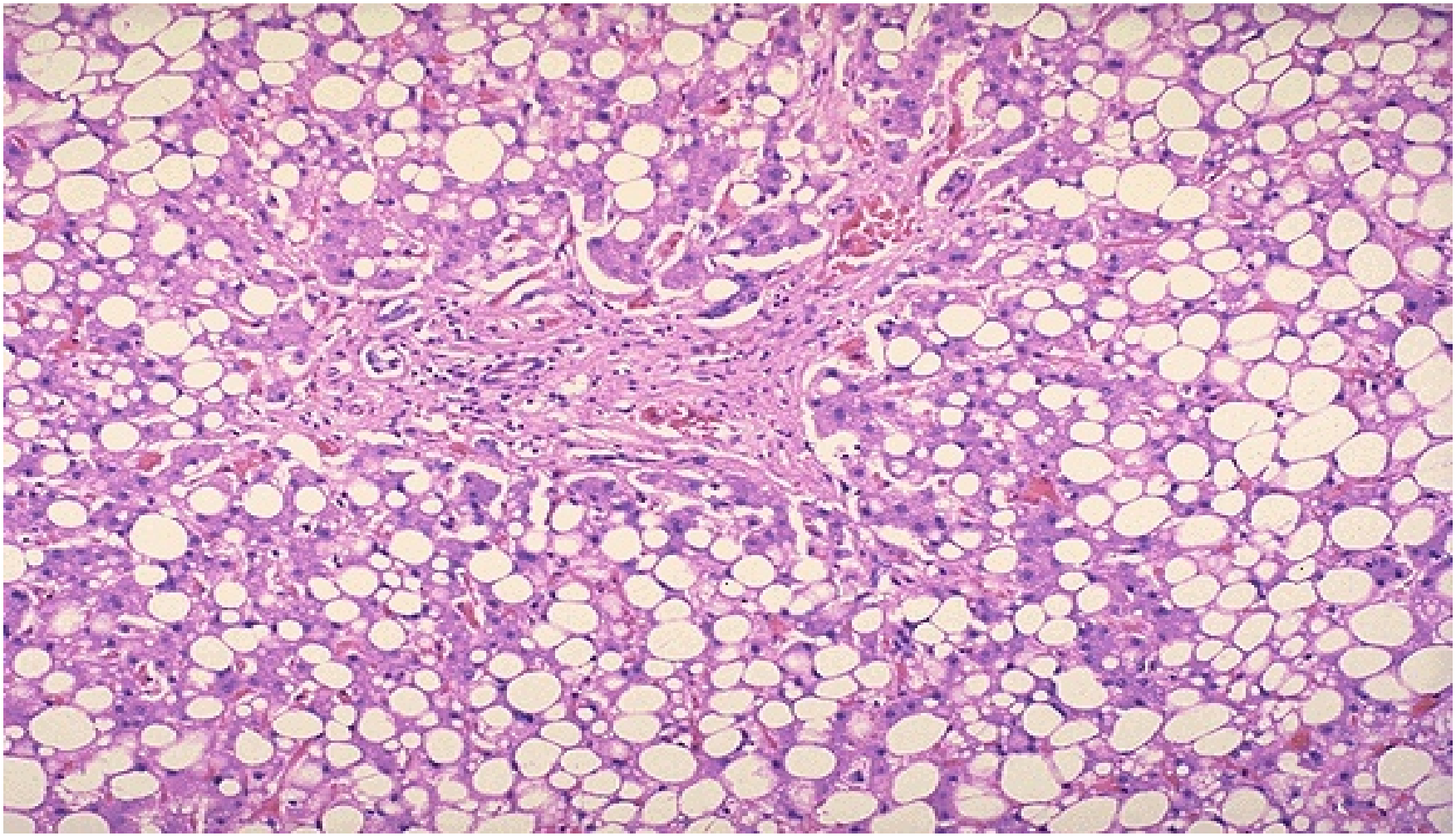
3-Steatosis (fatty change)

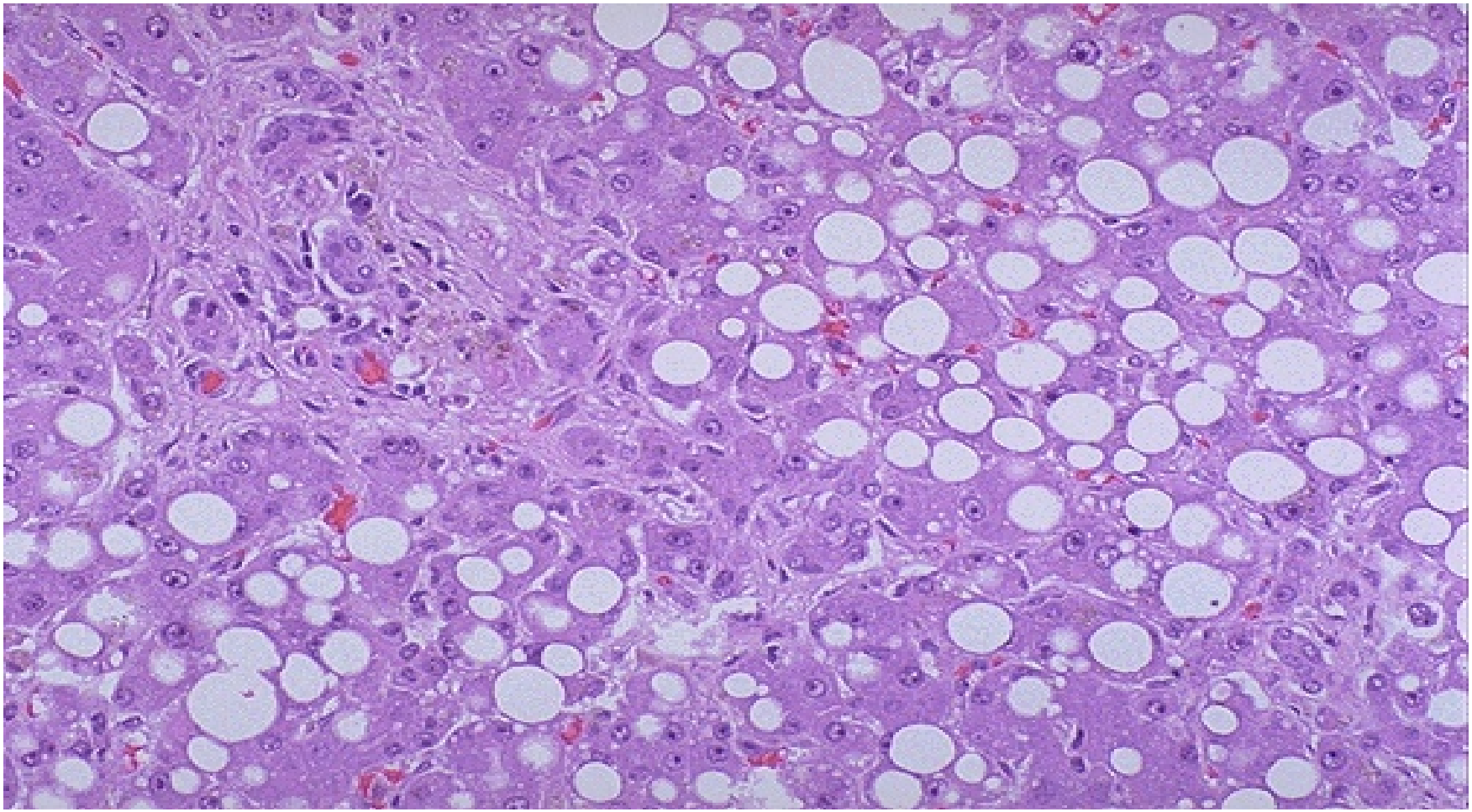
microvesicular:ALD,Reye syndrome, acute fatty change of pregnancy

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.

-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

acetominophen

halothane

anti TB drugs

CCL4 poisoning

Mushroom poisoning

2-Chronic liver disease

3-Hepatic dysfunction without overt cirrhosis

-Reye's syndrome

-Tetracyline toxicity

-Acute fatty liver of pregnancy

4-Hepatorenal syndrome

Renal failure in patients with severe liver disease with no morpholgic 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

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

-

- 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

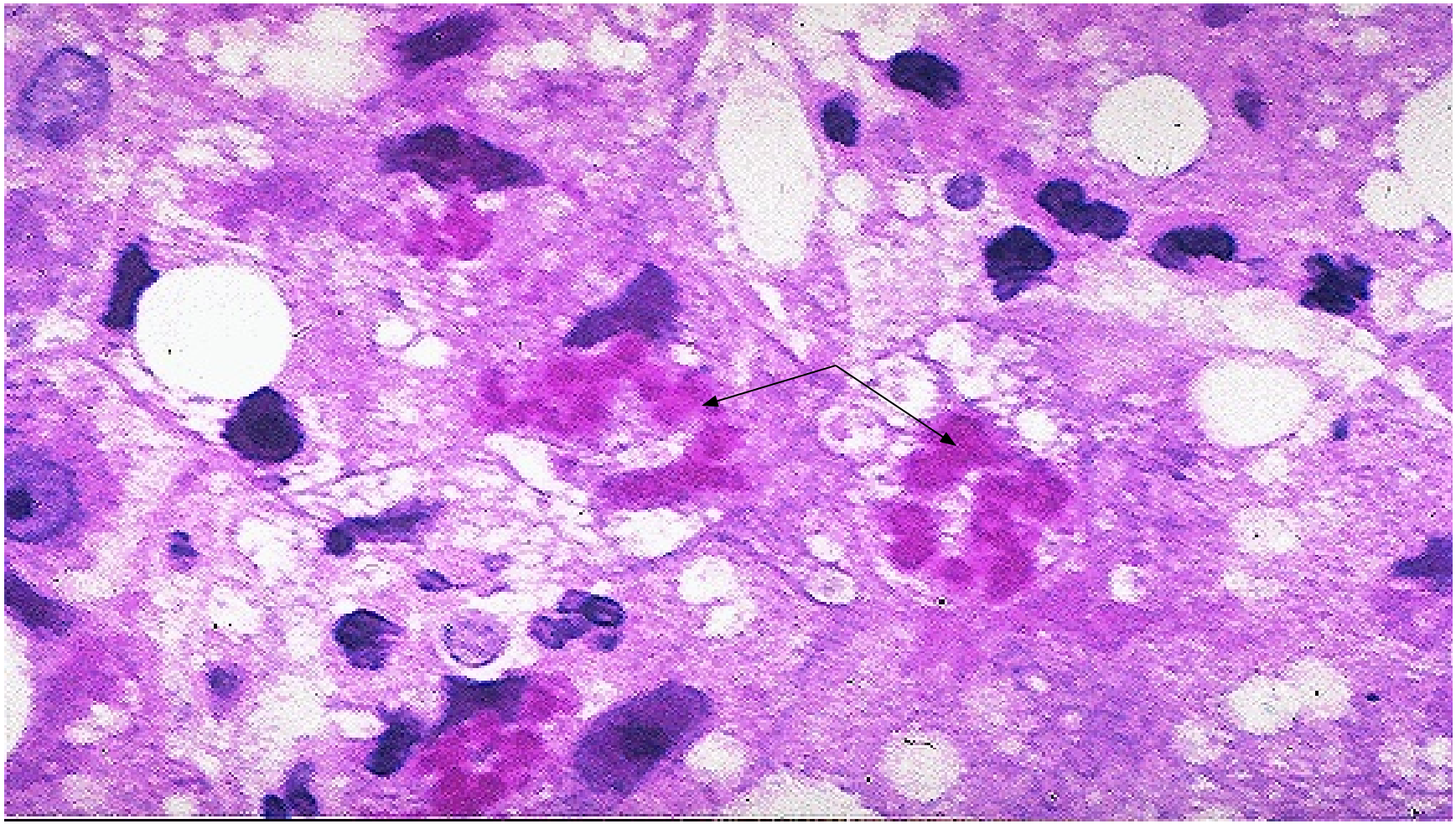
-Cholestasis

-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

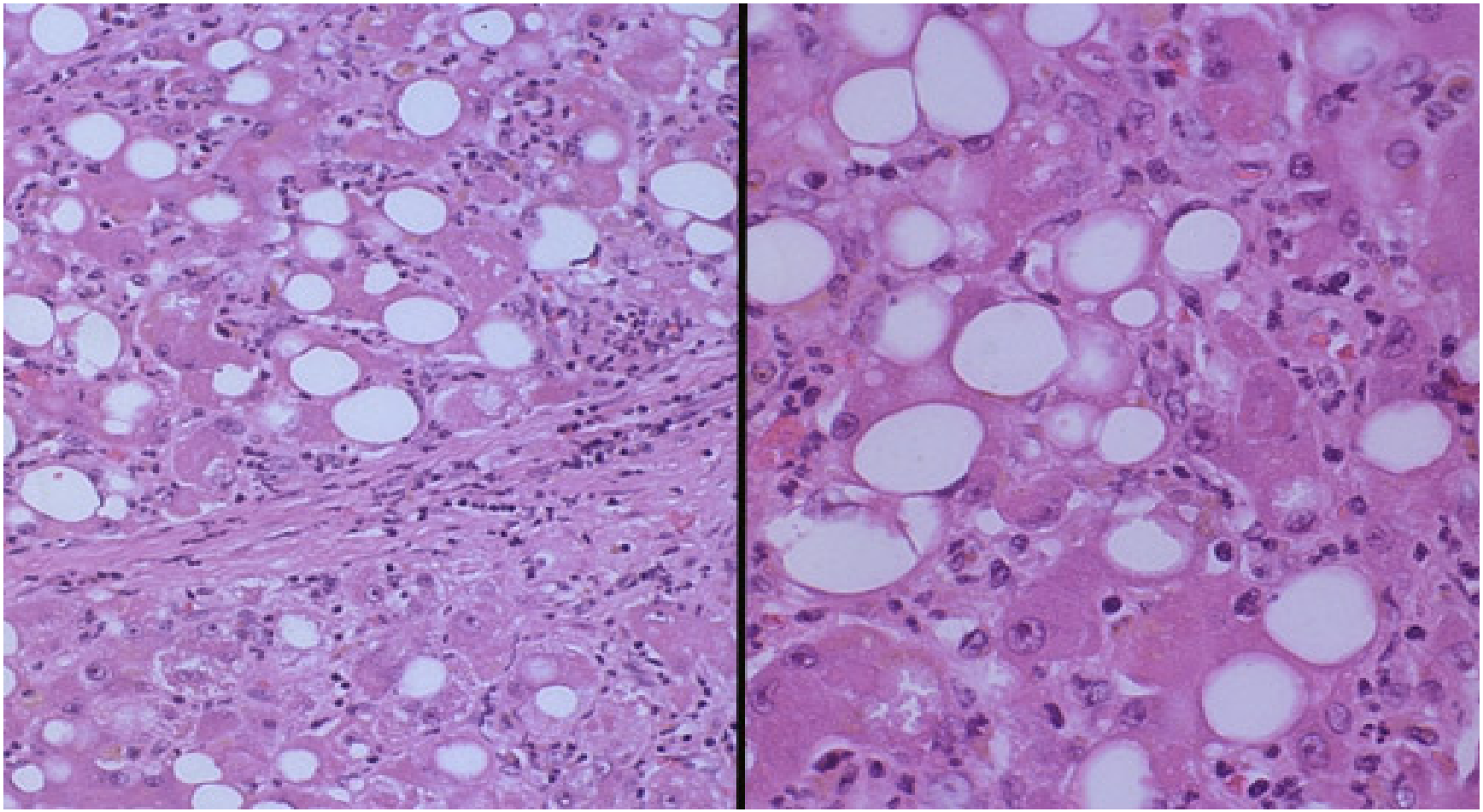
4-Fibrosis

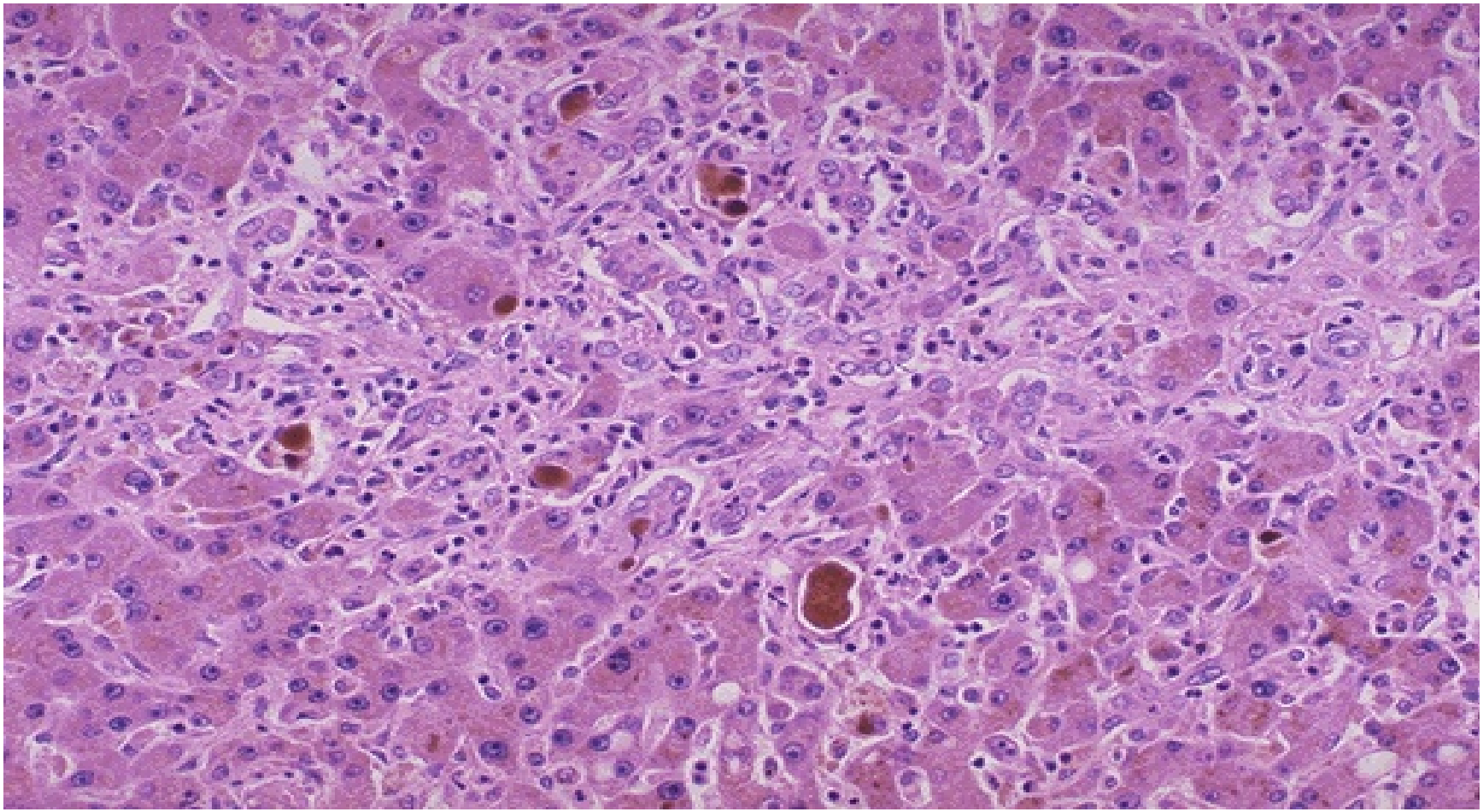
-Sinusoidal & perivenular fibrosis

-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

LECTURE 3

Cirrhosis

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

- **Main characteristics**

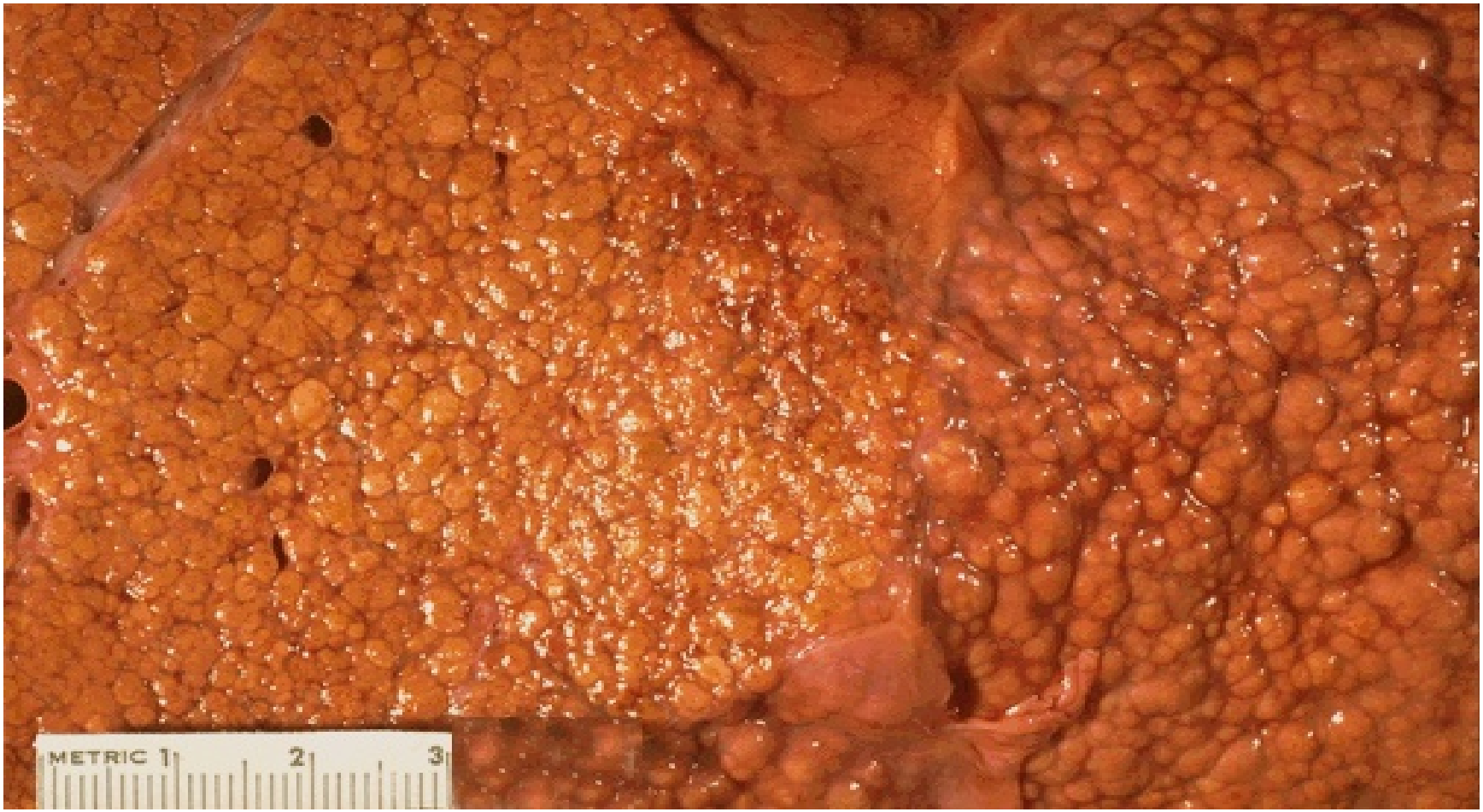
1. Bridging fibrous septae
2. Parenchymal nodules encircled by fibrotic bands
3. Diffuse architecture disruption

- **Types :**

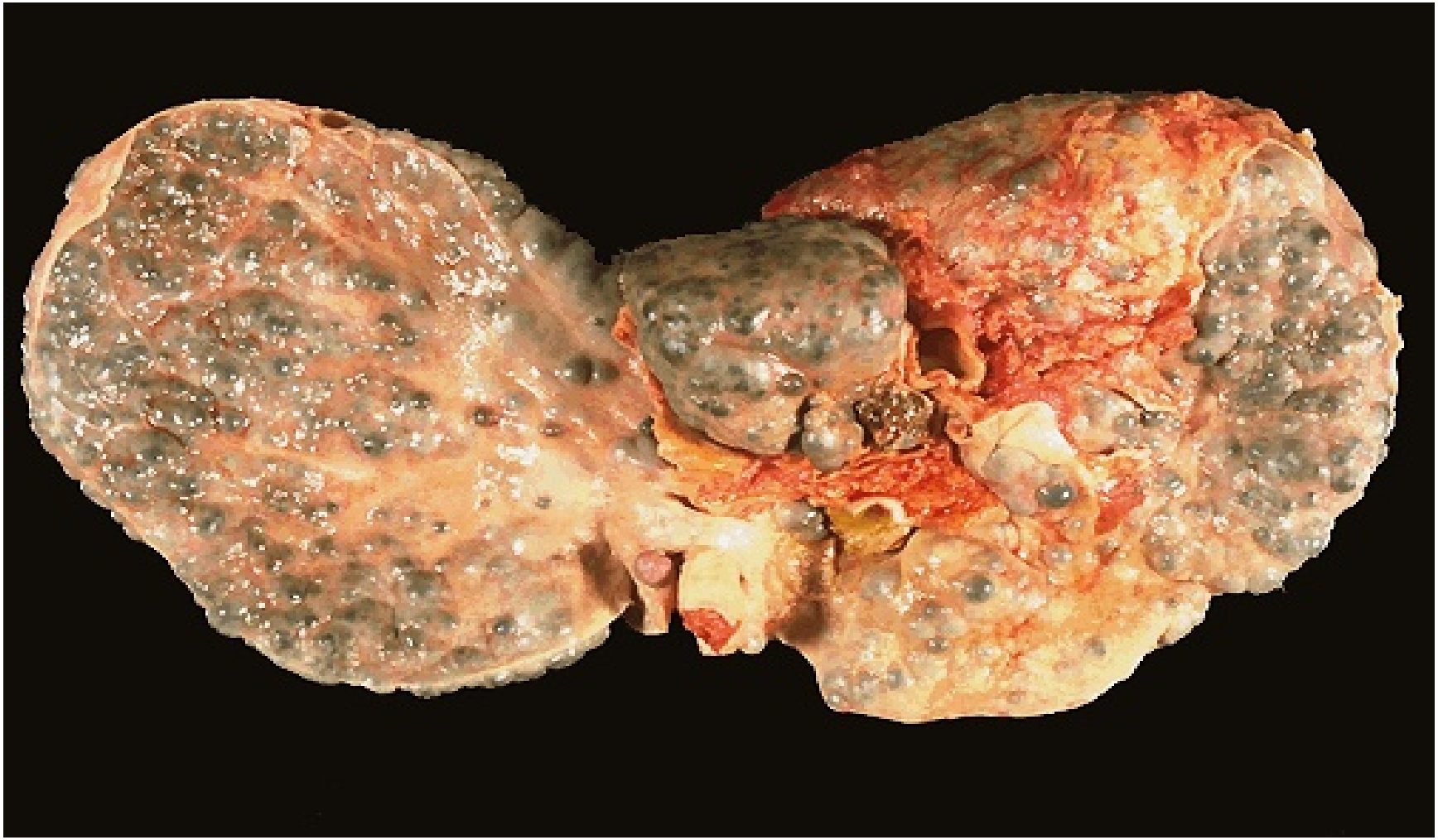
Micronodules < 3mm in diameter

Macronodules > 3 mm in diameter

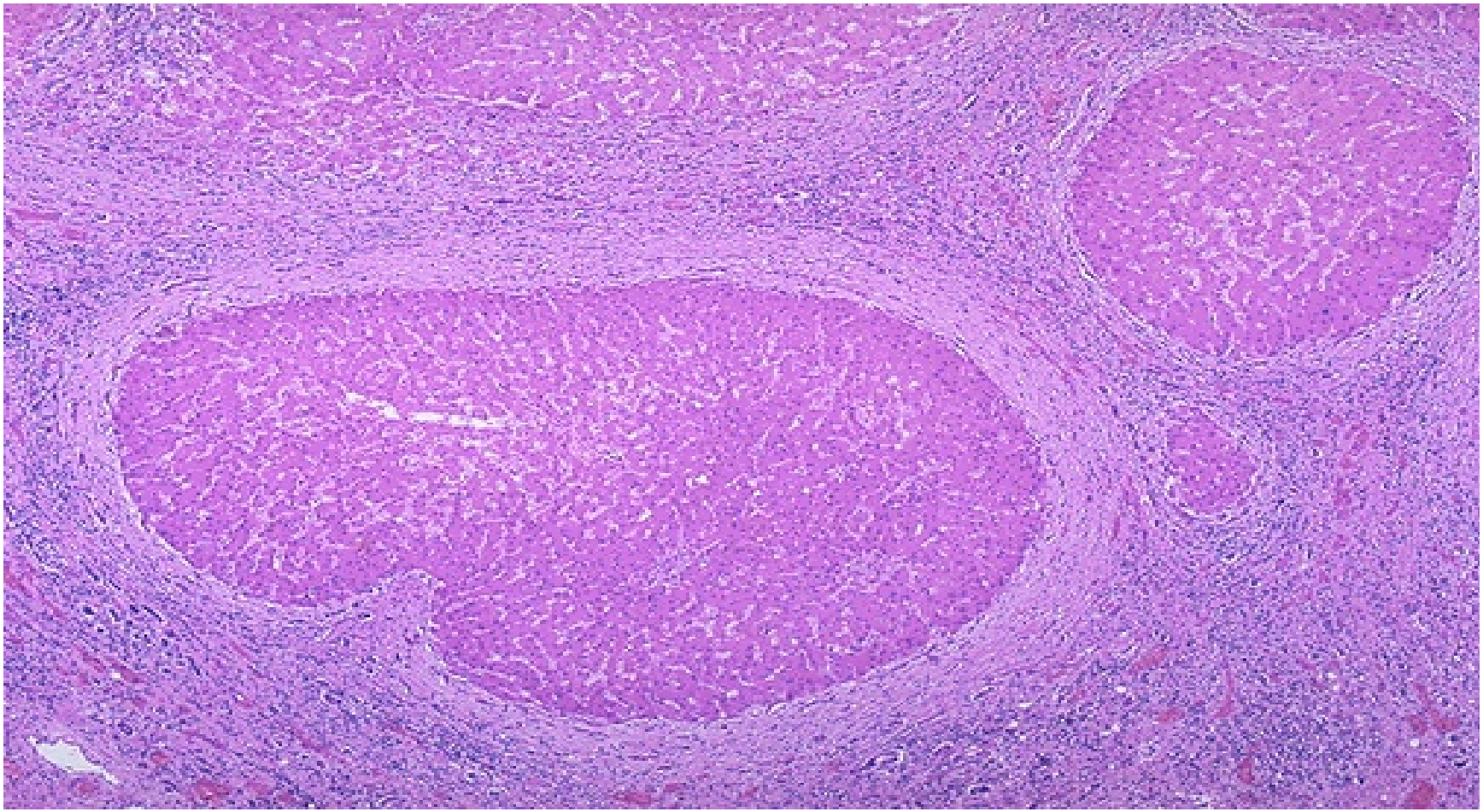
Micronodular cirrhosis



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-I, 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 CANCR

Pathogenesis

1-Sinusoidal ↑ 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 ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds

-Sites:

1-Around & within the rectum (Hemorrhoids)

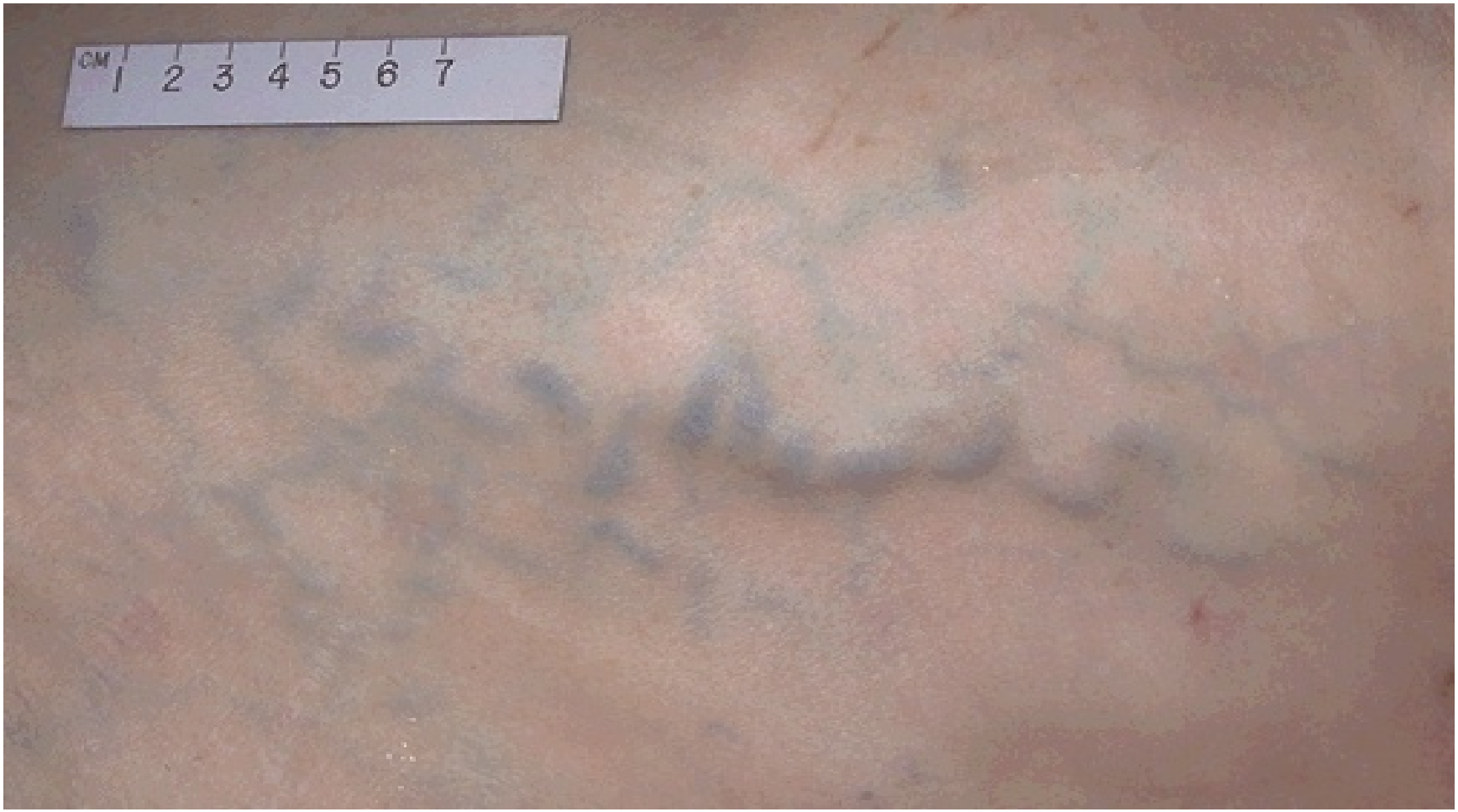
2-Gastroesophageal junction (varicies)

3-Retroperitoneum

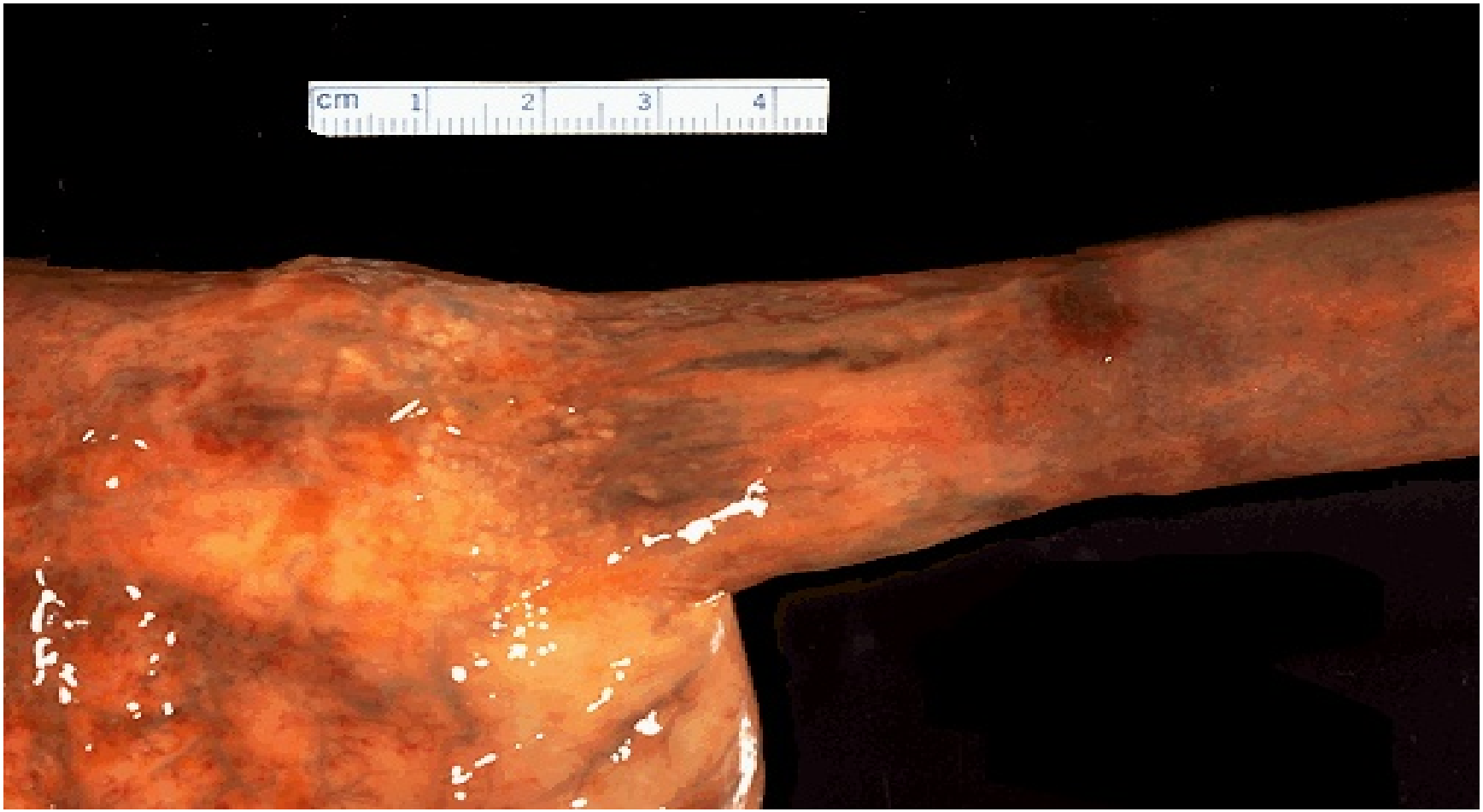
4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

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

caput medusae



Esophageal varicies



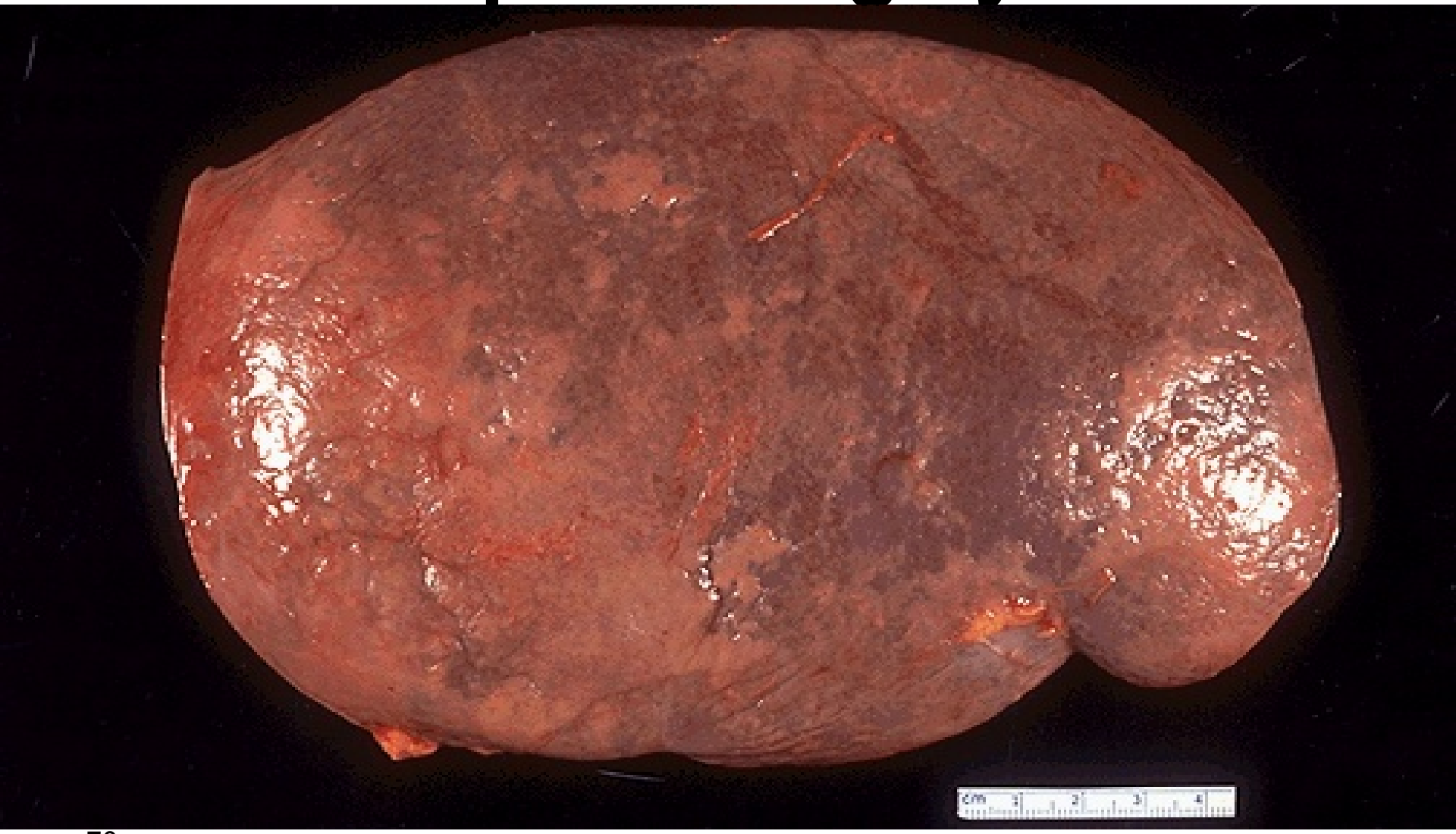
Splenomegaly

-Usu. 500-1000 gms (N <300gms)

-Not necessarily correlated with other features of portal ↑Bp

-May result in hypersplenism

splenomegaly



Hepatic encephalopthy

-It is a complication of acute & chronic hepatic failure

-Disturbance in brain function ranging from behavioural changes to marked confusion & sutpor to deep coma & death

-The changes may progress over hours or days

Neurological signs:

Rigidity
Hyper-reflexia
Non – specific EEG
Seizures
Asterixis (non-rhythmic rapid extension flexision 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