LECTURE 3

Cirrhosis

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

- **Main characteristics**

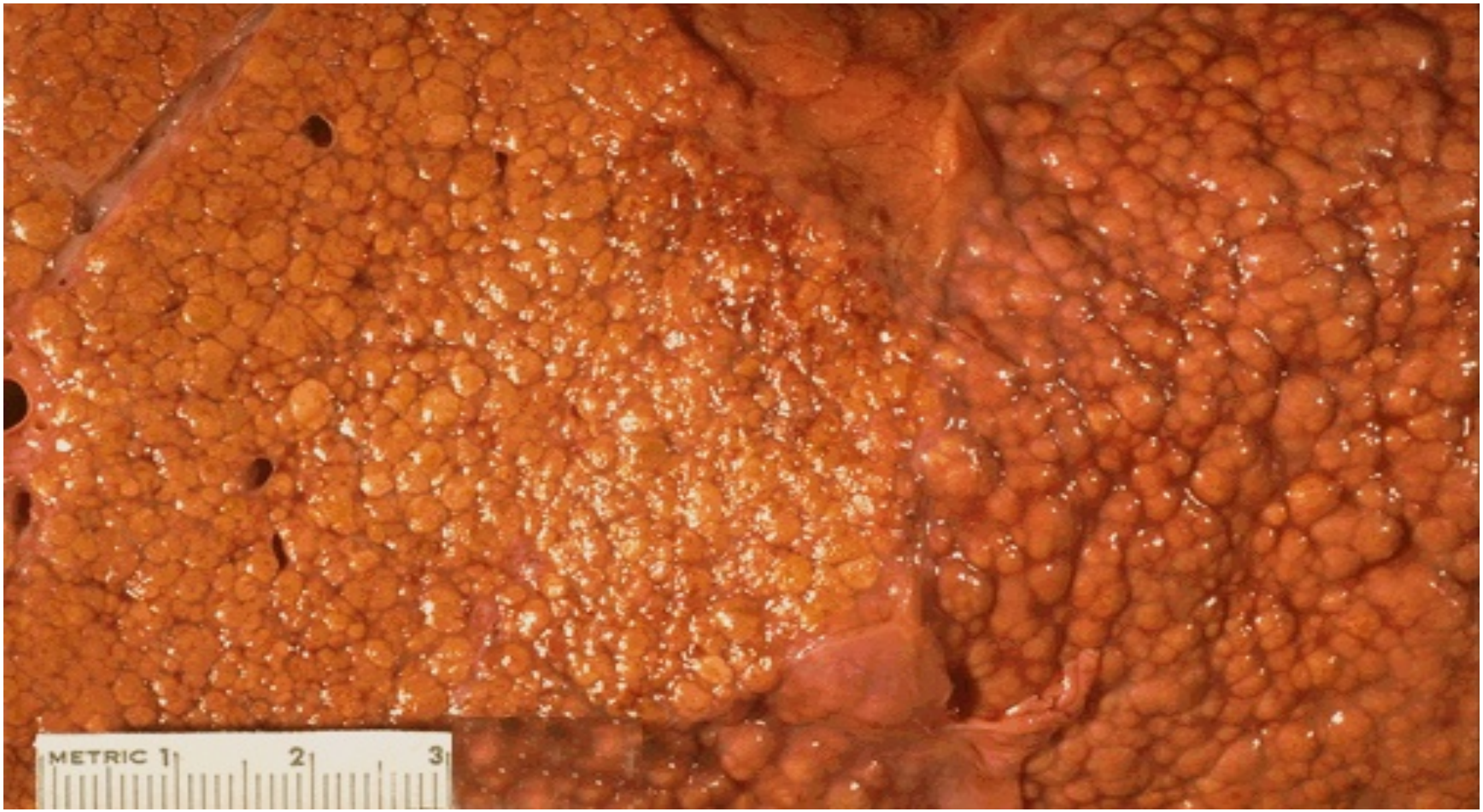
1. Bridging fibrous septae
2. Parenchymal nodules encircled by fibrotic bands
3. Diffuse architecture disruption

- **Types :**

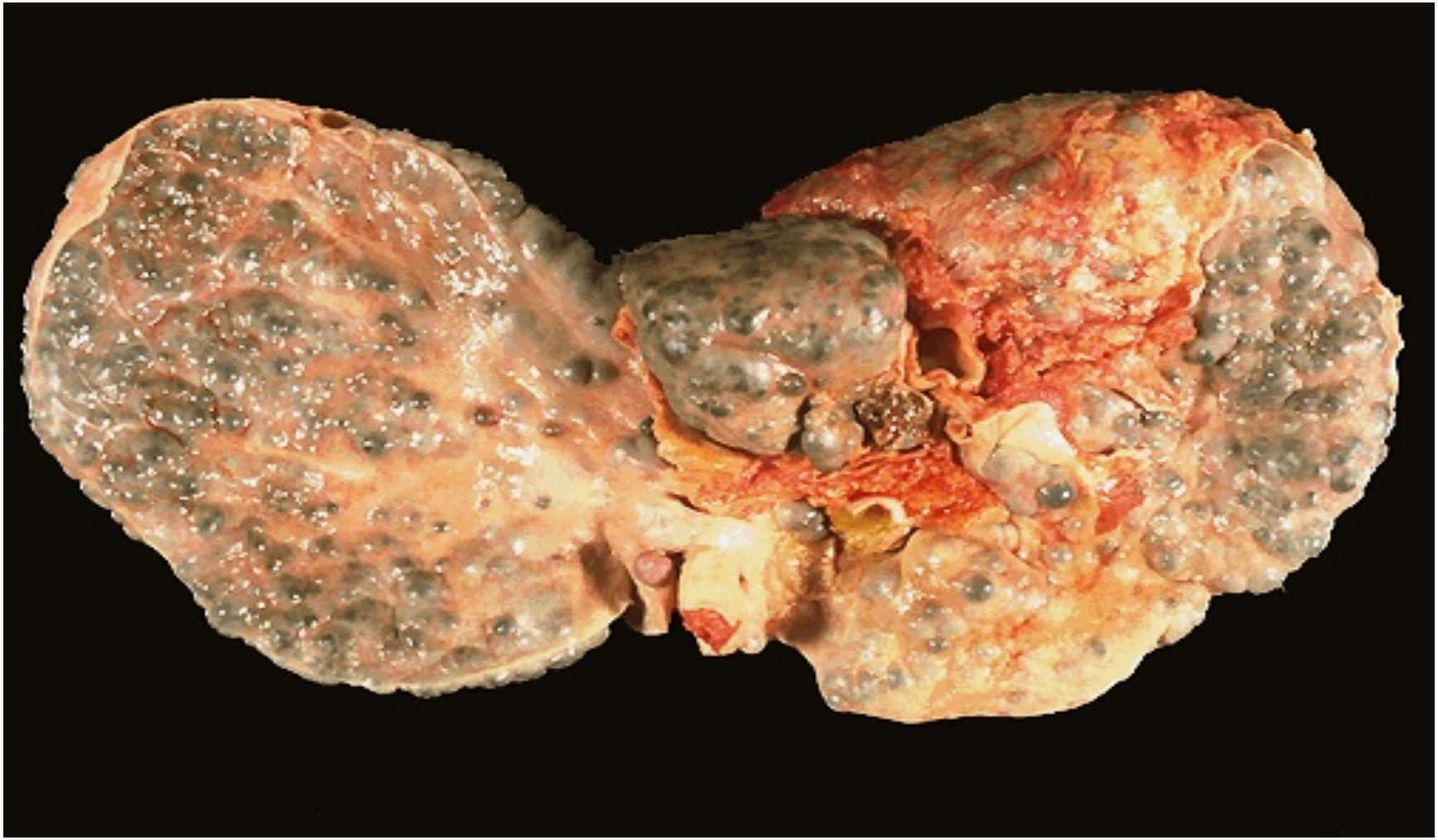
Micronodules < 3mm in diameter

Macronodules > 3 mm in diameter

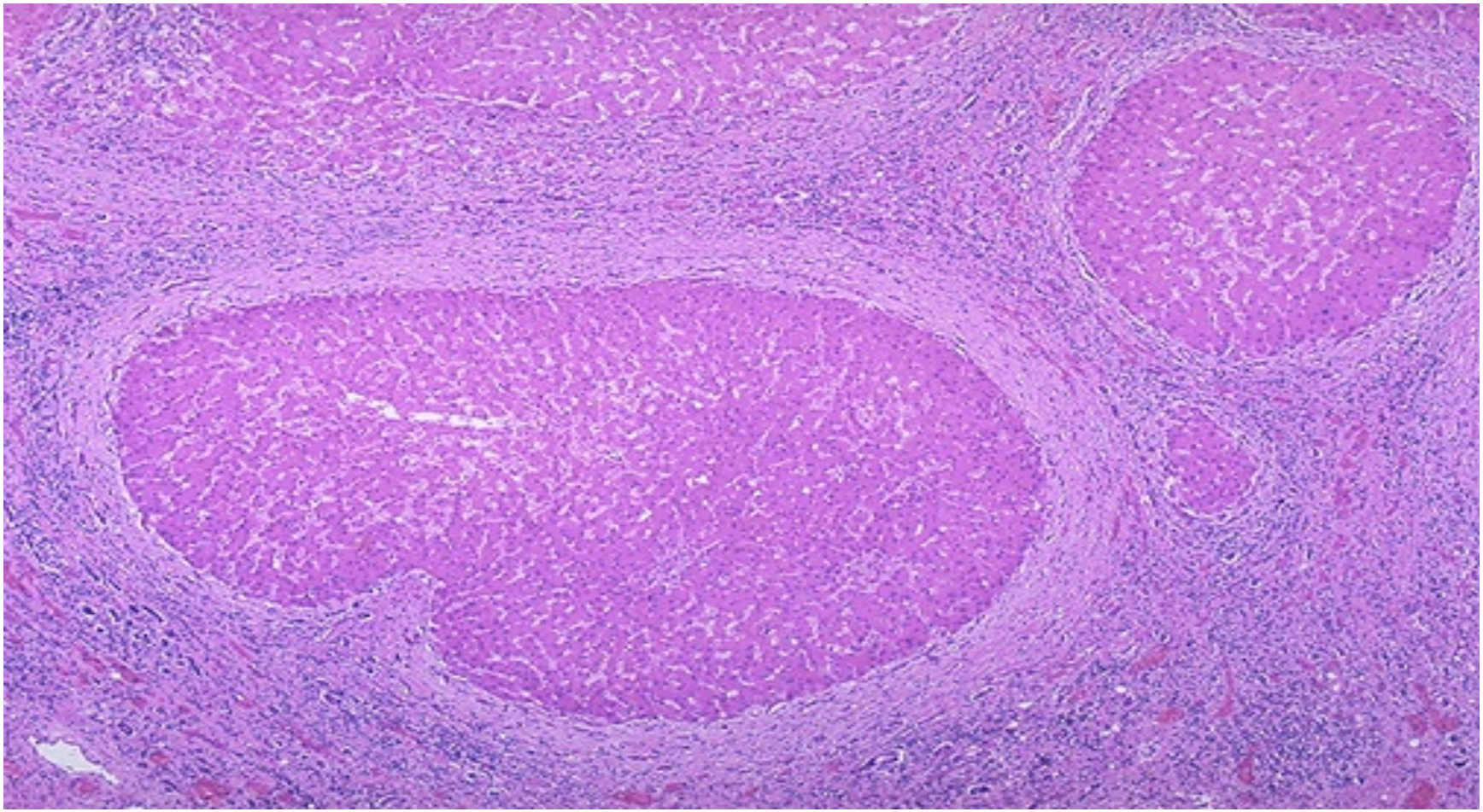
Micronodular cirrhosis



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

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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)

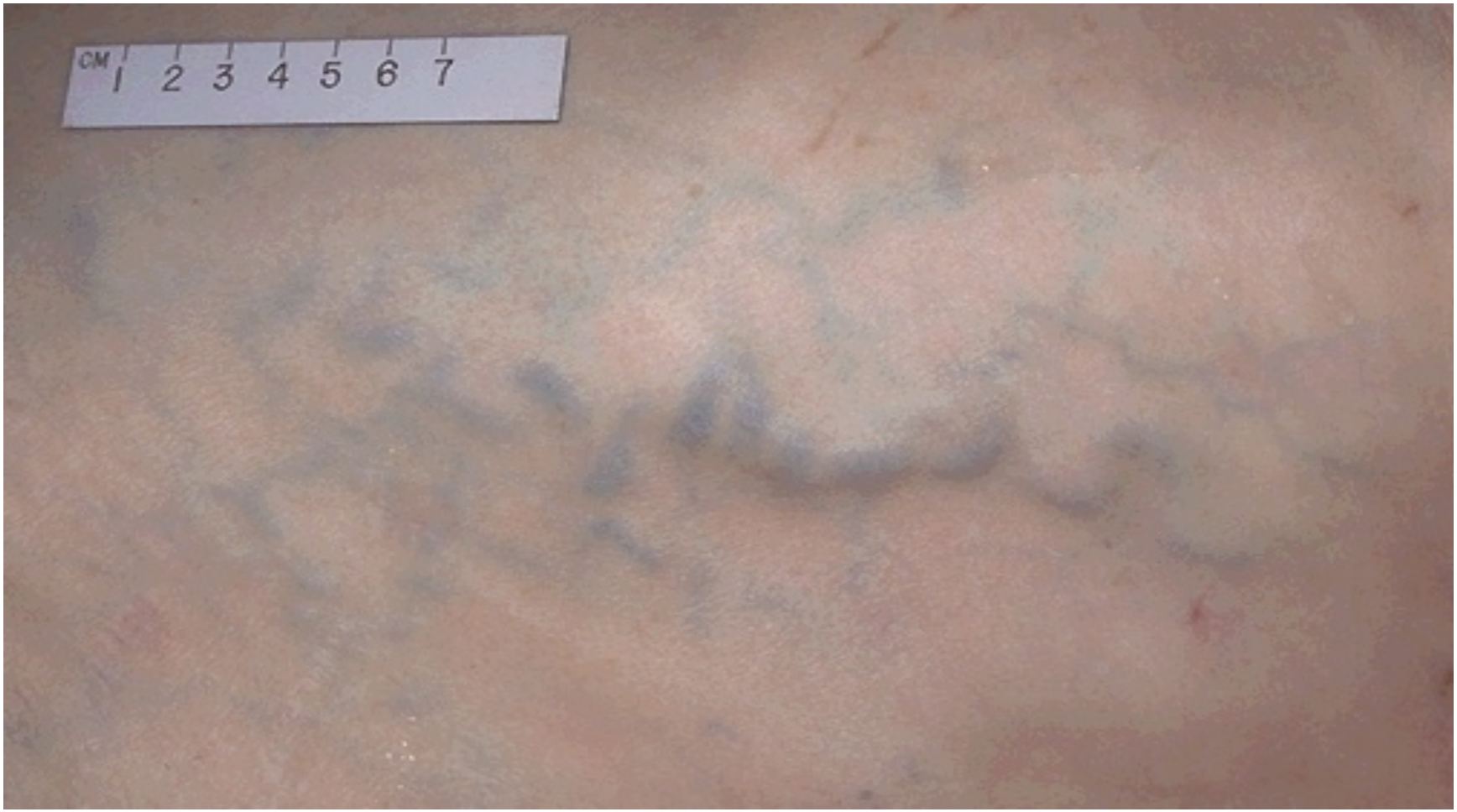
2-Gastroesophageal junction (varicies)

3-Retroperitoneum

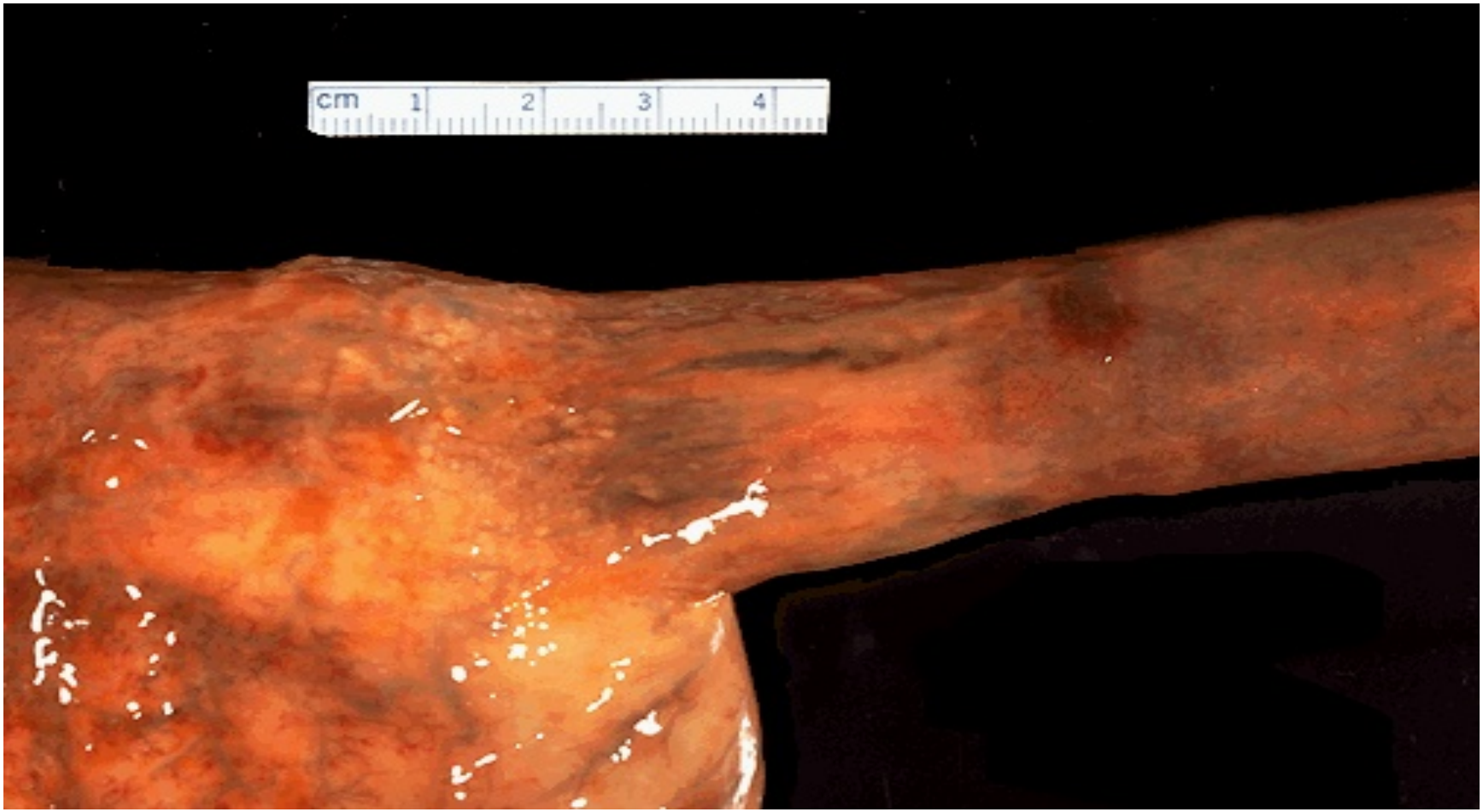
4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

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

caput medusae



Esophageal varicies



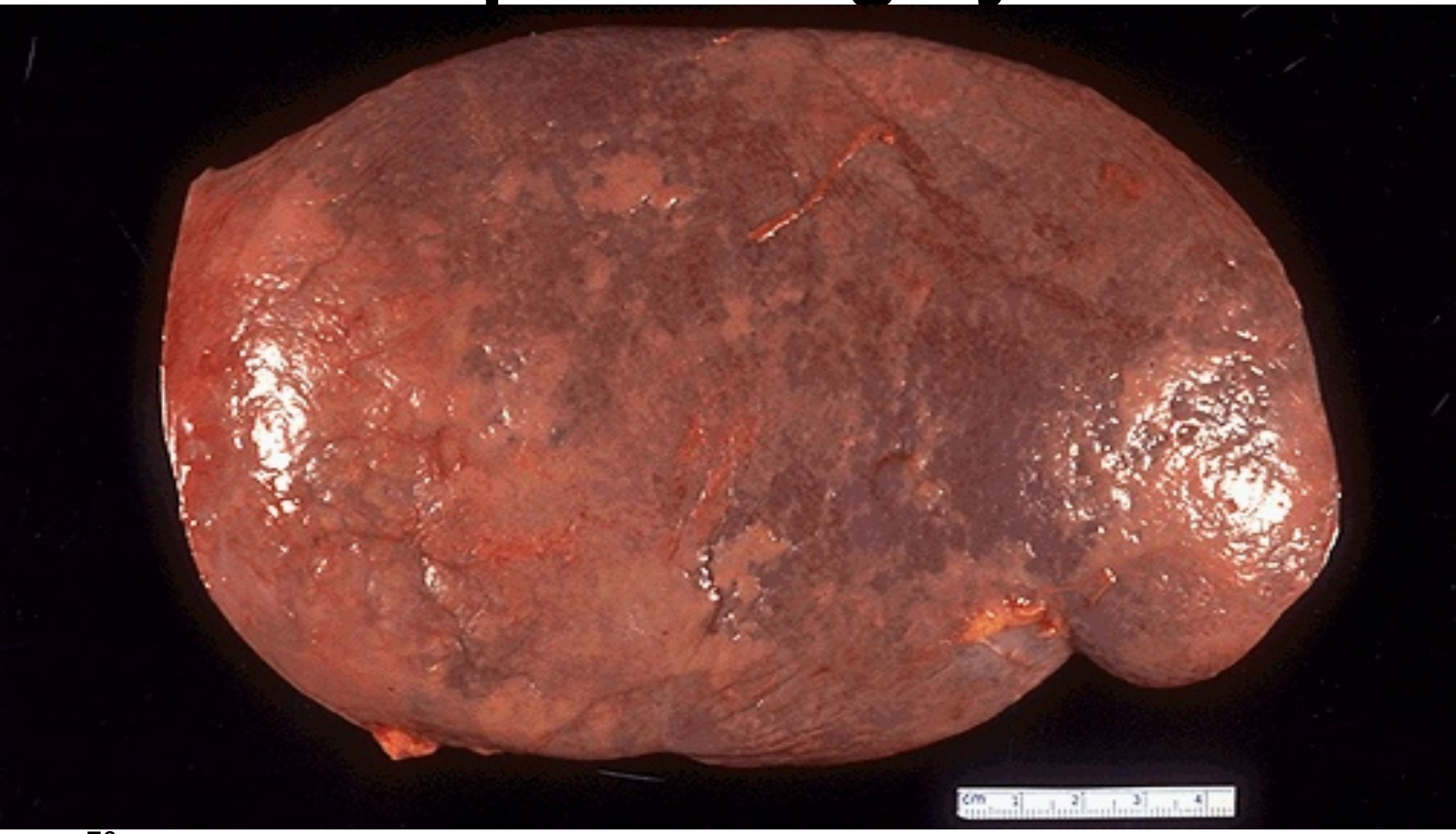
Splenomegaly

-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

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Exposure of Brain to toxic metabolic products

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

alteration in central nervous system AA metabolism