Liver, biliary tree & pancreas

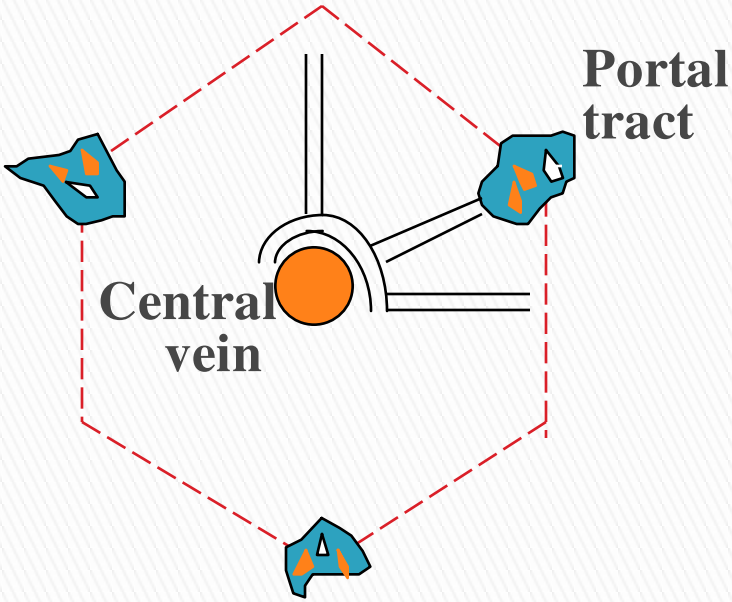
Dr. Nesreen Bataineh ,MD, FRCPath

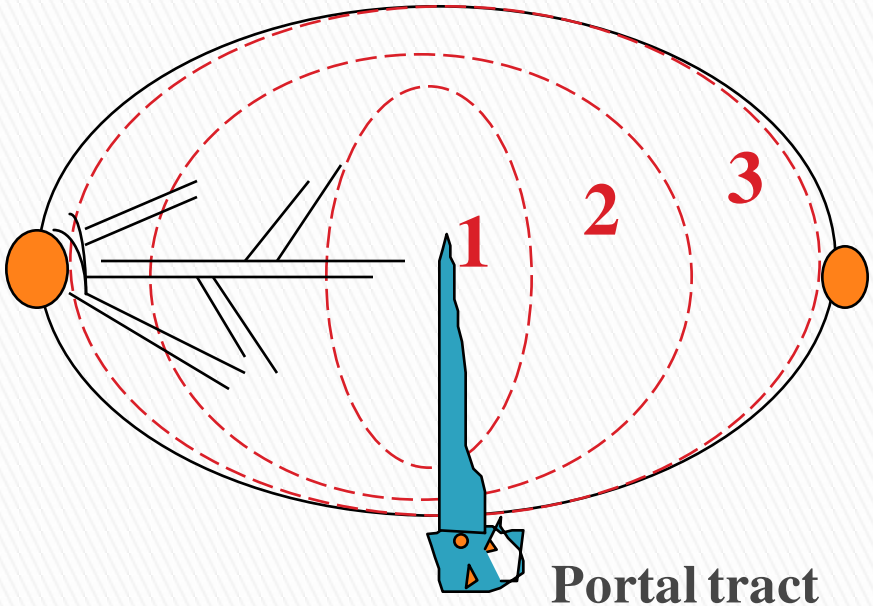
Outline

- Clinical syndromes of hepatic injury
- Diseases of liver
- Gallbladder diseases
- Disorders of extrahepatic bile ducts
- The pancreas

THE LIVER

LOBULES vs. ACINI

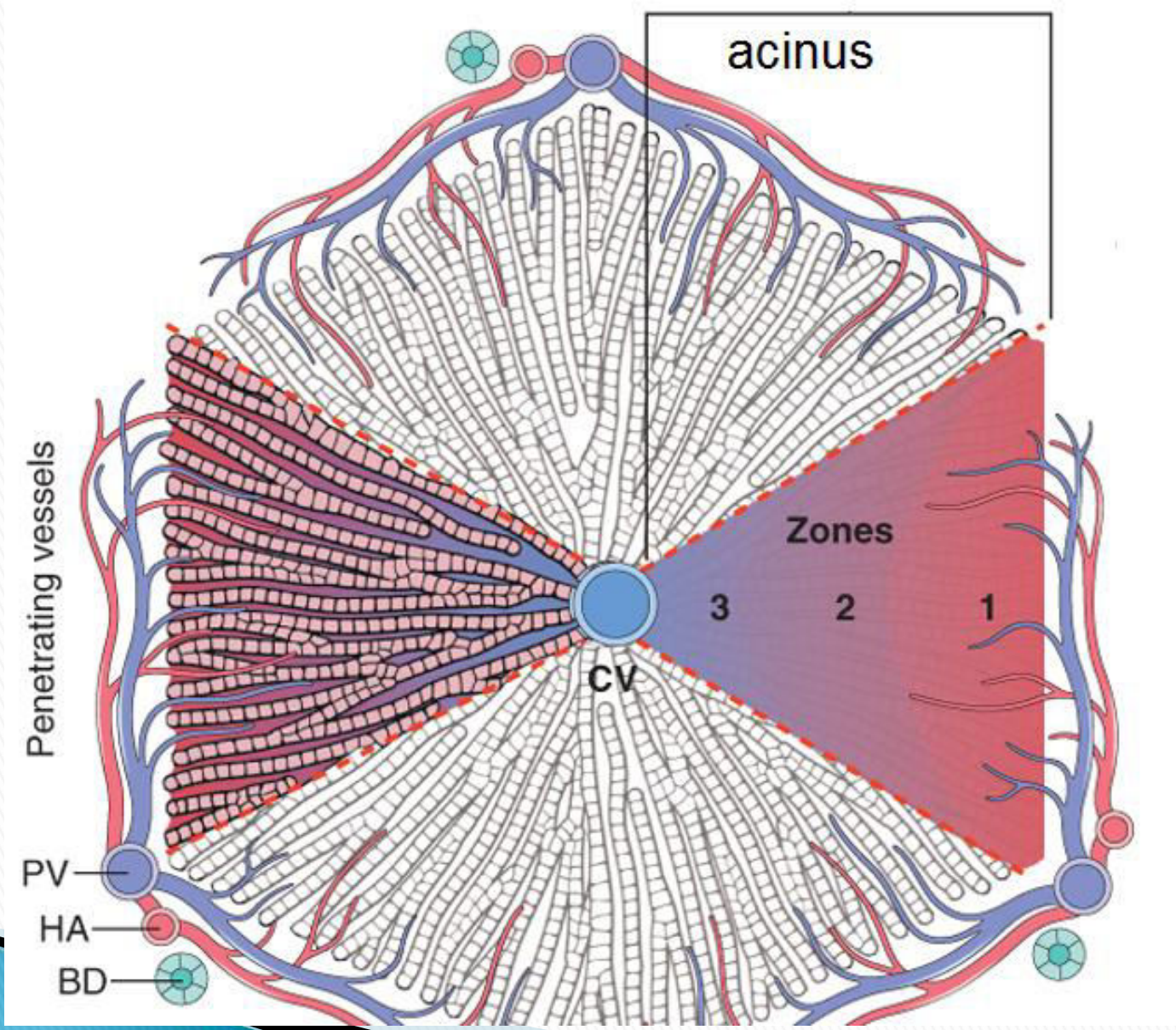




Traditional concept of liver histology: Centrilobular, periportal (peripheral) & midlobular zones

Acini are defined by micro-circulatory layout of liver: Central axis (portal tract & its afferent vessels), surrounded by 3 zones

THE LIVER



Liver diseases

- Acute hepatitis
- Chronic hepatitis
- Fatty liver disease
  - Steatosis & steatohepatitis
- Metabolic liver disease
- Diseases of intrahepatic biliary tracts
- Circulatory disorders
- Tumors and hepatic nodules

Clinical syndromes of liver disease

- **Major clinical syndromes of liver disease:**
  - Hepatic failure
  - Cirrhosis
  - Portal hypertension
  - Jaundice & Cholestasis

Hepatic Failure

- The most severe clinical consequence of liver disease, due to progressive **chronic** damage (*usually*) or sudden (**acute**) and massive destruction.

Hepatic Failure

- 80% to 90% of hepatic function must be lost before hepatic failure ensues. But this % can be lowered by some ***precipitating factors:***
  - Systemic infections
  - Electrolyte disturbances
  - Stress (major surgery, heart failure …)
  - Gastrointestinal bleeding

Hepatic Failure

- **Causes of liver failure fall into three categories:**
  - *Acute liver failure with massive hepatic necrosis*
  - ***Chronic liver disease***
  - *Hepatic dysfunction without overt necrosis*

I. Acute liver failure & massive hepatic necrosis

- *Uncommon*, but life-threatening.
- Often requires liver transplantation.

- **Causes:**
- Drugs:
  - Acetaminophen, CCL4 & mushroom poisoning…
- Fulminant viral hepatitis:
  - As HAV & HBV infection.

Acute liver failure & massive hepatic necrosis

- **Course of the disease:**

→ Acute liver failure:

- Progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 wks.

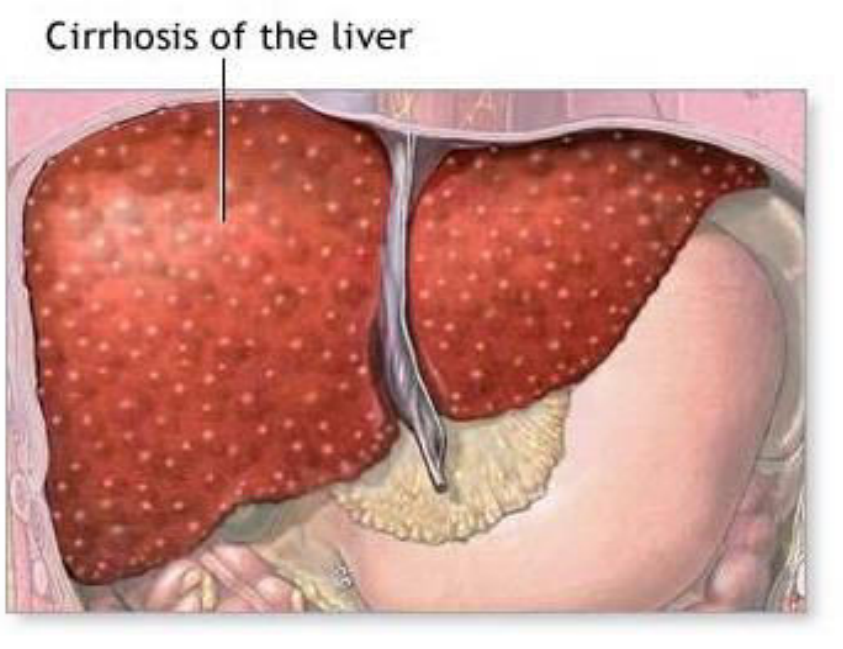
→ Subacute failure:

- A course extending as long as 3 months.

- **Histopathology: Massive hepatic necrosis**

II. Chronic liver disease

- The **most common** route to hepatic failure
- The end stage of chronic liver damage ending in *cirrhosis*.



III. Hepatic dysfunction without overt necrosis

- Hepatocytes may be viable but unable to perform normal metabolic function:
  - Acute fatty liver of pregnancy
  - Tetracycline toxicity
  - Reye syndrome

Clinical Features of hepatic failure

Jaundice

Hypoalbuminemia & peripheral edema

Hyperammonemia

Hypoglycemia, weight loss, & muscle waisting

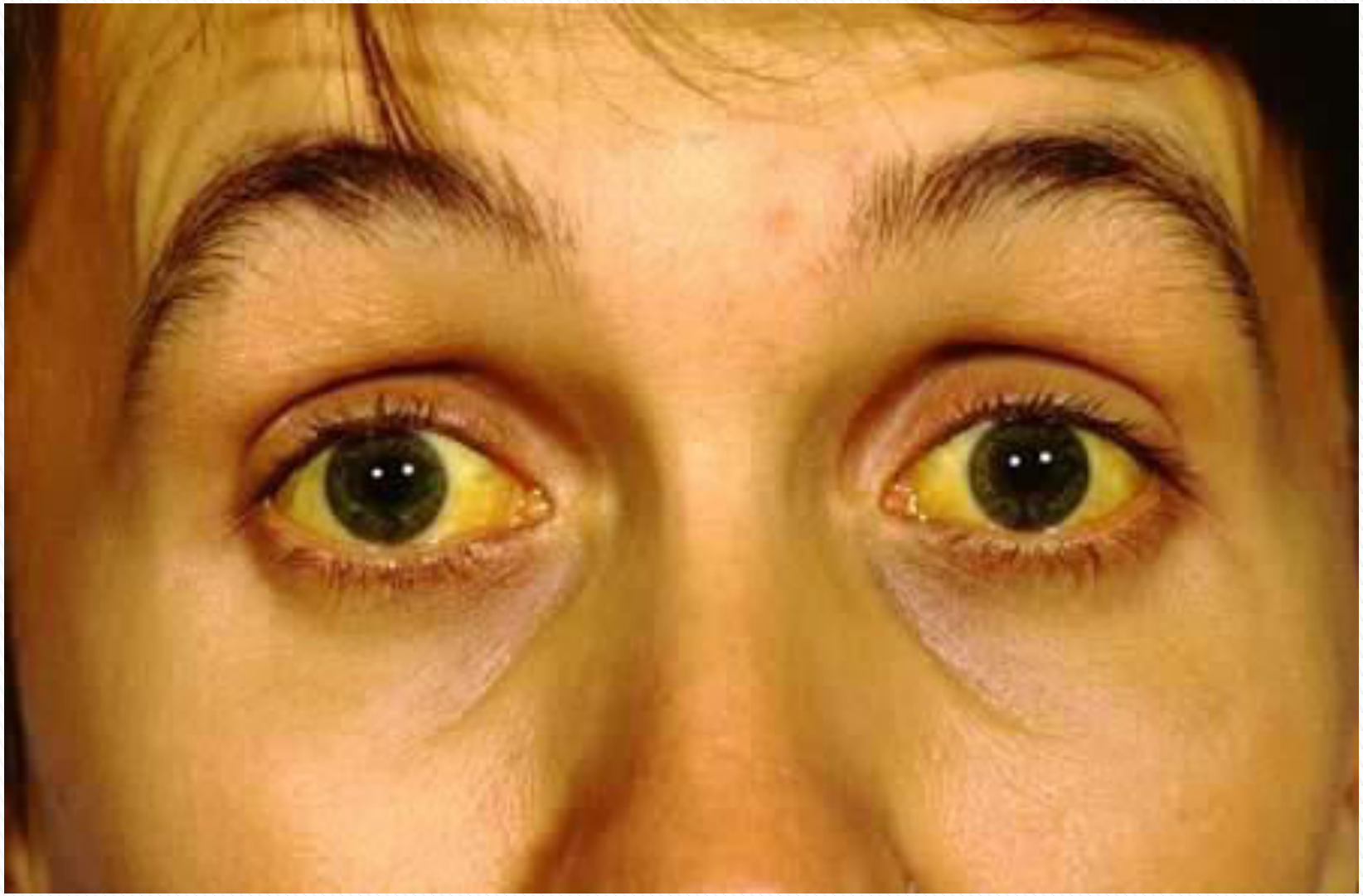
Fetor hepaticus "musty" or "sweat & sour"

- Formation of mercaptans by action of GI bacteria on sulfur containing amino acid methionine & with P-S shunting → Lungs

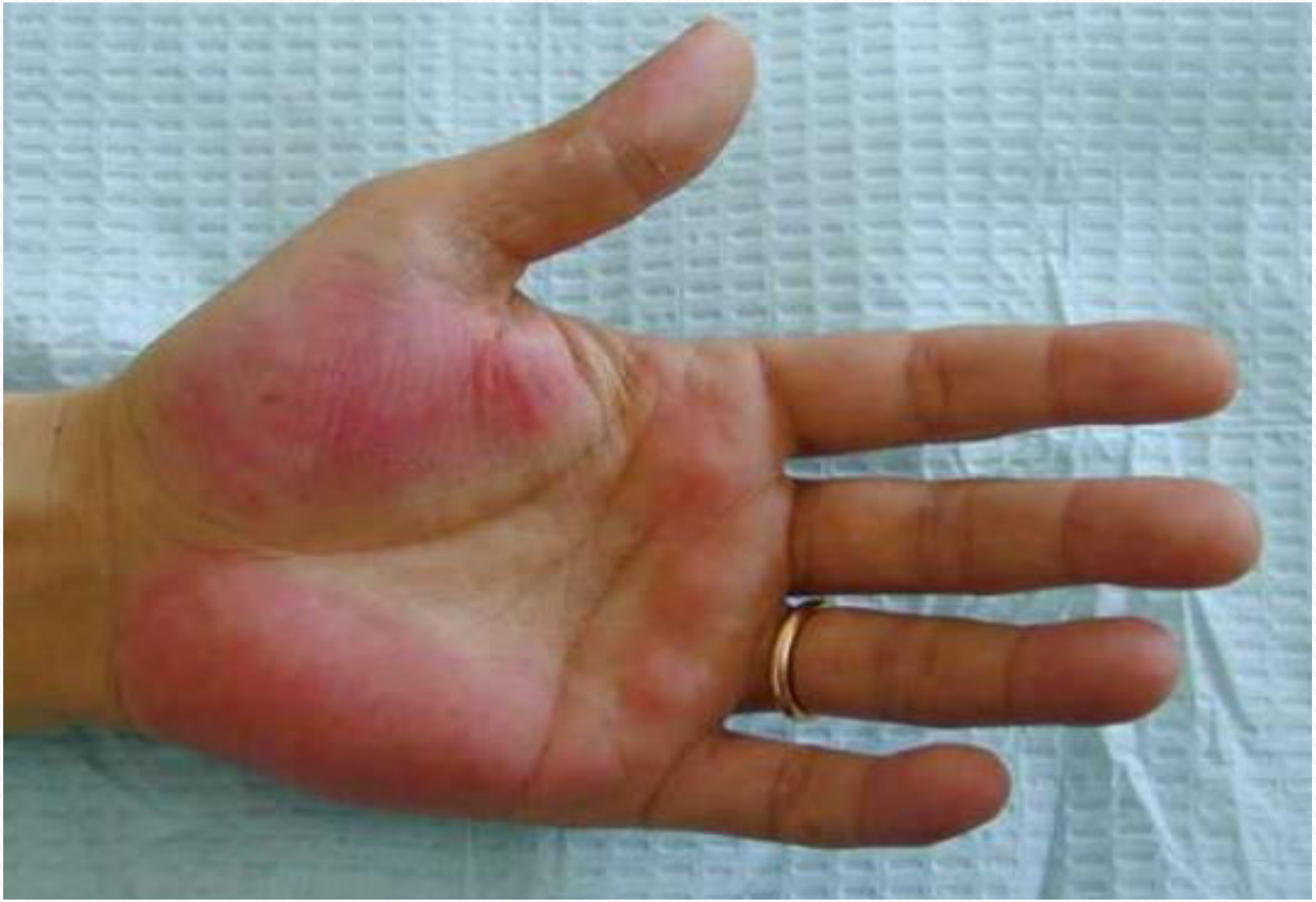
Hyperestrogenemia, esp. in chronic liver disease:

- Palmar erythema (local vasodilatation)
- Spider angiomas of the skin
- In the male, hypogonadism and gynecomastia

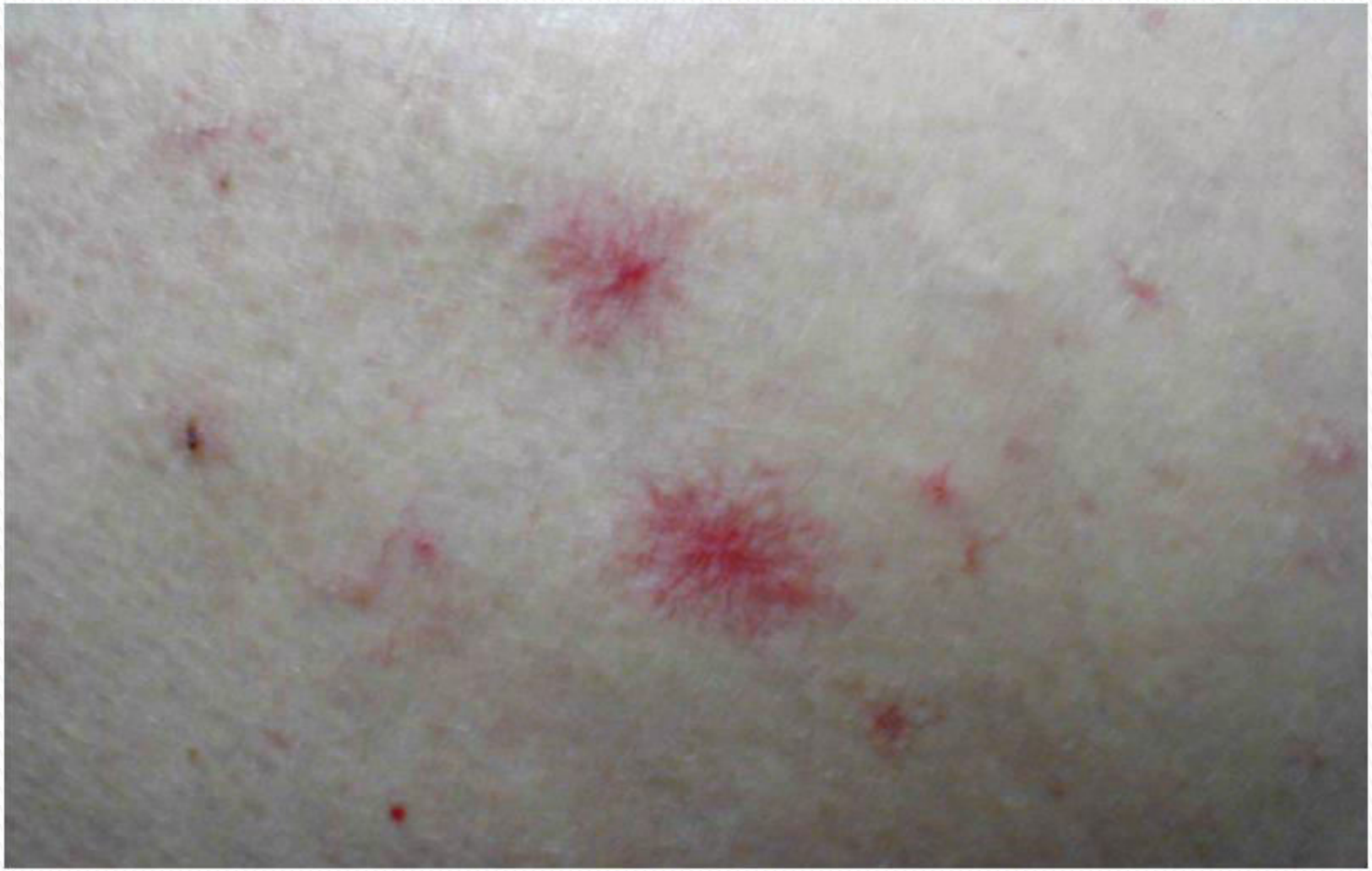
Jaundice



Palmar erythema



Spider angioma

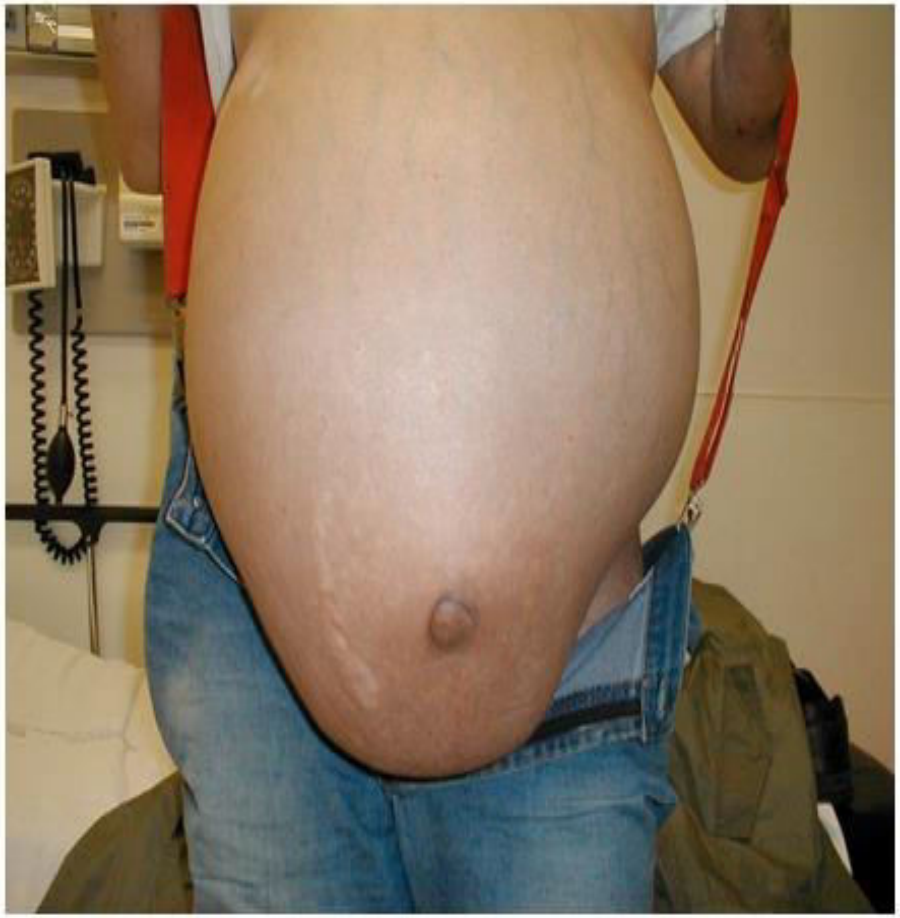


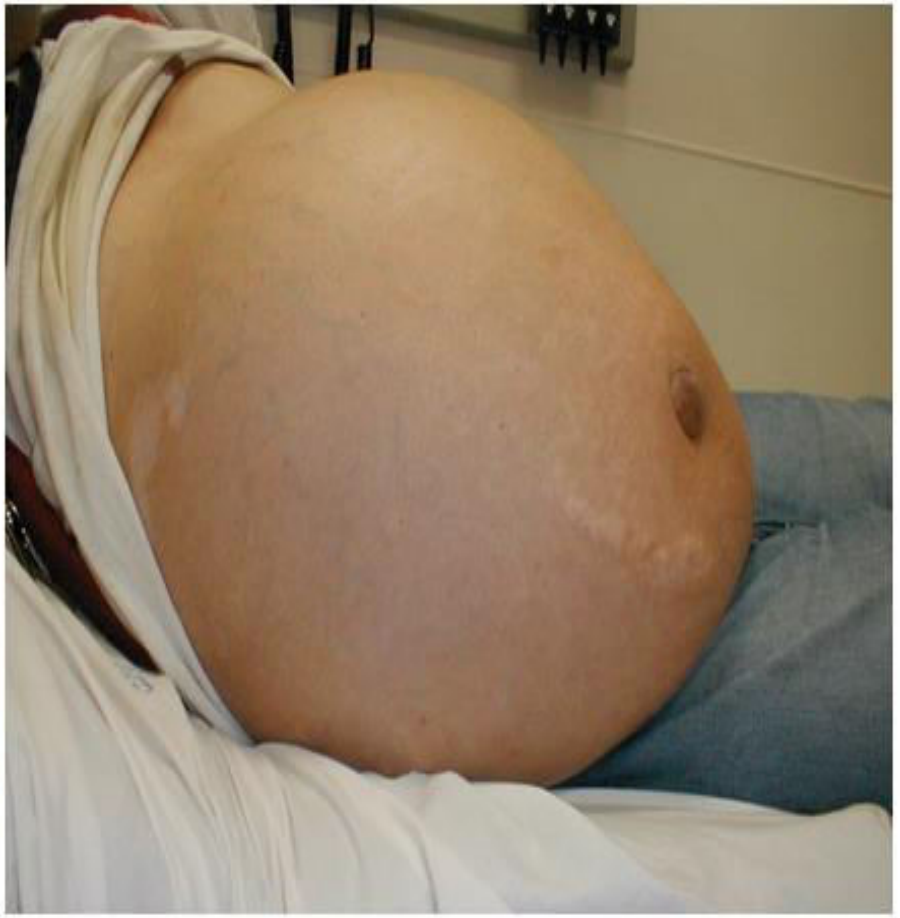
A central, pulsating, dilated arteriole from which small vessels radiate

Complications of hepatic failure

- Ascites
- Portal hypertension
- Coagulopathy
  - Impaired hepatic synthesis of clotting factors
  - Bleeding tendency & GI hemorrhage
- Hepatic encephalopathy
- Hepatorenal syndrome
- Portopulmonary Hypertension & Hepatopulmonary Syndrome.
- Multiple organ failure (↑ *toxic metabolites*)

Ascites





Hepatic Encephalopathy

- A complication of acute & chronic liver failure.

A spectrum of disturbances in brain function
Fluctuating neurologic signs ▪Rigidity, hyper-reflexia, EEG changes ▪Asterixis (flapping tremor) → *characteristic* ▪Rarely seizures
Behavioral abnormalities
Confusion and stupor
Deep coma and death

Pathogenesis

Severe loss of hepatocellular function & Porto-systemic shunt

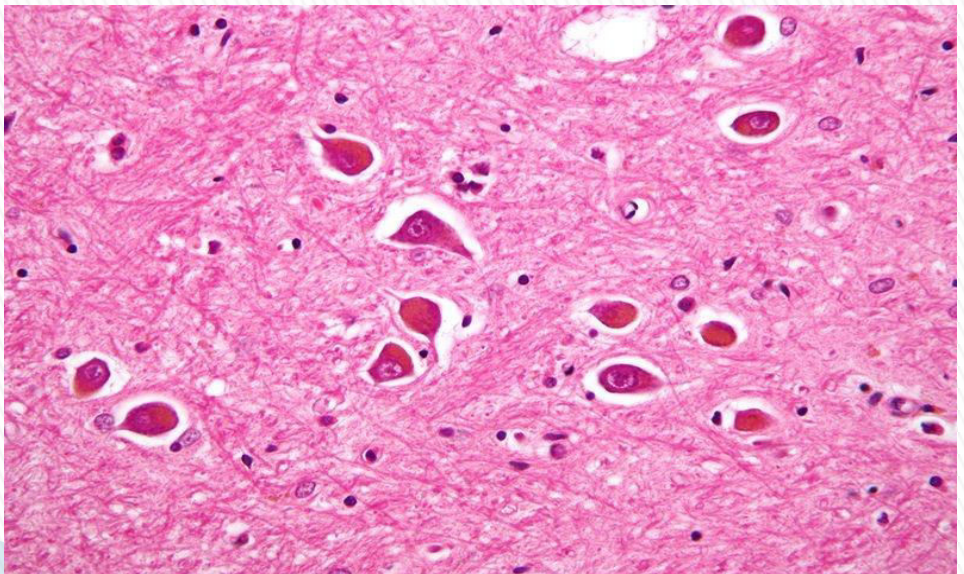
The net result is exposure of the brain to an altered metabolic milieu

Elevated levels of blood ammonia*

Deranged neurotransmission due to altered amino acid metabolism in the brain**

Morphology

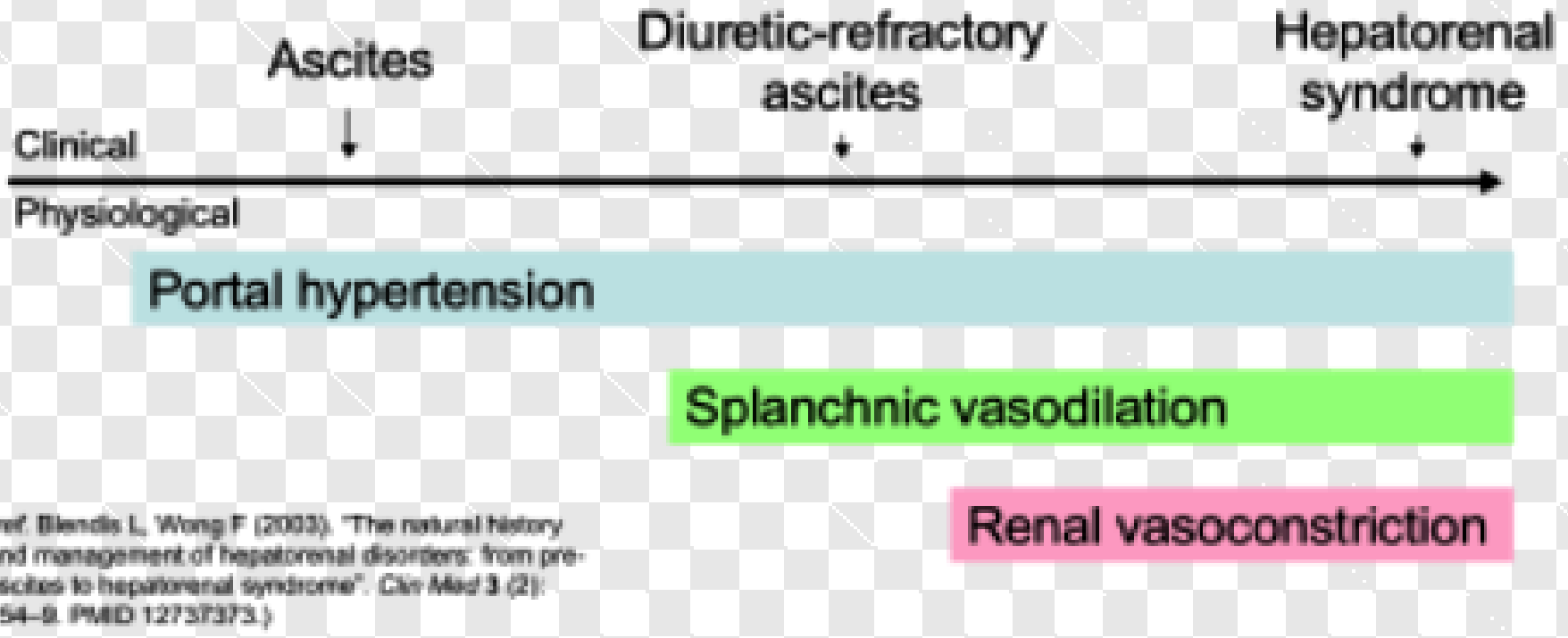
- Minor morphologic changes in the brain:
  - Brain edema
  - Non-specific astrocytic reaction
- *Reversible* if underlying hepatic dysfunction is corrected



Hepatorenal Syndrome

- The development of renal failure *without primary abnormalities* of the kidneys themselves *.
- **Pathogenesis** (*not clear*):
  - Splanchnic VD and systemic VC → severe reduction of renal blood flow.
  - Kidney function improves if hepatic failure is reversed.

Hepatorenal Syndrome



(ref: Blendis L, Wong F (2003). "The natural history and management of hepatorenal disorders: from pre-ascites to hepatorenal syndrome". *Clin Med* **3** (2): 154–9. PMID 12737373.)

Clinical features of hepatorenal syndrome

- Oliguria
- Rising BUN & creatinine values
- The ability to concentrate urine is retained*
- May lead to death

Cirrhosis

- The end stage of chronic liver disease

- **Definition:**
  - A **diffuse** process characterized by *fibrosis* and the conversion of normal liver architecture into *structurally abnormal nodules.*

- Focal injury with scarring is **not** cirrhosis

Three main characteristics

- **Bridging fibrous septa**
  - Delicate bands or broad scars around multiple adjacent lobules.
- **Parenchymal nodules** encircled by fibrotic bands:
  - Micronodular cirrhosis, Small nodules < 3 mm
  - Macronodular cirrhosis, nodules > 3mm

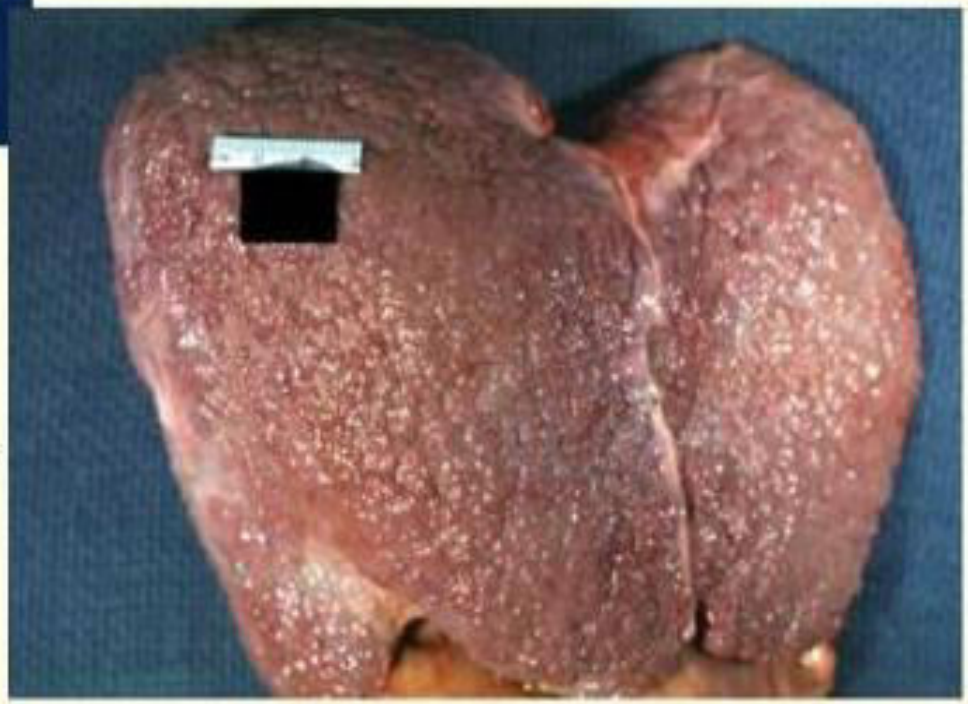
→ The nodules mostly contain proliferating (regenerating) hepatocytes

- **Disruption of the architecture of the entire liver.**

Classification of cirrhosis

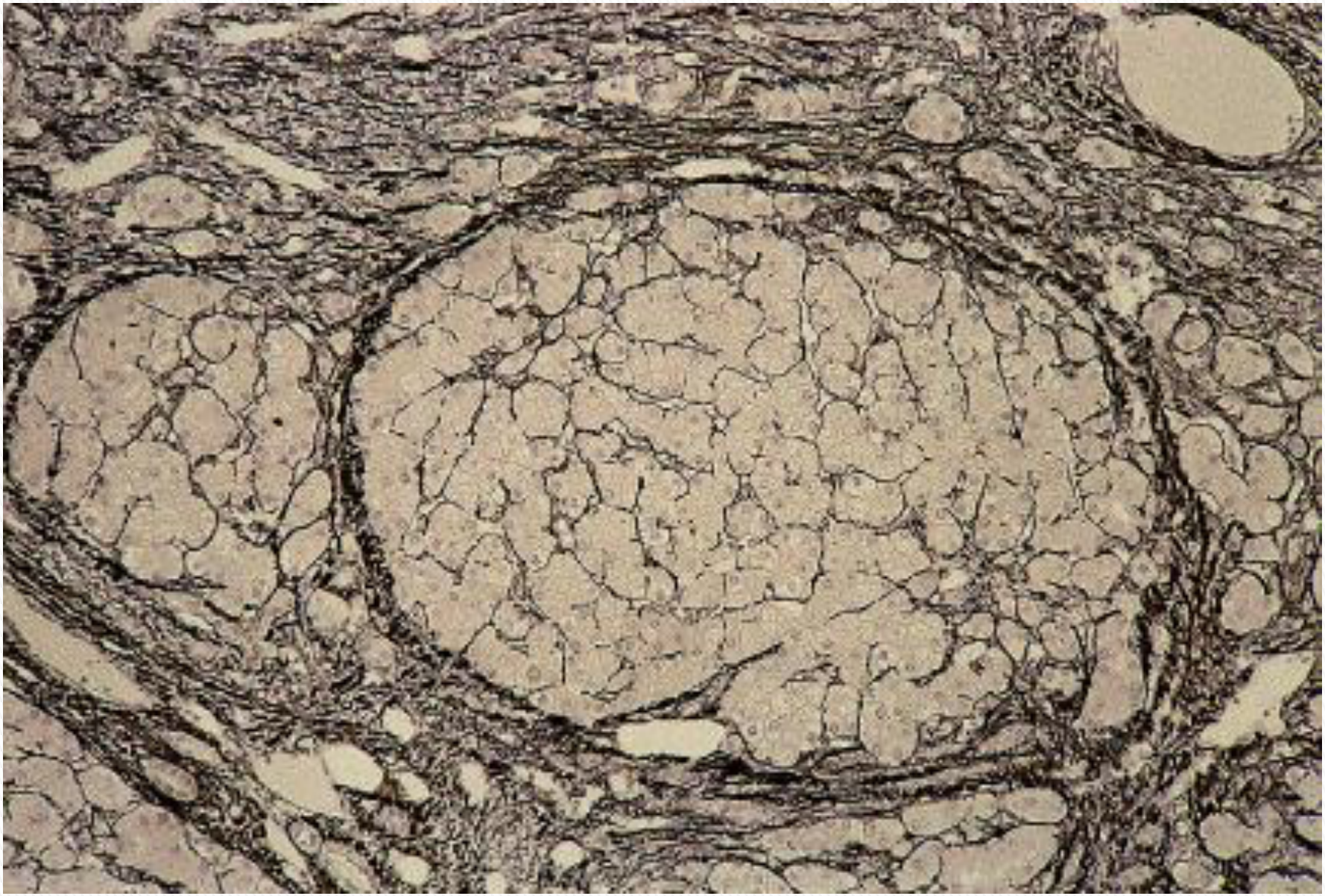
- **Micronodular cirrhosis**
  - Alcoholic liver disease
  - Hemochromatosis
- **Macronodular cirrhosis**
  - Cirrhosis due to viral hepatitis
- **Mixed micro- & macronodular**
  - Most cases

Micronodular Cirrhosis

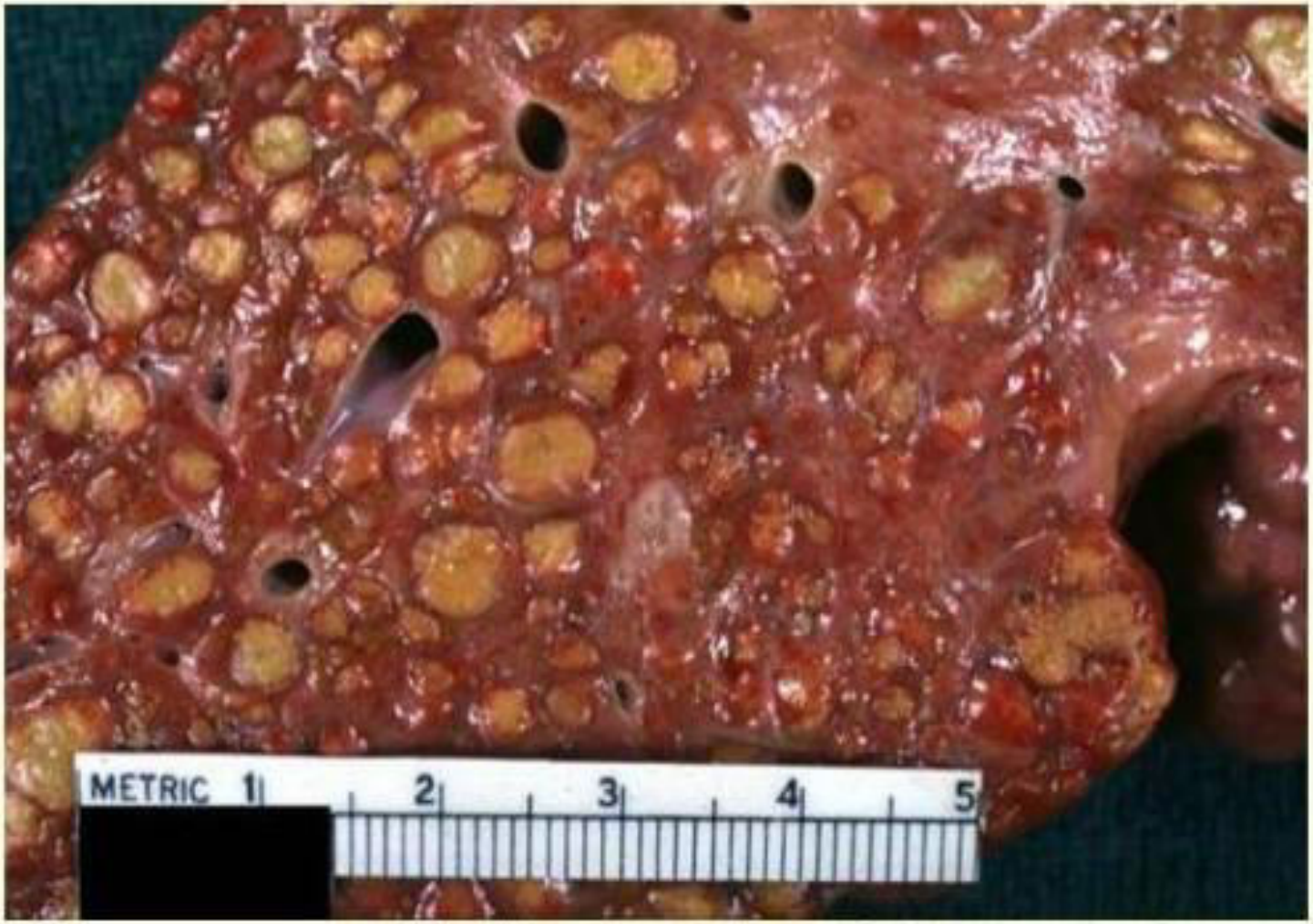


*Restricted use. Source: PEIR: University of Alabama at Birmingham, Department of Pathology

Micronodular cirrhosis

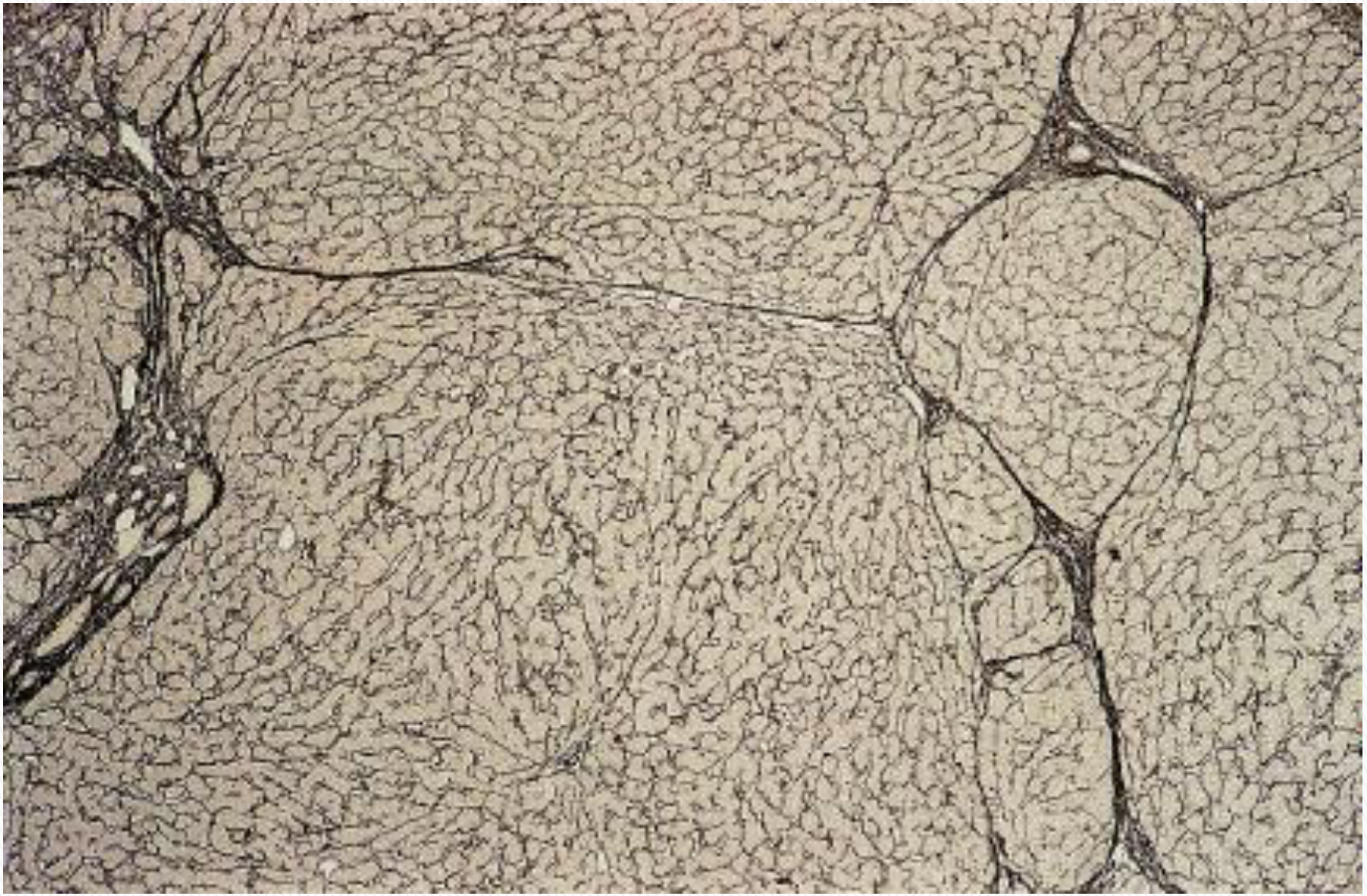


Macronodular Cirrhosis

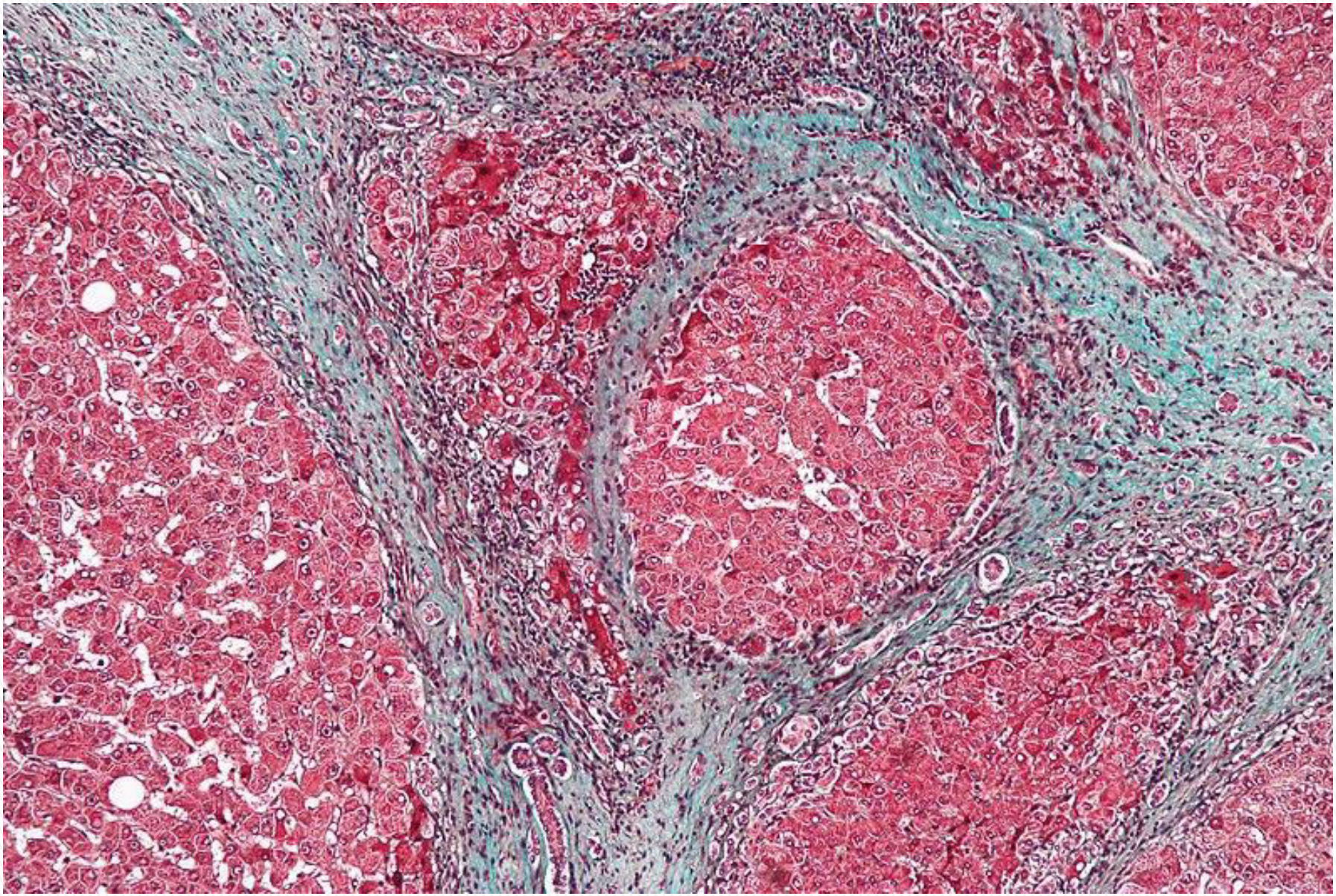


*Restricted use. Source: PEIR: University of Alabama at Birmingham, Department of Pathology

Macronodular cirrhosis



Mixed micro- & macronodular cirrhosis



Classification by etiology

Causes of cirrhosis	
Viral hepatitis HBV, HCV, HDV	60–70%
Alcoholic liver disease	10%
Biliary diseases	5–10%
Autoimmune hepatitis	5%
Hemochromatosis	5%
Wilson disease	Rare
Alpha1 antitrypsin deficiency	
Galactosemia, tyrosinemia	
Drug induced (α methyldopa)	
Cryptogenic cirrhosis∗	10–15%

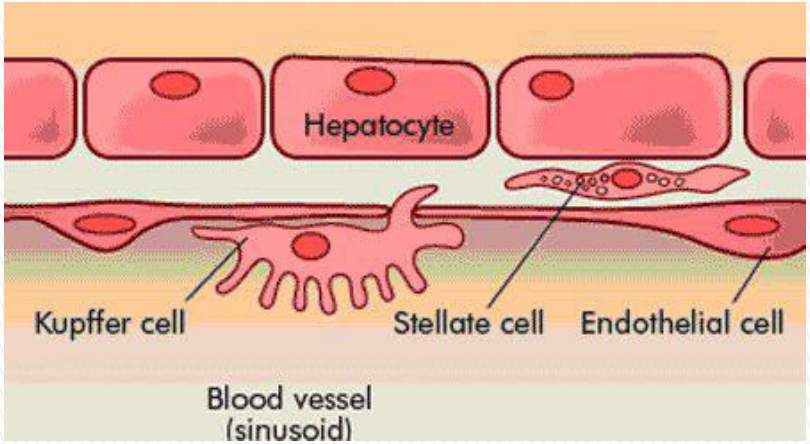
∗*Cryptogenic cirrhosis* is a "wastebasket" category due to difficulty in establishing an etiologic diagnosis once cirrhosis is well established.

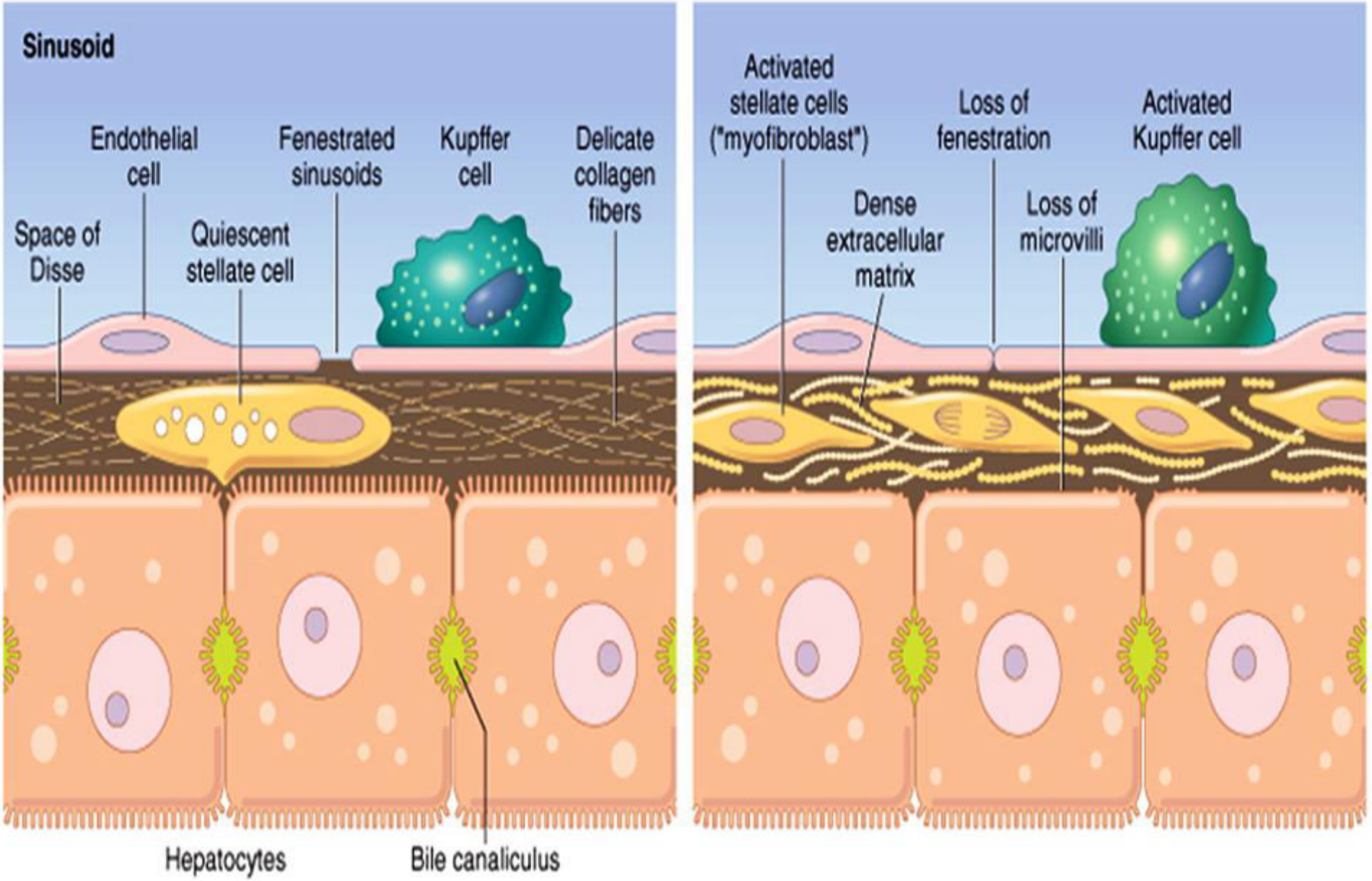
Pathogenesis of cirrhosis

The major mechanisms
Progressive hepatocellular death
Hepatocellular regeneration
Progressive fibrosis ▪Types I & III collagens deposited in the space of Disse. Also may come from portal triad area. ▪Fibrous bands separate nodules of hepatocytes
Vascular reorganization: ▪Inflammation+thrombosis → areas of hypo- & hyperperfusion + Loss of sinusoidal endothelial cell fenestrations & hepatocytes microvilli + Vascular shunts between portal vein-hepatic vein and hepatic artery-portal vein with defect in liver function

Pathogenesis of cirrhosis

- **The major source of excess collagen:**
- The perisinusoidal stellate cells (Ito cells or fat-storing cells) in the space of Disse.
- They normally store vitamin A and fat
- In cirrhosis, they become activated, and transform into *myofibroblast-like* cells




Sinusoid
Endothelial cell
Fenestrated sinusoids
Kupffer cell
Delicate collagen fibers
Space of Disse
Quiescent stellate cell
Hepatocytes
Bile canaliculus
Activated stellate cells ("myofibroblast")
Loss of fenestration
Activated Kupffer cell
Dense extracellular matrix
Loss of microvilli

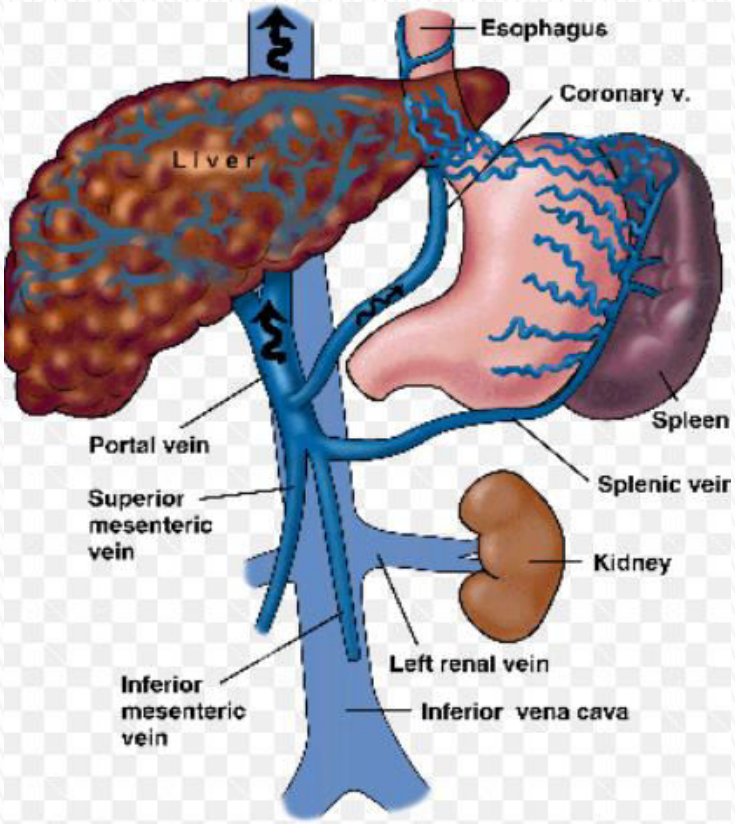
Clinical Features of cirrhosis

- May be clinically *silent*.
- Nonspecific manifestations:
  - Anorexia, weight loss & weakness*
- Complications of cirrhosis:
  - Hepatic failure
  - Portal hypertension
  - Hepatocellular carcinoma


ومن يتهيب صعود الجبال
يعش أبد الدهر بين الحفر

Portal Hypertension

- Increased resistance to portal blood flow, portal vein pressure > 12 mmHg (N 5–10).



Causes of portal hypertension

Pre-hepatic

Portal or splenic vein thrombosis

Intrahepatic

Sinusoidal	**Cirrhosis** (***most common***)
Presinusoidal *	Idiopathic, Schistosomiasis Sarcoidosis, Milliary TB, PBC, Nodular regenerative hyperplasia
Postsinusoidal	Sinusoidal obstruction syndrome

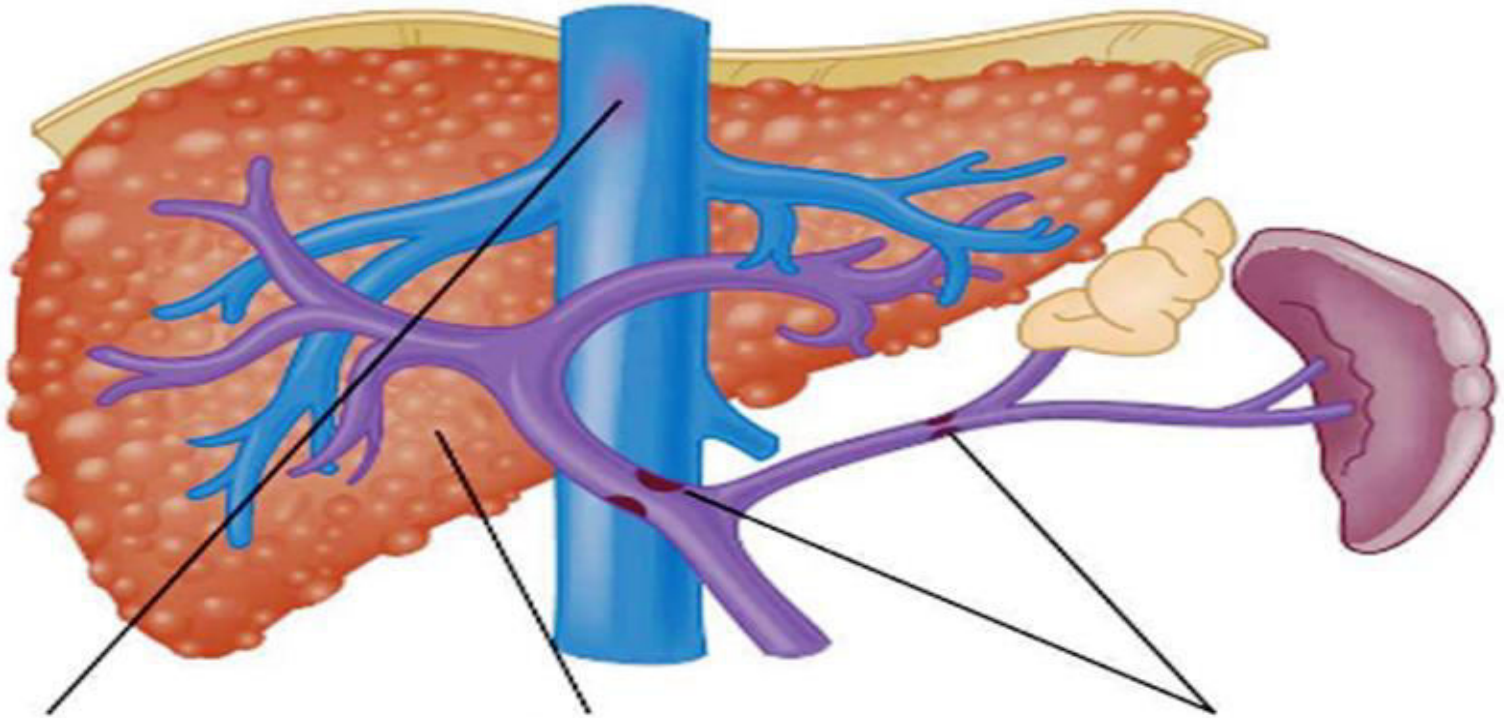
Post-hepatic

Severe right-sided heart failure

Constrictive pericarditis

Hepatic vein or IVC outflow obstruction (Budd-Chiari syndrome)

Causes of portal HTN



Posthepatic
Budd-Chiari syndrome
Constrictive pericarditis
Inferior vena caval obstruction
Right-sided heart failure
Severe tricuspid regurgitation

Intrahepatic
Presinusoidal
- Idiopathic portal hypertension
- Primary biliary cirrhosis
- Sarcoidosis
- Schistosomiasis

Sinusoidal
- Alcoholic cirrhosis
- Alcoholic hepatitis
- Cryptogenic cirrhosis
- Postnecrotic cirrhosis

Postsinusoidal
- Sinusoidal obstruction syndrome

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis

Mechanism of portal HTN in cirrhosis

- Increased resistance to portal flow at the level of the sinusoids.
- Compression of central veins by perivenular fibrosis and expanded parenchymal nodules.
- Porto-systemic anastomoses in the fibrous bands also impose arterial pressure on the normally low-pressure portal venous system.

Clinical consequences of portal HTN

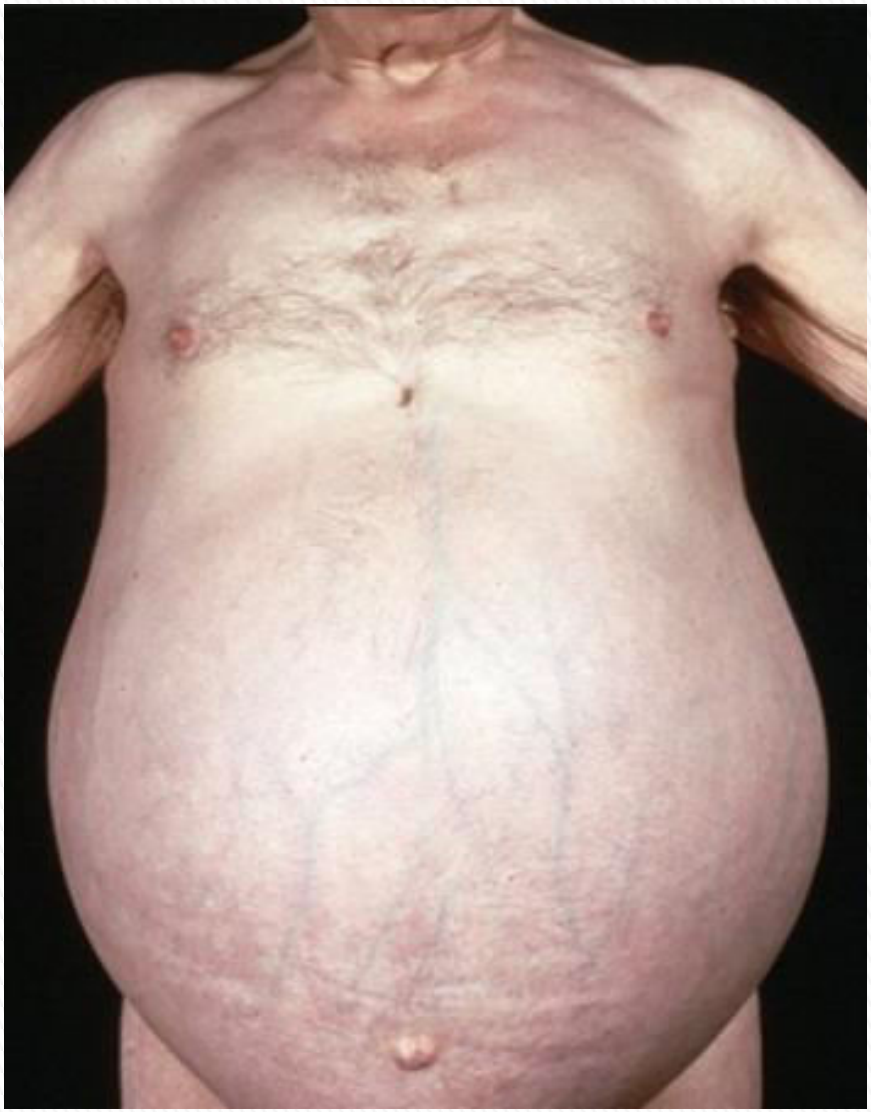
- Ascites
- Portosystemic venous shunts
- Congestive splenomegaly*
  - *Hypersplenism*
- Hepatic encephalopathy

Ascites

Definition:

- *Collection of excess fluid in the peritoneal cavity.*
- Clinically detectable when at least 500 mL accumulate.
- Many liters may accumulate and cause *massive abdominal distention.*
- Long-standing ascites may lead to seepage of fluid through transdiaphragmatic lymphatics to produce **hydrothorax**, more often on the **Rt** side.

Ascites



Normal composition of ascitic fluid

- A serous fluid having < 3 gm/dL protein (largely albumin)*.
- The **same concentrations** of solutes as glucose, sodium, & potassium as in the blood.
- Scant number of mesothelial cells.
- Mononuclear leukocytes.

- *Neutrophils* suggest infection (acute or spontaneous bacterial peritonitis).
- *RBCs* suggest dissiminated intra-abdominal CA or trauma.

Portosystemic Shunt

- The rise in portal venous pressure leads to bypasses between the systemic and portal circulations at site of anastomosis

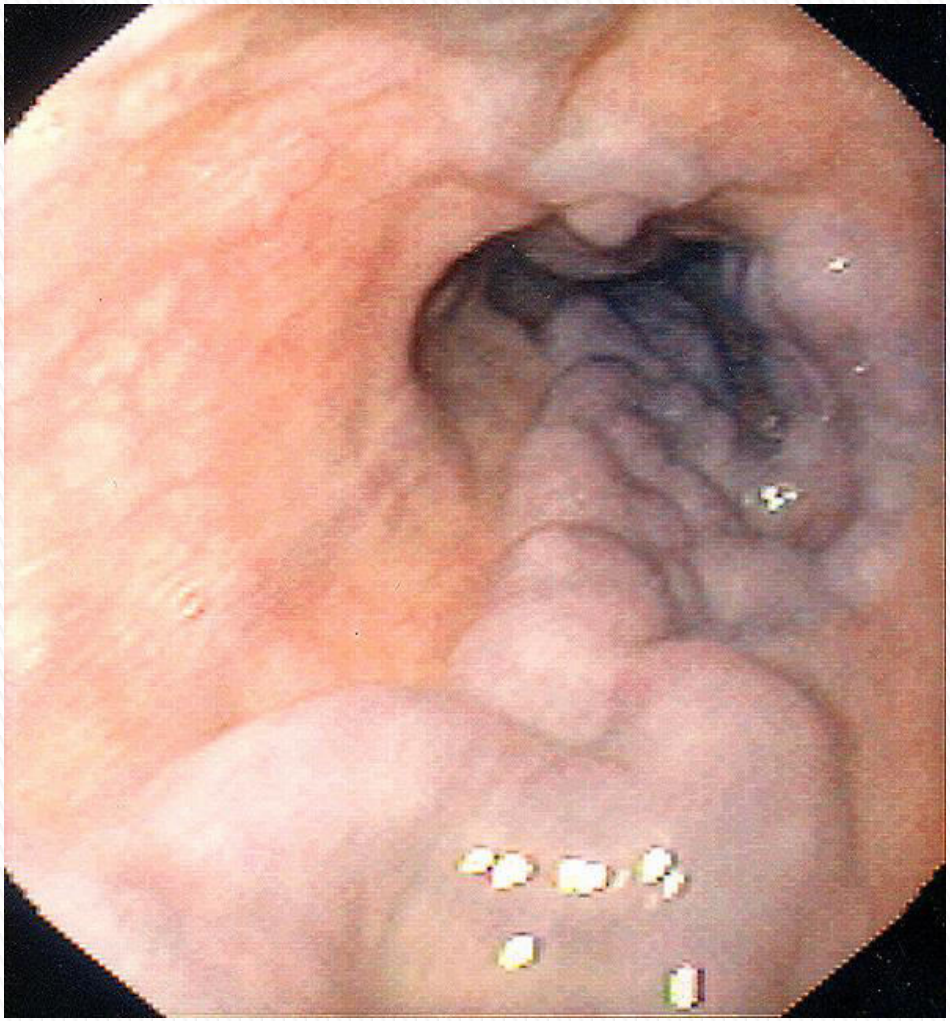
- **Sites**:
  - Hemorrhoids
  - Esophagogastric varices
  - The retroperitoneum
  - Periumbilical and abdominal wall collaterals

Portosystemic Shunt

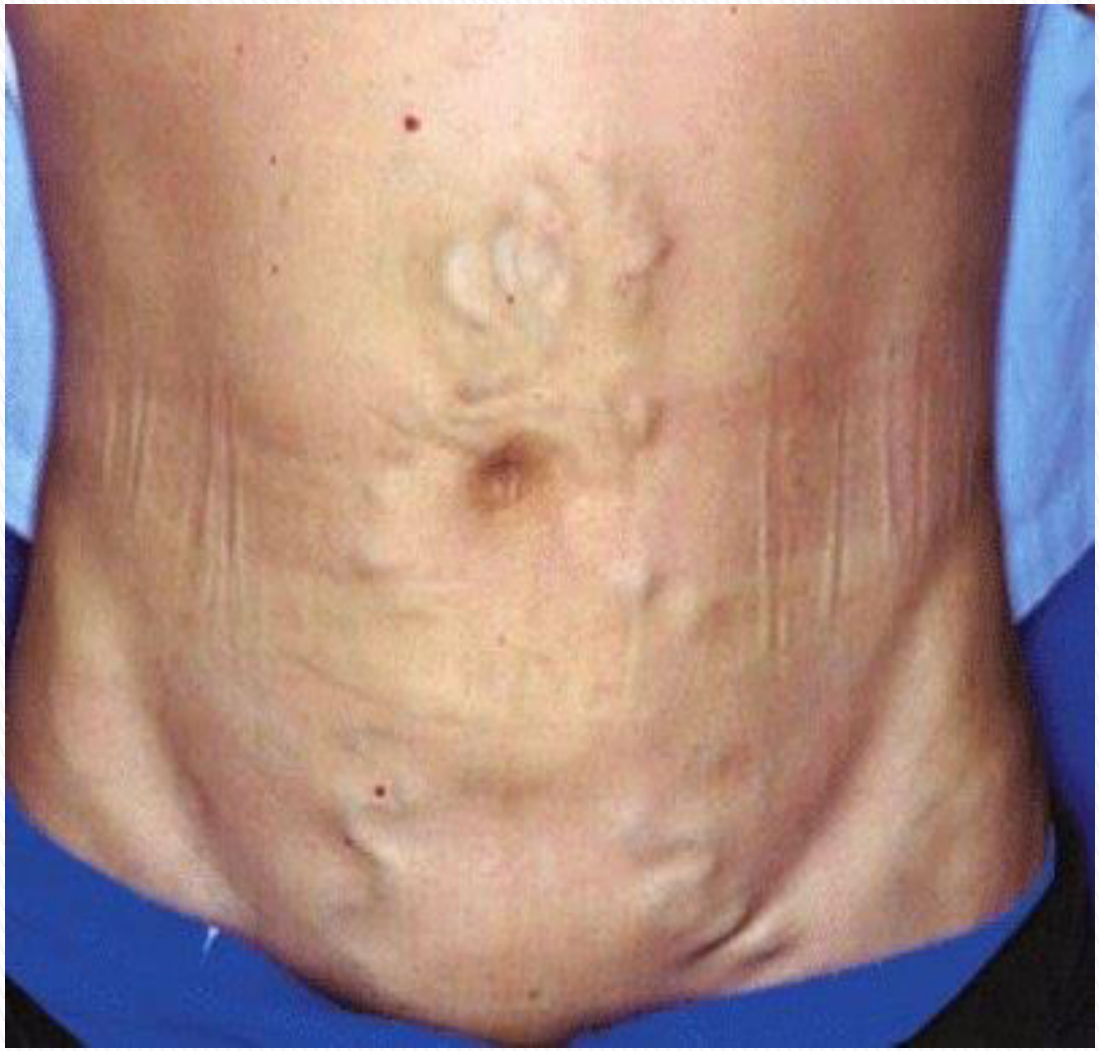
- **Esophagogastric varices:**
  - 65% of those with advanced cirrhosis.
  - Cause massive hematemesis and death in about half.

- **Abdominal wall collaterals:**
- Dilated subcutaneous veins extending outward from the umbilicus *(caput medusae)*

Esophageal varices-endoscopy



Caput medusa



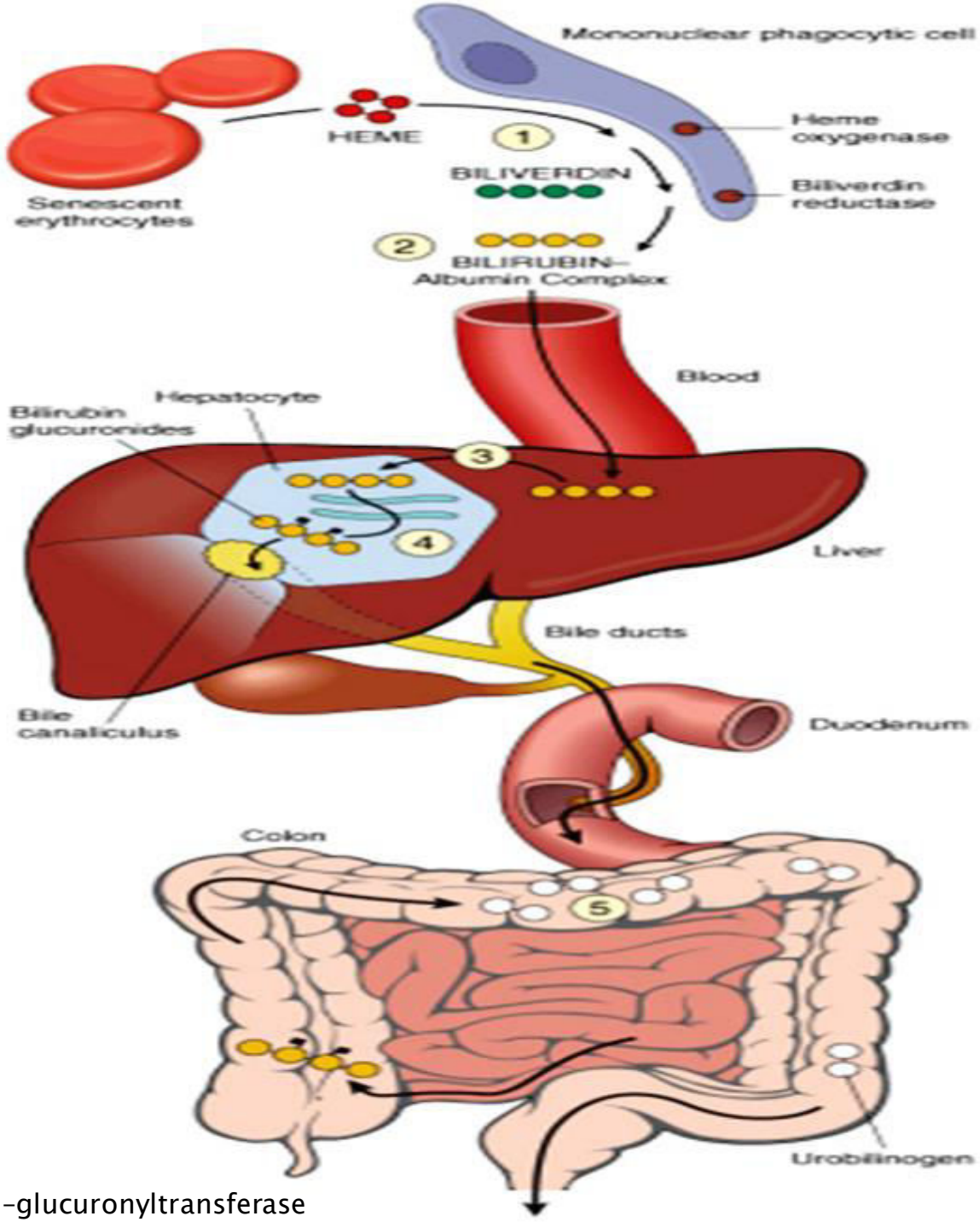
Jaundice and Cholestasis

- **Jaundice (icterus):**
  - A common manifestation of liver disease.
  - *A yellow discoloration of skin and sclerae due to elevated bilirubin serum levels > 2.0 mg/dL (N 0.3-1.2 mg/dL)*

- **Cholestasis:**
  - *Systemic retention of bilirubin & other solutes eliminated in bile (bile salts and cholesterol).*

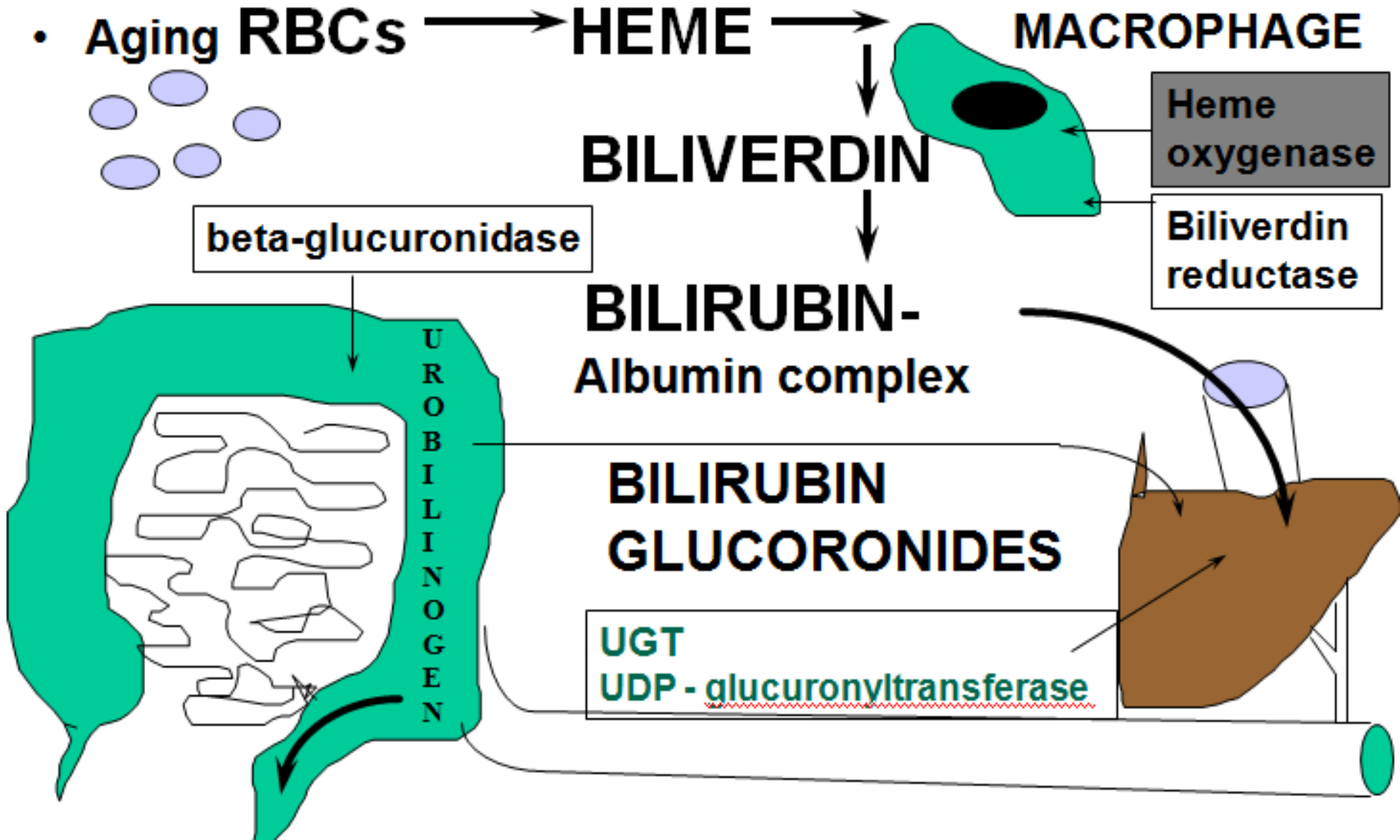
Bilirubin metabolism

https://www.youtube.com/watch?v=RwvbO-40xw



Bilirubin uridine diphosphate-glucuronyltransferase

BILIRUBIN METABOLISM



Pathogenesis

- Jaundice occurs when the equilibrium between bilirubin production and clearance is disturbed*:

- **Unconjugated hyperbilirubinemia**
  - Excessive production of bilirubin
  - Reduced hepatic uptake
  - Impaired conjugation
- **Conjugated hyperbilirubinemia**
  - Decreased hepatocellular excretion
  - Impaired bile flow (Intrahepatic & extrahepatic)

Cholestasis

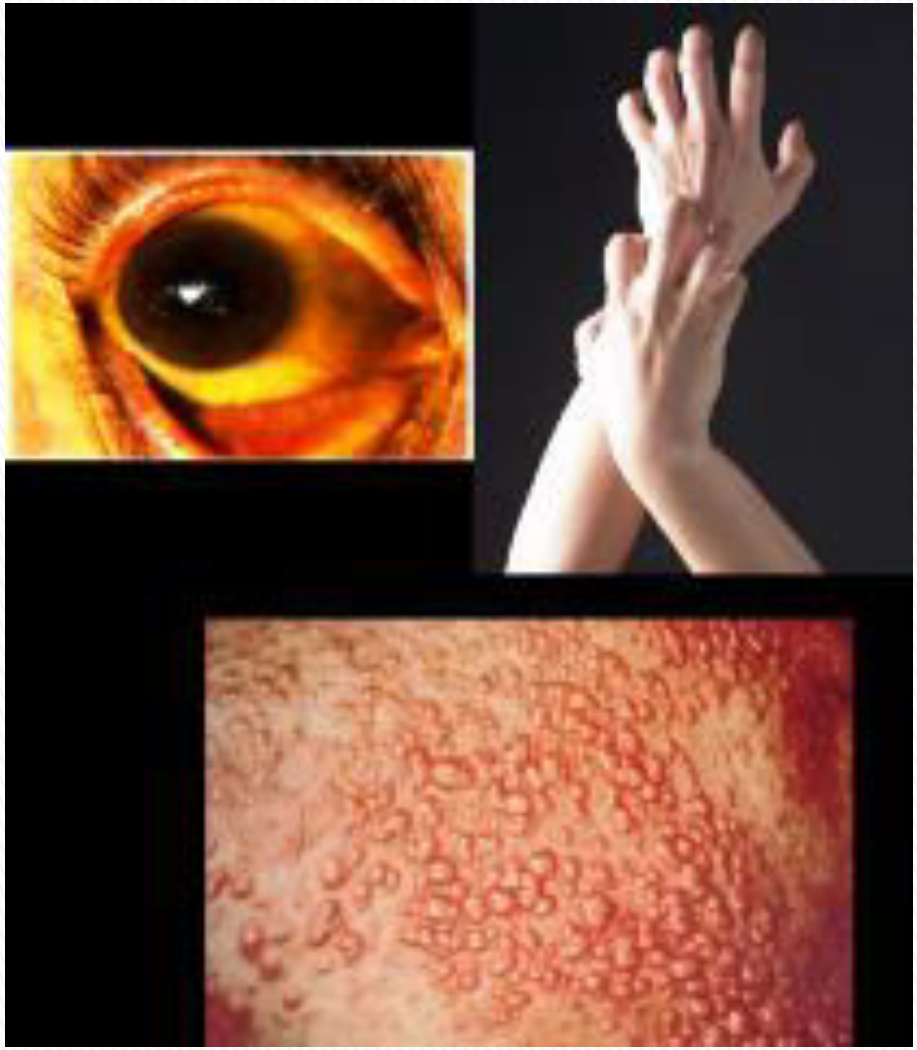
- Systemic retention of bilirubin & other solutes eliminated in bile (bile salts, bile acids & cholesterol).
- Impaired intra-* **OR** extrahepatic bile flow.
- ***Extrahepatic obstruction:***
  - Gallstone, stricture, tumor
  - Amenable for surgical correction
- ***Intrahepatic cholestasis:***
  - Medical jaundice
  - Not amenable for surgical correction

Manifestations of cholestasis

- **Jaundice** due to conjugated hyperbilirubinemia
- **Pruritus** is the presenting symptom, due to deposition of bile acids in skin.
- **Skin xanthomas** (accumulations of cholesterol)
- Intestinal malabsorption especially of fat soluble vitamins (A,D,K).

- Increased alkaline phosphatase, γ-glutamyl transpeptidase, Serum 5'-nucleotidase*.

Manifestations of cholestasis



Laboratory Evaluation of Liver Disease

Hepatocyte integrity

Cytosolic hepatocellular enzymes

- Serum aspartate aminotransferase (AST)
- Serum alanine aminotransferase (ALT)
- Serum lactate dehydrogenase (LDH)

Elevated in liver disease as hepatitis

Hepatocyte function

Proteins secreted into the blood

- Serum albumin
  - Decreasesd in liver disease
- Prothrombin time (factors V, VII, X, prothrombin, fibrinogen)
  - Elevated in liver disease

Hepatocyte metabolism

- Serum ammonia
  - Elevated in liver disease

Lab evaluation of liver disease

Biliary excretory function

Substances secreted in bile

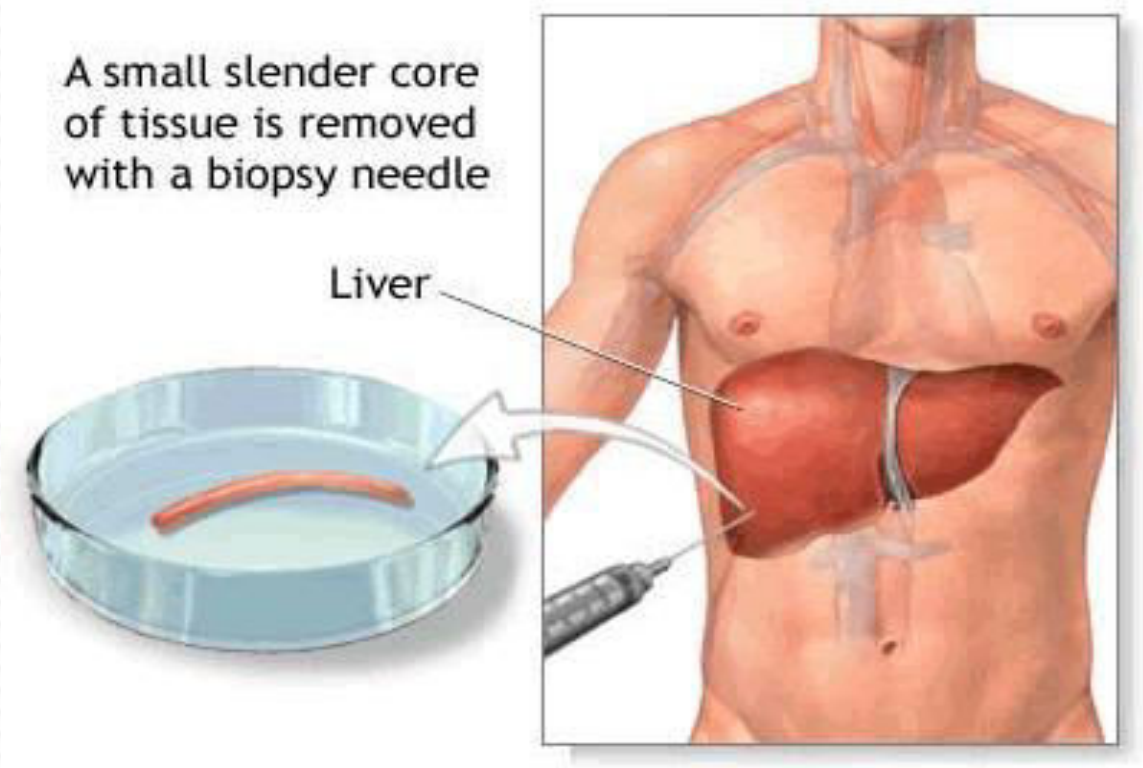
- Serum bilirubin
  - Total: unconjugated plus conjugated
  - Direct: conjugated only
  - Delta: covalently linked to albumin
- Urine bilirubin
- Serum bile acids

Plasma membrane enzymes (from damage to bile canaliculus)

- Serum alkaline phosphatase
- Serum γ-glutamyl transpeptidase
- Serum 5'-nucleotidase

LAB evaluation of liver disease

- Liver biopsy represents the gold standard for diagnosis of liver disease



Inflammatory disorders of liver

- **HEPATITIS:**

"Injury to hepatocytes associated with an influx of acute or chronic inflammatory cells ±scarring"

  - ***Viral hepatitis*** (most common)→ A,B,C,D,E
  - *Autoimmune hepatitis*
  - *Drug-induced hepatitis*
  - *Alcoholism*
  - *Wilson disease, alpha 1 antitrypsin deficiency*

- **Other infections.**
- **Liver abscess.**

Viral hepatitis

- A term reserved for infection of the liver by hepatotropic viruses (a small group of viruses having a particular affinity for the liver).

- Hepatitis A virus (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)
- Hepatitis E virus (HEV)
- Hepatitis G virus (HGV), not pathogenic

Other hepatic viral infections

- **Systemic viral infections can involve the liver:**
- Infectious mononucleosis (Epstein–Barr virus)
  Mild hepatitis during the acute phase
- Cytomegalovirus or herpesvirus infections,
  in newborns or immunosuppressed
- Yellow fever, in tropical countries
- Infrequently, rubella, adenovirus, or enterovirus in children and the immunosuppressed.

Clinical Features

Clinical syndromes of hepatitis viruses*:

- *Asymptomatic acute infection*
- *Acute hepatitis: anicteric or icteric*
- *Chronic hepatitis ± progression to cirrhosis*
- *Chronic carrier state*
- *Fulminant hepatitis*

- Serologic studies are critical for the diagnosis of viral hepatitis & identification of virus types.

Asymptomatic Infection

- Incidentally discovered
- Minimally elevated serum aminotransferases
- Serological evidence of the disease (the presence of antiviral antibodies).

Acute Viral Hepatitis

- Any one of the hepatotropic viruses.
- Acute HCV can be easily missed.
- Divided into four phases:

1. An incubation period
2. A symptomatic preicteric phase
3. A symptomatic icteric phase (with jaundice and scleral icterus)
4. Convalescence

- Elevated serum aminotransferase levels