Hepatobiliary pathology

LEC 2

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II- Chronic viral hepatitis:

- **Def : symptomatic**, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, with histologically documented inflammation and necrosis.
- **Causes:** Although the hepatitis viruses are responsible for most cases, there are **many other causes** of chronic hepatitis; They include :
- **Wilson disease,**
- **α_1-antitrypsin deficiency,**
- **chronic alcoholism,**
- **drugs (isoniazid , α-methyldopa, methotrexate),**
- **autoimmunity.**

Morphology of chronic hepatitis

Most of **morphologic changes** in chronic hepatitis are **shared** with acute hepatitis.

But the following changes are **only seen with chronic hepatitis**.

a. inflammation is limited to the portal tracts & consist of lymphocytes , macrophages, rare neutrophils & eosinophils.

b. lymphoid aggregates are often seen in the portal tract.

c. continuous **periportal necrosis** & **bridging necrosis**…….**progressive liver damage**

d. deposition of **fibrous tissue** (irreversible injury).

e. **cirrhosis** which is usually of macro nodular type.

Morphology

- **The hallmark** of serious **chronic liver damage** is the deposition of fibrous tissue.
- At first, only portal tracts exhibit increased fibrosis, but with time **periportal fibrosis** occurs, followed by linking of fibrous septa between lobules **(bridging fibrosis).**
- **Continued loss of hepatocytes and fibrosis results in cirrhosis, with fibrous septa and hepatocyte regenerative nodules.**

Specific morphology in chronic hepatitis:

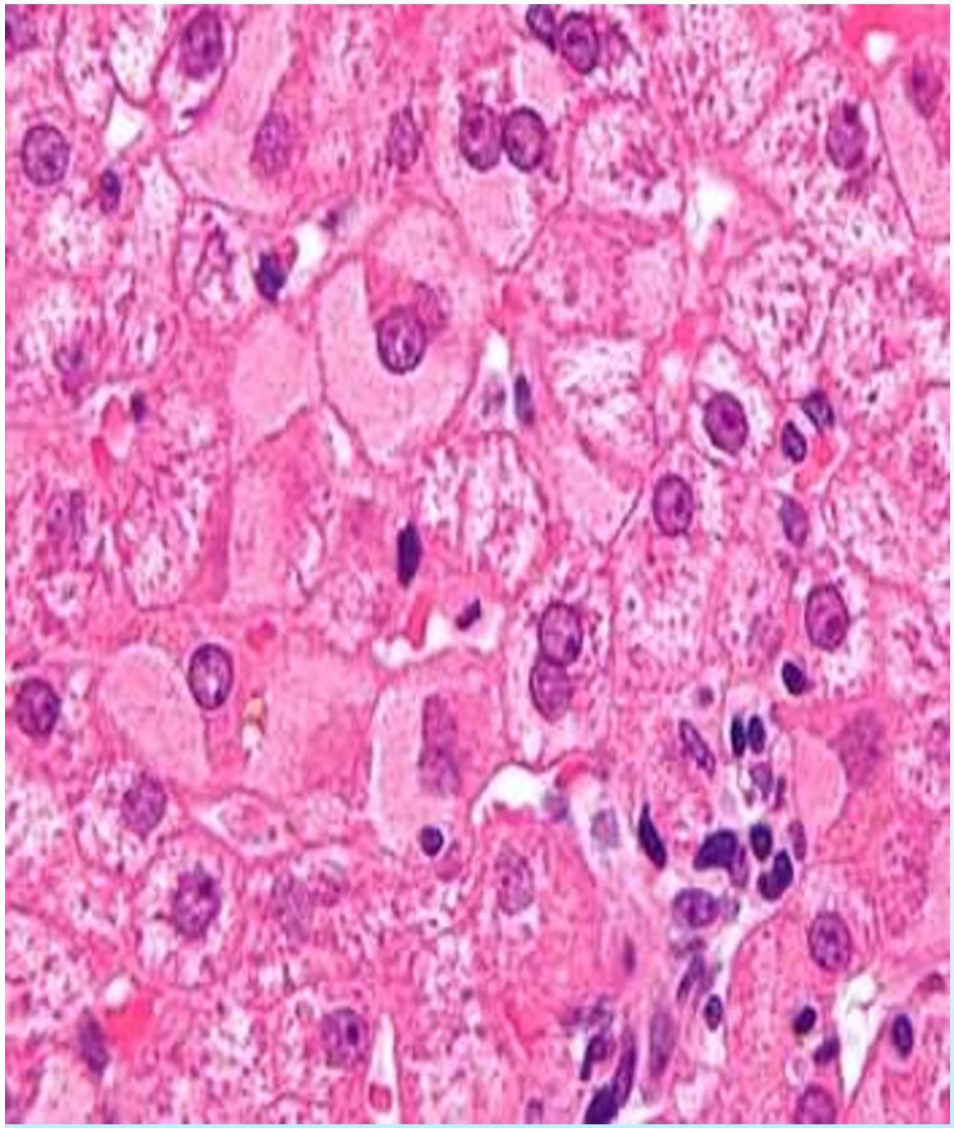
In chronic HBV infection may generate **"ground-glass"** hepatocytes

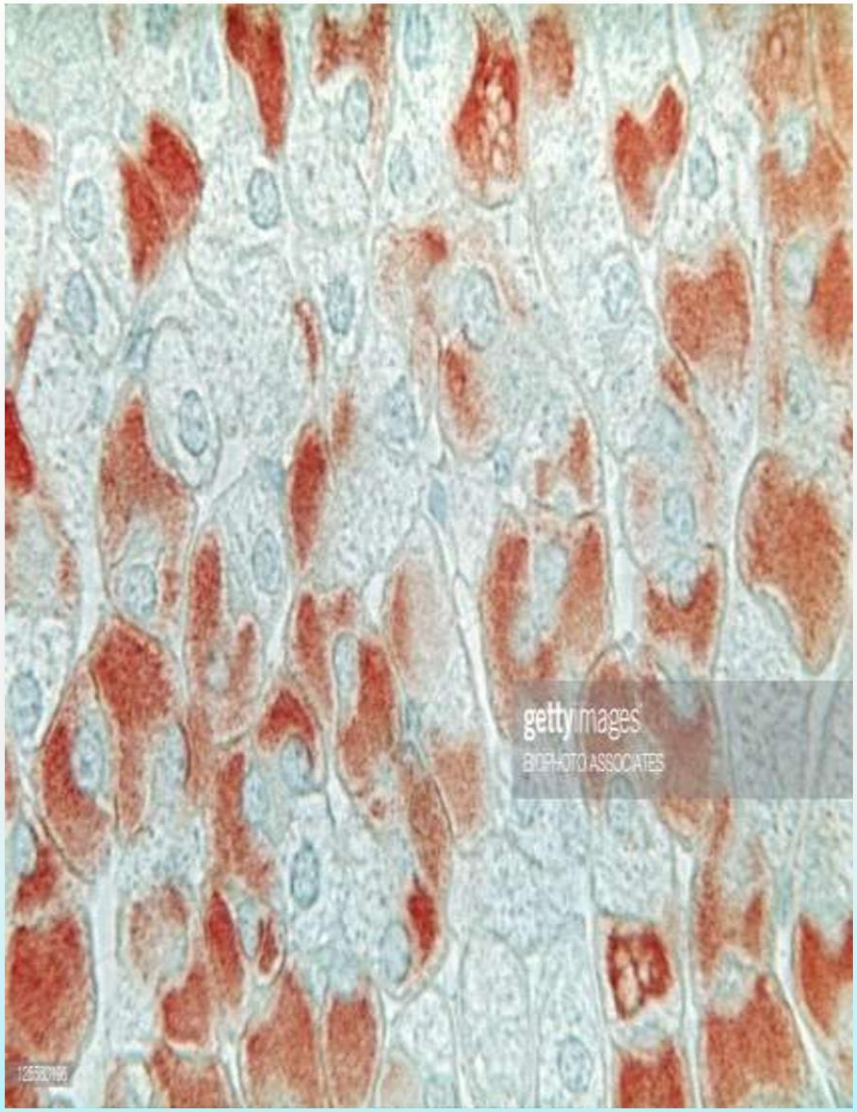
- Other HBV-infected hepatocytes may have **"sanded"nuclei,**

. **Ground glass hepatitis:** this is seen **in HBV**. The hepatocytes show a fine granular eosinophilic cytoplasm shown by electron microscope to contain massive quantities of HBs Ag in the form of spheres & tubules.

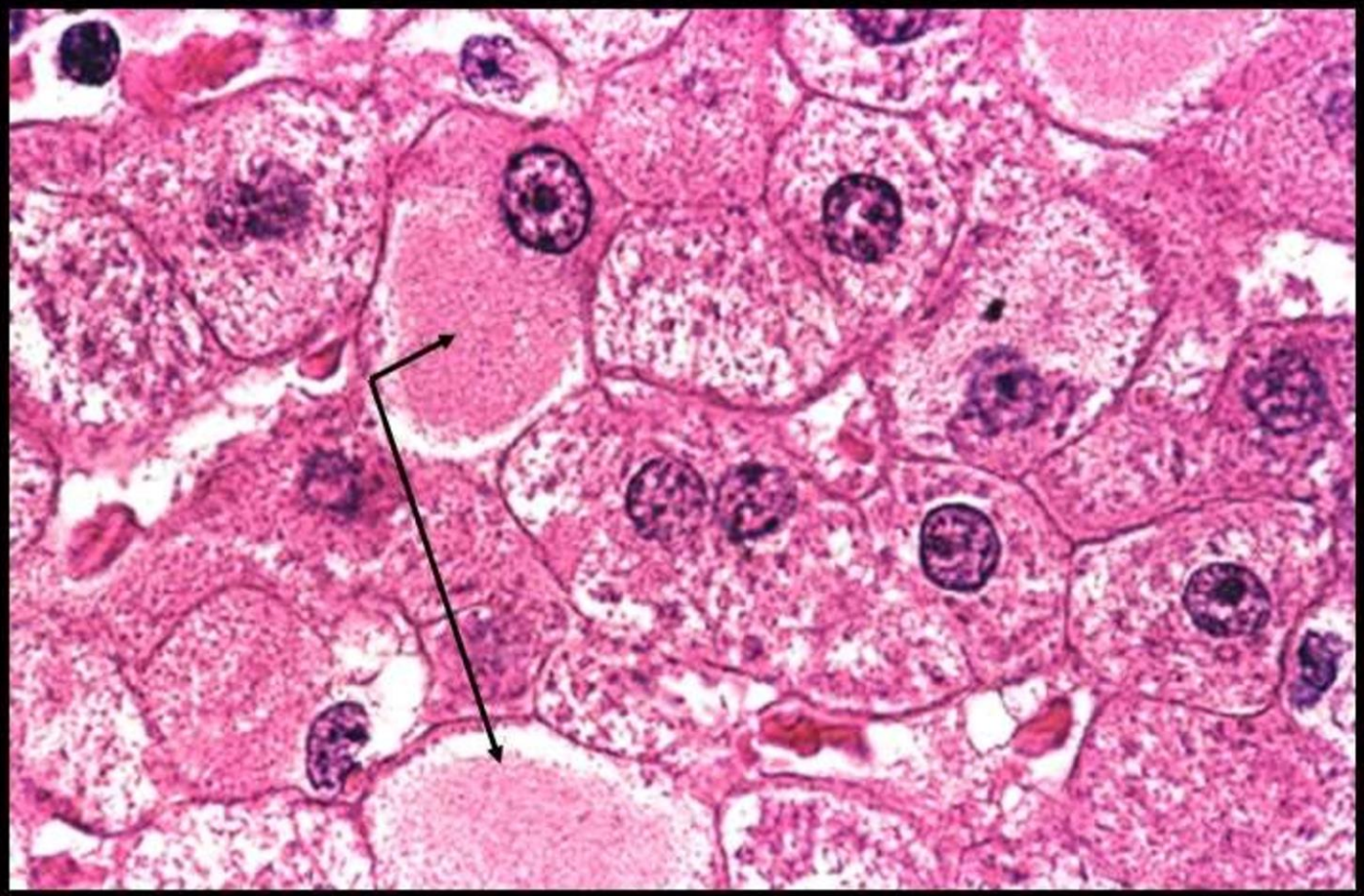
Sanded nuclei: also seen in HBV infection due to abundant intranuclear HBc Ag .

Chronic Hepatitis B infection; **ground-glass"** hepatocytes may be immunostained by antibodies to HBsAg stained brown.



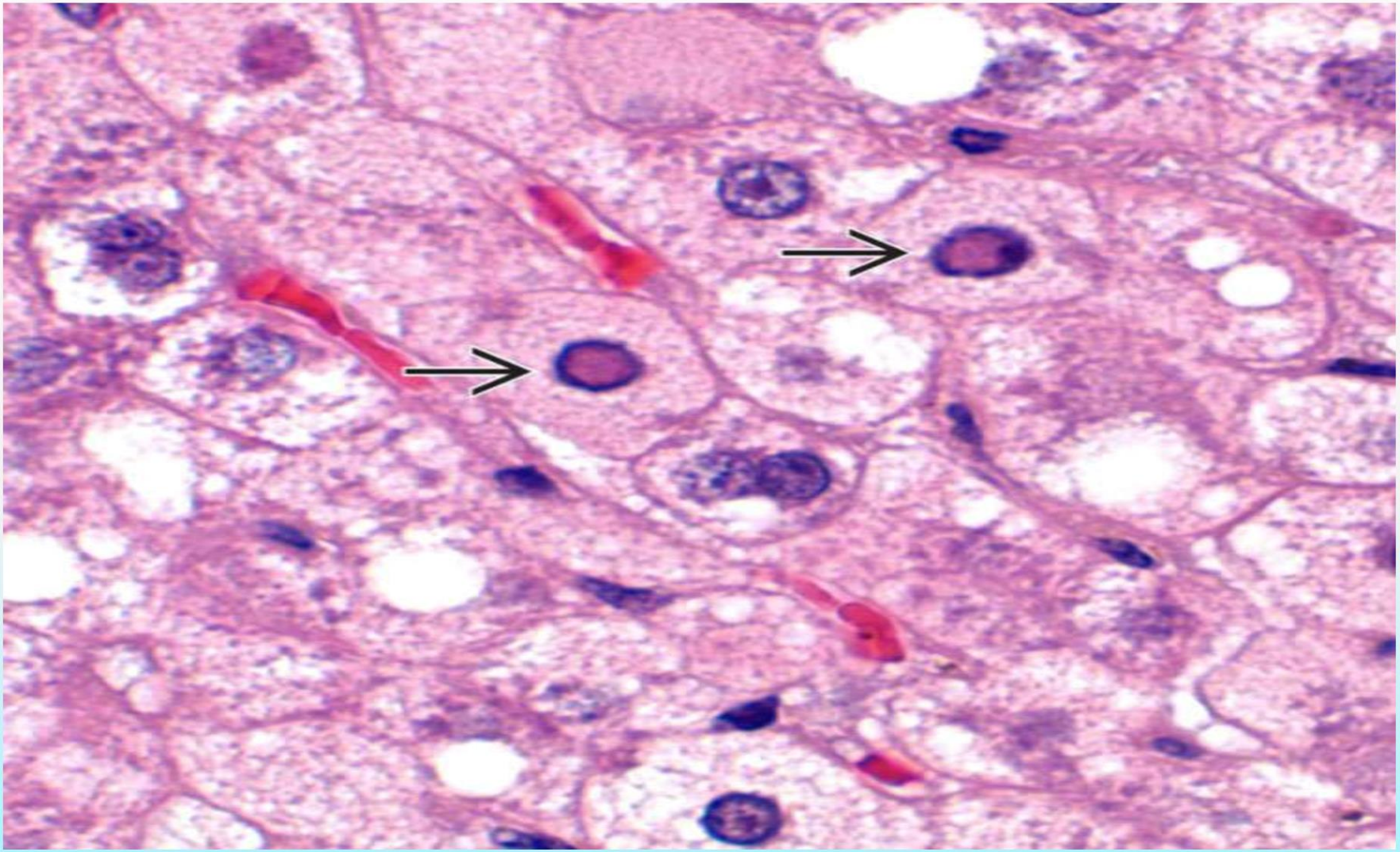


Chronic viral hepatitis B showing ground glass hepatocytes



Ground glass hepatocytes, characterized by more pale, eosinophilic, and homogeneous cytoplasm than surrounding normal (more granular) hepatocytes. Note (artifactual) cleft between "ground glass" cytoplasm and hepatocellular cell membrane. The change corresponds to extensive endoplasmic reticulum hyperplasia and massive accumulation of HBsAg. (H&E)

Sanded NucleiHepatitis B-infected hepatocytes may have pale pink, finely granular intranuclear inclusions (sanded nuclei image)



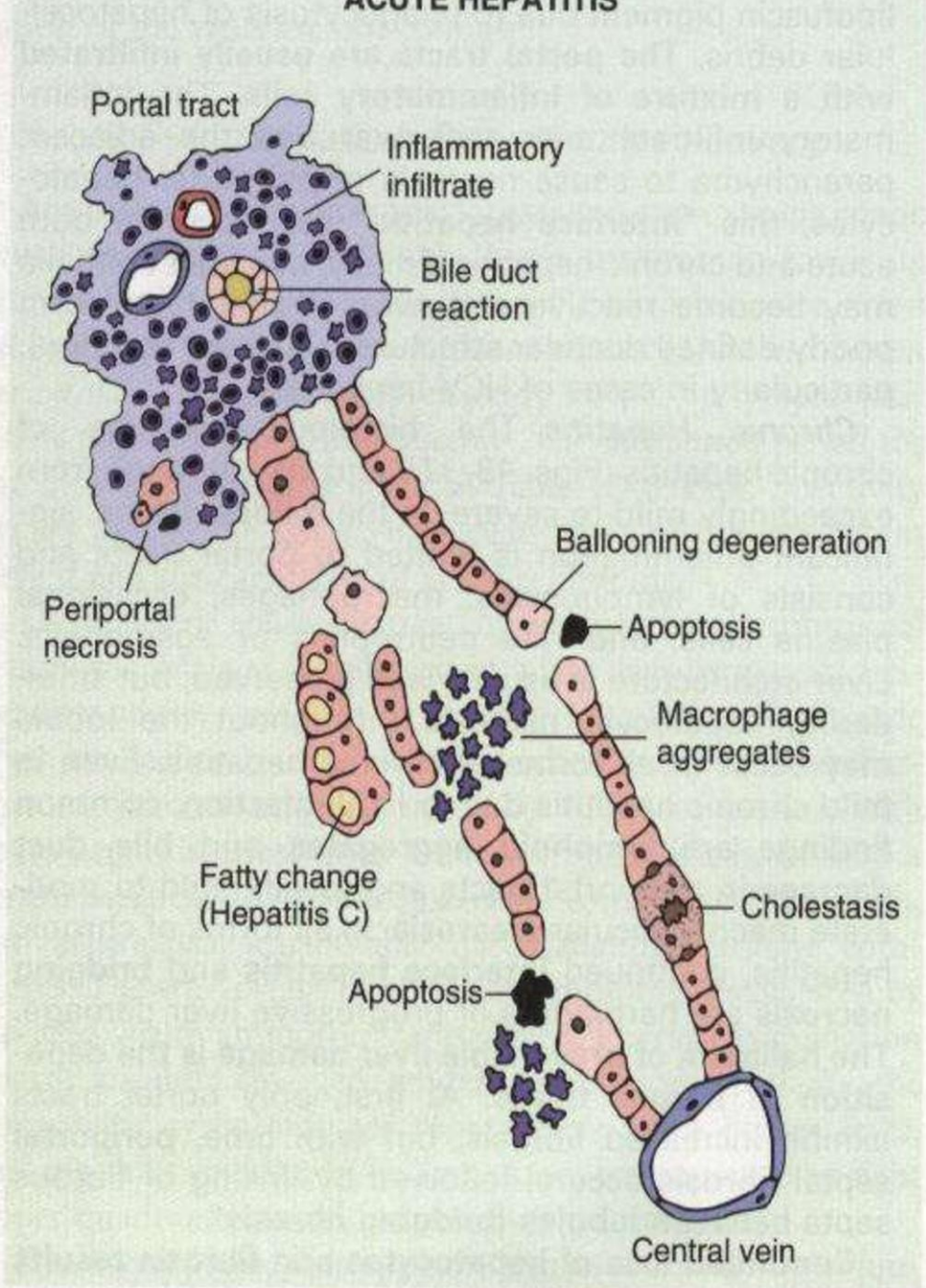
Specific morphology associated with HCV

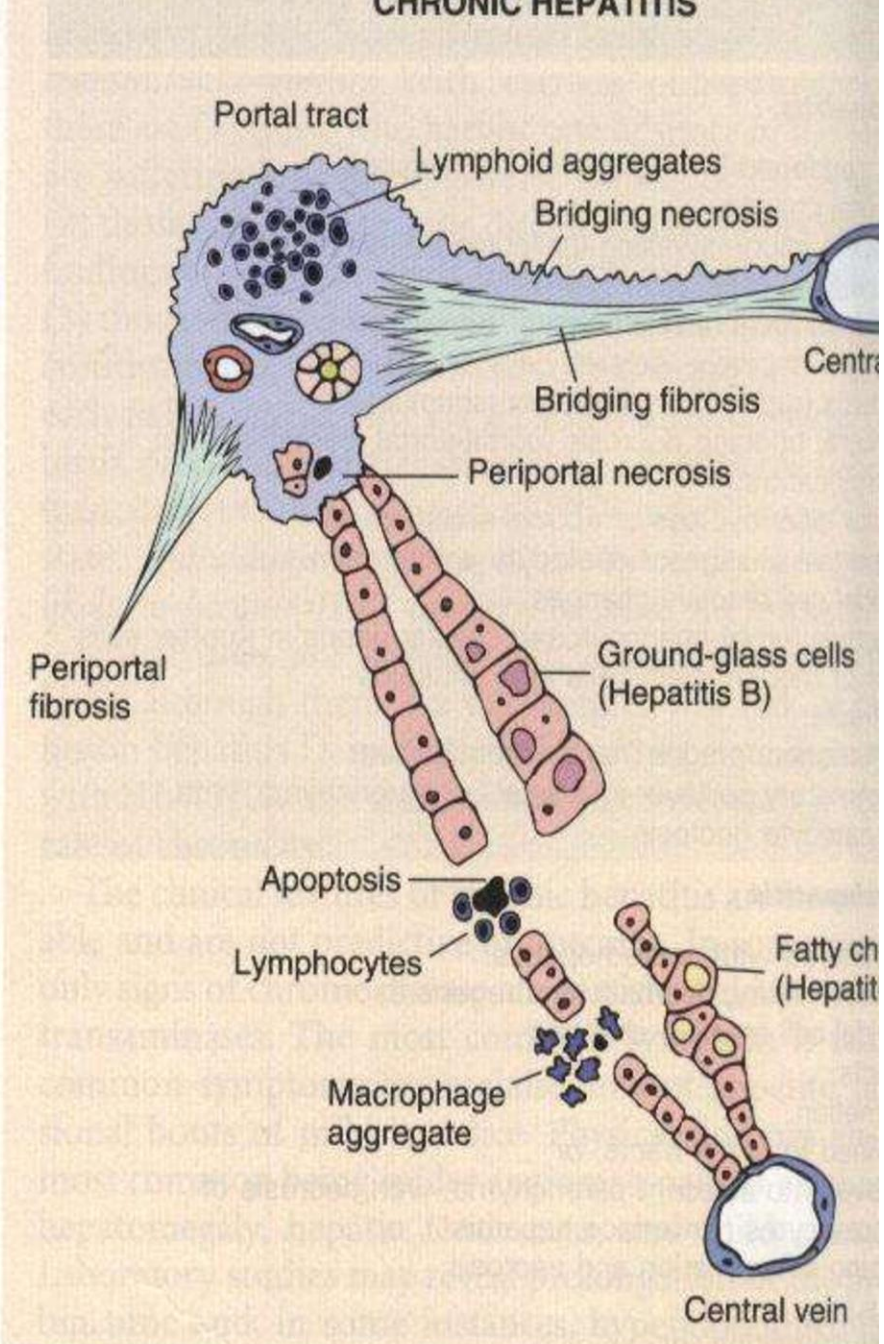
- **Chronic hepatitis C commonly shows**:

1-lymphoid aggregates or fully formed lymphoid follicles .

2-fatty change

3- Bile duct injury


ACUTE HEPATITIS
Portal tract
Inflammatory infiltrate
Bile duct reaction
Ballooning degeneration
Periportal necrosis
Apoptosis
Macrophage aggregates
Fatty change (Hepatitis C)
Cholestasis
Apoptosis
Central vein


CHRONIC HEPATITIS
Portal tract
Lymphoid aggregates
Bridging necrosis
Bridging fibrosis
Periportal necrosis
Periportal fibrosis
Ground-glass cells (Hepatitis B)
Apoptosis
Lymphocytes
Macrophage aggregate
Central vein

NON-Viral hepatitides

Infectious (non-viral) Hepatitis:

(1) Bacterial infection.(Gram-Negatives Follow acute cholangitis or) Staph aureus (toxic shock)

(2) Fungal infection.

(3) Parasitic infections: (hydatid cyst)

(4) Granulomatous infections. Like tuberculosis, leprosy

AUTOIMMUNE
ALCOHOLIC HEPATITIS

INFLAMMATIONS OF THE LIVER

AUTOIMMUNE HEPATITIS

Chronic hepatitis of variable severity,

histologically indistinguishable from chronic viral hepatitis

Patients have variety of immunologic abnormalities

Female predominance (70%)

No serologic viral markers

Elevated serum IgG >2.5 gm/dl

High titers of autoantibodies (80%) including ANA, anti-smooth muscles.

Increased frequency of HLA-B8 or HLA-DRw

Other forms of autoimmune diseases may be present (60%), e.g. RA,

Overall risk for cirrhosis is 5%

Rx: good response to immunosuppressive therapy

Alcoholic liver disease

Excessive alcohol consumption is the leading cause of liver disease & death in most western countries.

Chronic alcohol consumption leads to three distinctive alcoholic liver disease :

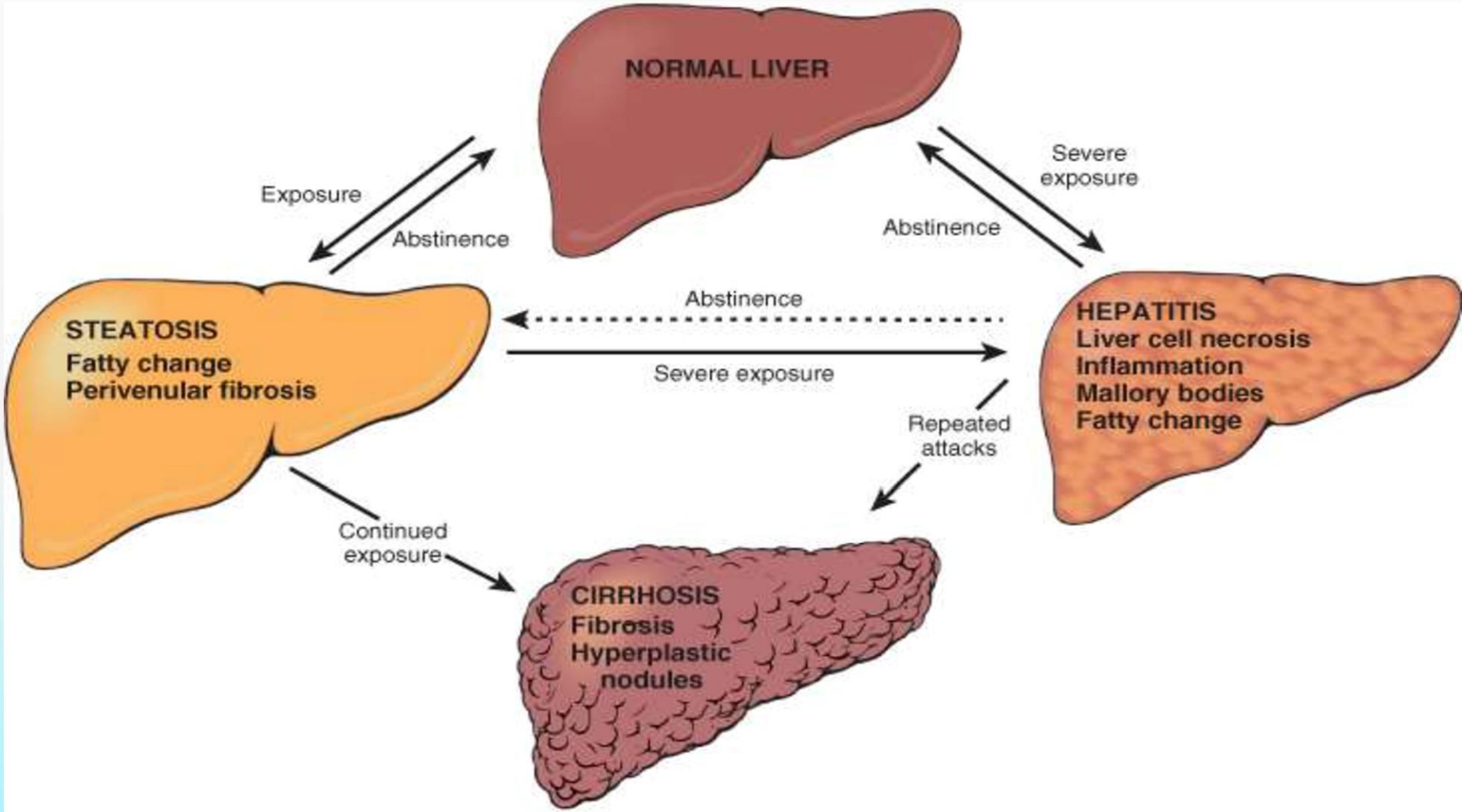
1-Hepatic steatosis (fatty liver) (50%).

2-Alcohol hepatitis. (20%).

3-Hepatic cirrhosis. (10%).

TOXIN-INDUCED LIVER DISEASE

ALCOHOLIC LIVER DISEASE



Morphology of hepatic steatosis

Grossly:

Large fatty liver (up to 4-6 kg), soft, yellowish, greasy, Little or no fibrosis at first.

Microscopically:

small lipid droplets occur (microvesicular changes).

large lipid droplets (macrovesicular) globules

the nucleus is displaced to the periphery of the cell.

ALCOHOLIC LIVER DISEASE

Steatosis (fatty changes)

Lipid droplets accumulate in hepatocytes

2 histologic types:

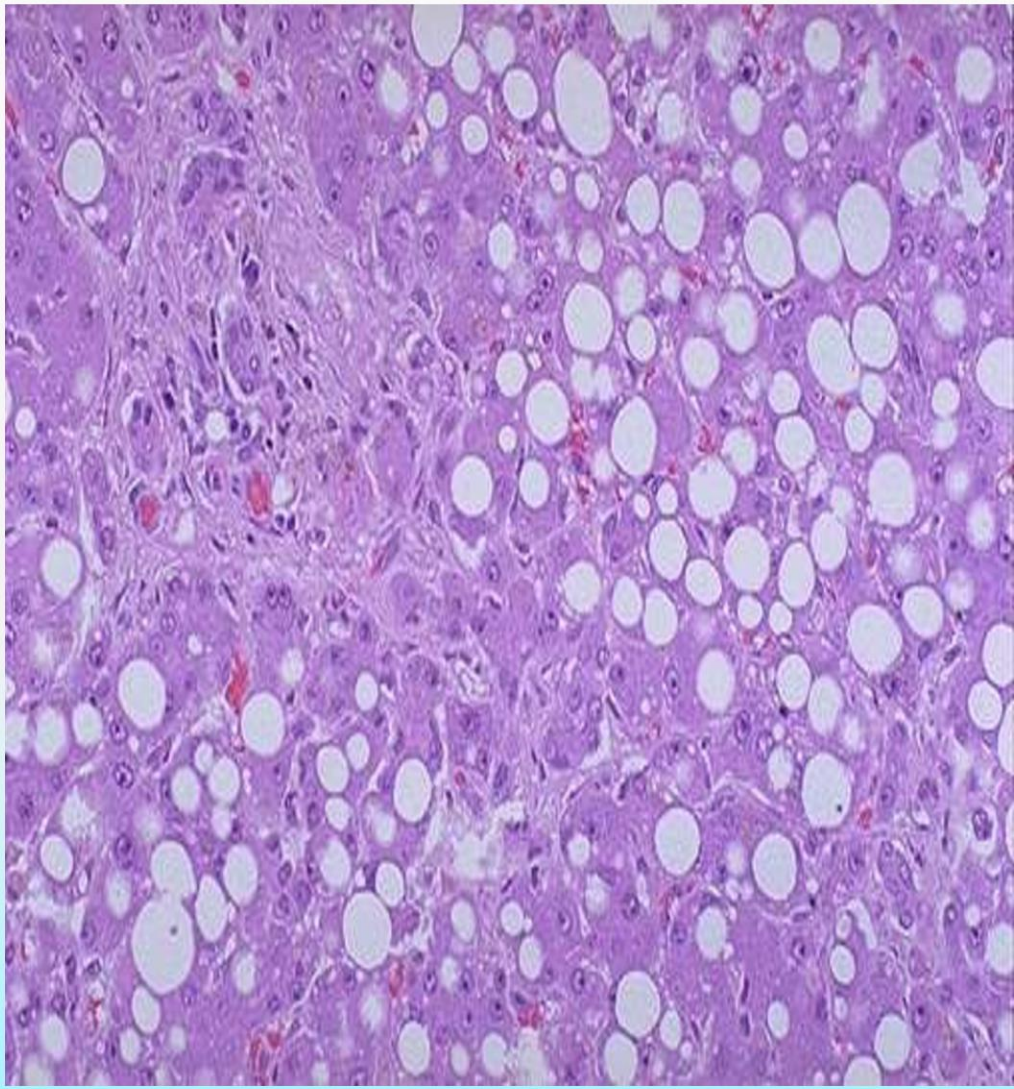
Microvesicular

Macrovesicular

Initially centrilobular

Later panlobular

Completely reversible if there is abstention



Morphology of Alcoholic hepatitis

Grossly:

Large fatty liver (up to 4-6 kg), soft, yellowish, greasy, Little or no fibrosis at first.

Microscopically:

1-Hepatocyte swelling (Ballooning degeneration).

2-Macrovesicular steatosis.(reversible with moderate alcohol intake).

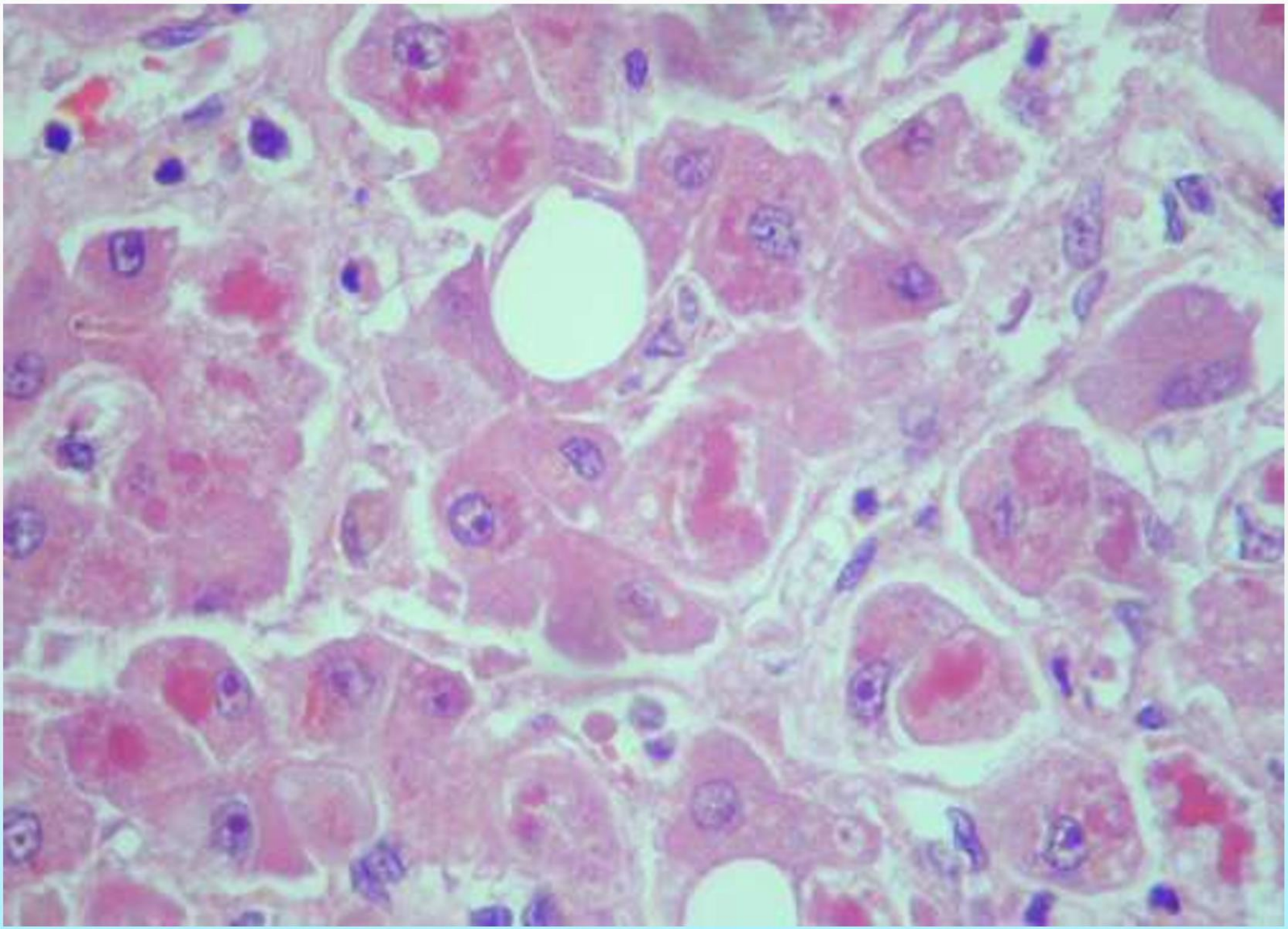
3-Mallory bodies: amorphous eosinophilic, cytoplasmic inclusions due to accumulation of cytokeratin filaments

4-Neutrophilic reaction: around degenerating hepatocytes

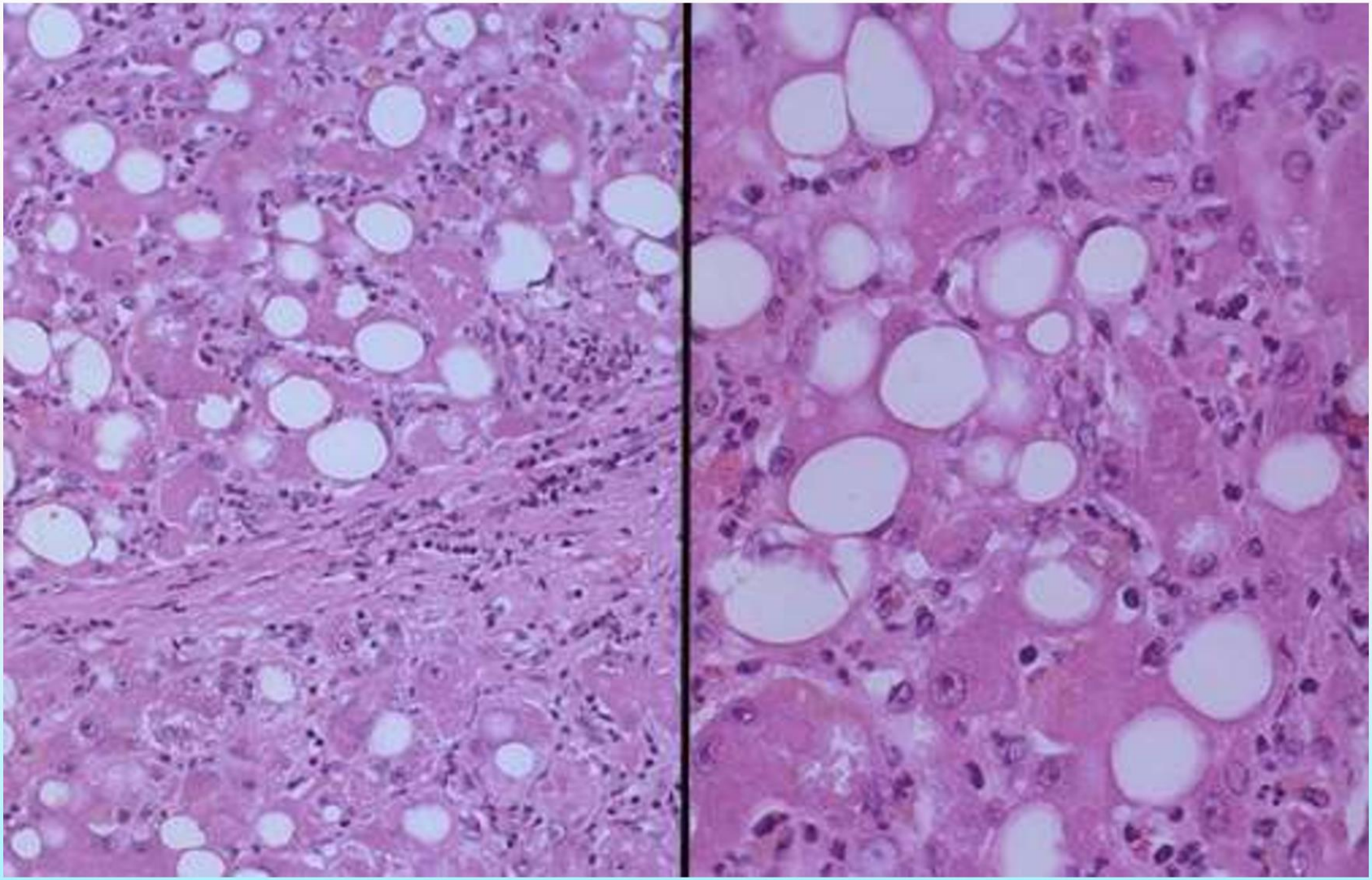
5-portal lymphocytes & macrophages

6-Fibrosis: starts as sinusoidal & perivenular then periportal

MALLORY'S HYALINE



ALCOHOLIC HEPATITIS



Morphology of Alcoholic cirrhosis

Grossly:

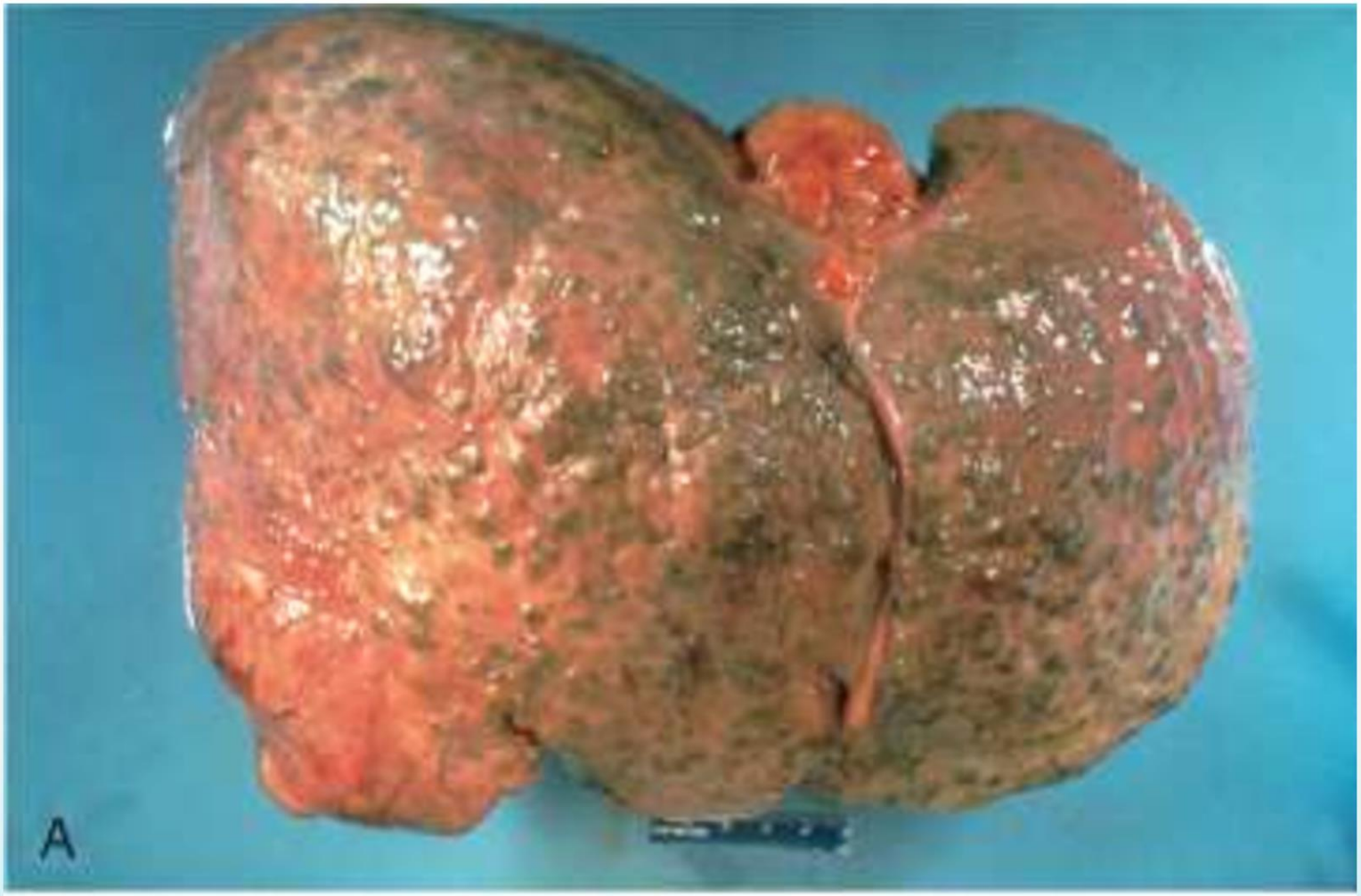
Cirrhotic liver appears yellow and enlarged more than 2kg, at the first 1-2 years, after years appear brown, shrunken, non fatty less than 1 kg

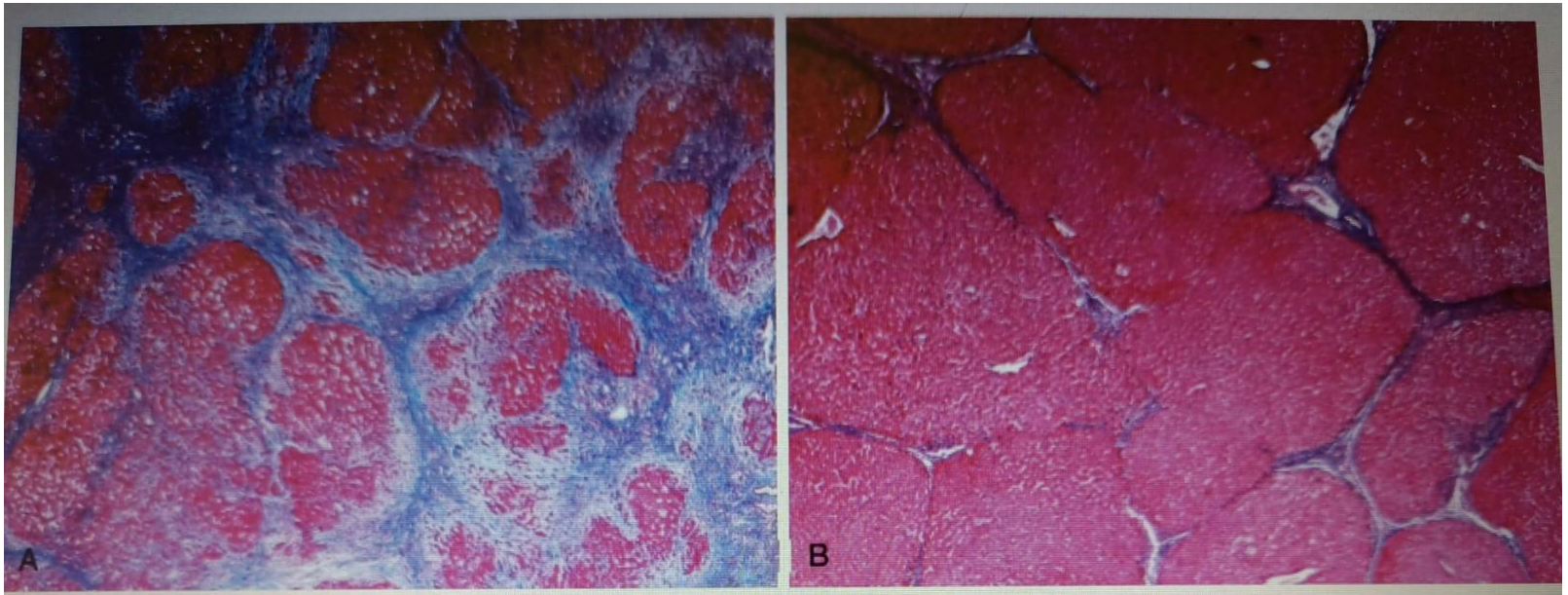
Microscopically:

At first, delicate fibrous tissue extent from central-portal, central - central, portal –portal.

With time, the regenerating hepatocytes with the fibrosis lead to form micronodules then macronodules

The final and irreversible form usually evolves slowly.





g. 16.6 Alcoholic cirrhosis in an active drinker (A) and following long-term abstinence (B). A, Thick bands of collagen separate rounded cirrhotic nodu After 1 year of abstinence, most scars are gone (Masson trichrome stain). *(Courtesy of Drs. Hongfa Zhu and Isabel Fiel, Mount Sinai School of Medicine, N k, New York.)*

CLINICAL FEATURES OF ALCOHOLIC LIVER DISEASE

Hepatic steatosis

Asymptomatic

Mild ↑ serum bilirubin & alk. phosphatase

Alcoholic hepatitis

Minimal to severe manifestations

Nonspecific symptoms

Increase in serum bilirubin, alk. phosphatase, WBCs

Alcoholic cirrhosis

Similar to other forms of cirrhosis

METABOLIC LIVER DISEASES
NONALCOHOLIC FATTY LIVER DISEASE(NAFLD)

A condition in which fatty liver develops in individuals who do not drink alcohol.

May present as steatosis or as nonalcoholic steatohepatitis (NASH) which is similar to ASH.

Is considered as a significant contributar to the group of patients with cryptogenic cirrhosis.

NAFLD & NASH are consistently associated with insulin resistance .

METABOLIC LIVER DISEASES
NONALCOHOLIC FATTY LIVER DISEASE(NAFLD)

Causes:

1- Type 2 D.M.

2-Obesity.

3-Dyslipidemia (increase triglycerides, low HDL, high LDL).

CIRRHOSIS

- PORTAL-to-PORTAL (bridging)

FIBROSIS

- The “normal” hexagonal “ARCHITECTURE” is replaced by

NODULES

Cirrhosis

This is the end stage of chronic liver diseases

Def: a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal regenerative nodules,

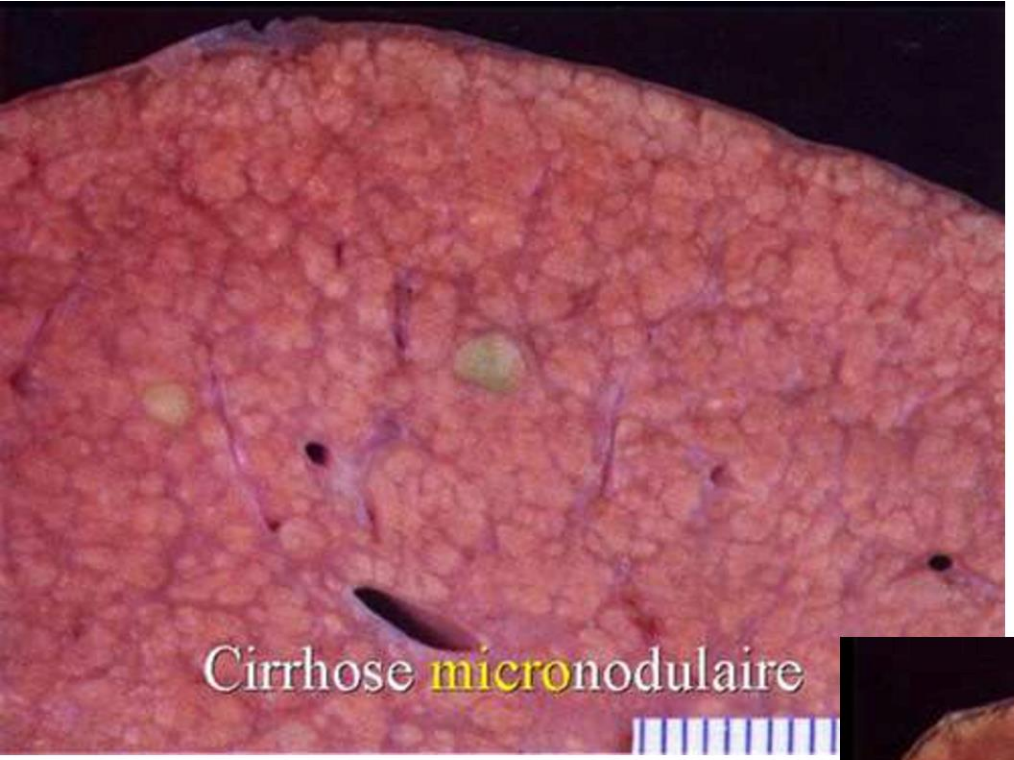
It is mainly characterized by three main histological modifications which are:

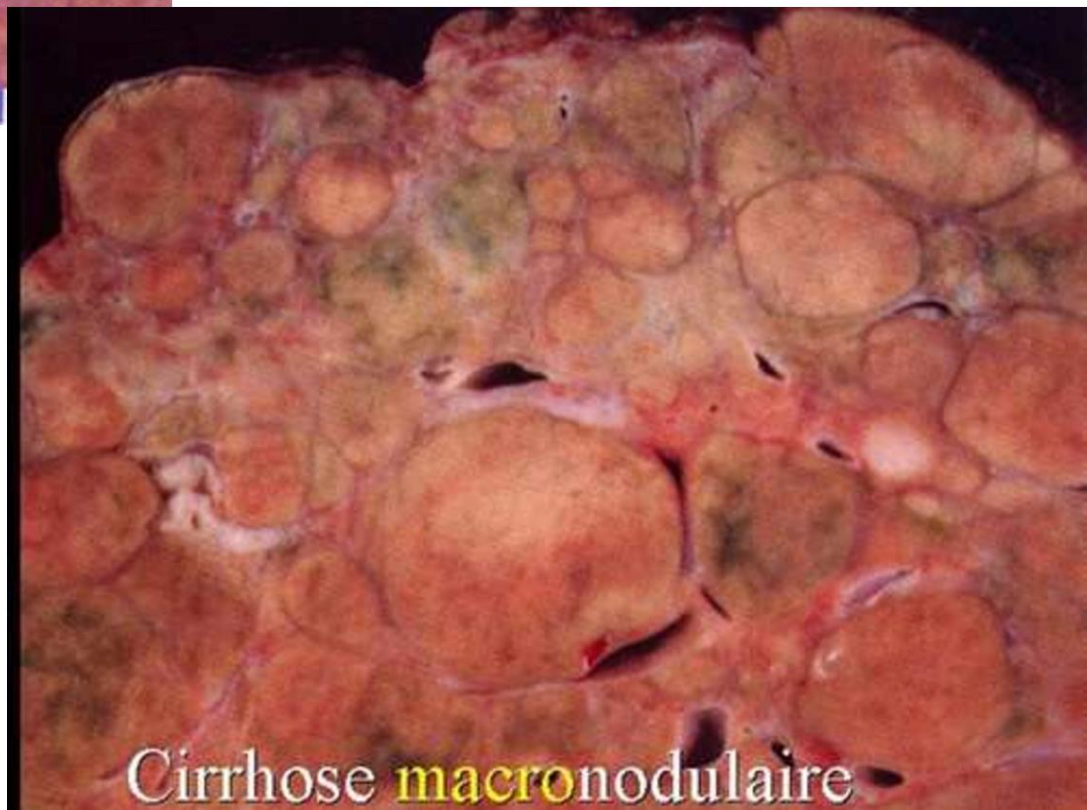
1. ***Bridging fibrous septa:*** in the form of delicate bands or broad scars around multiple adjacent lobules; long-standing fibrosis is generally irreversible
2. ***Parenchymal nodules:*** varying in size from micronodules (<3mm) to macronodules (several centimeters); these nodules are encircled by fibrosis and contain proliferating hepatocytes.
3. ***Disruption of the architecture of the entire liver:*** the parenchymal cell injury and fibrosis are diffuse, extending throughout the liver; focal injury with scarring doesn`t constitute cirrhosis

- **Classification of Cirrhosis. :**
- Many classifications of liver cirrhosis
- **A. Morphological classification**: Macronodular, Micronodular, Mixed
- **B. Histologic classification**: Portal, Post-necrotic, Post Hepatitic, Biliary, Congestive.
-

C. Etiological classification (most commonly used)

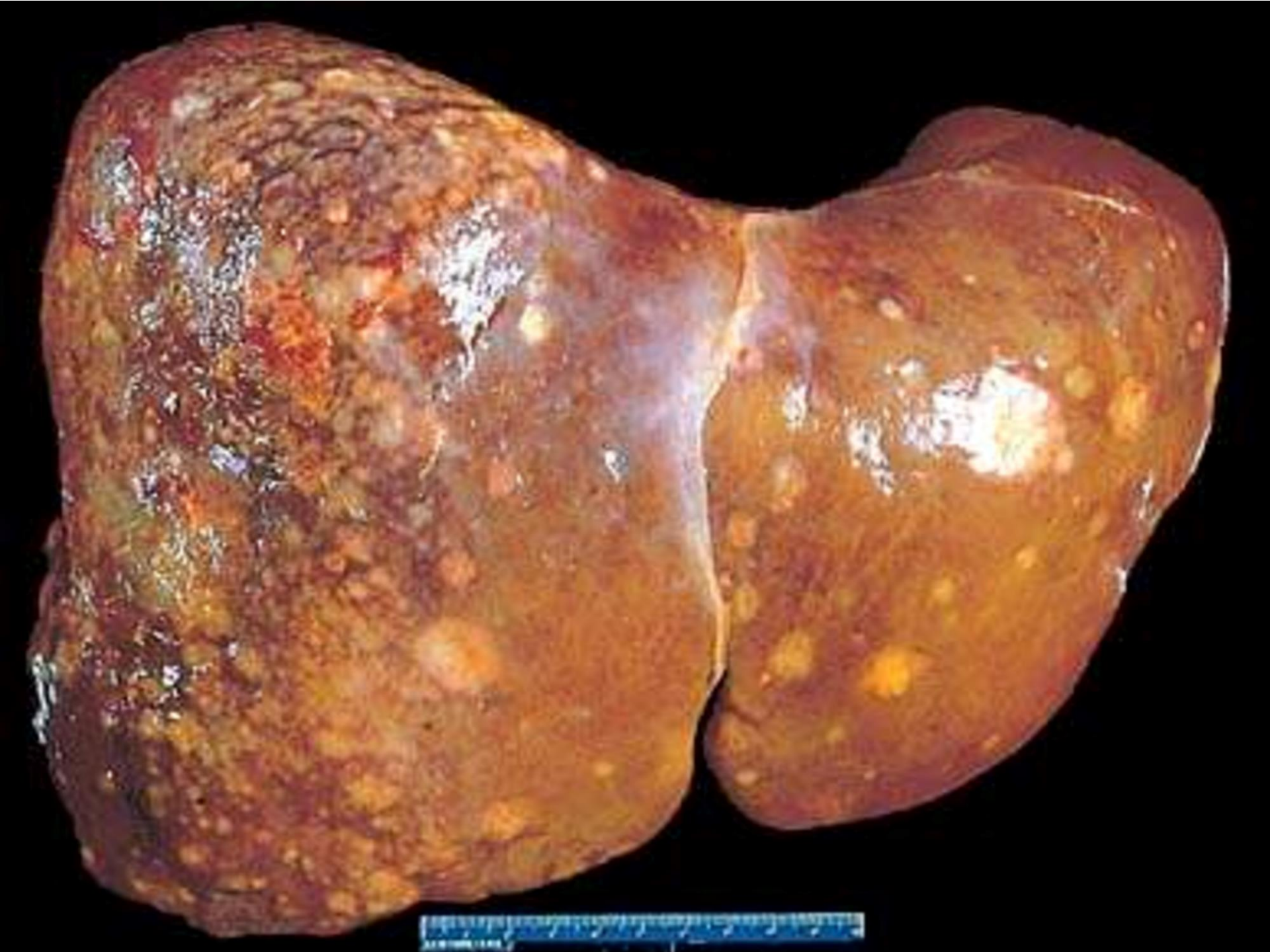
- Cirrhosis is classified according to etiology.
- 1. Alcoholic liver diseases (60% to 70%)
- 2. Viral hepatitis 10%
- 3. Biliary diseases 5% to 10%
- 4. Hereditary hemochromatosis 5%
- 5. Wilson disease rare.
- 6. Alph1- antitrypsin deficiency rare
- 7. Cryptogenic cirrhosis (idiopathic) 10% to 15%.
- 8. Others infrequent causes include (galactosemia, trypsinosis, drugs, syphilis, cardiac cirrhosis)

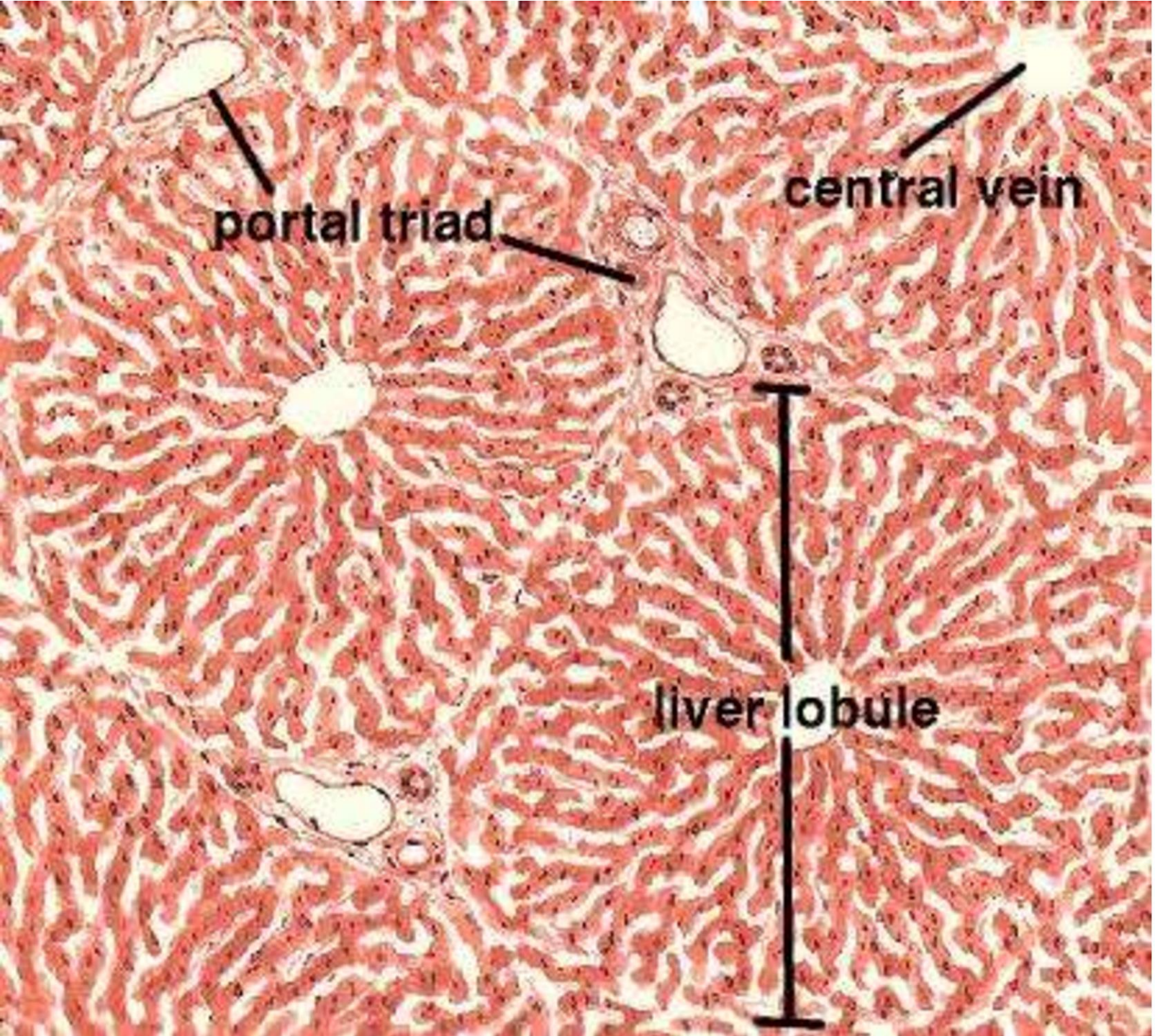

Cirrhose micronodulaire


Cirrhose macronodulaire

ALL CIRRHOSIS IS:

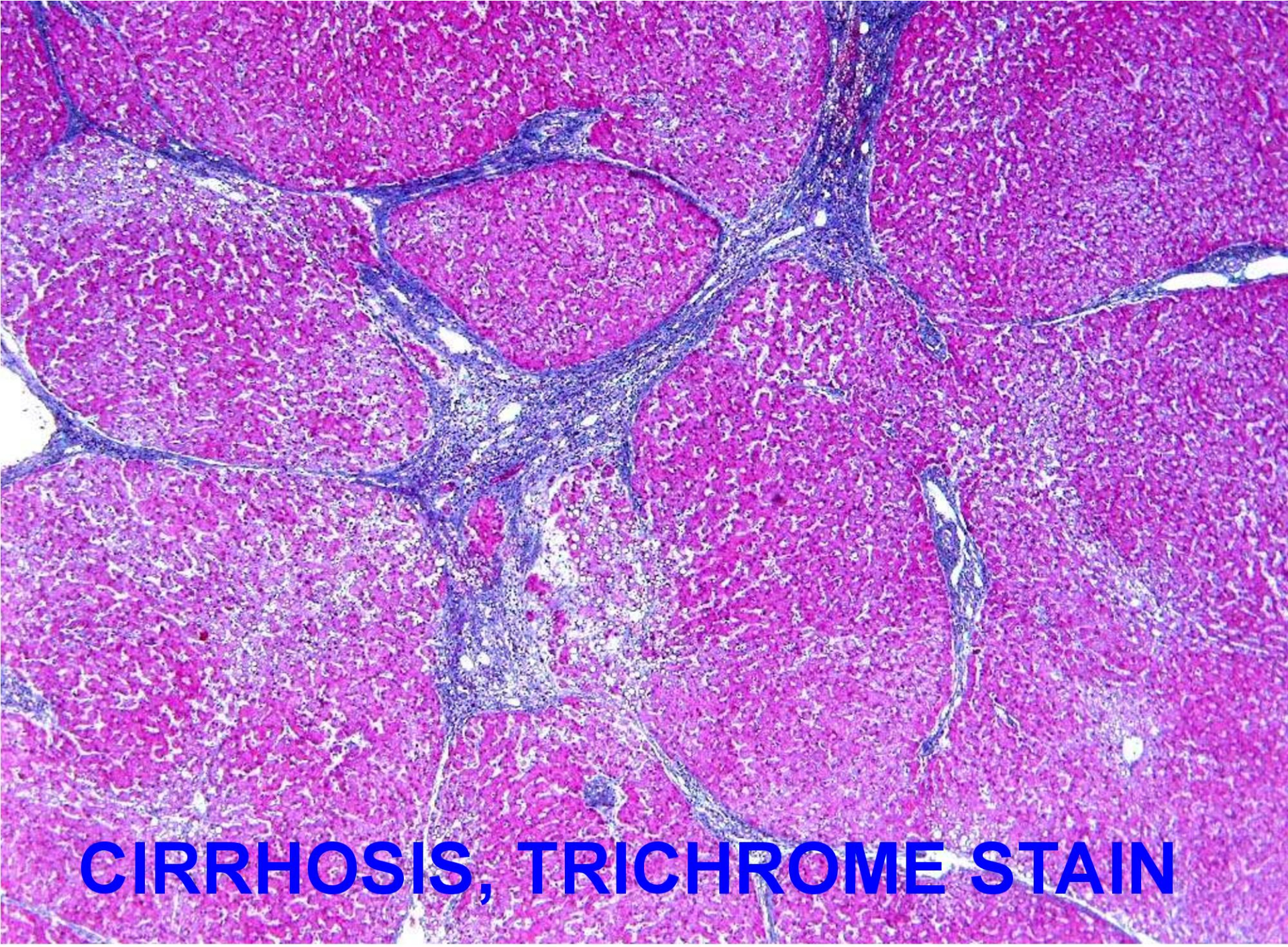
- **IRREVERSIBLE**
- The end stage of ALL chronic liver disease, often many years,
- Associated with a HUGE degree of nodular regeneration, and therefore represents a significant "risk" for primary liver neoplasm, i.e., Hepatocellular Carcinoma





NO

FIBROUS TISSUE BETWEEN PORTAL AREAS


CIRRHOSIS, TRICHROME STAIN

Pathogenesis of cirrhosis

. **Three major mechanisms that are combined to create cirrhosis.**

1. **Hepatocellular death.**
2. **Regeneration (normal tissue response).**
3. **Progressive fibrosis. Due to excessive collagen deposition.**

In normal liver the collagen (type I, III, IV) are limited to portal tracts & around the central veins & occasionally in the parenchyma.

In cirrhosis, types of collagen are I & III which are deposited in the all parts of the lobule & sinusoidal.

Endothelial cells loose their fenestration & this process converts the hepatic sinusoids from fenestrated to non fenestrated sinusoids, which impair the exchange of electrolytes & proteins between hepatocytes & plasma in particular (albumin, clotting factors, and lipoproteins).

- The major cause of excess collagen in cirrhosis appear to be the ITO cell: fat storing perisinusoidal sellate cells, which lies in the space of Disse.
- These cells which are normally function as vitamin A & fat storage cells, during the development of cirrhosis they become activated & transform into myofibroblasts like cells.
- The stimuli for synthesis & deposition of collagen may come from several sources. Include. Chronic inflammation, direct stimuli by toxins.
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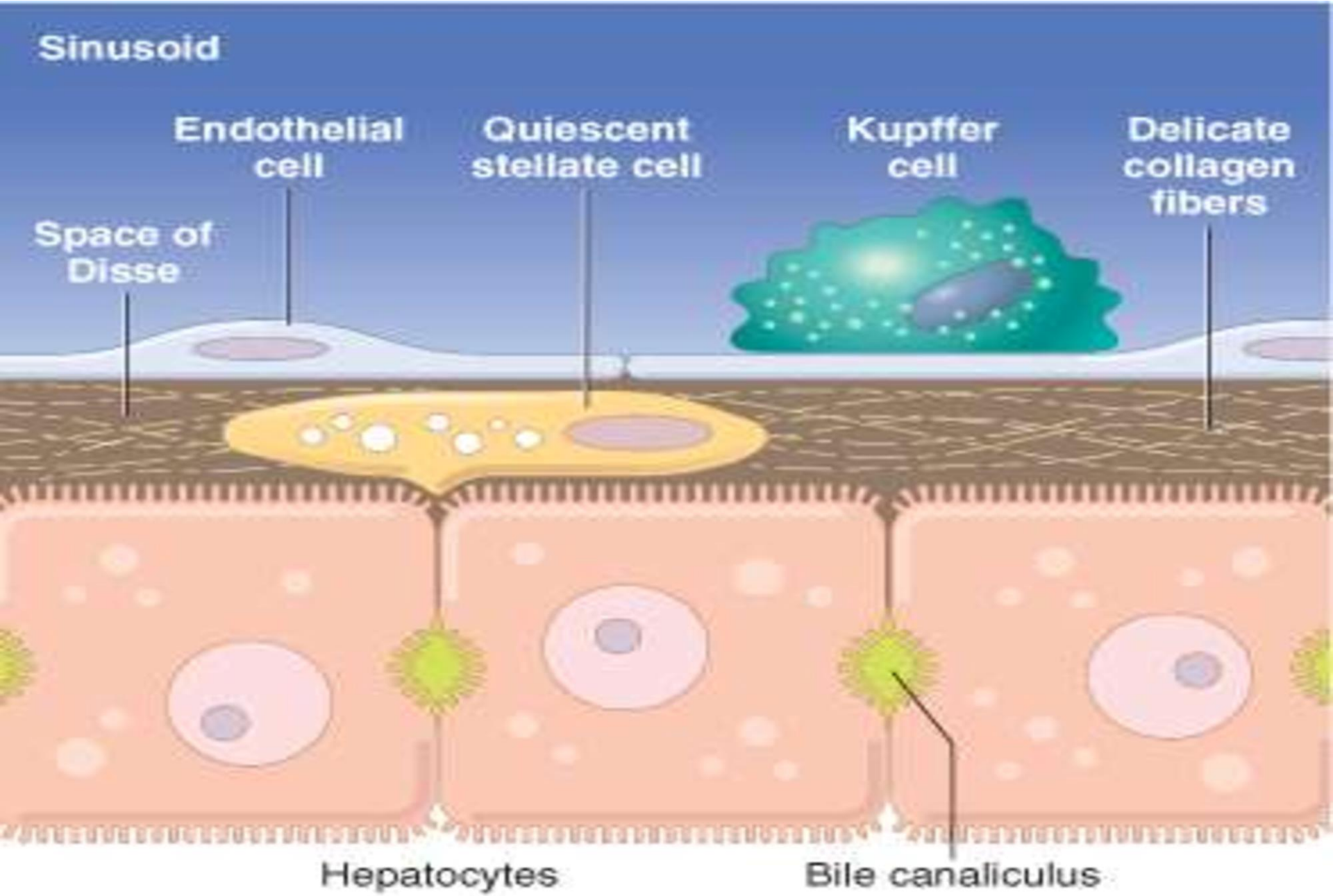
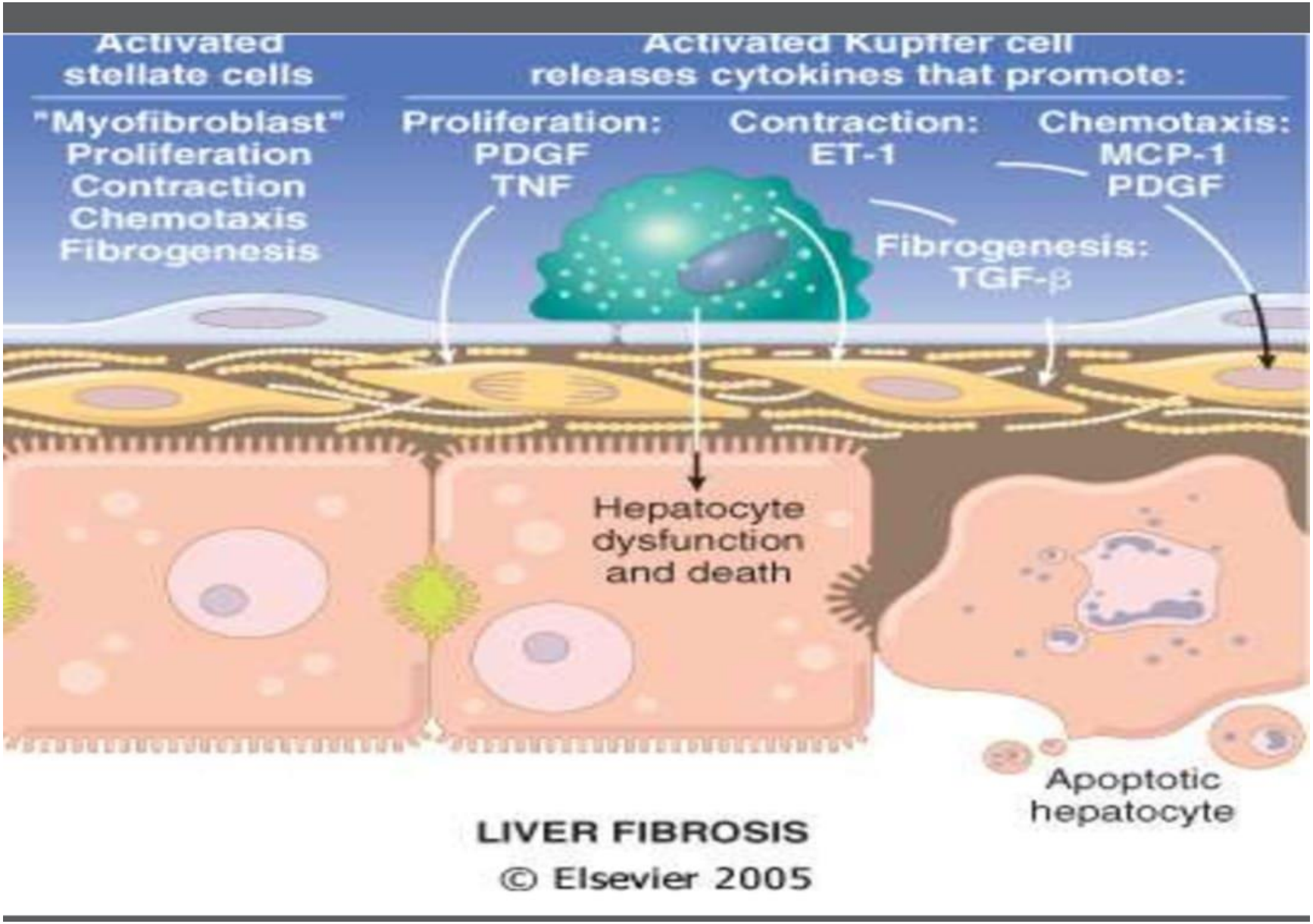


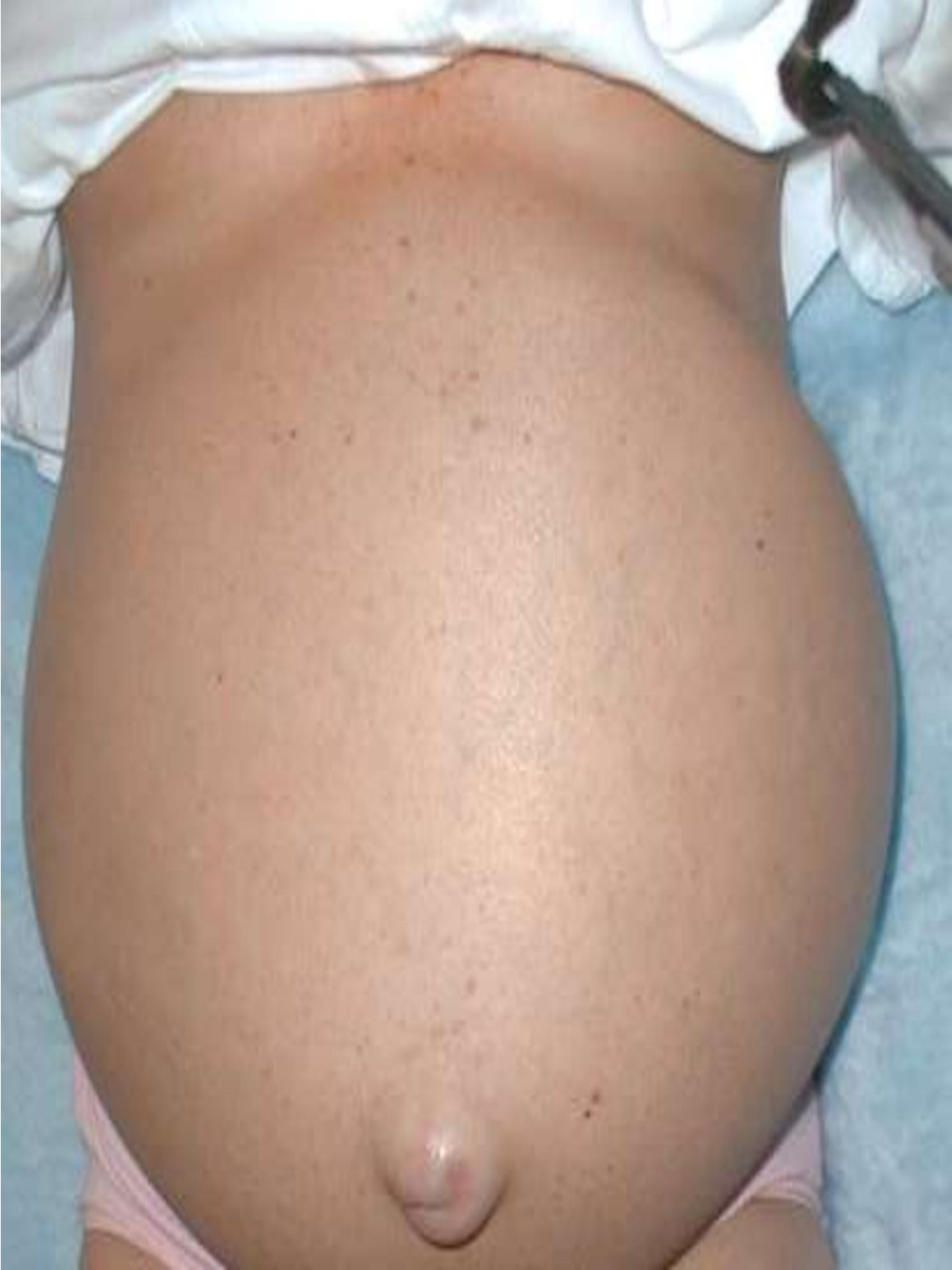
NORMAL LIVER



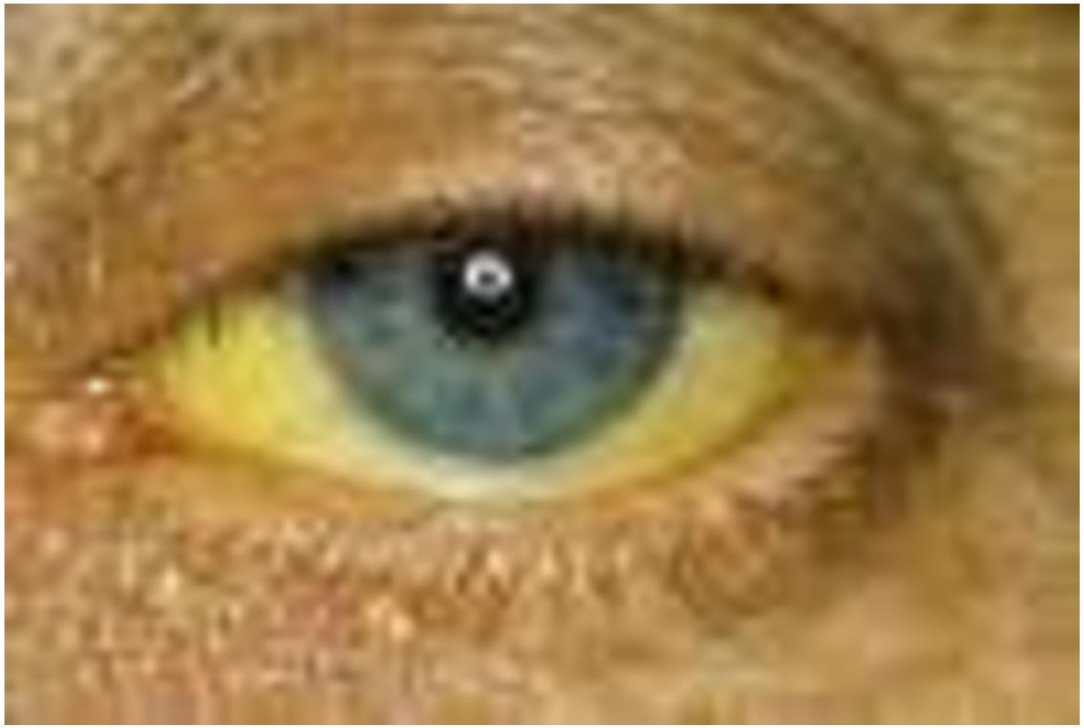
LIVER FIBROSIS

Common Clinical/Pathophysiological Events

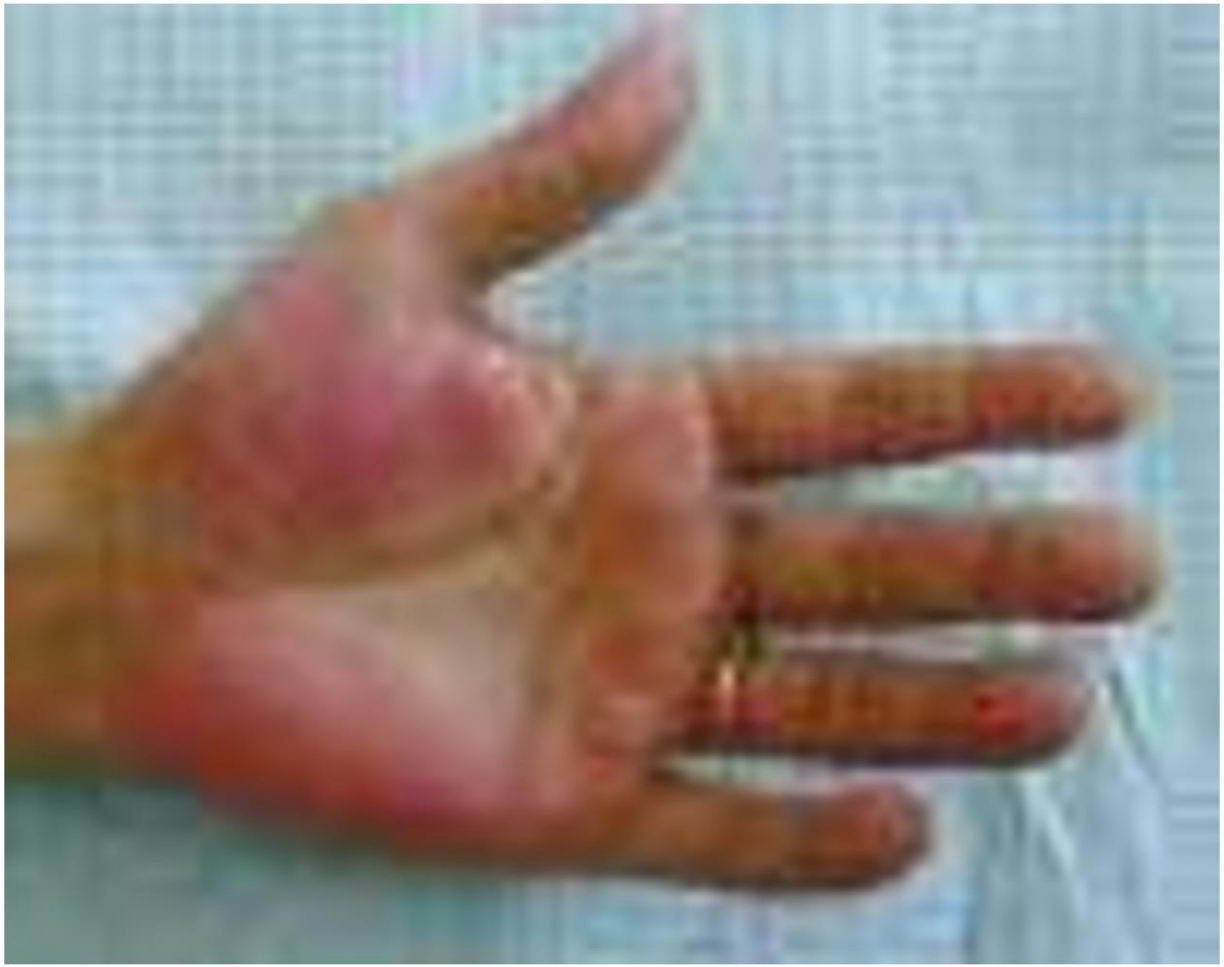
- Portal Hypertension WHY?
- Ascites WHY?
- Splenomegaly WHY?
- Hepatomegaly? Jaundice WHY?
- Anemia WHY?
- "Estrogenic" effects WHY?
- Coagulopathies (II, VII, IX, X) WHY?
- Encephalopathy WHY?



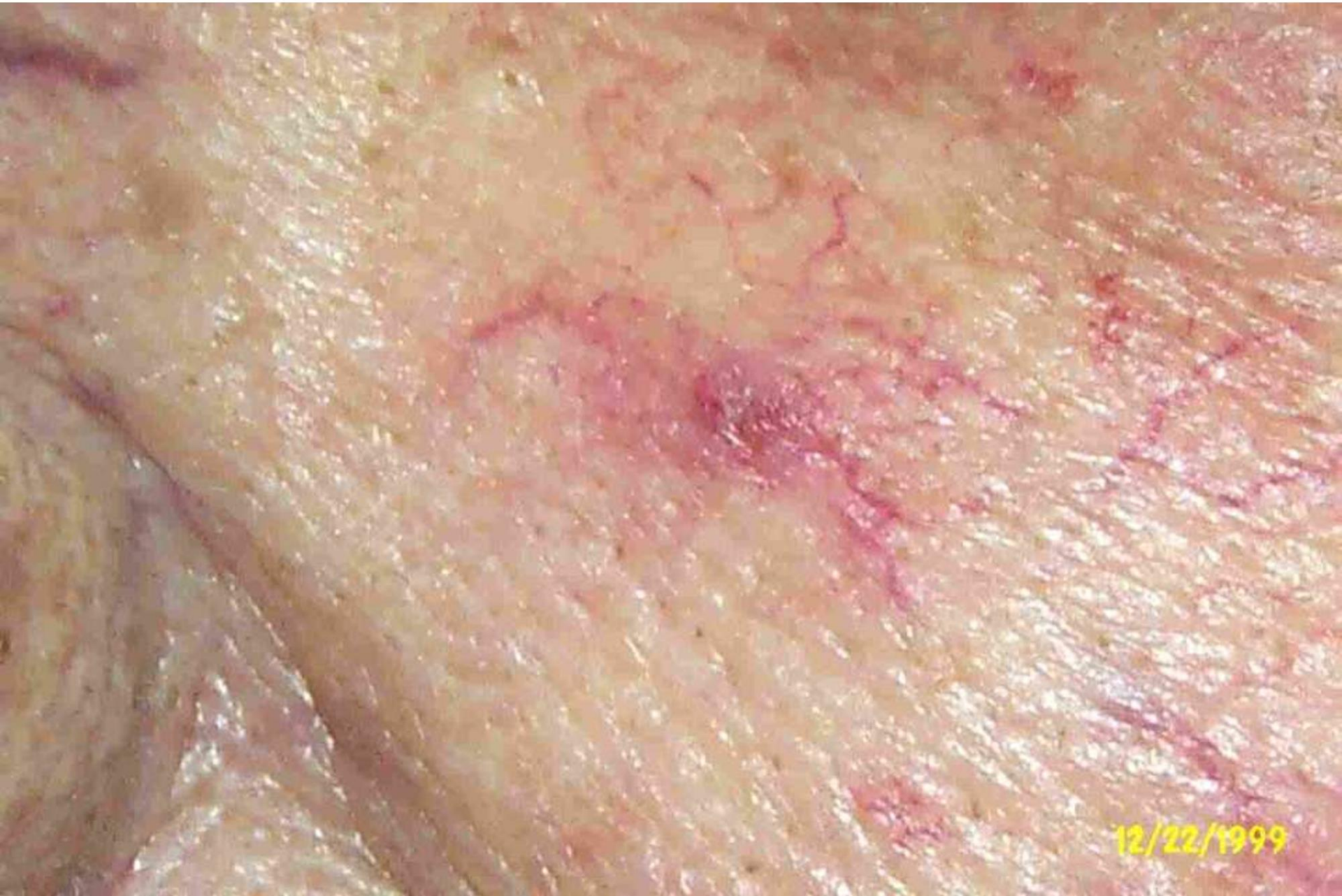
Jaundice and cholestasis



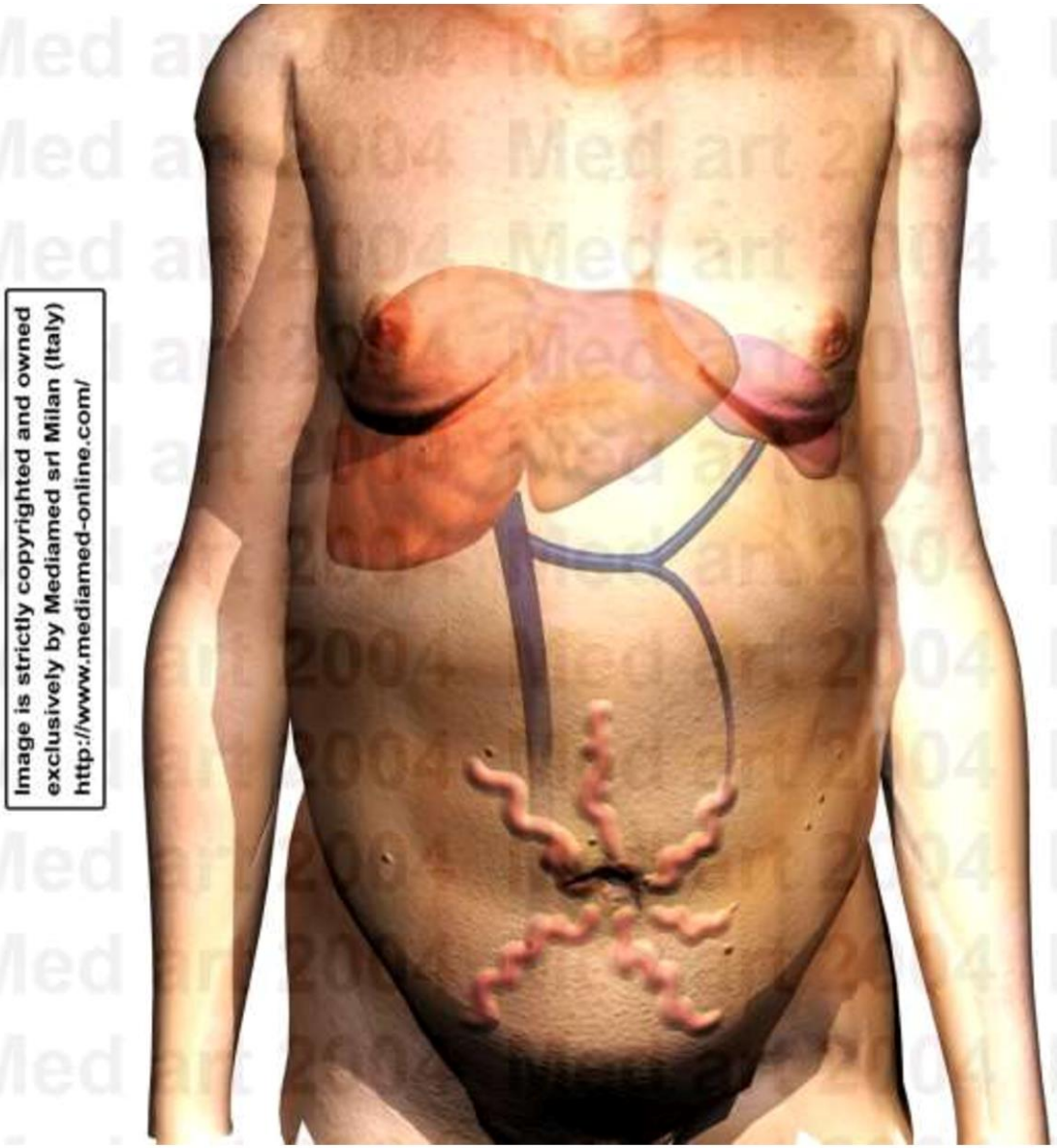
Palmer erythema



“SPIDER” ANGIOMA, CIRRHOSIS



Caput medusae-abdominal skin



The mechanisms of death in most patients with cirrhosis (fatal COMPLICATIONS).

- **(1) Progressive liver failure.**
- **(2) Portal hypertension.**
- **(3) Development of hepatocellular carcinoma.**

PATHOLOGY OF THE LIVER

JAUNDICE

- **Jaundice: yellowish discoloration of skin & sclera (icterus) due to systemic retention of bilirubin (> 2 mg/dl)** (normal level is less than 1.2mg/dl).

- Mechanisms of jaundice:
- **Equilibrium between bilirubin production & clearance is disturbed:**
- (1) Excessive production of bilirubin.
- (2) Reduced hepatic uptake for bilirubin.
- (3) Impaired conjugation of bilirubin inside the liver.
- ..These three mechanisms are produced unconjugated hyperbilirubinemia.
- (4) Decreased hepatic hepatocellular excretion.
- (5) Impaired bile flow.
- These two mechanisms are produced conjugated hyperbilirubinemia.
- More than one mechanism may operate to produce jaundice, especially in hepatitis.

JAUNDICE

- Hemolytic (UN-conjugated)
- Obstructive (Conjugated)

Pathophysiology of jaundice:

There are two types of bilirubin present normally in our body.

1. Unconjugated bilirubin.

- Present in the blood & is tightly bind to albumin.
- Insoluble in water at physiologic pH.....Cannot be excreted in the urine even when blood levels are high.
- is neurotoxic (kernicterus, which is means deposition of unconjugated bilirubin in the basal ganglia).
- This type of bilirubin is increase in cases of hemolytic diseases

- 2. Conjugated bilirubin is conjugated in the liver, water soluble, non neurotoxic & easily excreted in the urine. This type of bilirubinis increased in hepatocellular diseases, post hepatic obstruction in biliary tract (like in carcinoma head of pancreas.

- **Types of jaundice**:
- (1) **Prehepatic jaundice**. (unconjugated hyperbilirubinemia, hemolytic jaundice)
- (2) **Hepatic jaundice.** (Both unconjugated & conjugated hyperbilirubinemia).
- This type is due to hepatocellular diseases.
- (3) **Post hepatic jaundice**. (Obstructive, surgical jaundice). This type is usually due to obstruction in the pathway of bilirubin beyond the liver. & the common cause is carcinoma head of pancreas.