College of medicine
Department of pathology
3rd year

Hepatobiliary system

LEC. 2

Dr. Methaq Mueen

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**

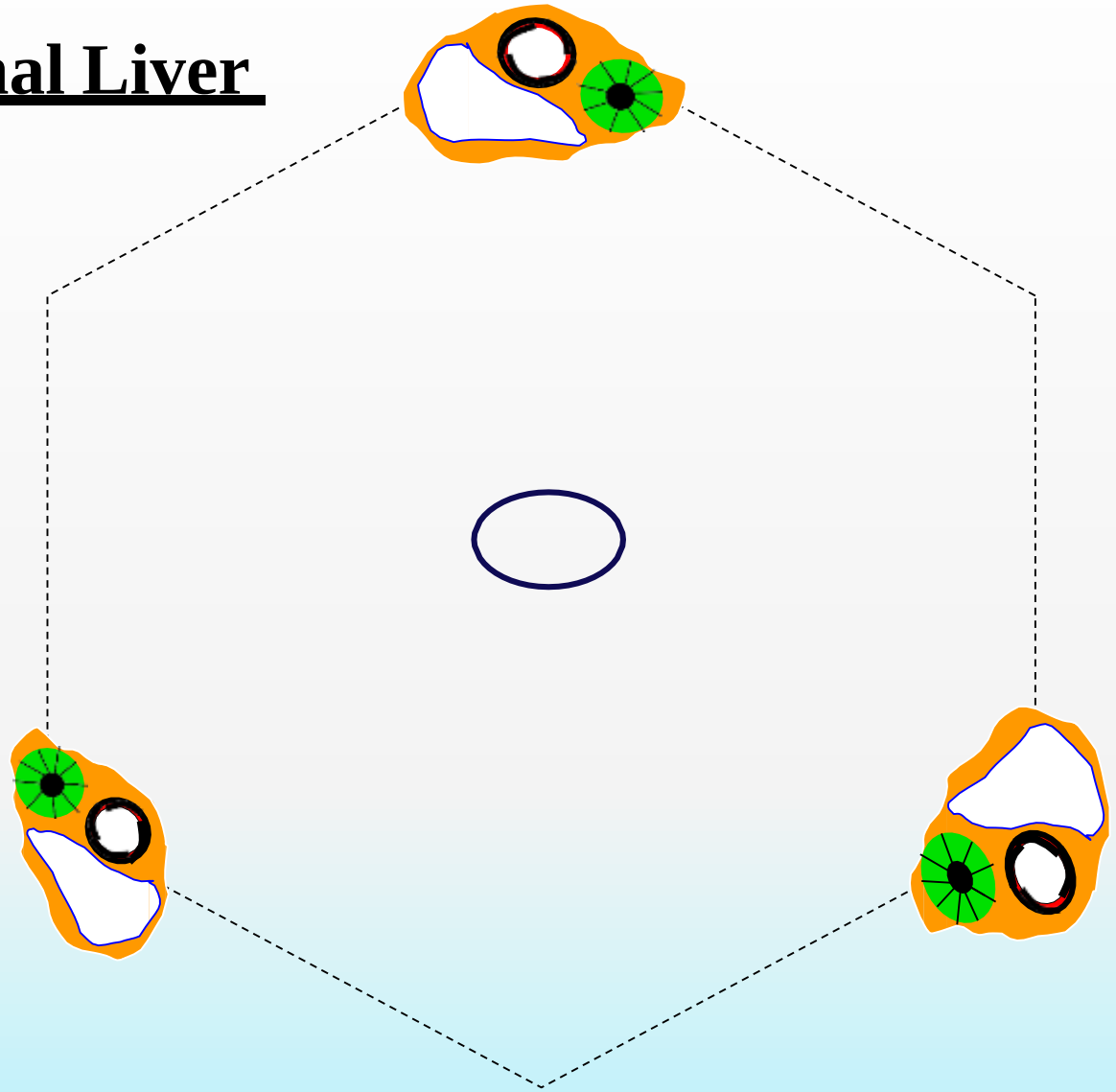
d. deposition of **fibrous tissue** (irreversible injury).

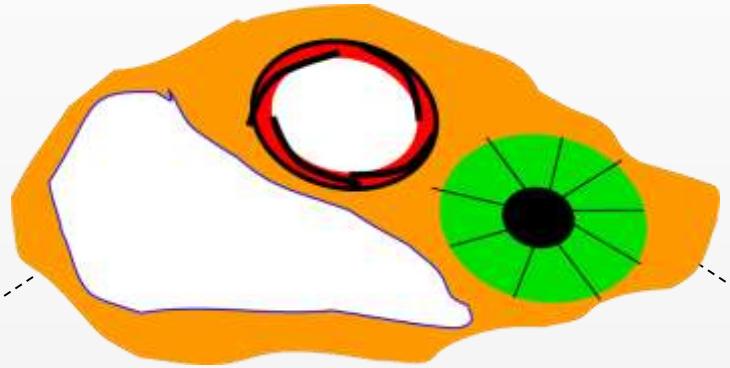
e. **cirrhosis** which is usually of macro nodular type.

Morphology

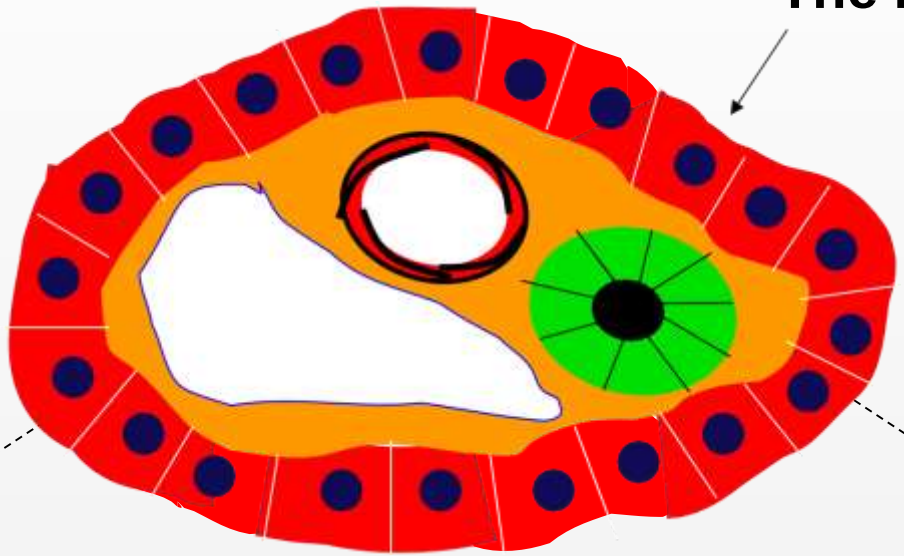
- **The hallmark** of serious **chronic liver damage** is the deposition of fibrous tissue.
- At first, only portal tracts exhibit increased fibrosis, but with time **periportal fibrosis** occurs, followed by linking of fibrous septa between lobules **(bridging fibrosis).**
- **Continued loss of hepatocytes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

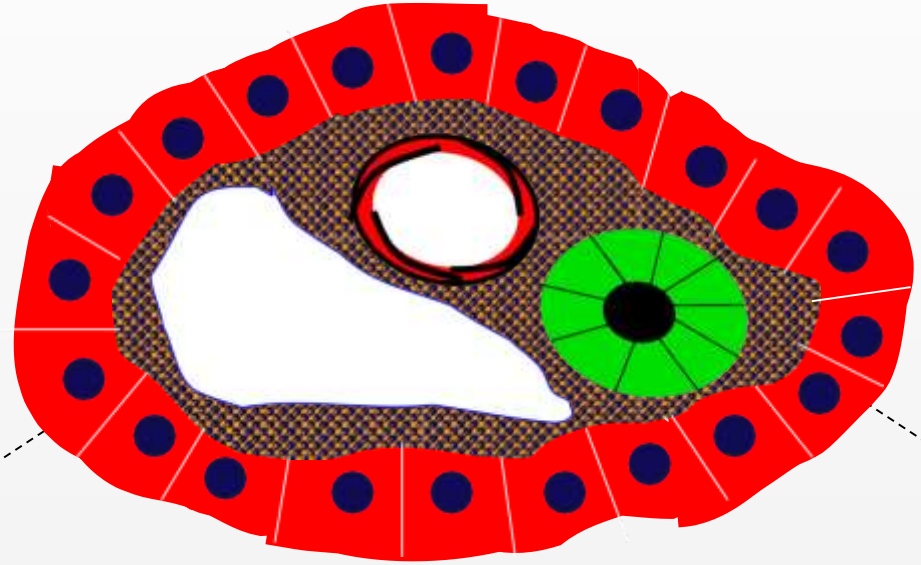
The Normal Liver Lobule:



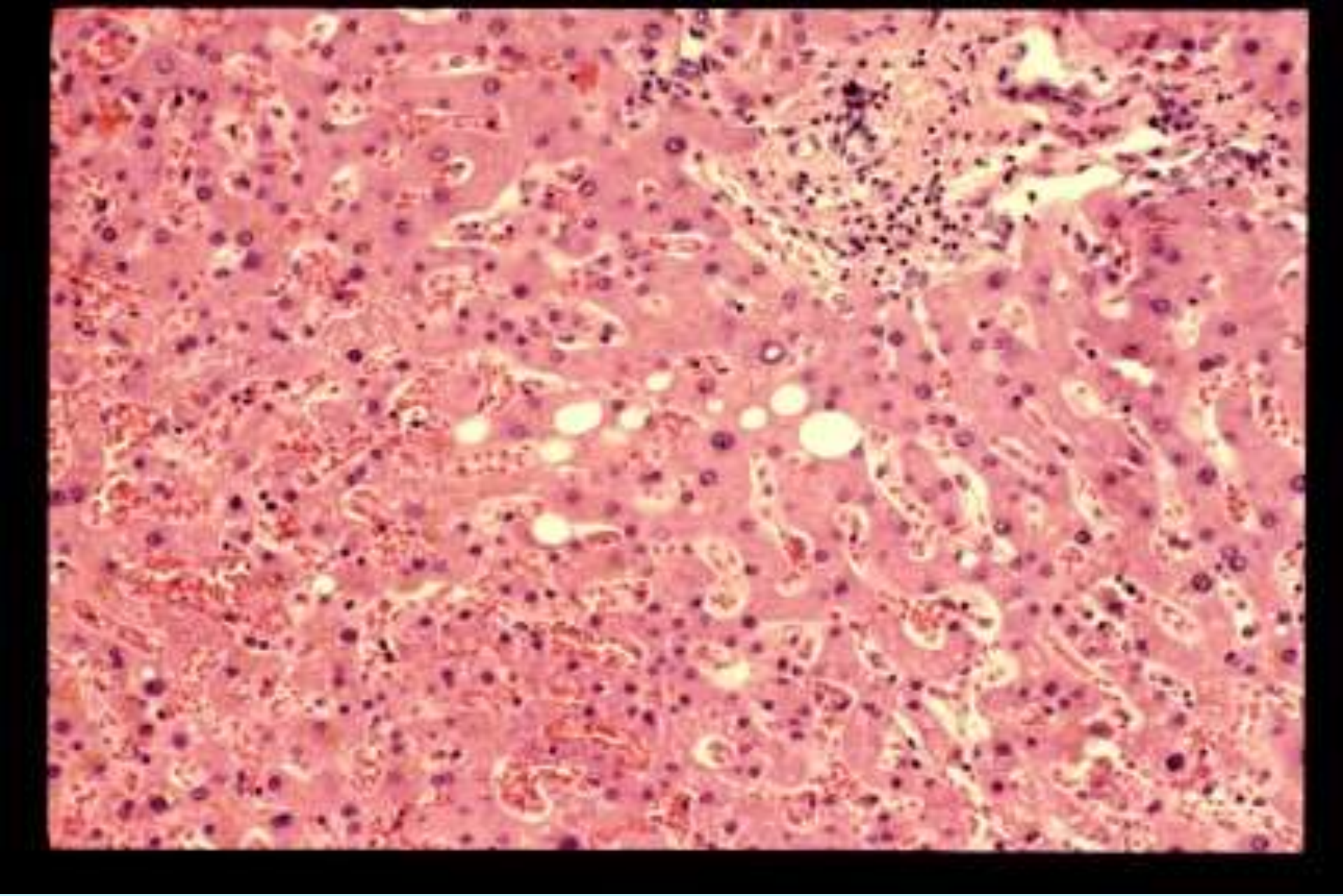


The Limiting Plate

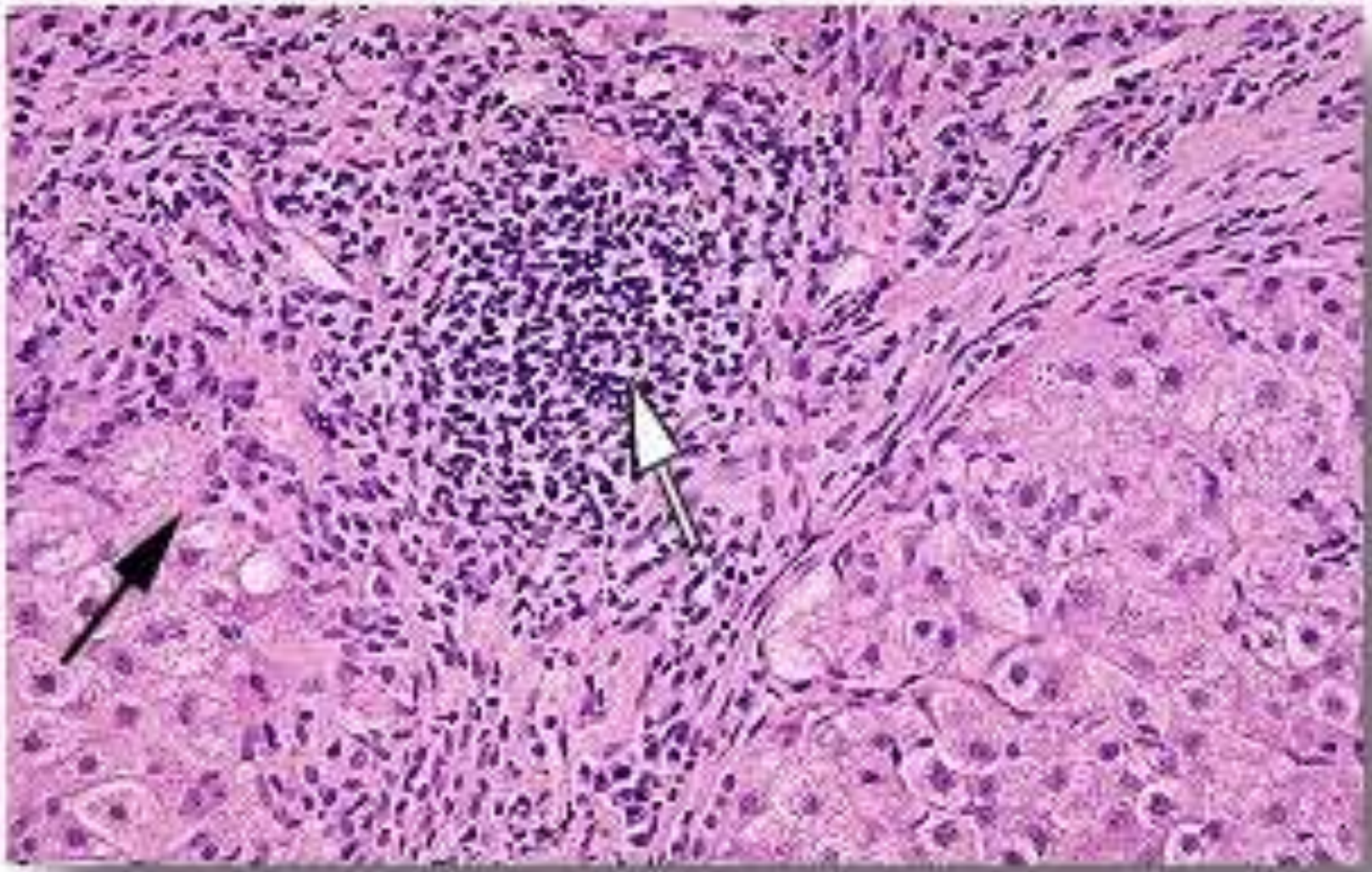




Portal inflammation
DEFINES
Chronic Hepatitis

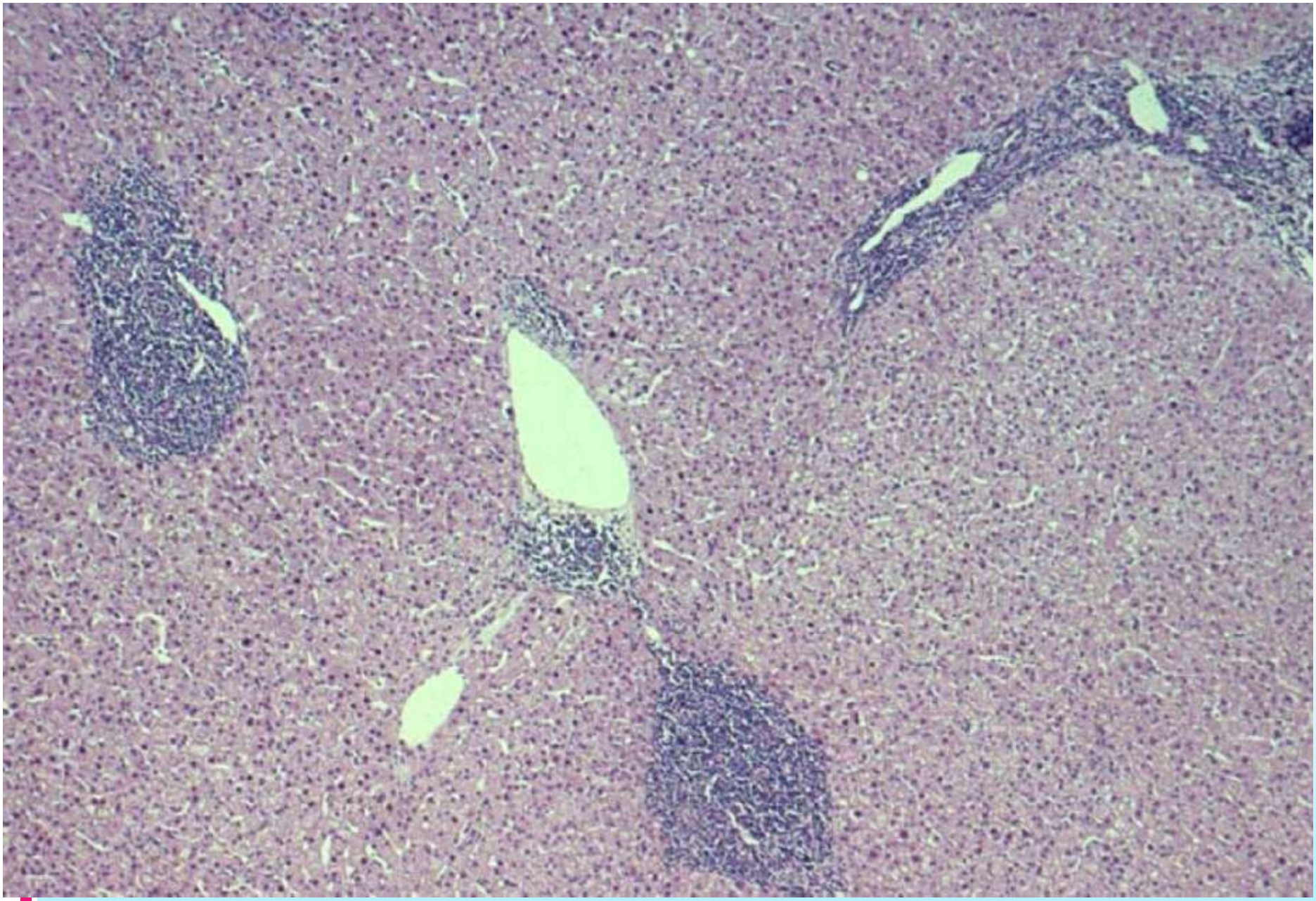


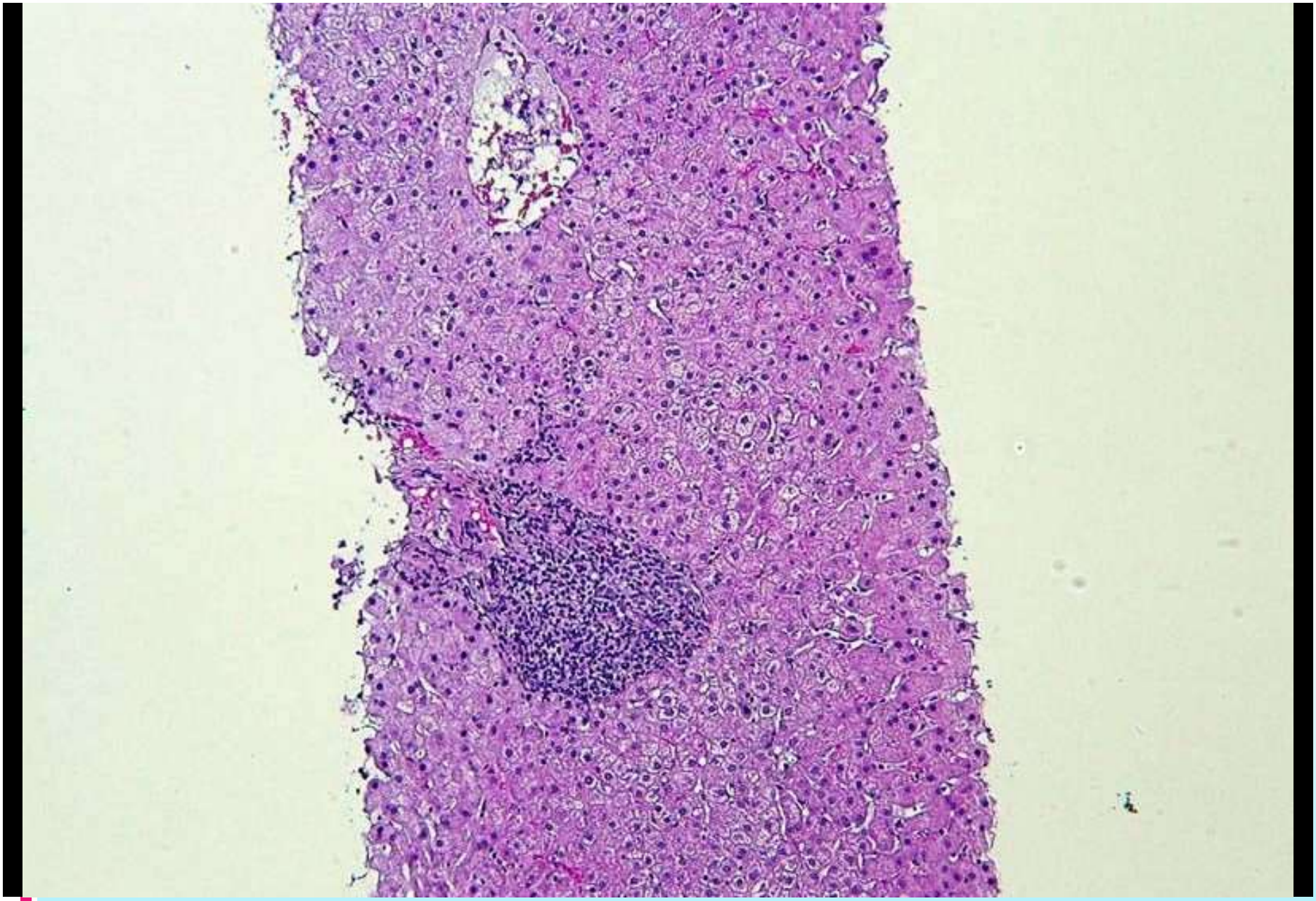
MILD portal tract inflammation

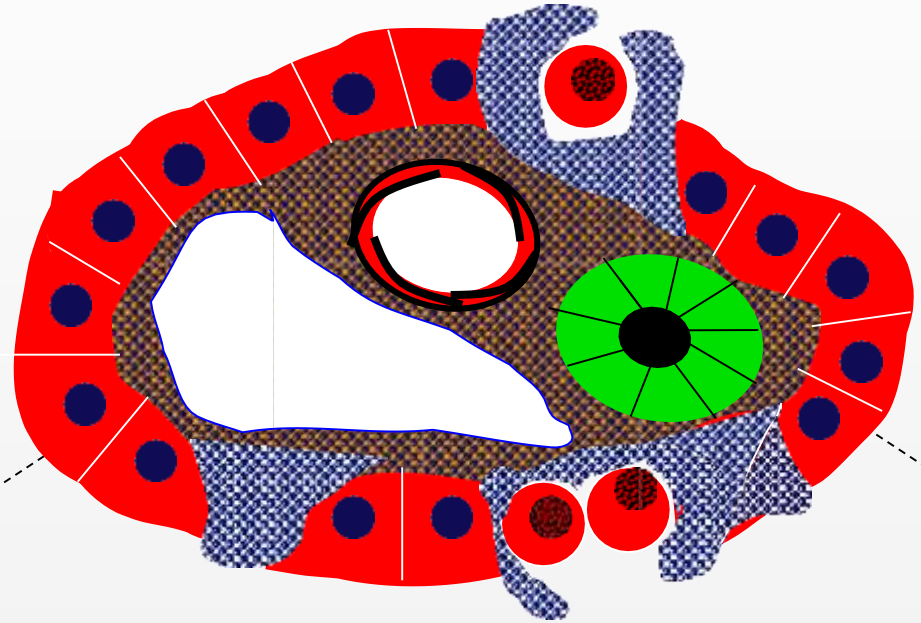


More severe portal infiltrates with sinusoidal infiltrates also.

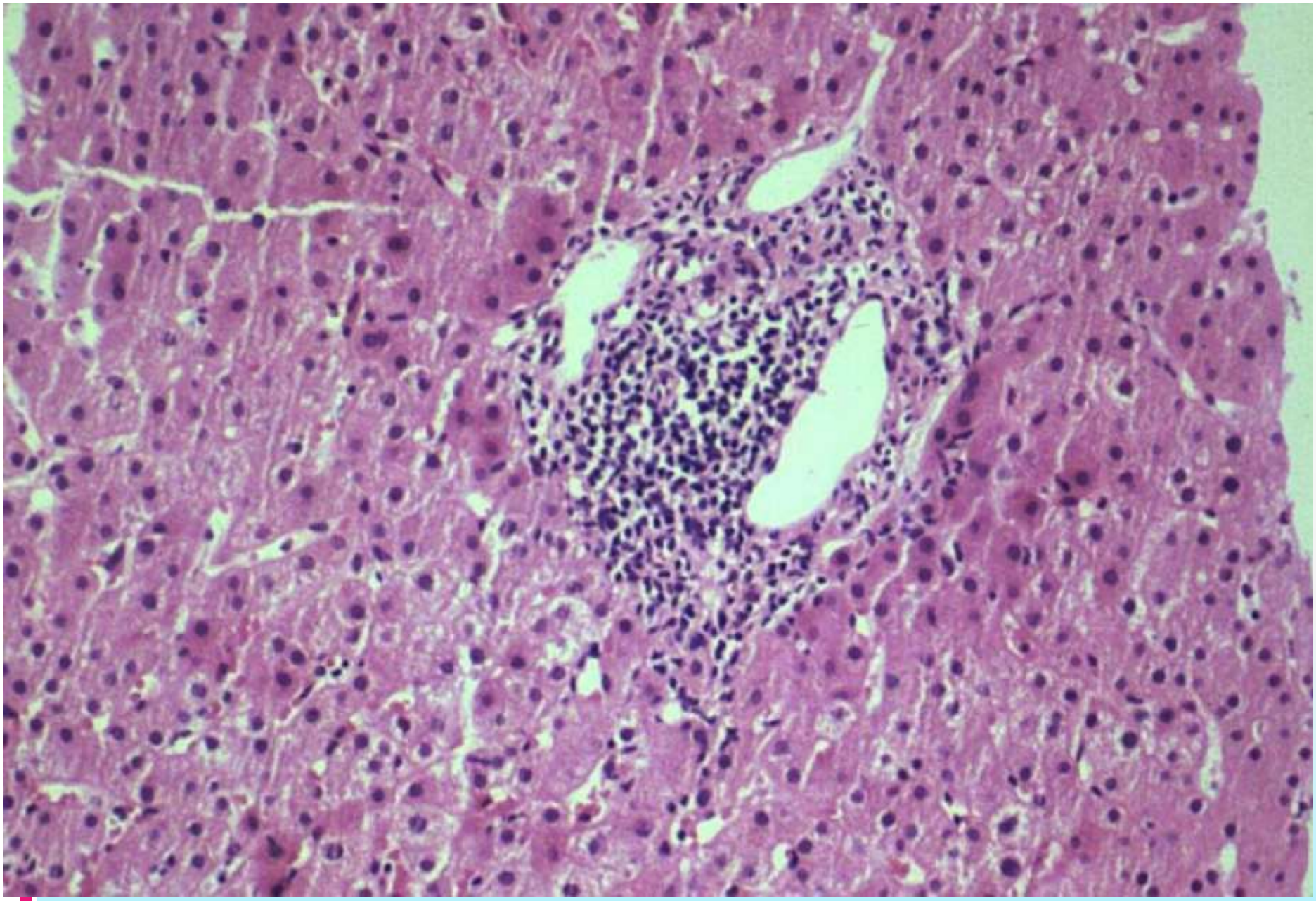
Understanding the “limiting plate” is important!

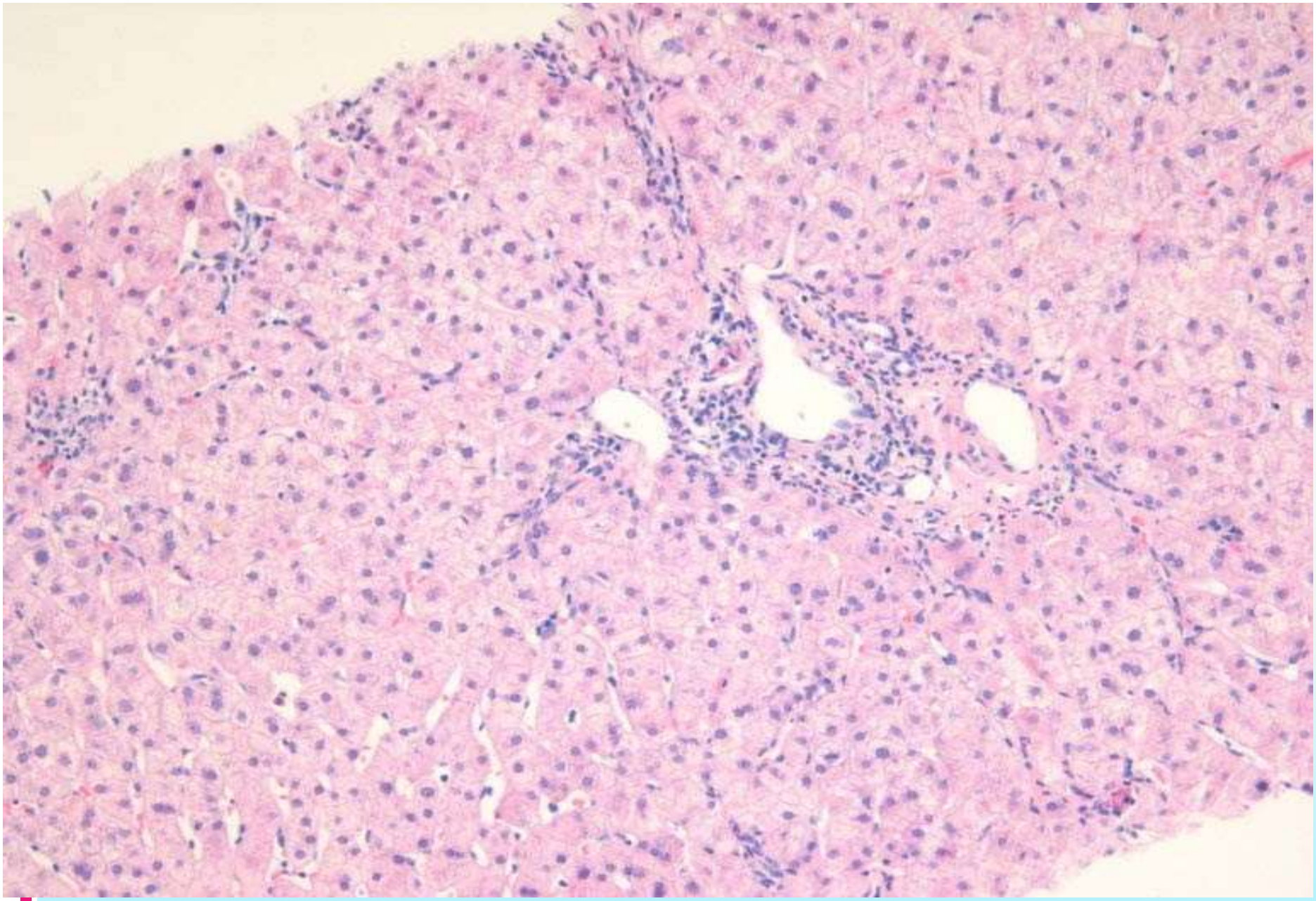


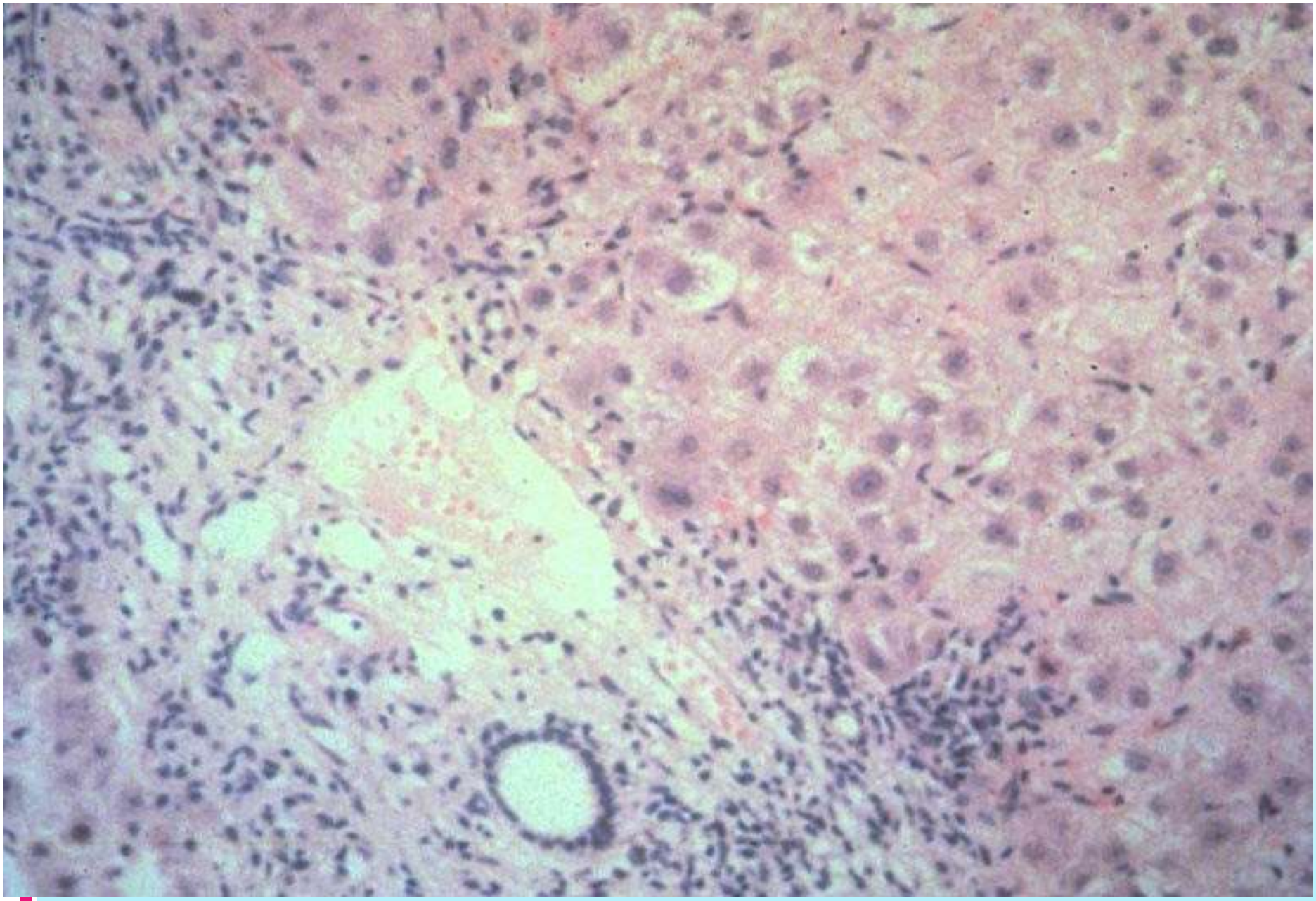




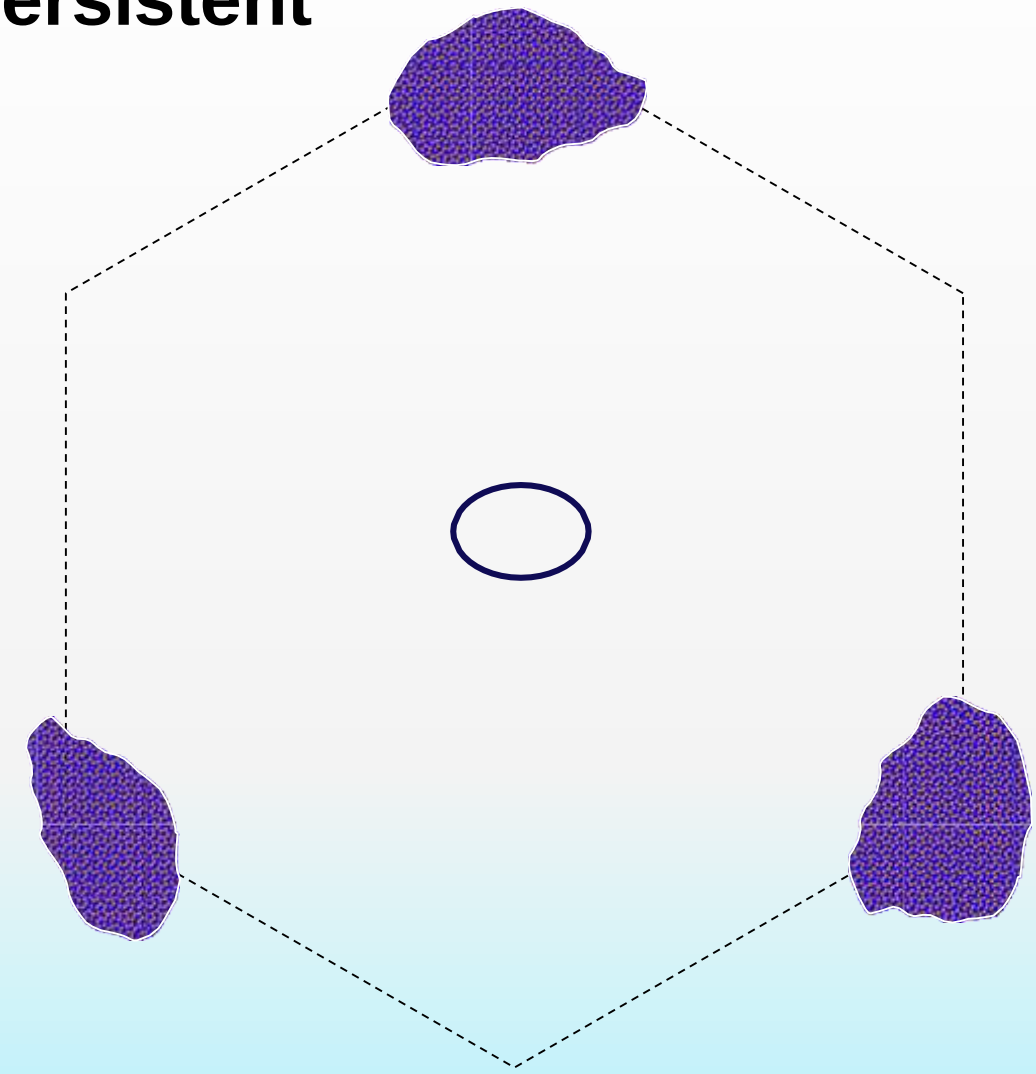
“Piecemeal Necrosis”
or, better,
“Interface Hepatitis”



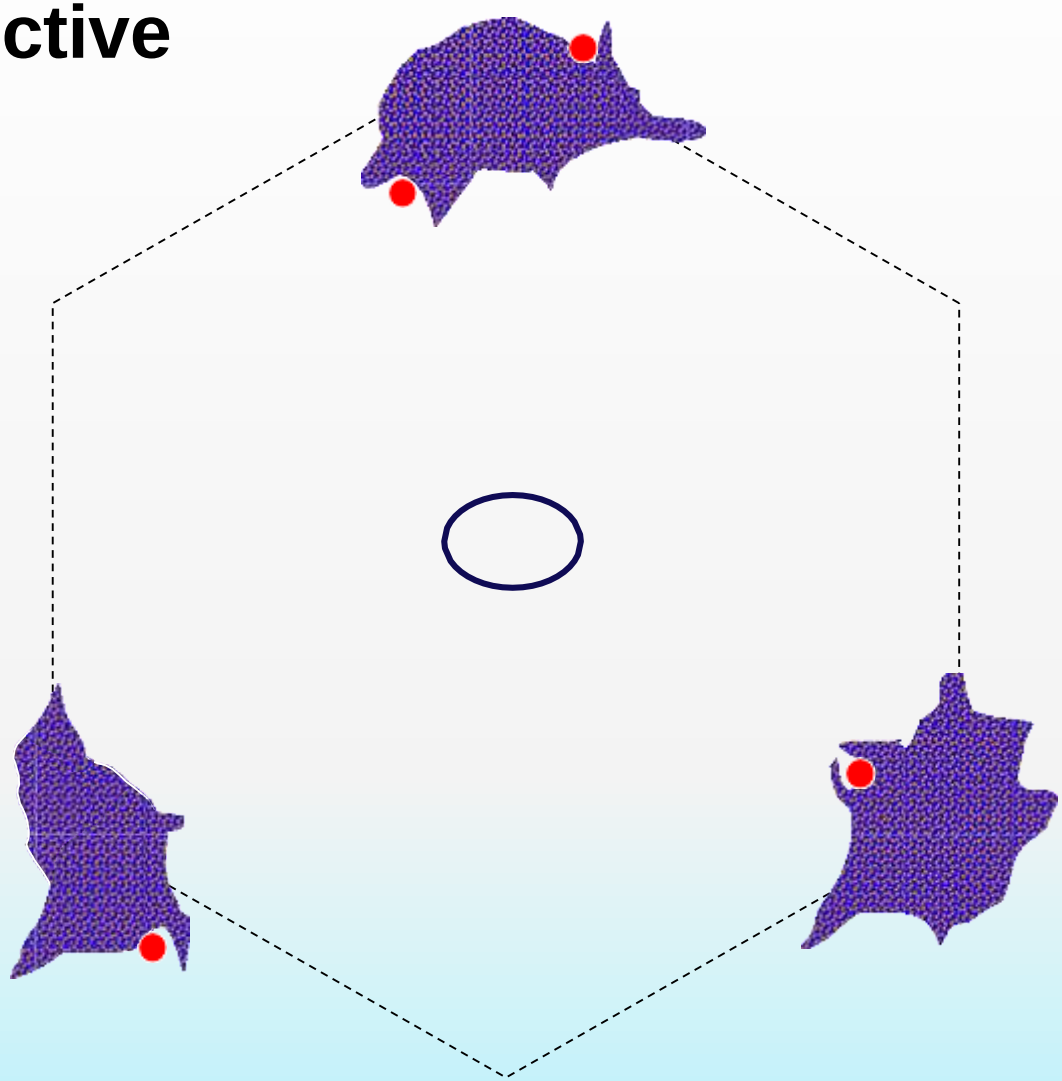




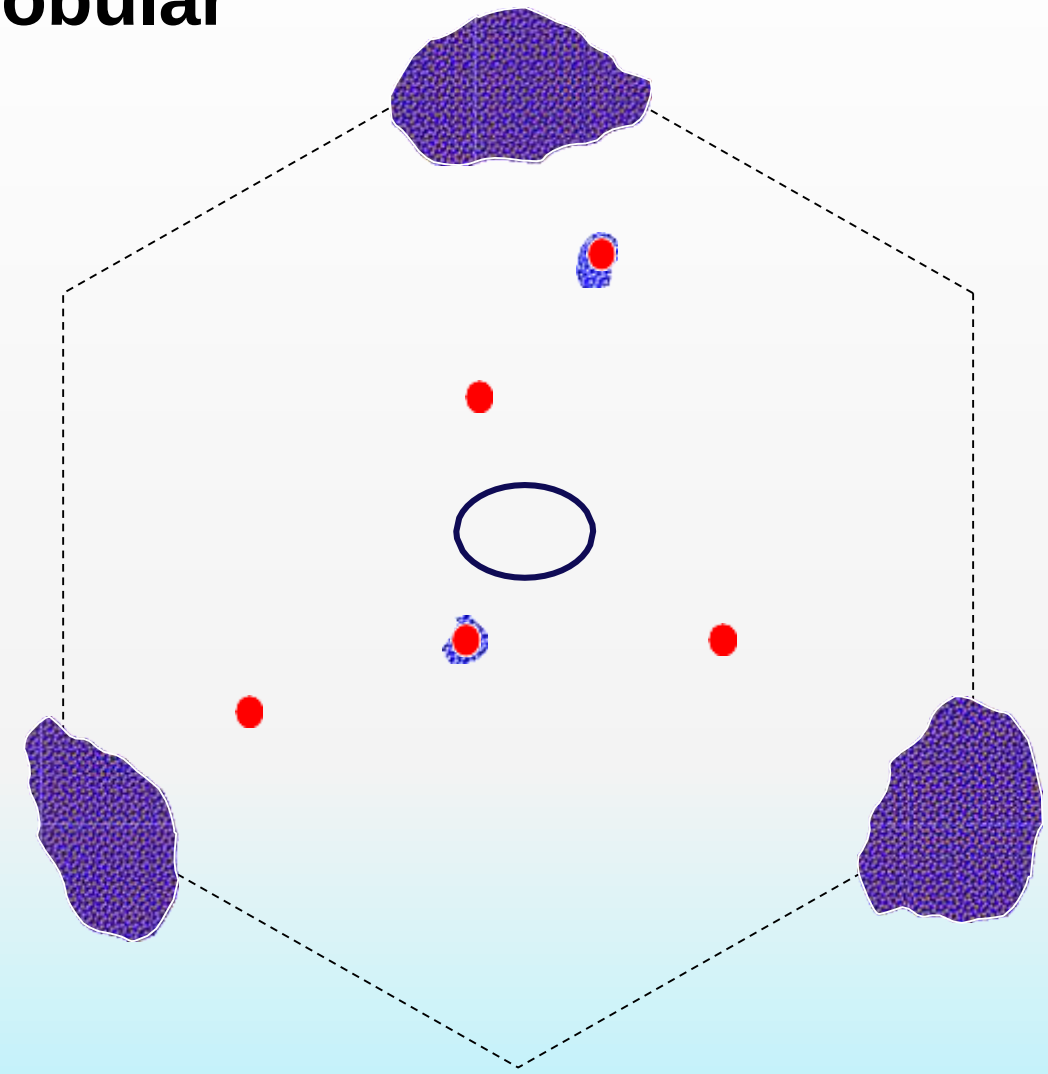
Chronic Persistent Hepatitis

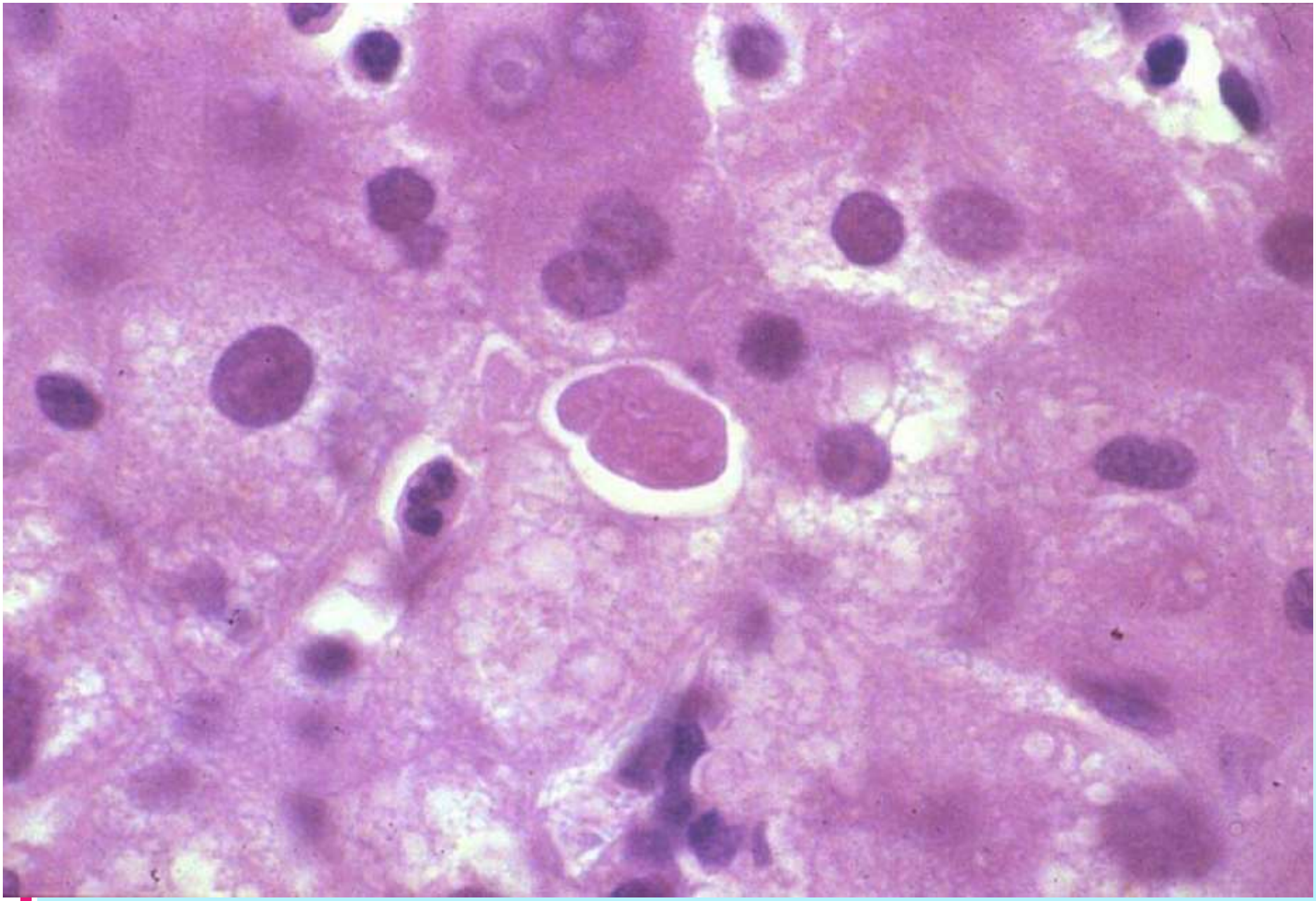


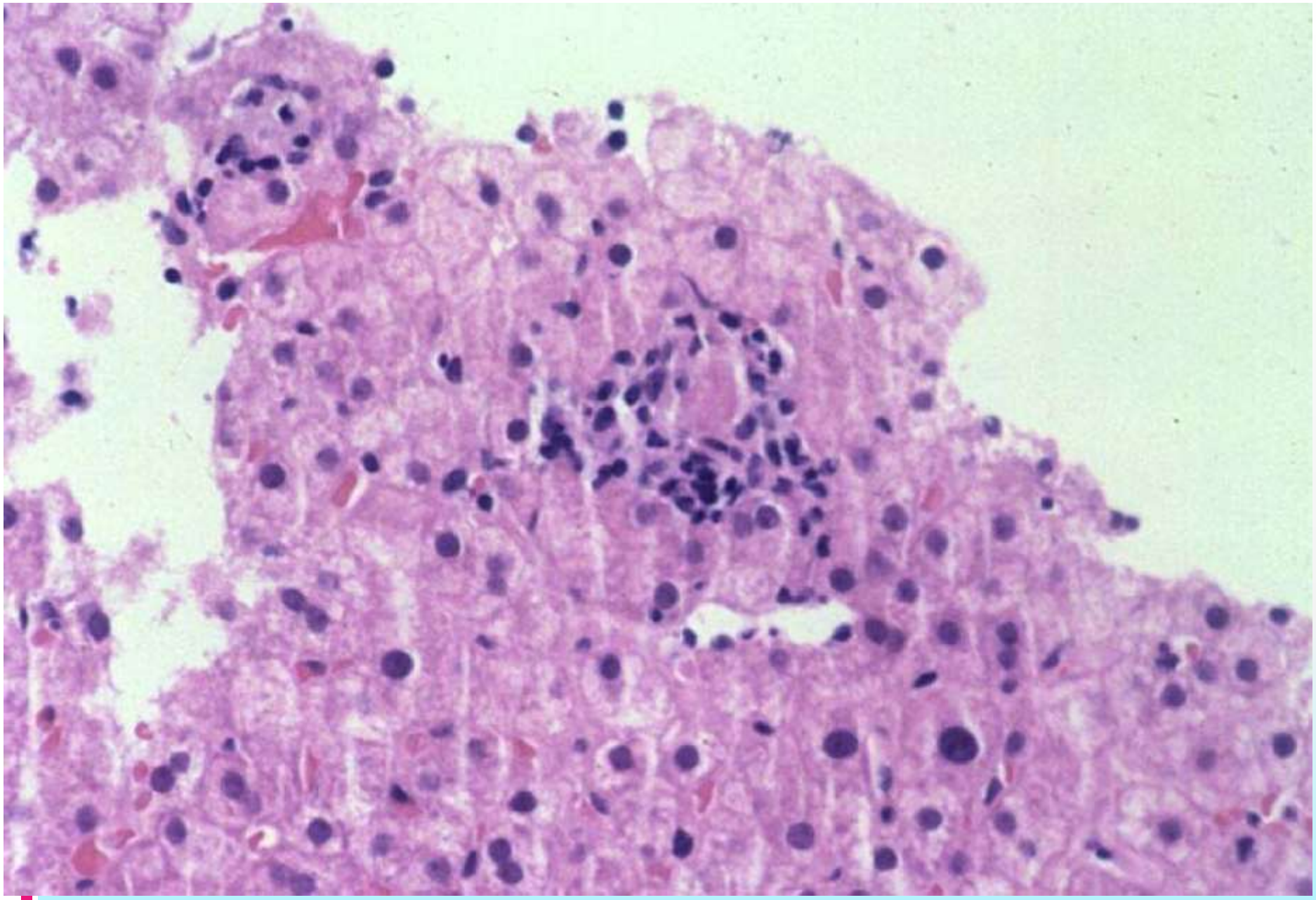
Chronic Active Hepatitis

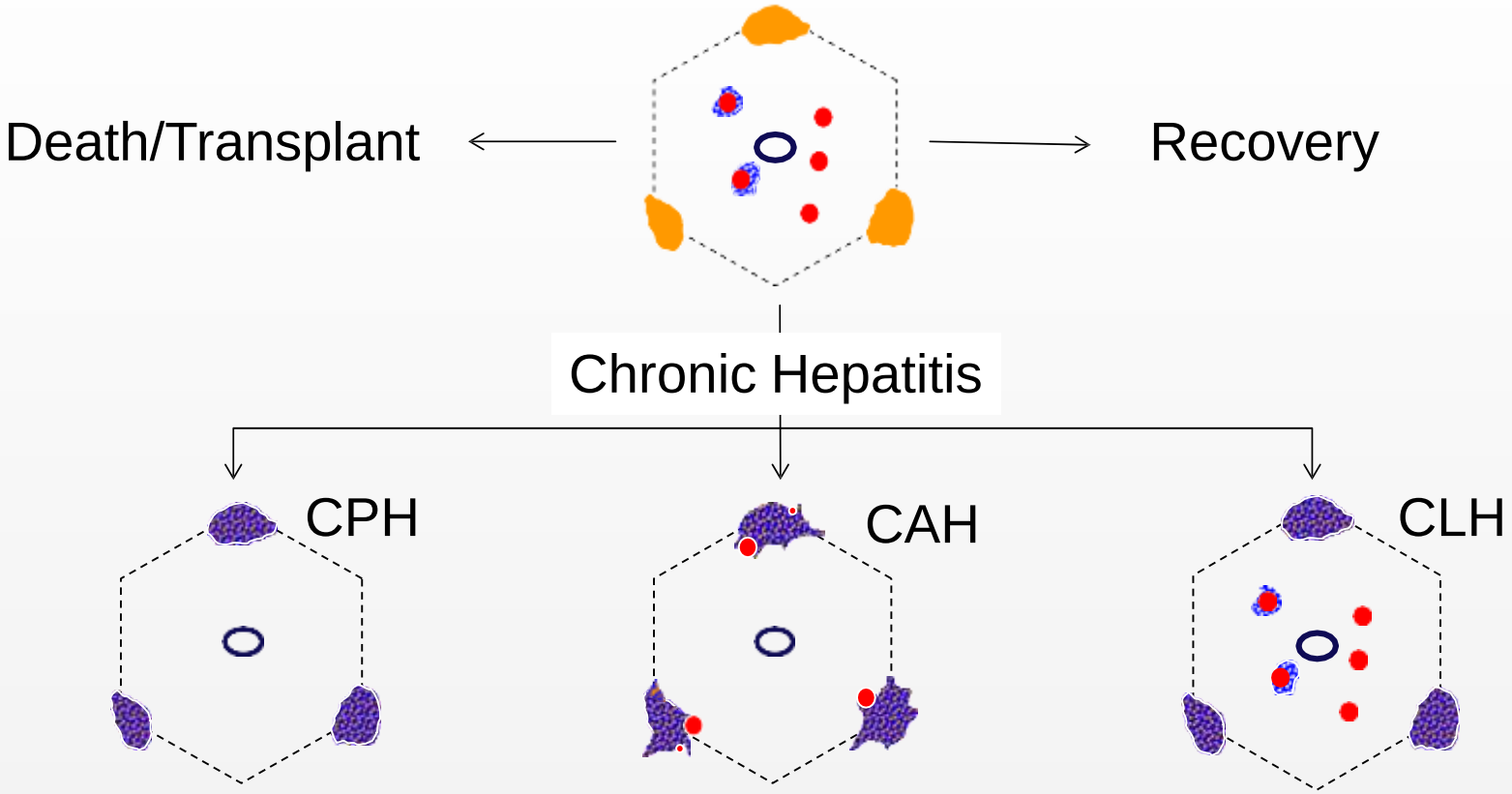


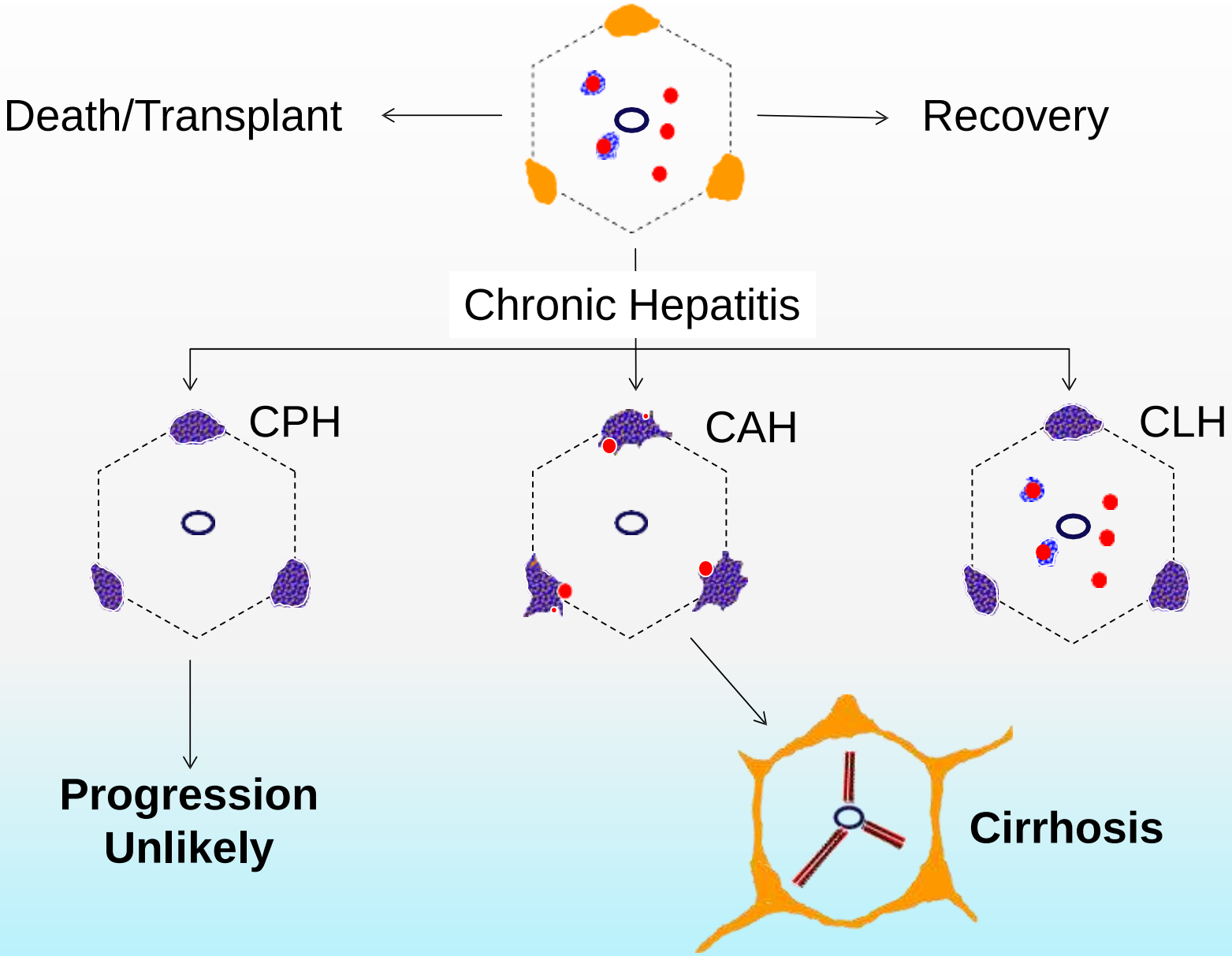
Chronic Lobular Hepatitis

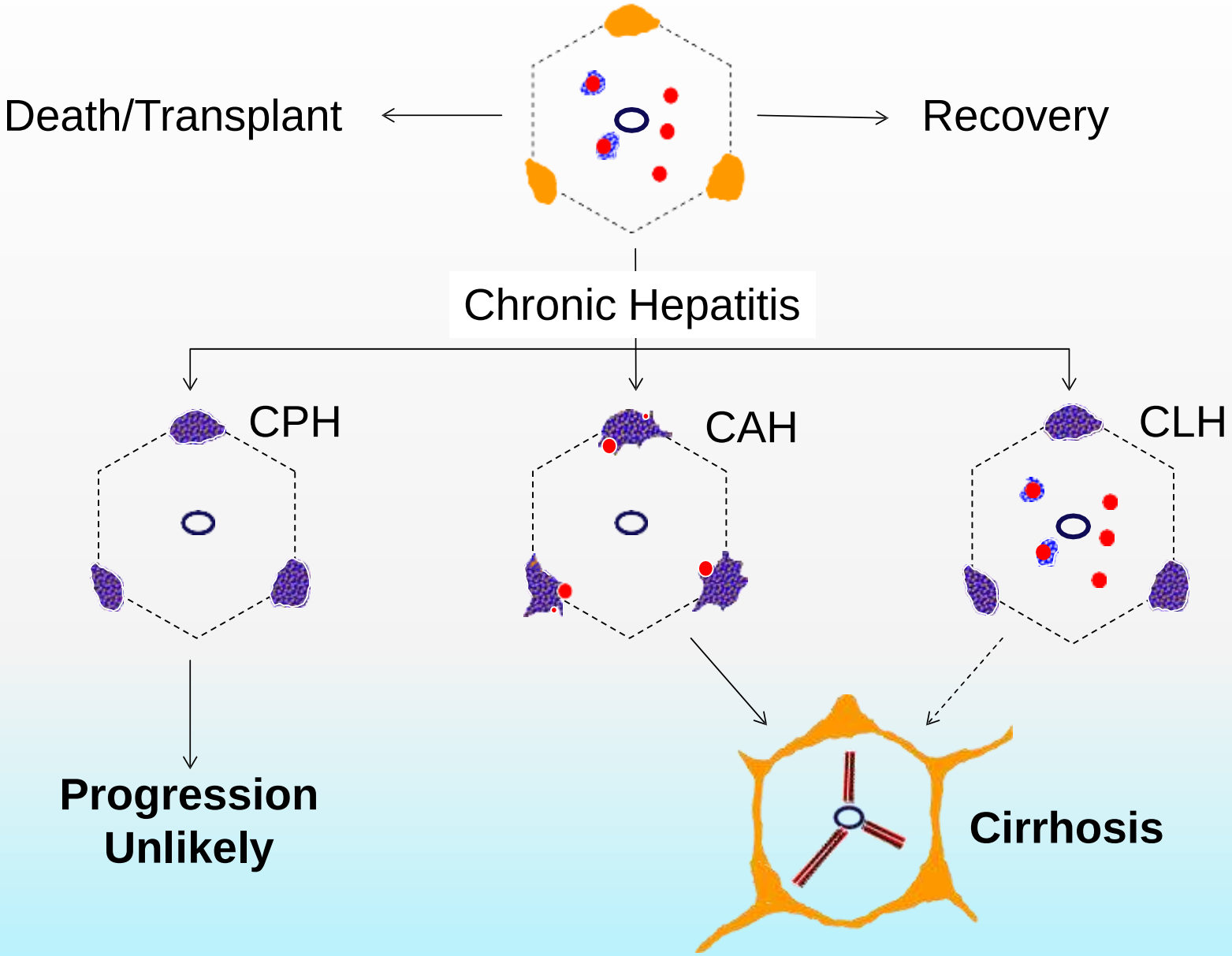







Death/Transplant
Recovery
Chronic Hepatitis
CPH
CAH
CLH


Death/Transplant
Recovery
Chronic Hepatitis
CPH
CAH
CLH
Progression Unlikely
Cirrhosis


Death/Transplant
Recovery
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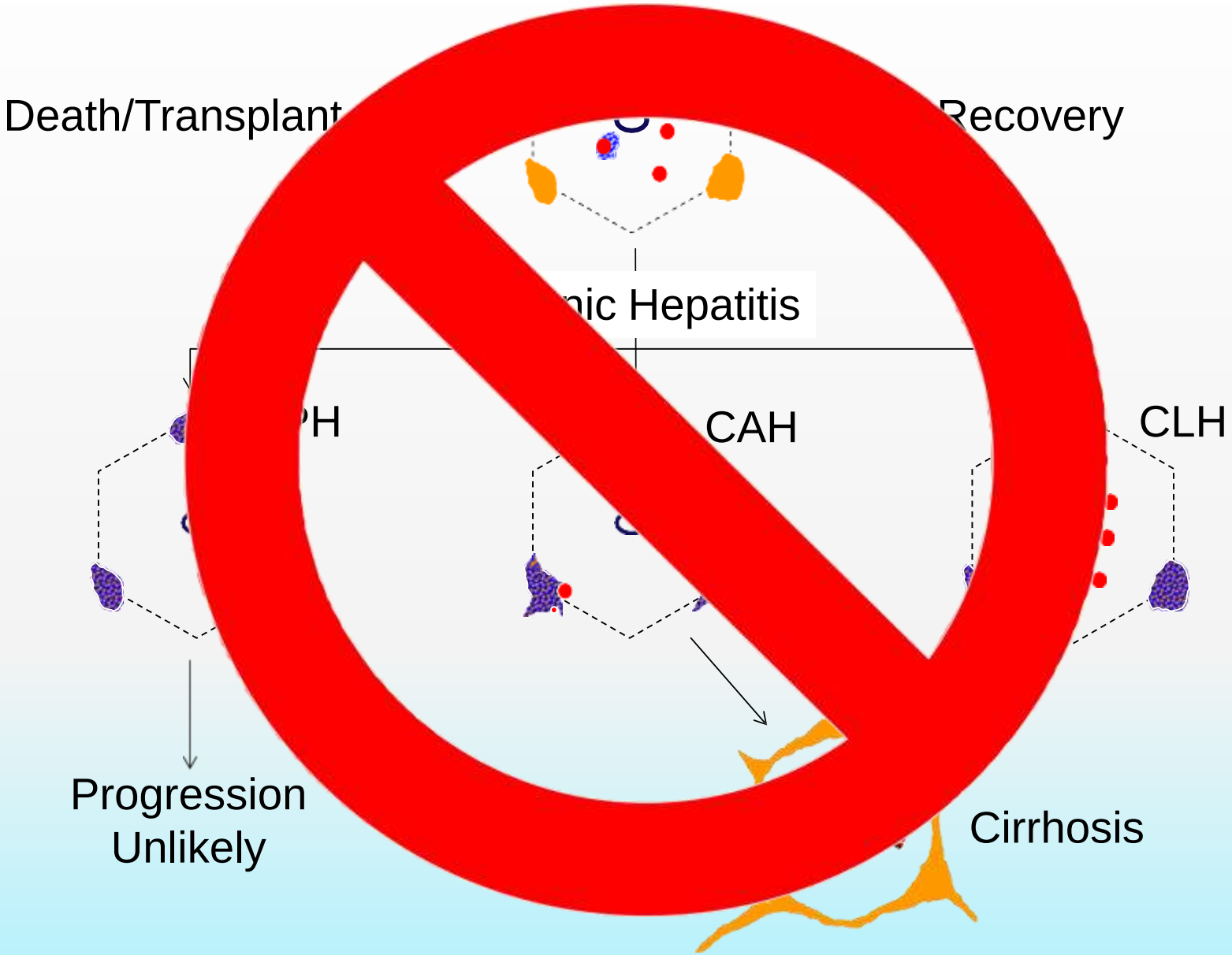
CLH
Progression Unlikely
Cirrhosis


Death/Transplant
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Unlikely
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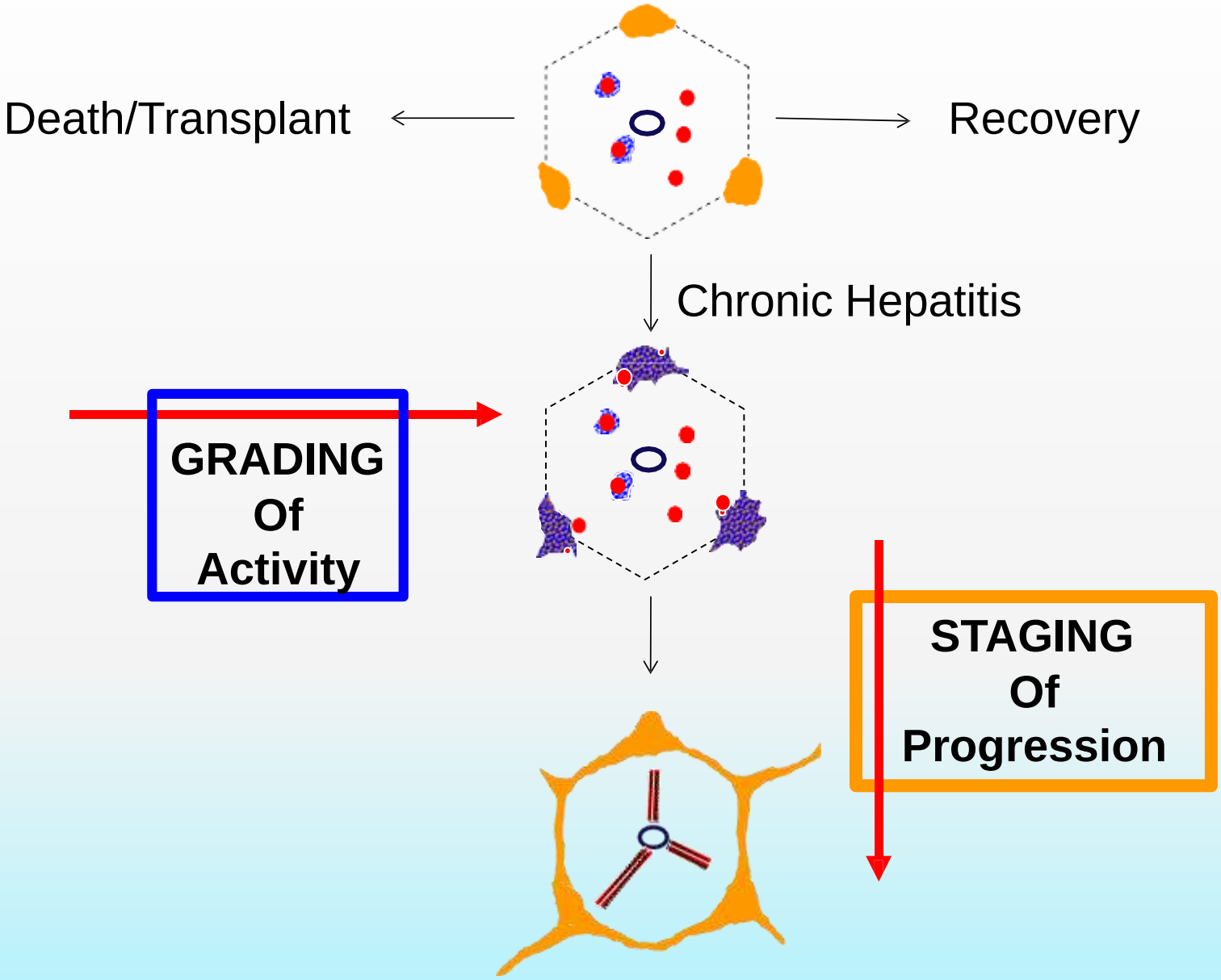
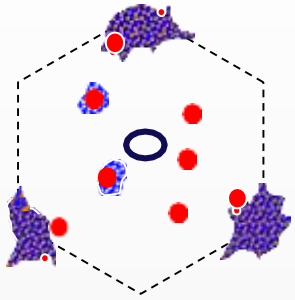
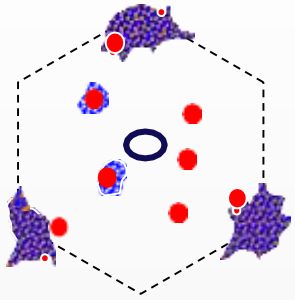

Death/Transplant
Recovery
Chronic Hepatitis
GRADING
Of
Activity
STAGING
Of
Progression

GRADING Of Activity



- Portal inflammation
- Interface hepatitis
- Lobular hepatitis
- Confluent necrosis

GRADING Of Activity



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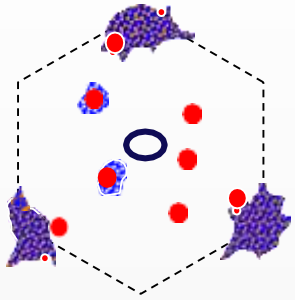

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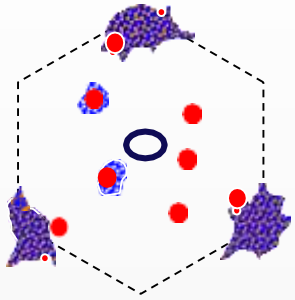
GRADING Of Activity



- Portal inflammation
- Interface hepatitis
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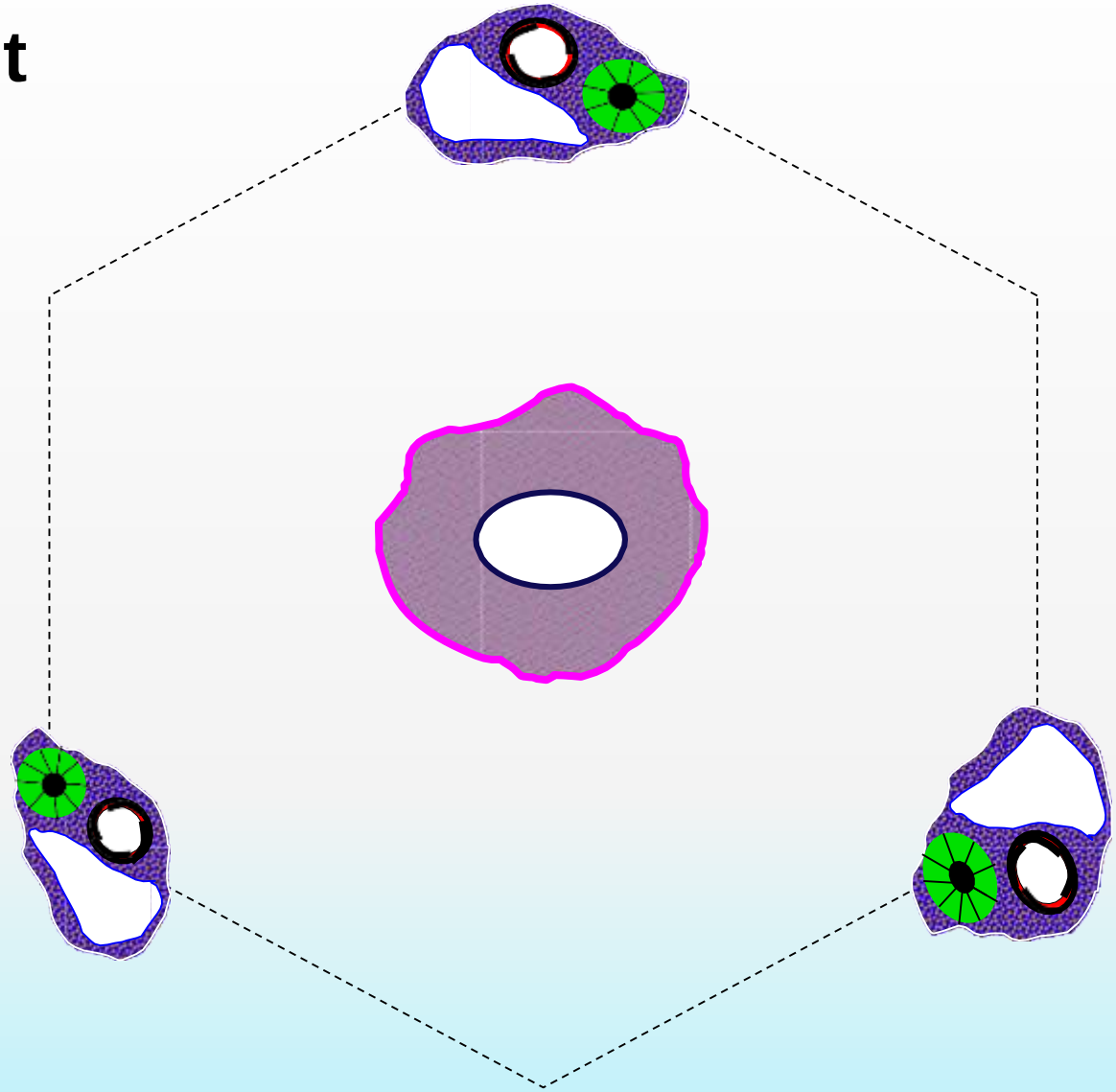
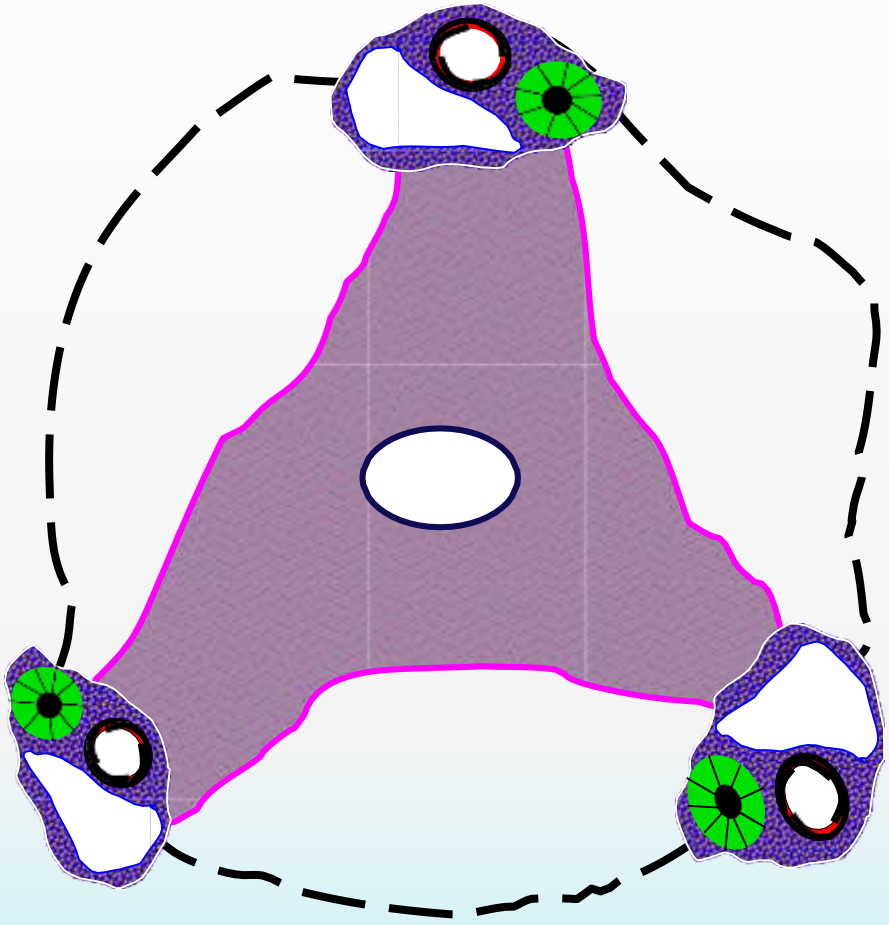
- Confluent necrosis

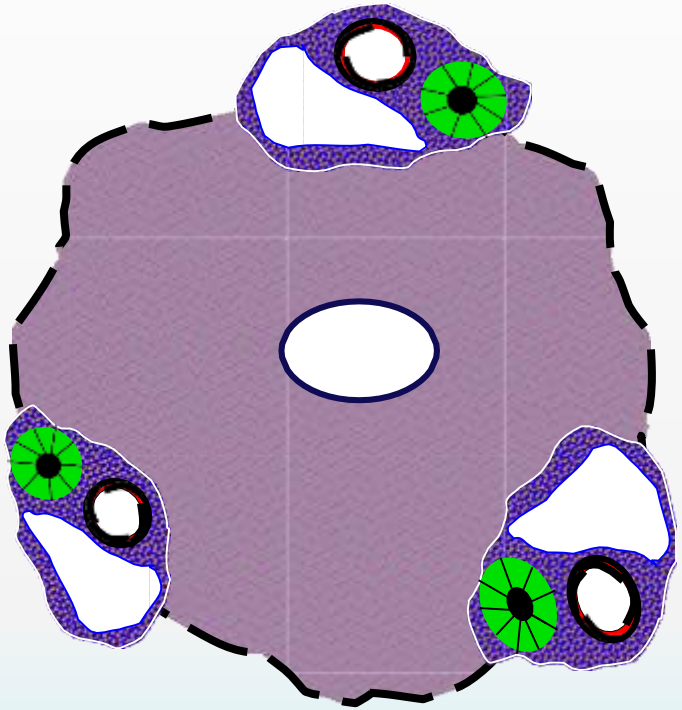
Confluent Necrosis

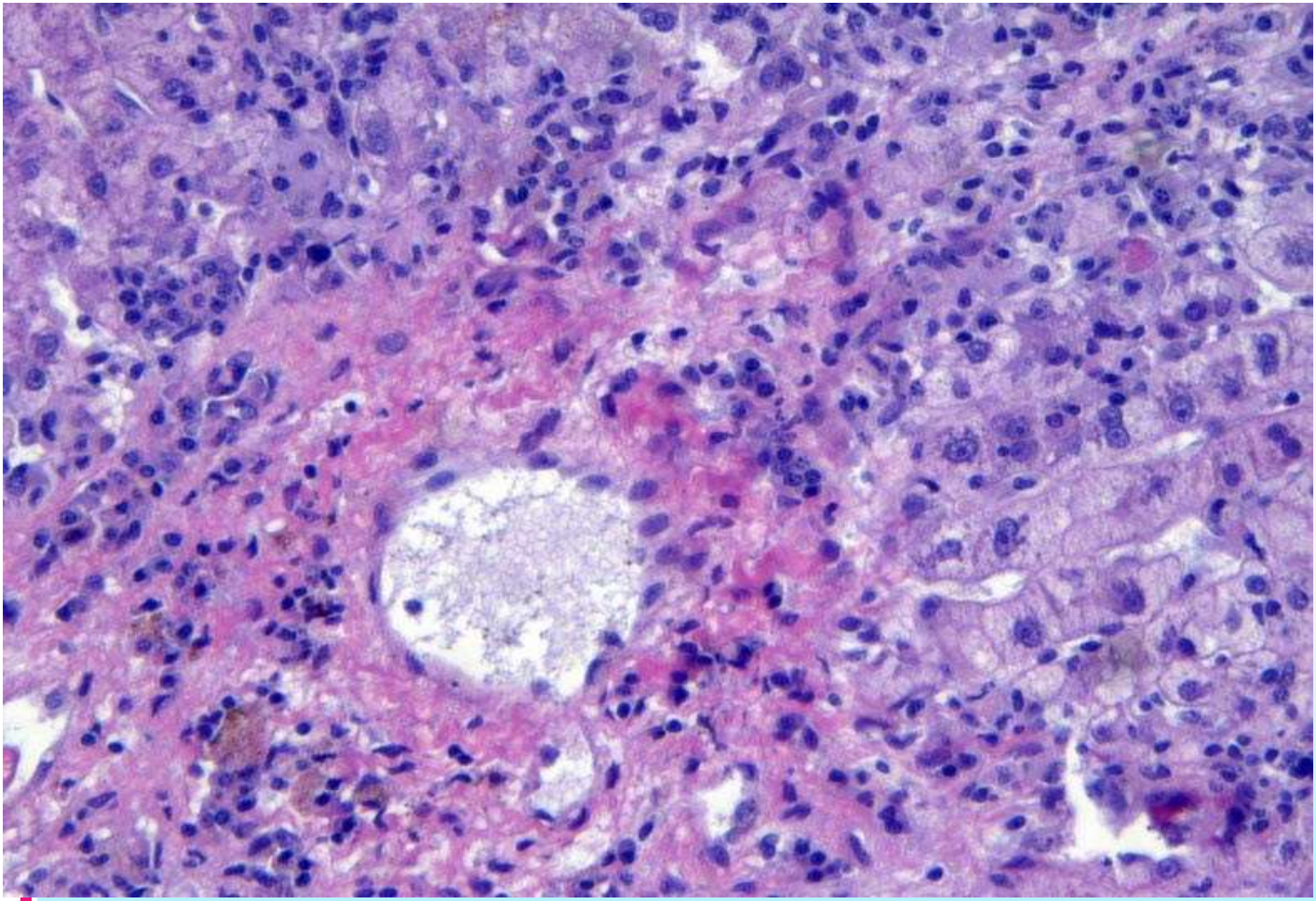


Confluent Necrosis

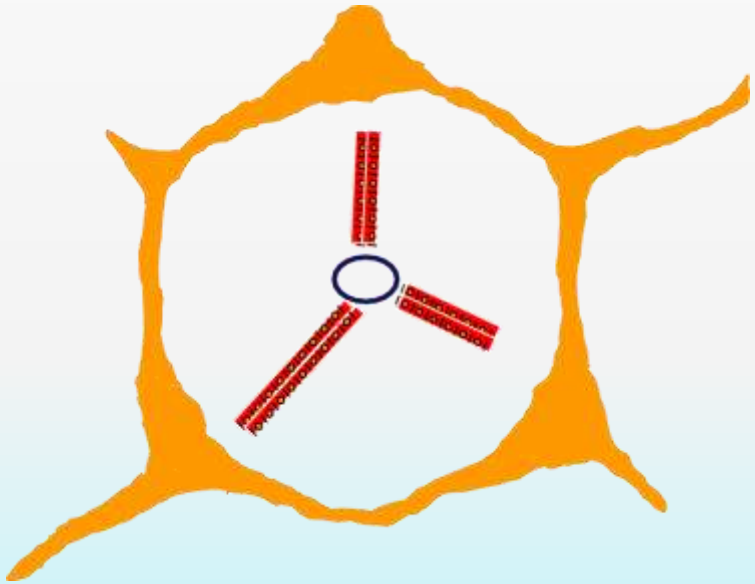


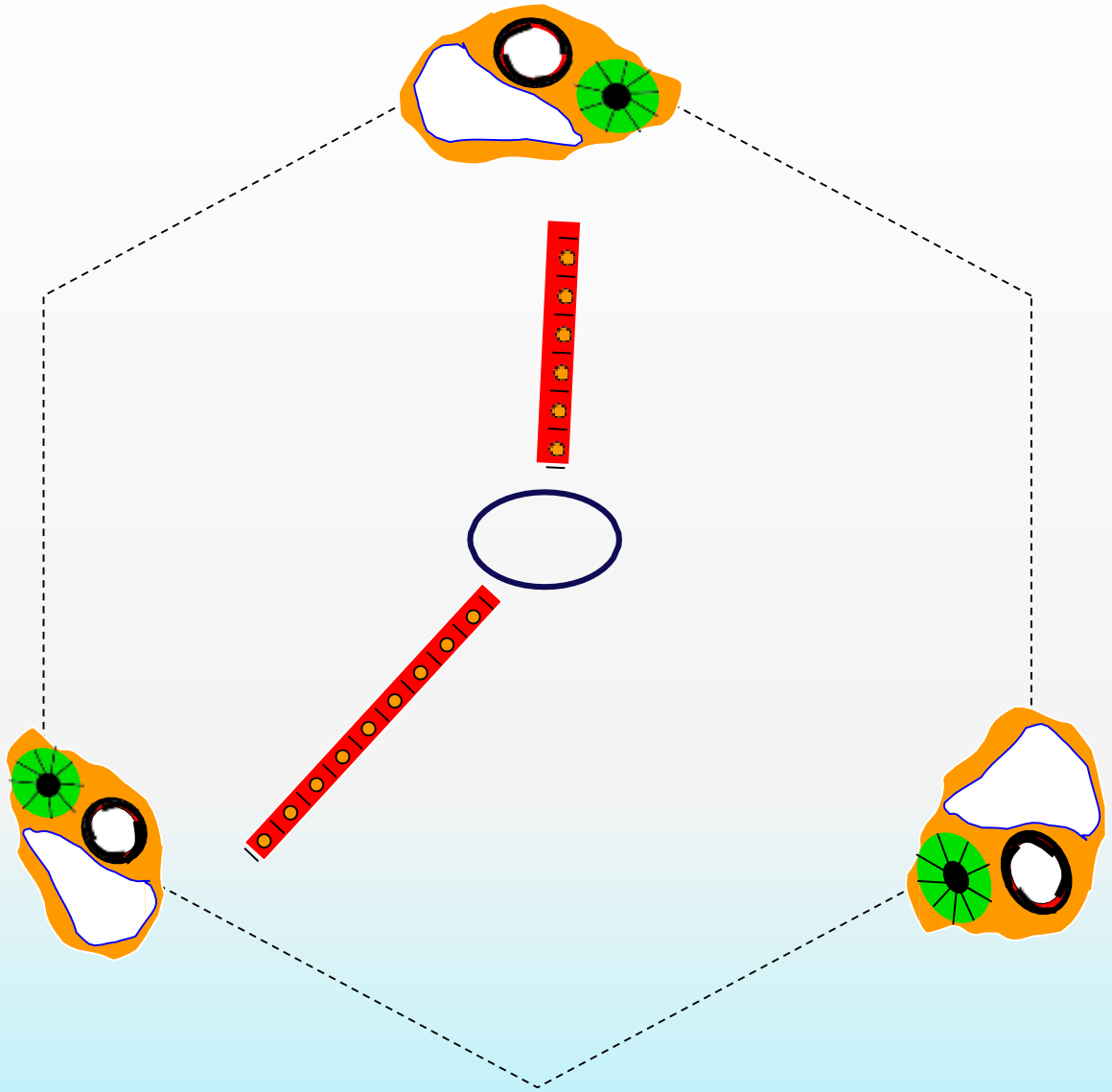
Confluent Necrosis

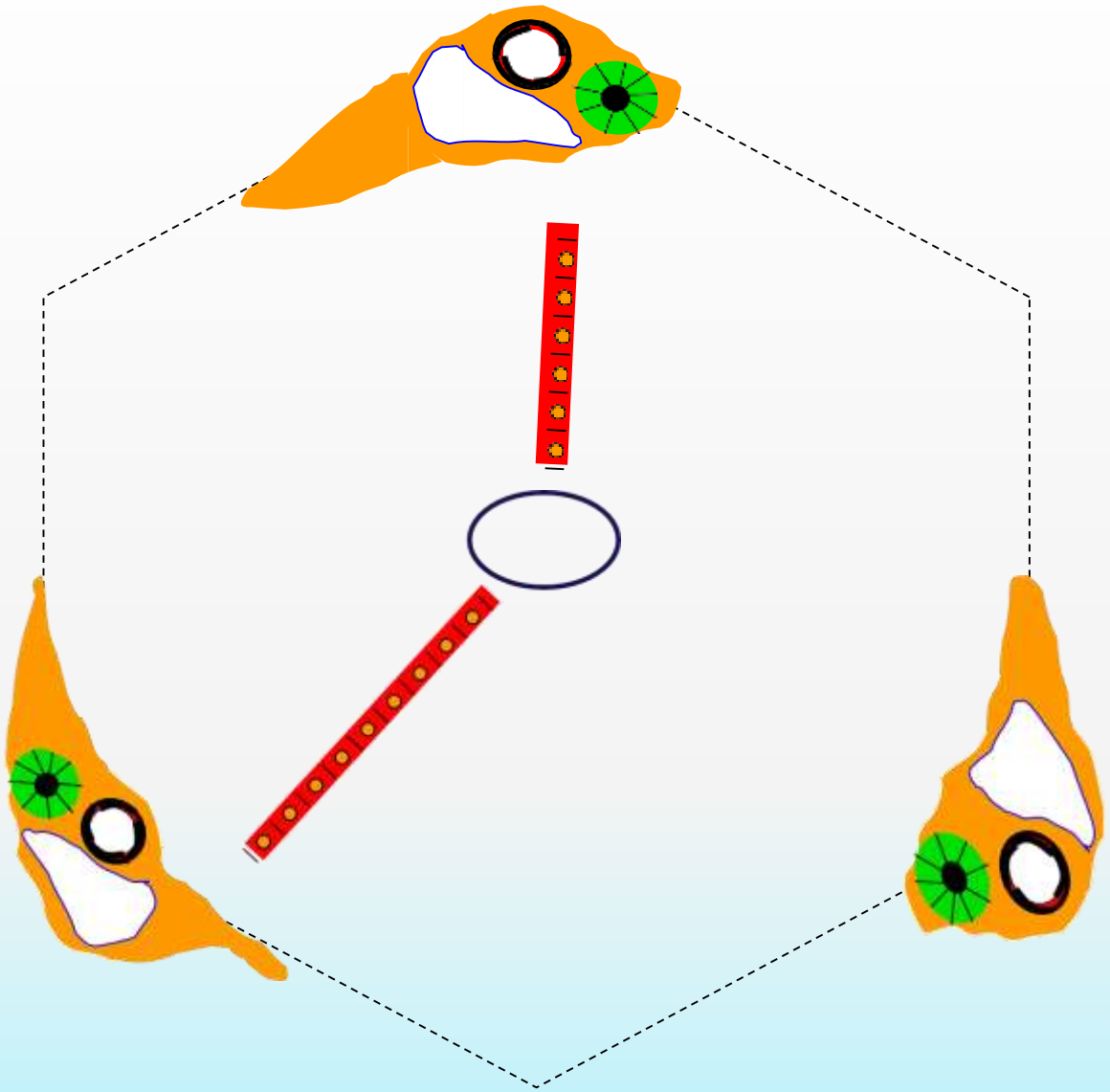


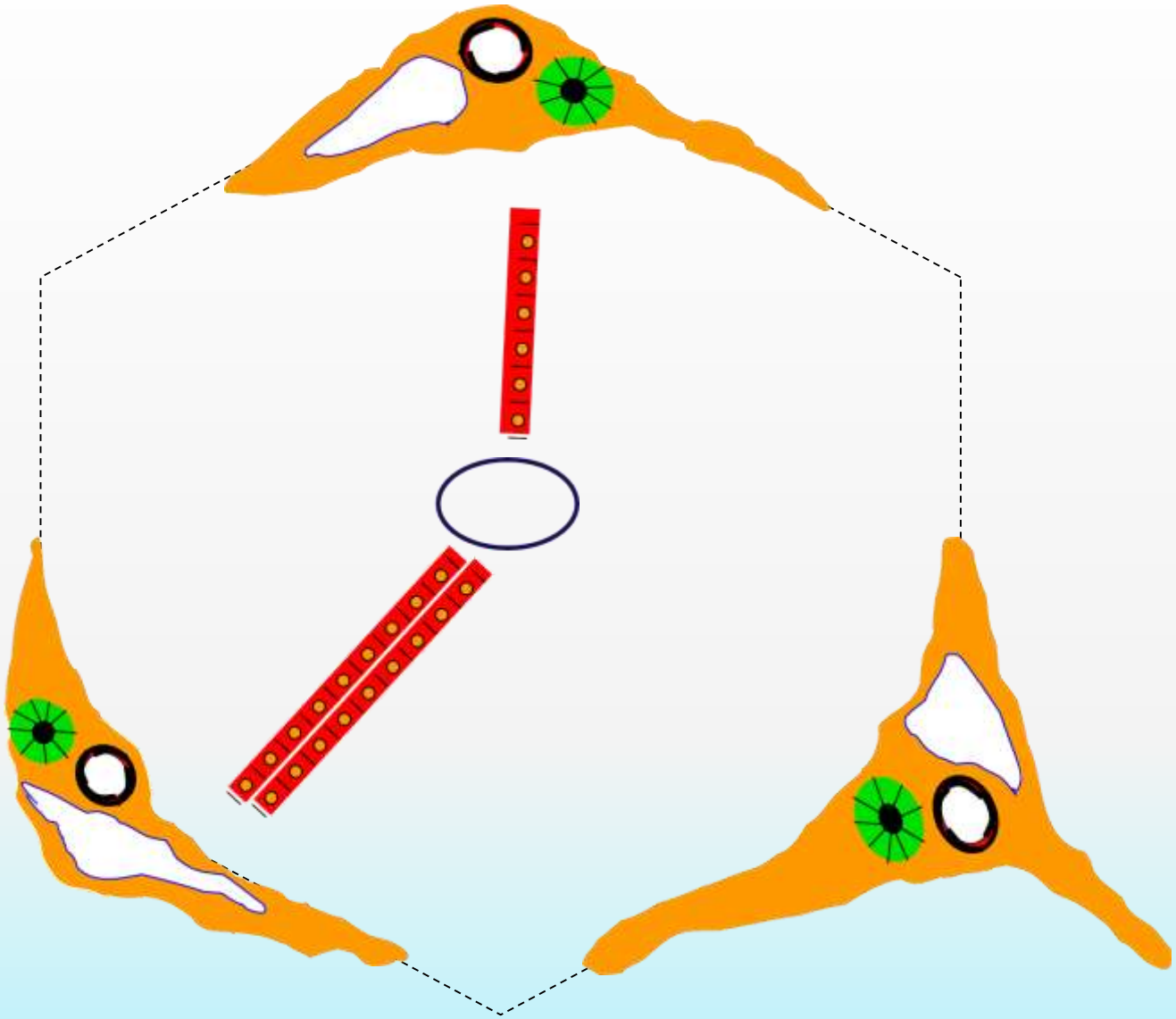


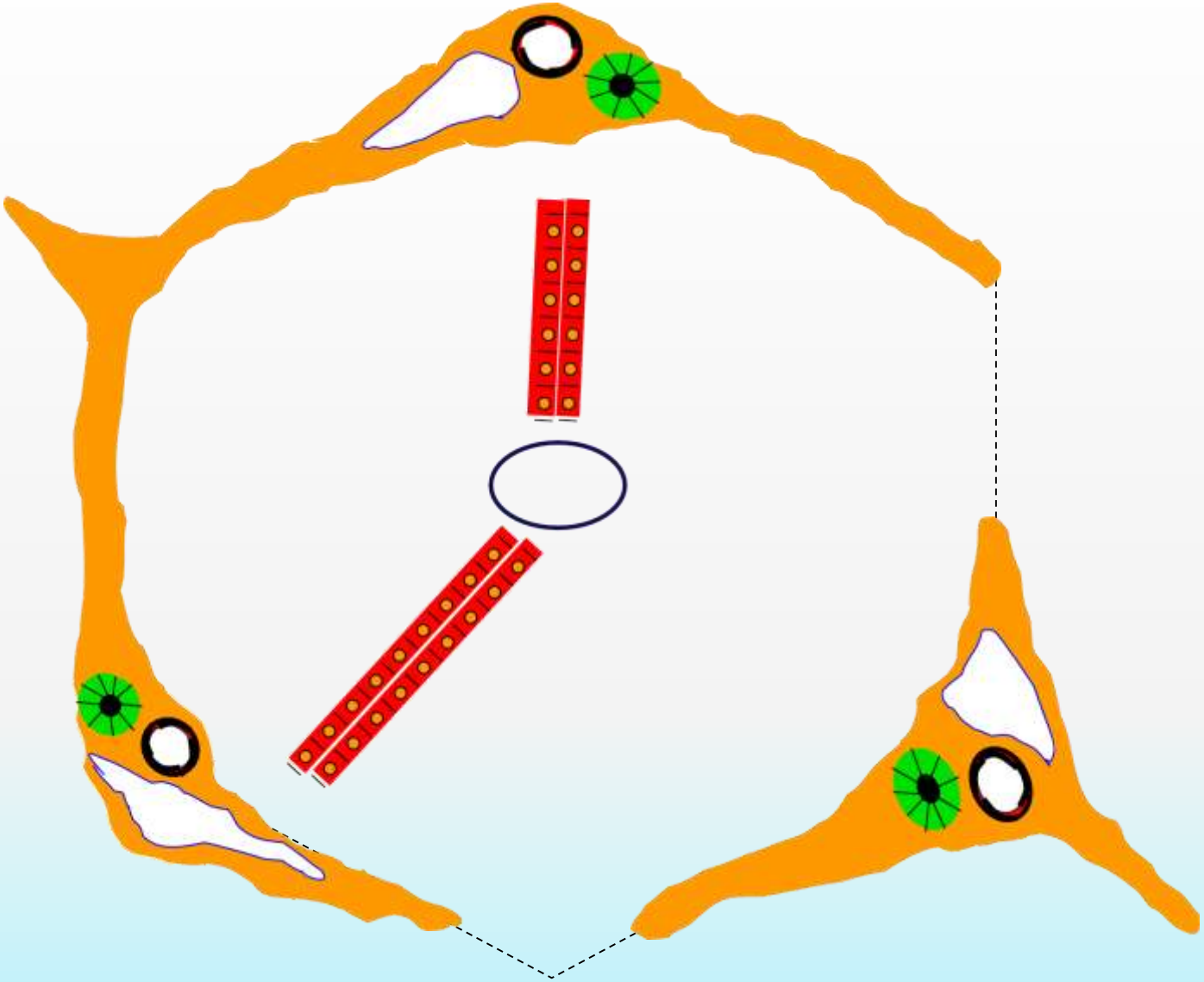
STAGING

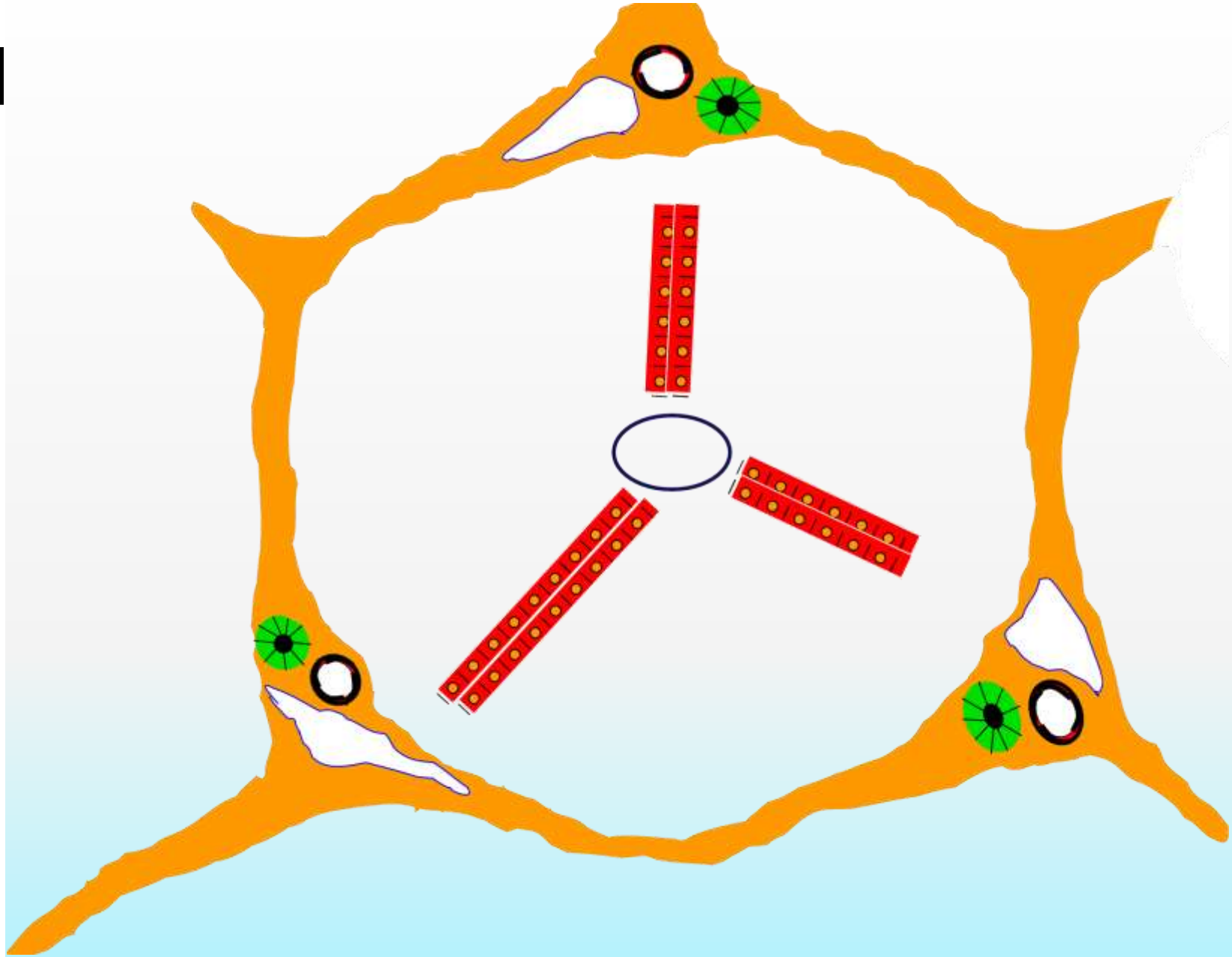


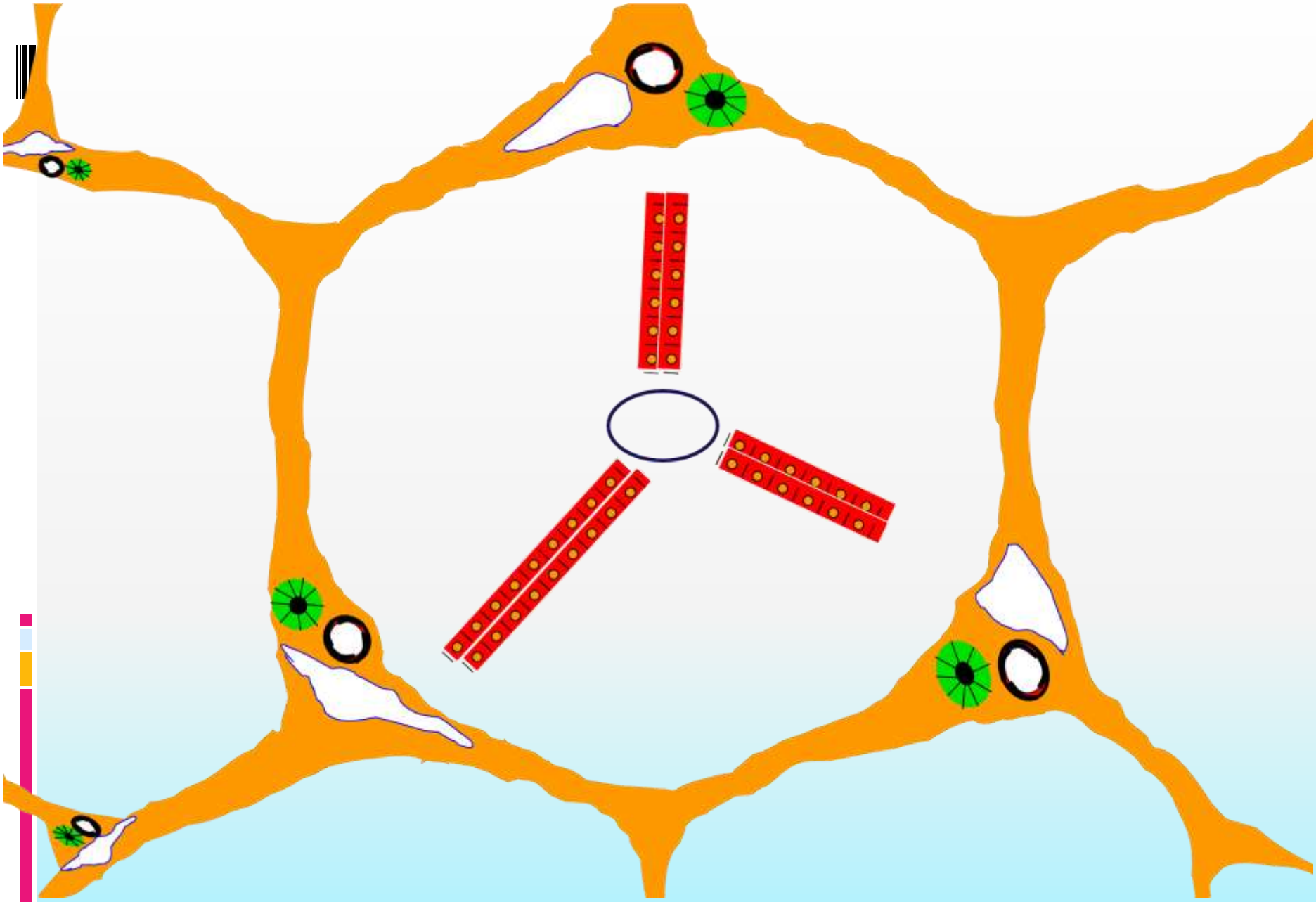


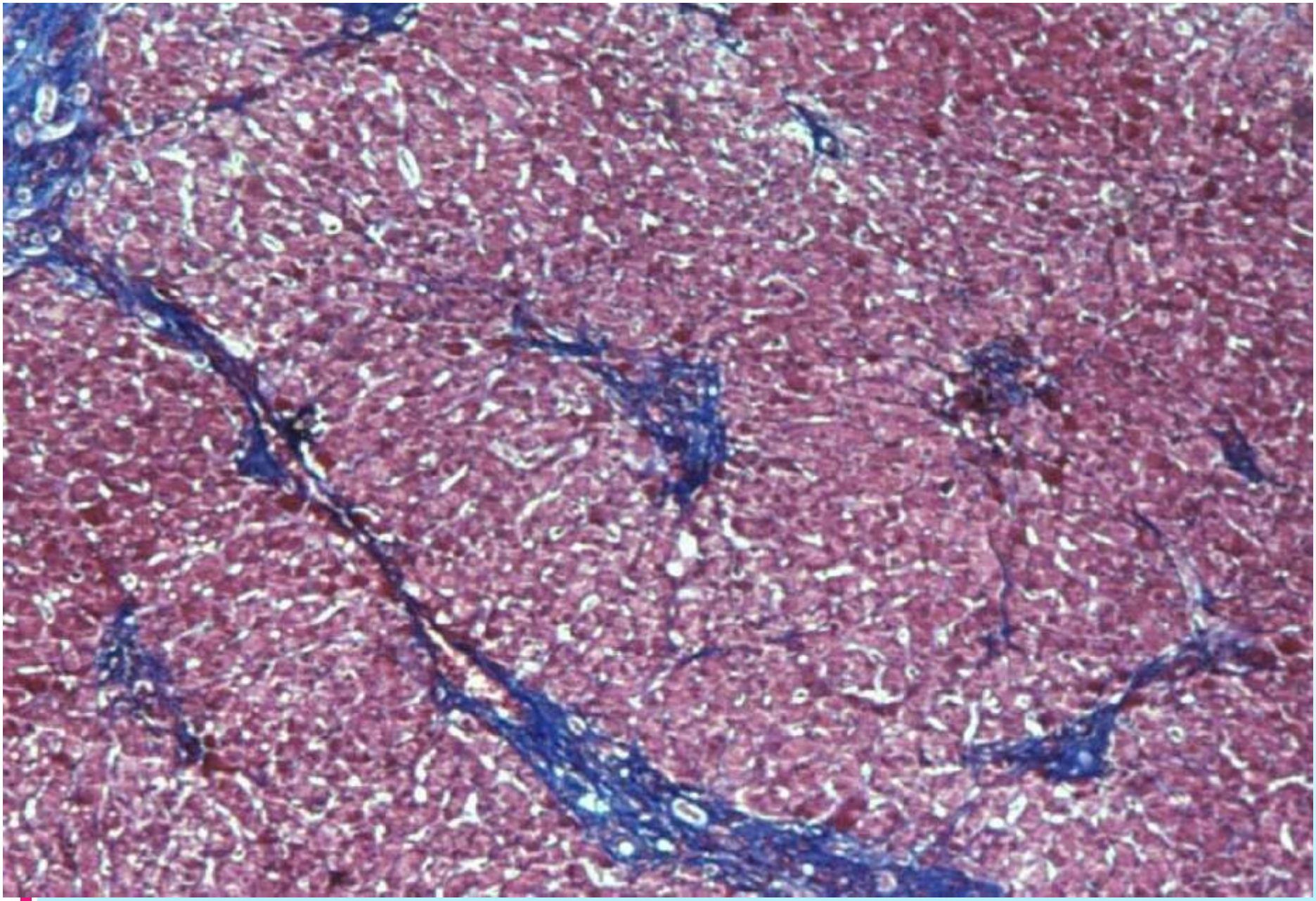


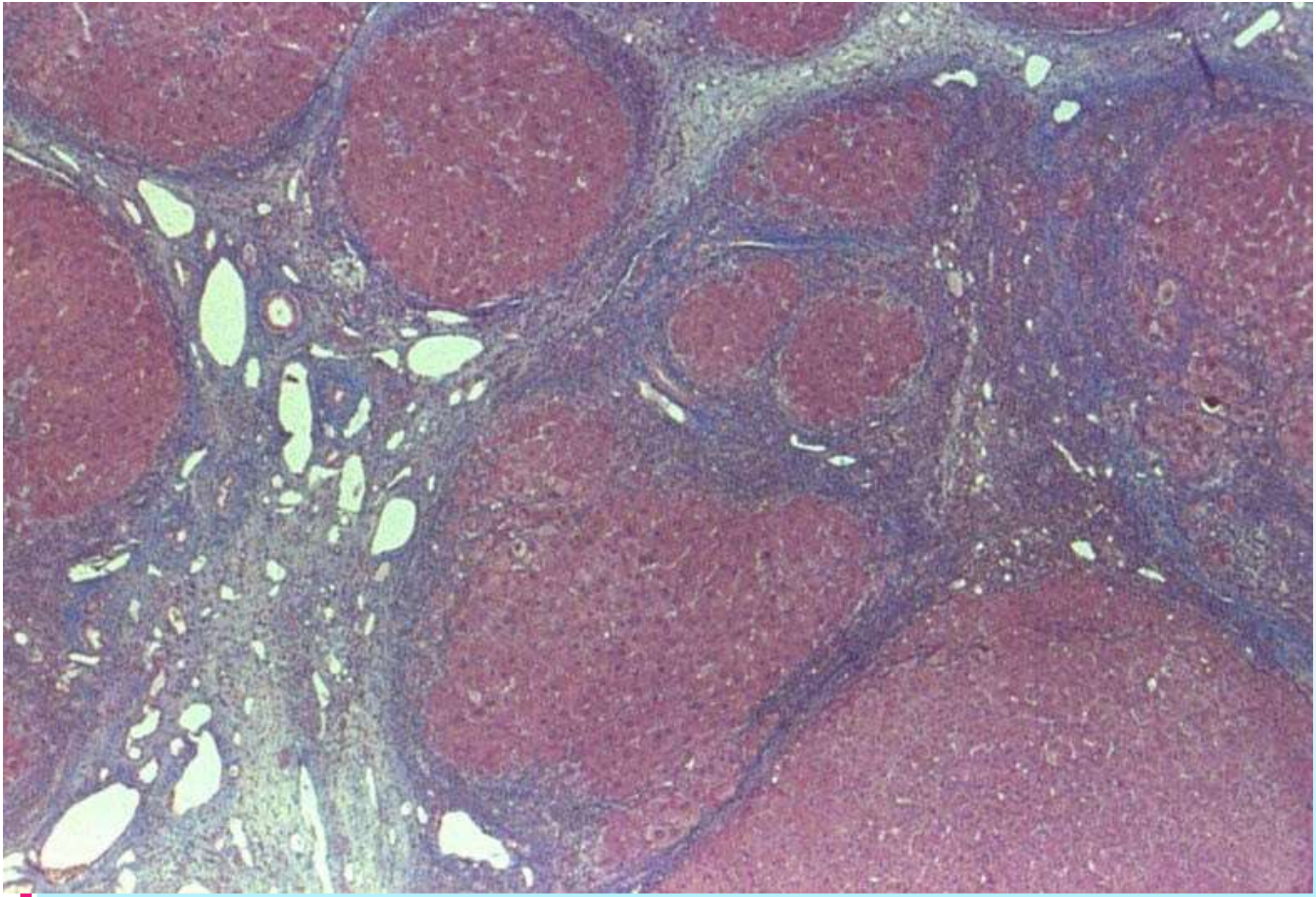












Specific morphology in chronic hepatitis:

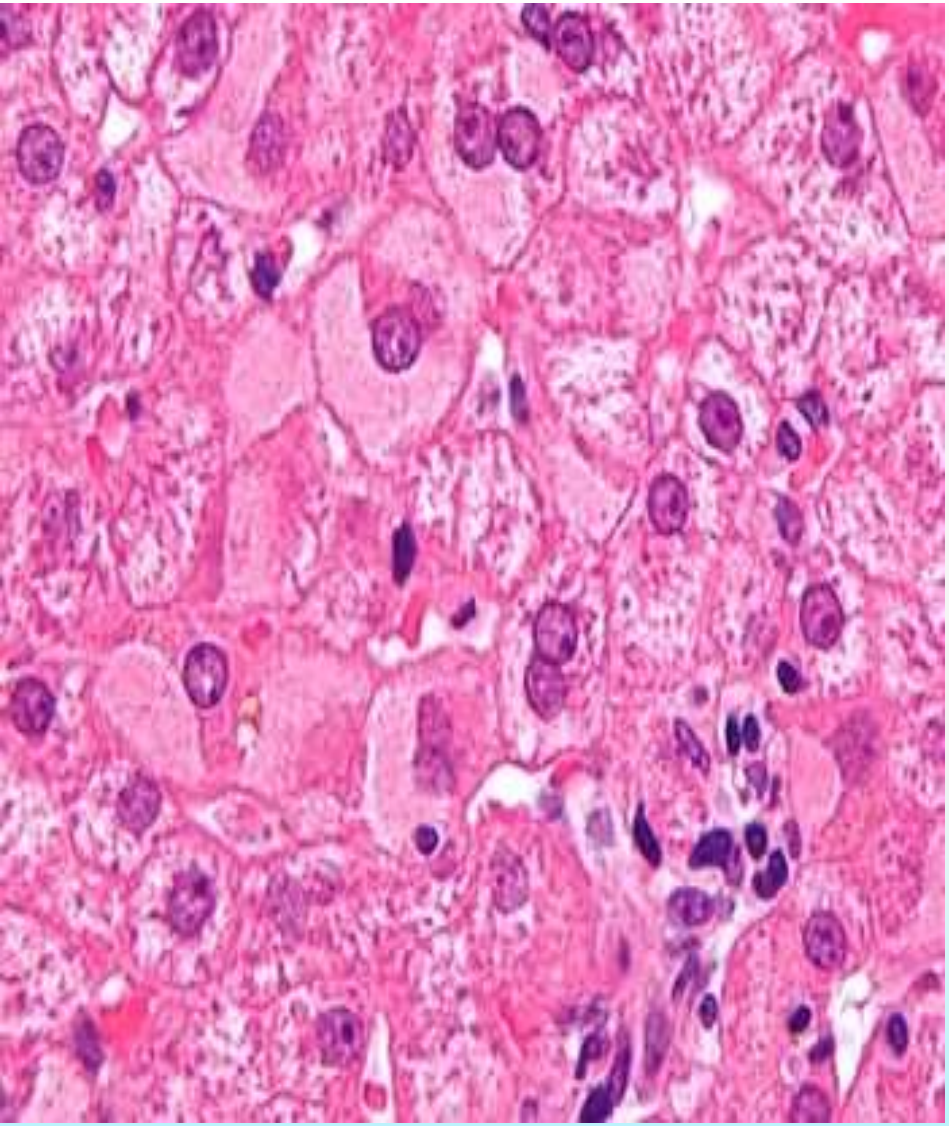
In chronic HBV infection may generate **"ground-glass"** hepatocytes

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

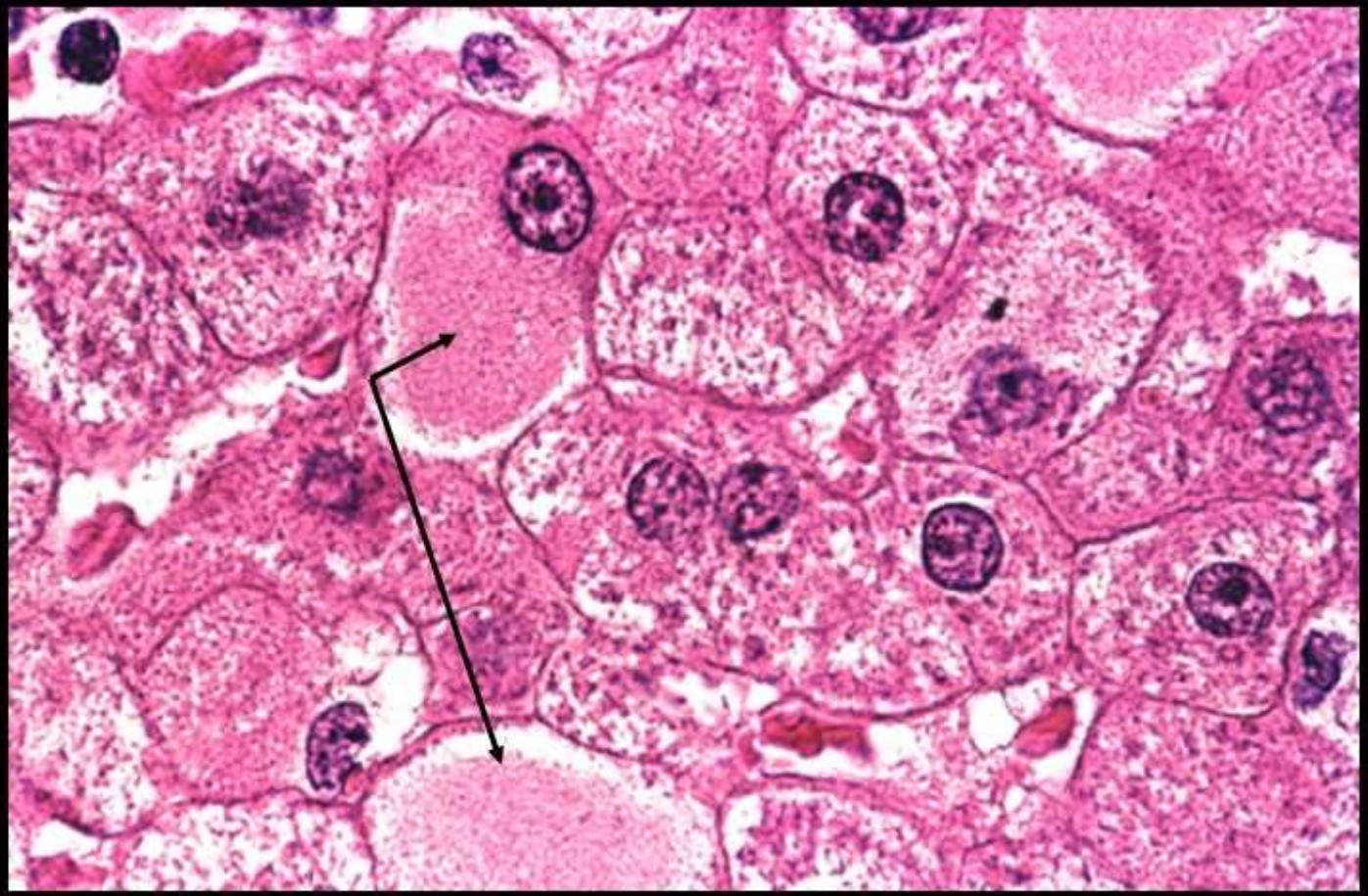
. Ground glass hepatitis: this is seen **in HBV**. The hepatocytes show a fine granular eosinophilic cytoplasm shown by electron microscope to contain massive quantities of HBs Ag in the form of spheres & tubules.

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.

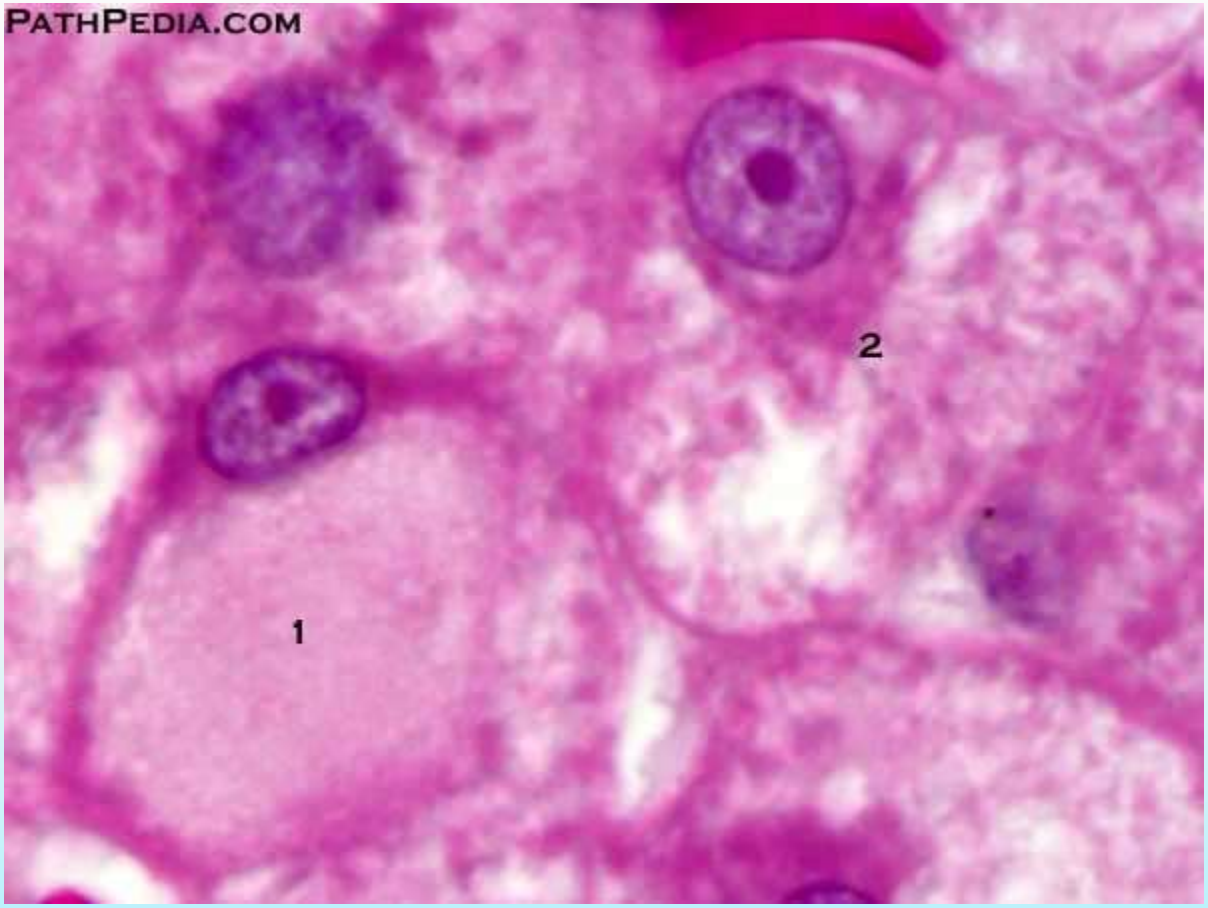


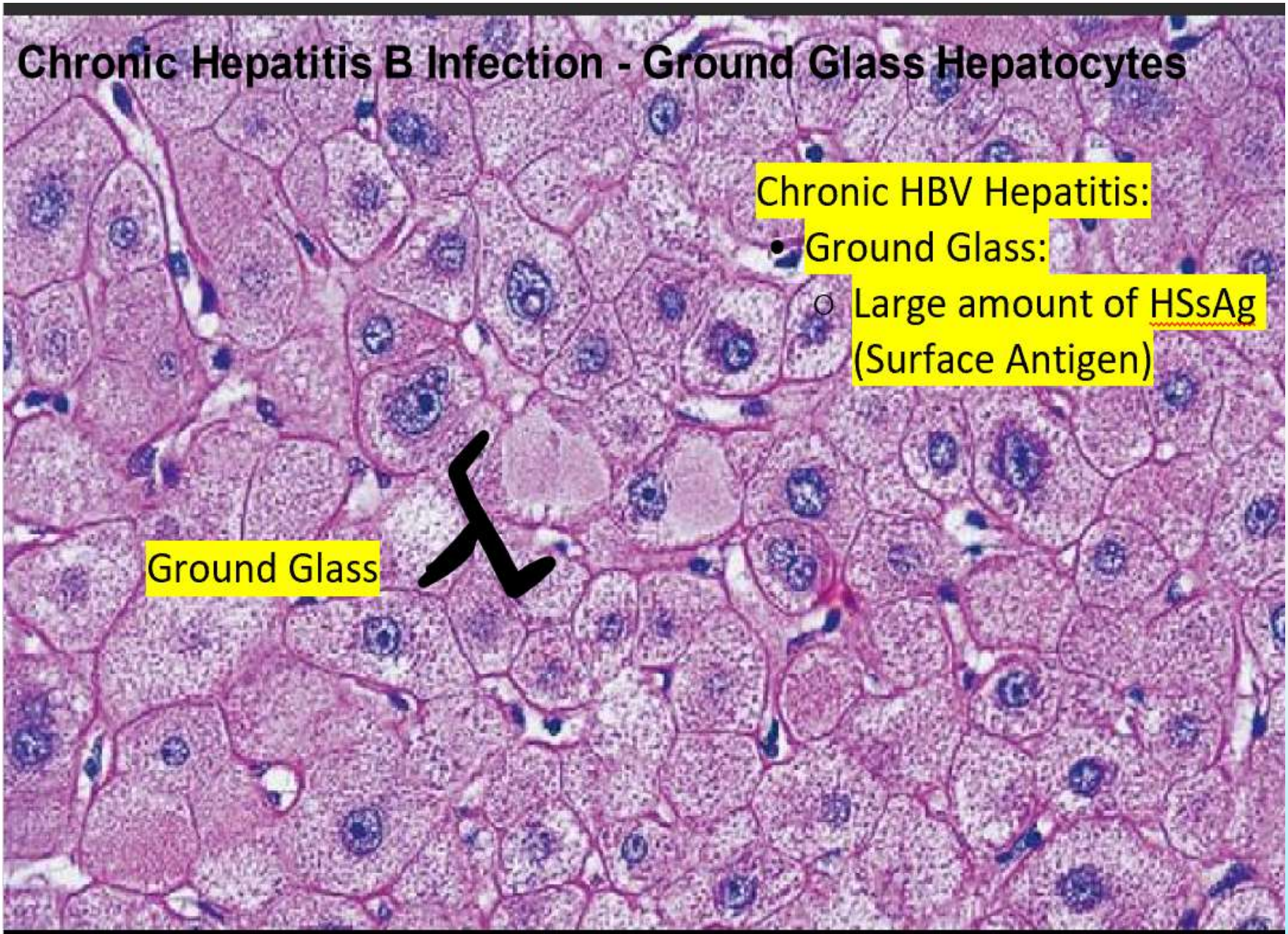
Chronic viral hepatitis B showing ground glass hepatocytes

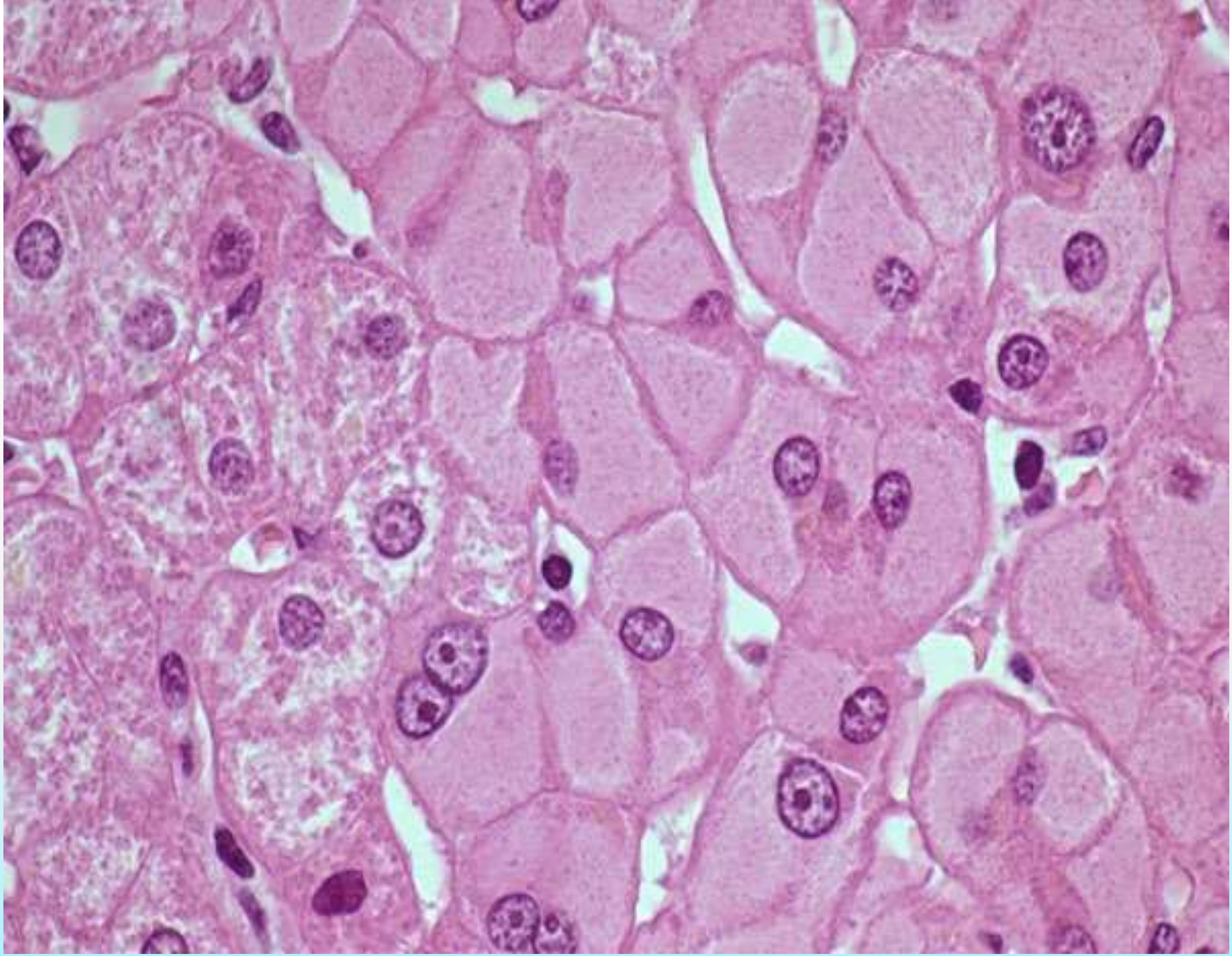


Ground glass hepatocytes, characterized by more pale, eosinophilic, and homogeneous cytoplasm than surrounding normal (more granular) hepatocytes. Note (artifactual) cleft between "ground glass" cytoplasm and hepatocellular cell membrane. The change corresponds to extensive endoplasmic reticulum hyperplasia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

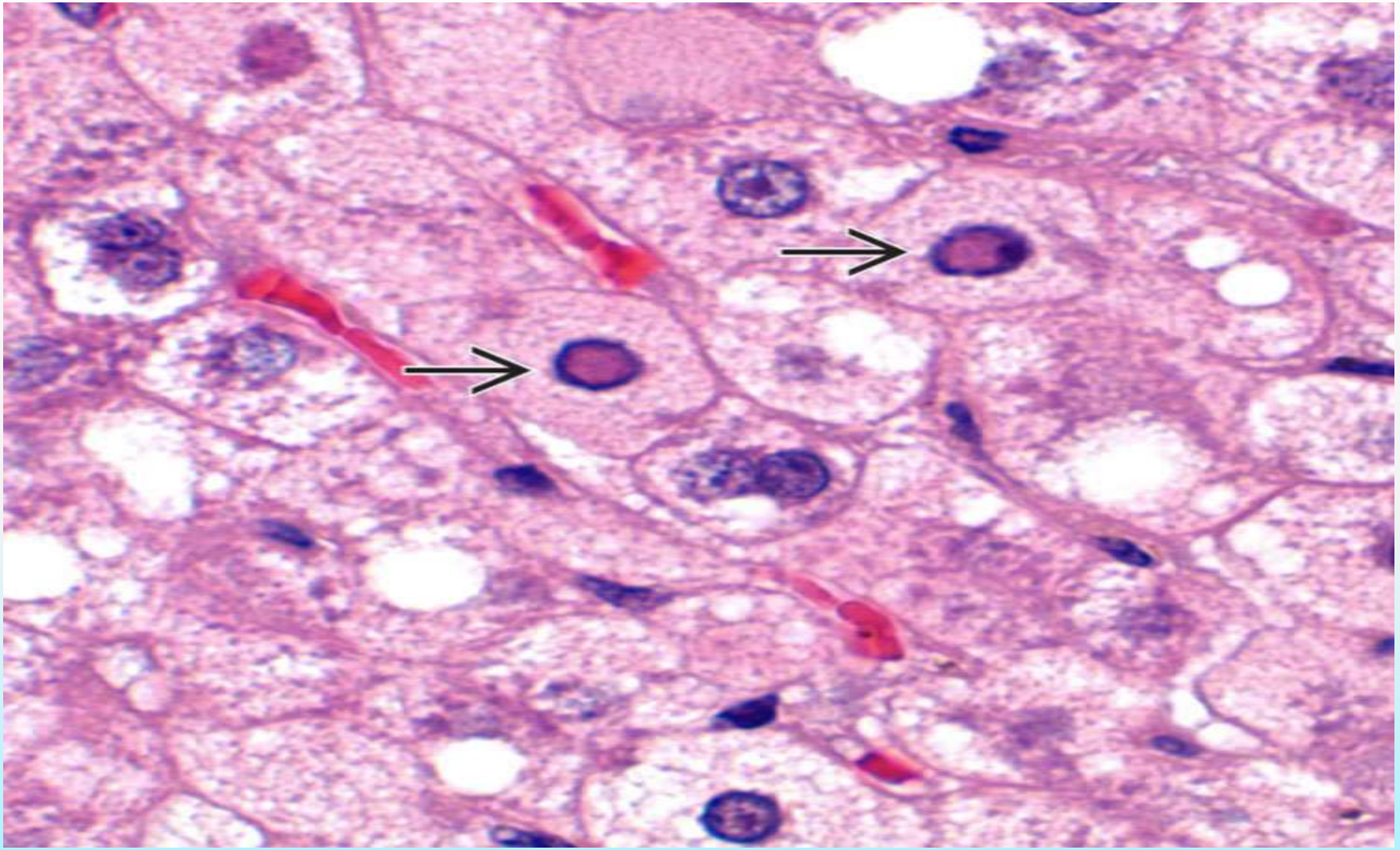
CHRONIC HEPATITIS B]. Note the contrasting morphologic features of a hepatocyte with ground-glass hepatitis B inclusion (#1) and a normal hepatocyte (#2) without such inclusions. The ground-glass appearance is due to the presence of hepatitis B surface antigen within proliferated endoplasmic reticulum throughout the cell. The inclusion may become so big that it pushes the nucleus to the side




Chronic Hepatitis B Infection - Ground Glass Hepatocytes
Chronic HBV Hepatitis:
• Ground Glass:
○ Large amount of HSsAg (Surface Antigen)
Ground Glass



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



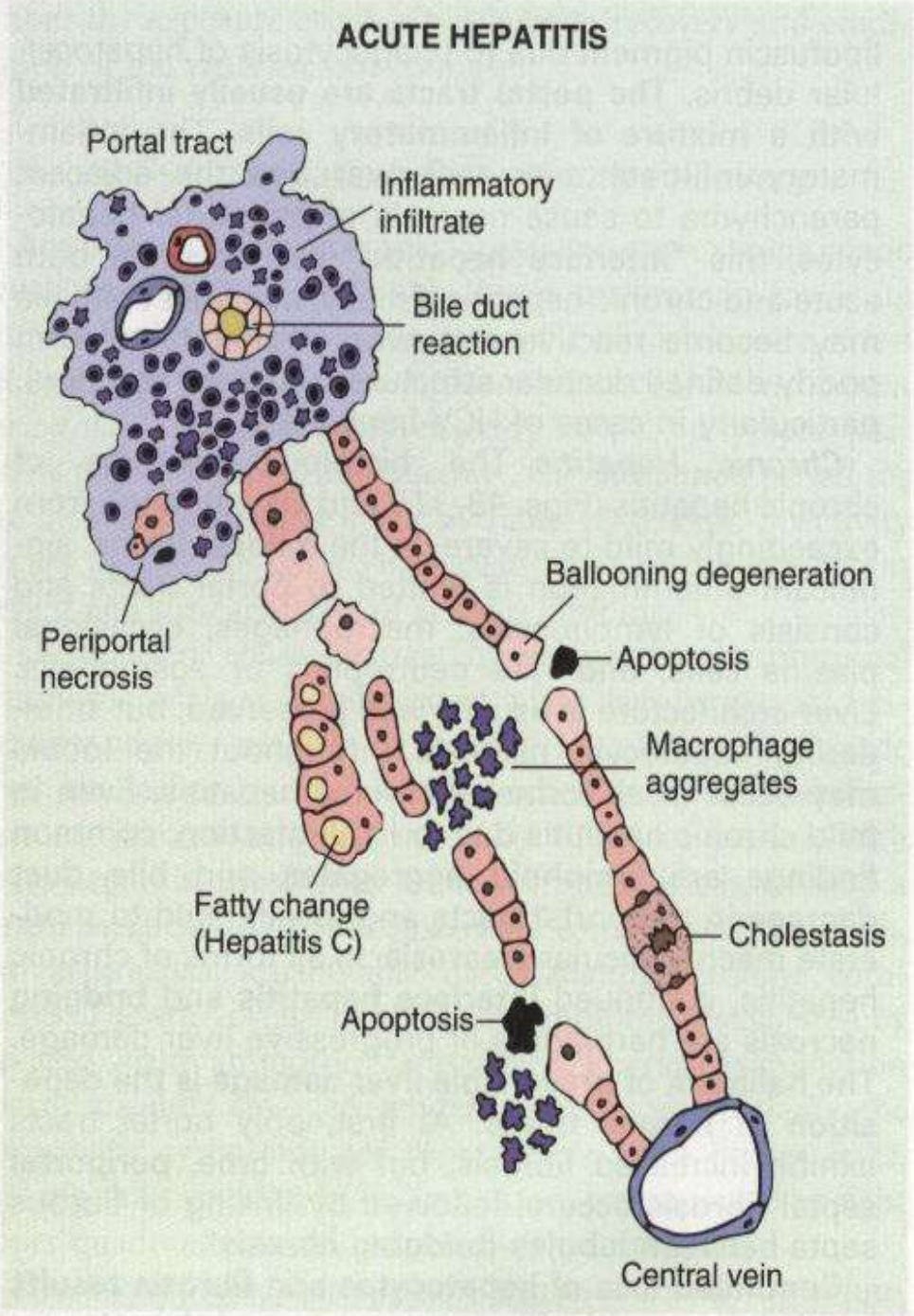
Specific morphology associated with HCV

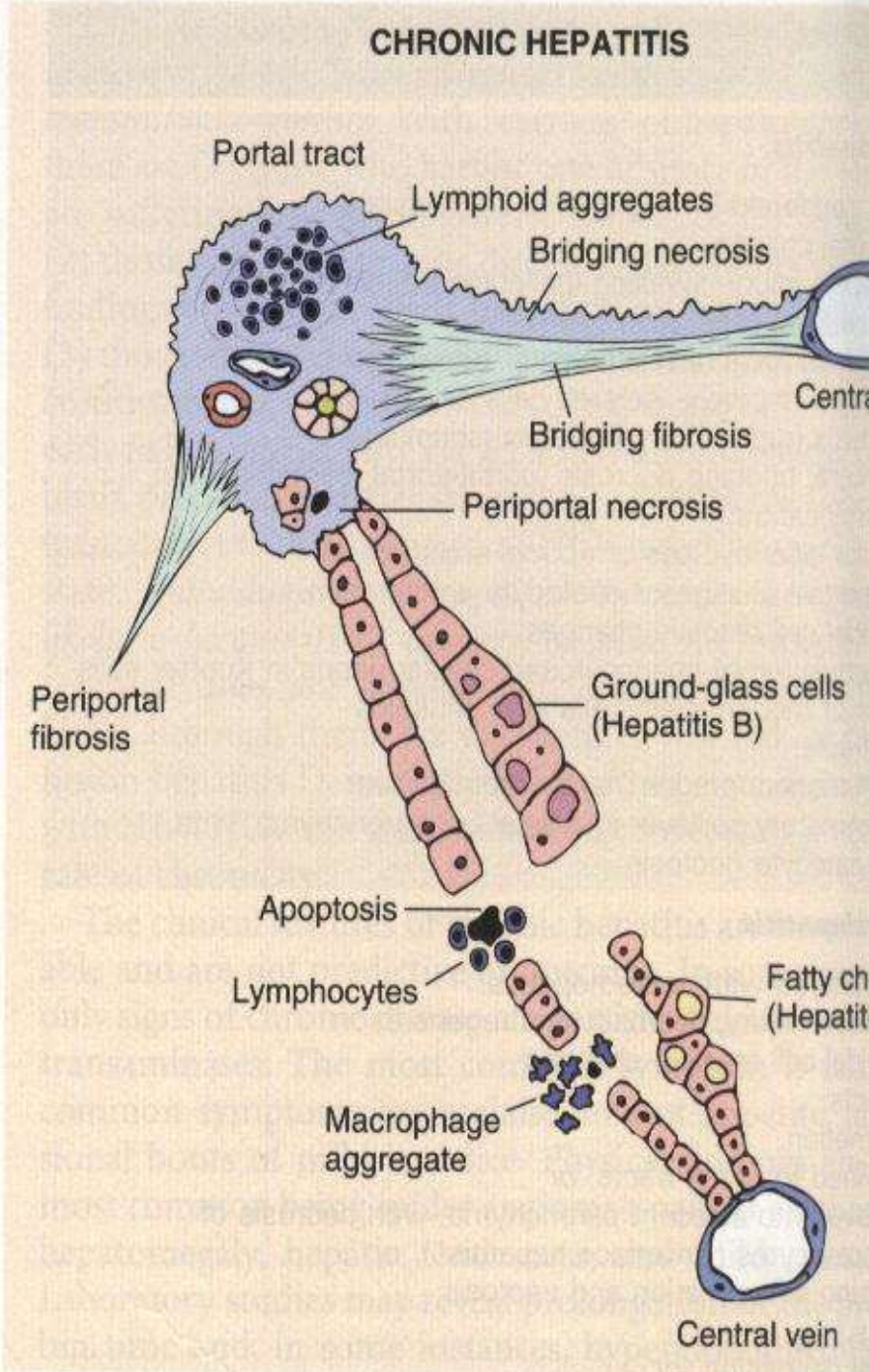
- **Chronic hepatitis C commonly shows**:

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

Acute viral hepatitis : clinical features

- It is the same for all types of hetatropic viruses
- The disease divided into 4 phases :
- Incubation period :no symptoms
- Symptomatic **preictreric** phase:
- Non specific symptoms, malaise , fatigability, nausea, loss of appetite, low grade fever, headache muscle and joint aches
- Symptomatic **icteric**(with jaundice):
- When jaundice appear all the previous symtoms disappear.
- convalescence

Chronic hepatitis C/F

Highly variable:

Fatigue

Malaise

Loss of appetite

Bouts of mild jaundice

Mild hepatomegaly and tenderness

persistent elevation of serum aminotransferase level

Clinical course: highly variable

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

Malaria

Schistosomes

Liver flukes (Fasciola hepatica)

(5)Ameba (abscesses)

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 :

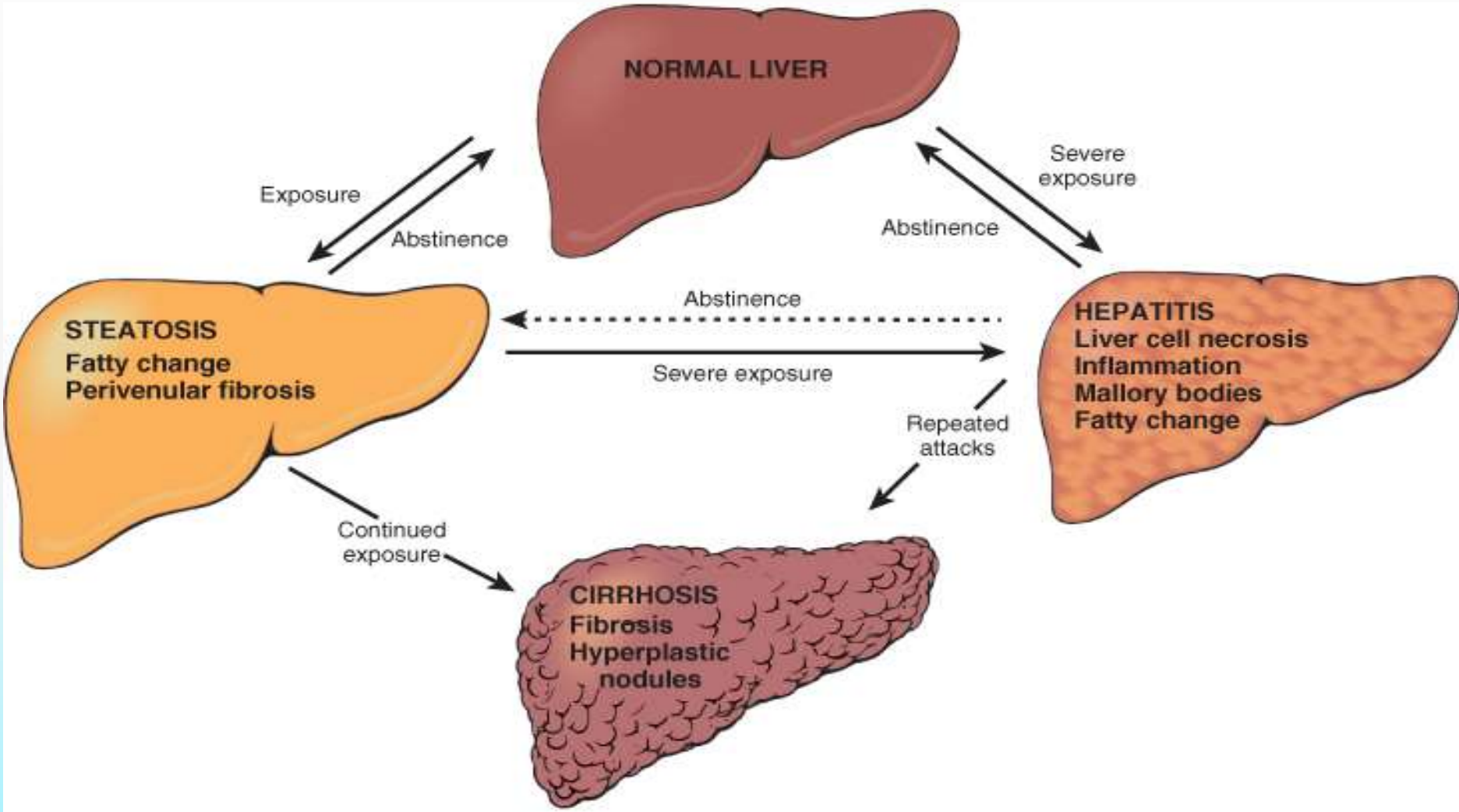
1-Hepatic steatosis (fatty liver) (50%).

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.

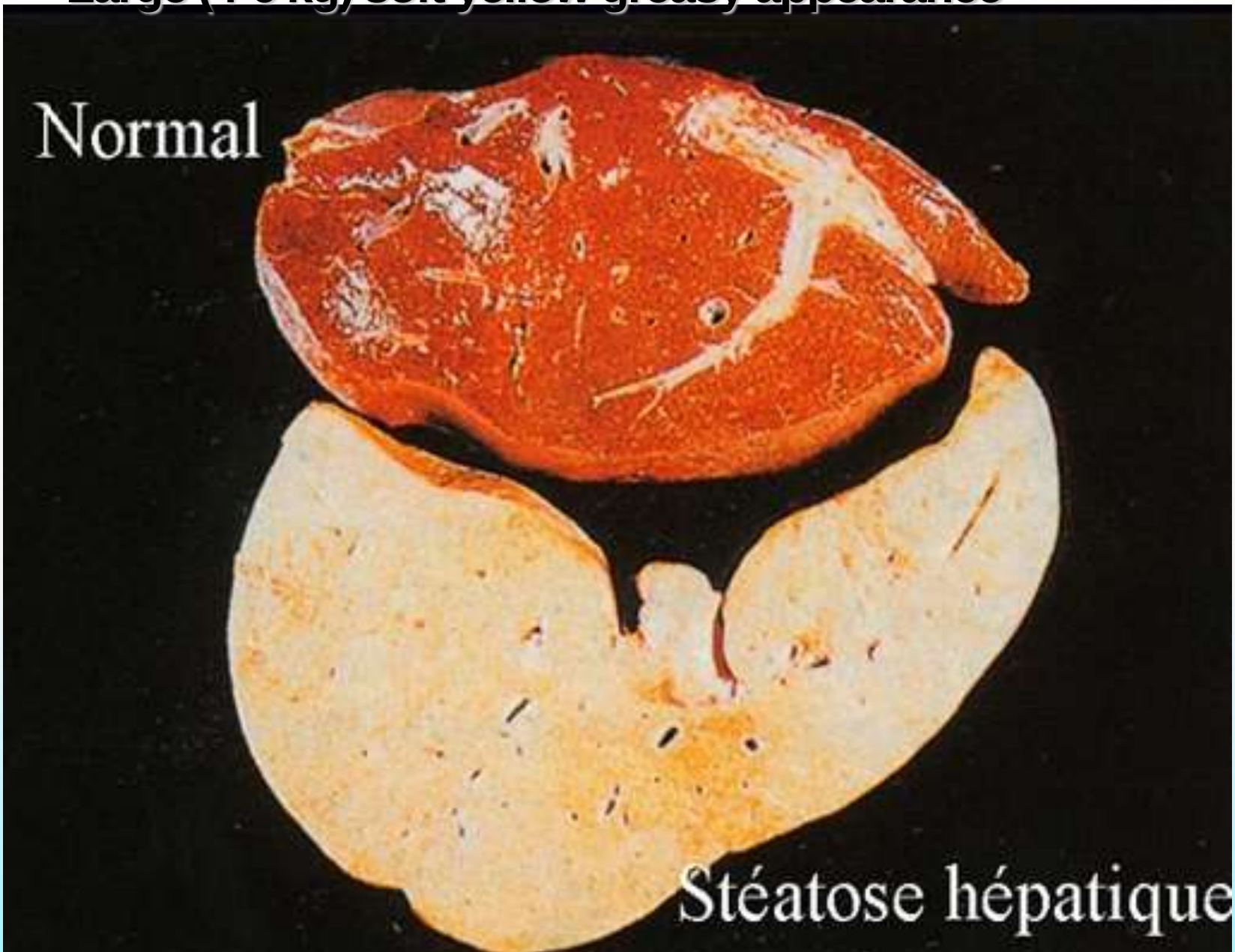
Microscopically:

small lipid droplets occur (microvesicular changes).

large lipid droplets (macrovesicular) globules

the nucleus is displaced to the periphery of the cell.

Large (4-6 kg) soft yellow greasy appearance



ALCOHOLIC LIVER DISEASE

Steatosis (fatty changes)

Lipid droplets accumulate in hepatocytes

2 histologic types:

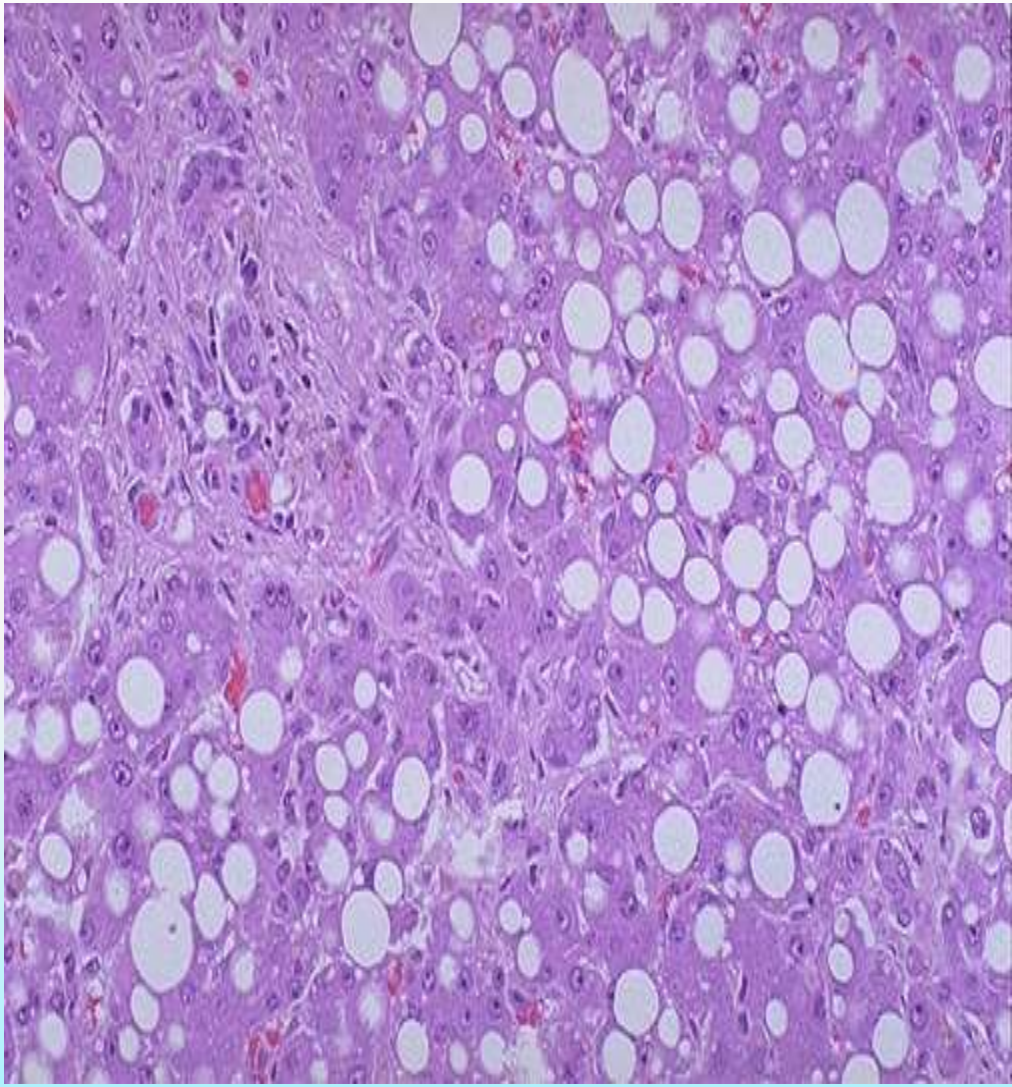
Microvesicular

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).

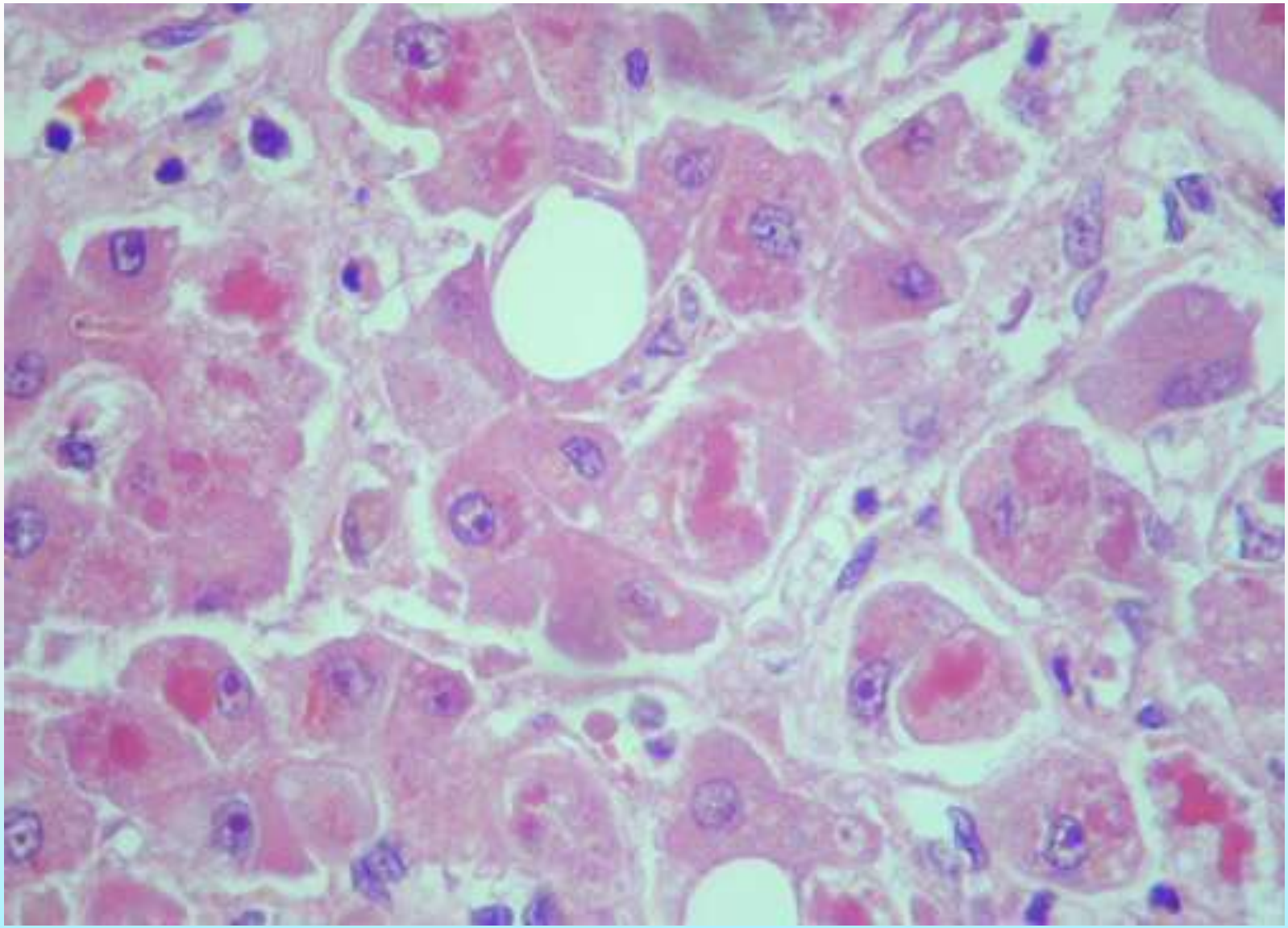
3-Mallory bodies: amorphous eosinophilic, cytoplasmic inclusions due to accumulation of cytokeratin filaments

4-Neutrophilic reaction: around degenerating hepatocytes

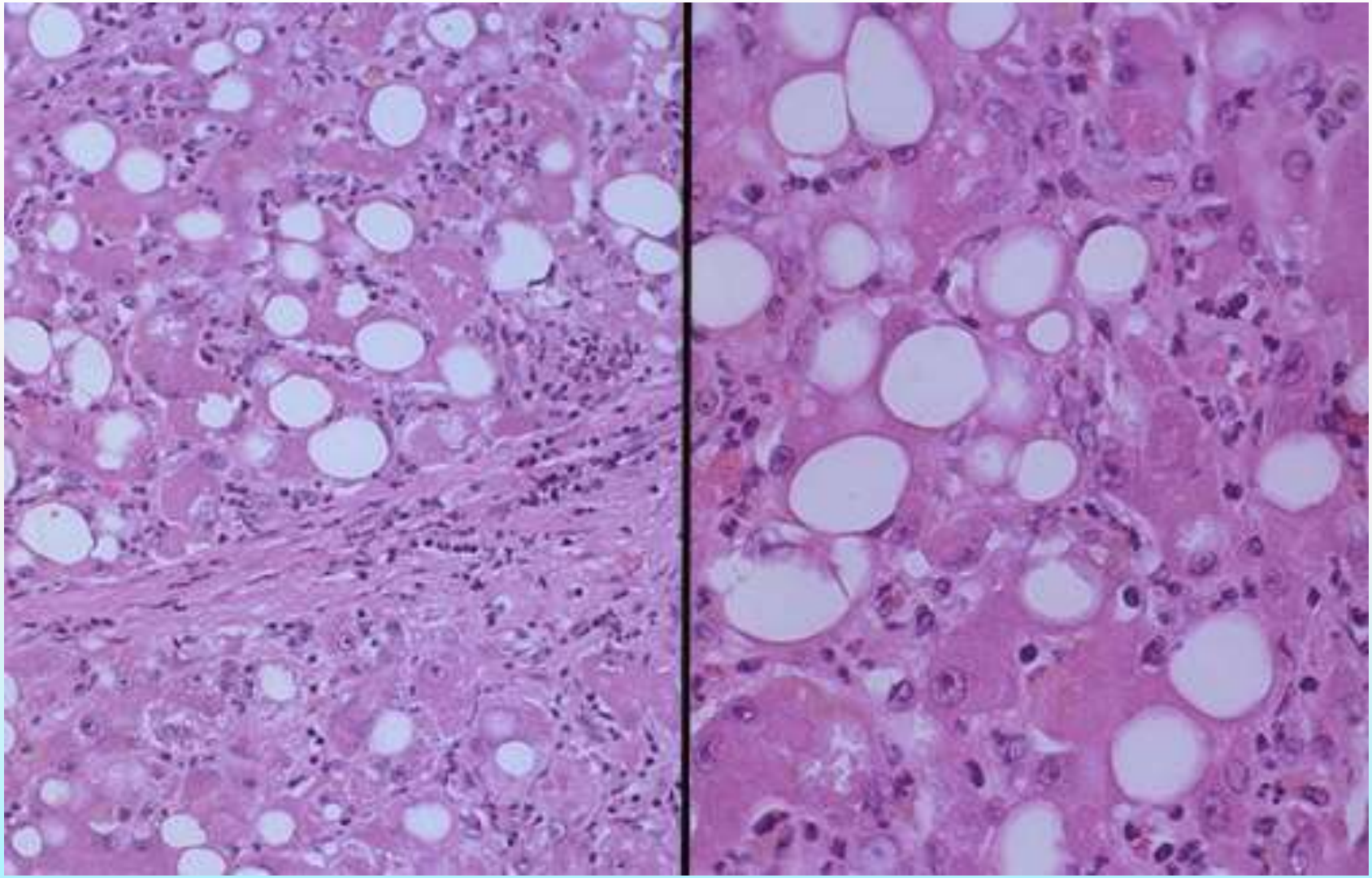
5-portal lymphocytes & macrophages

6-Fibrosis: starts as sinusoidal & perivenular then periportal

MALLORY'S HYALINE



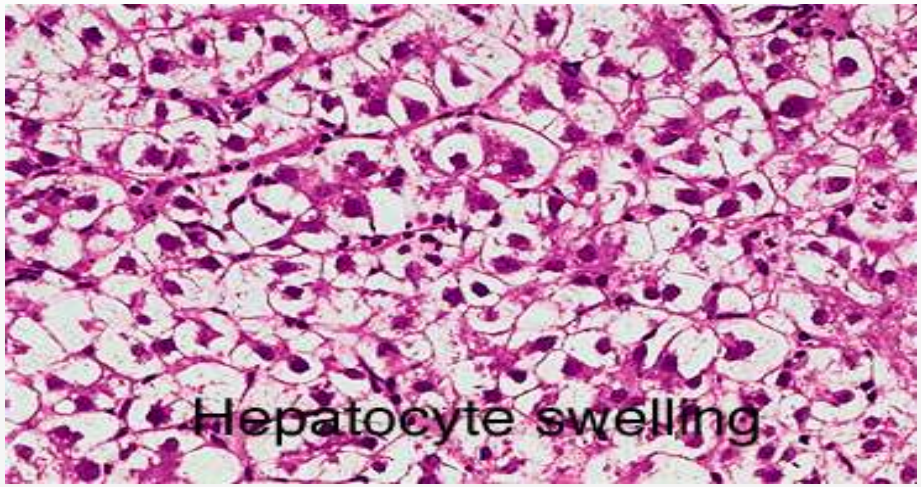
ALCOHOLIC HEPATITIS

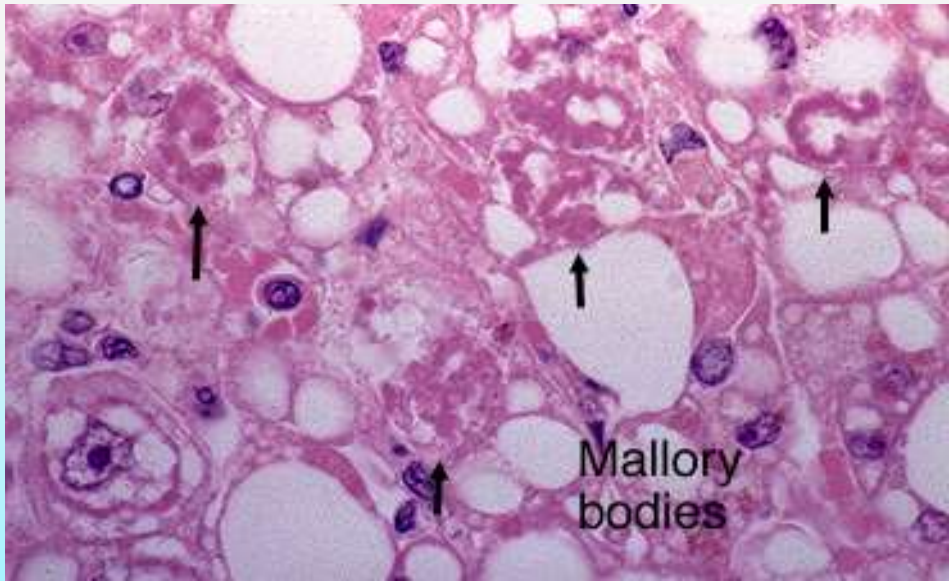


ALCOHOLIC LIVER DISEASE

ALCOHOLIC HEPATITIS

- Hepatocyte swelling (ballooning) due to accumulation of fat & water, and cell necrosis
- Mallory bodies: characteristic eosinophilic cytoplasmic inclusions (cytokeratin intermediate filaments)
- Neutrophilic reaction
- Fibrosis

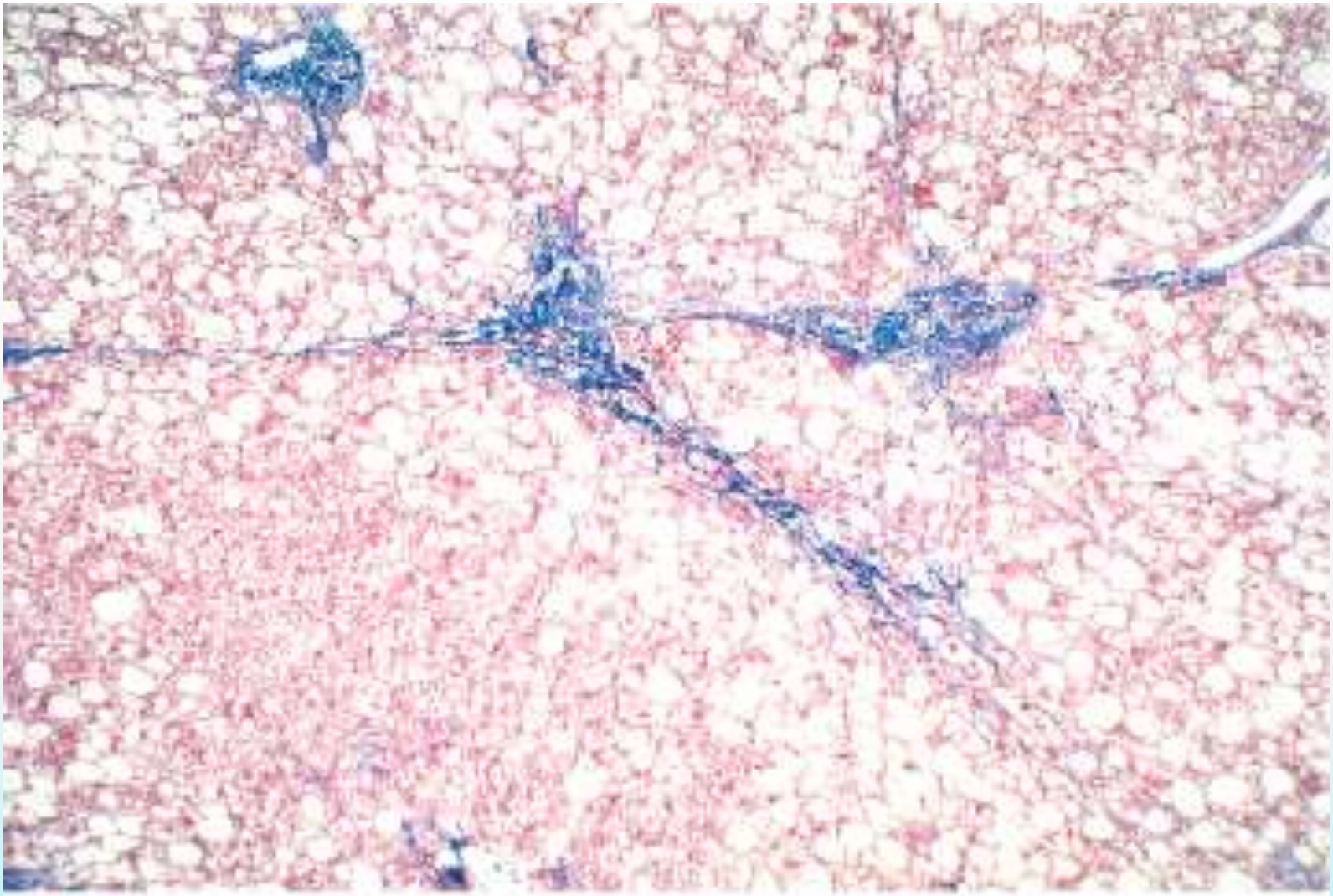




ALCOHOLIC LIVER DISEASE

ALCOHOLIC HEPATITIS

- **Mallory bodies:** characteristic eosinophilic cytoplasmic inclusions (cytokeratin intermediate filaments)



Morphology of Alcoholic cirrhosis

Grossly:

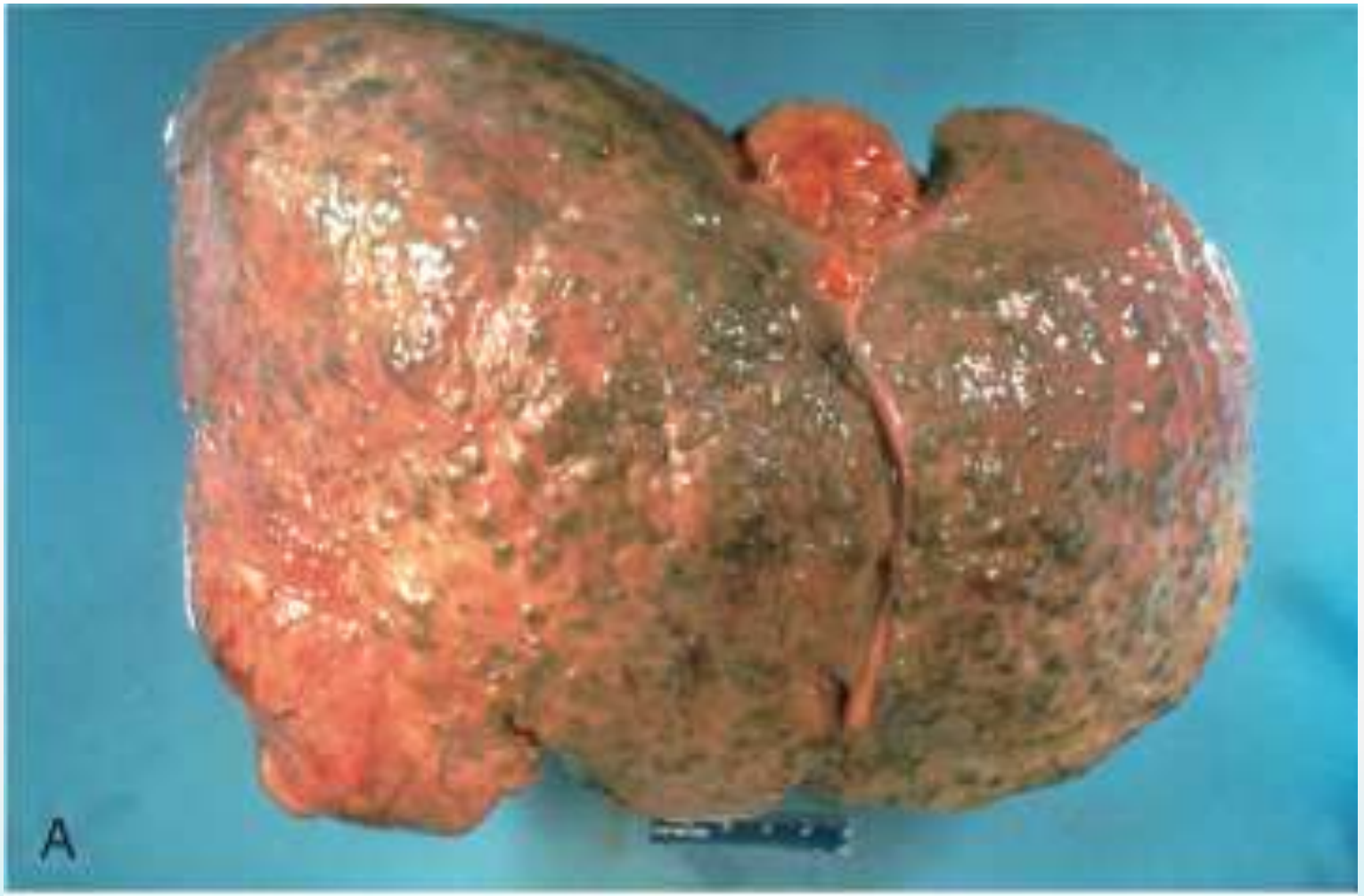
Cirrhotic liver appears yellow and enlarged more than 2kg, at the first 1-2 years, after years appear brown, shrunken, non fatty less than 1 kg

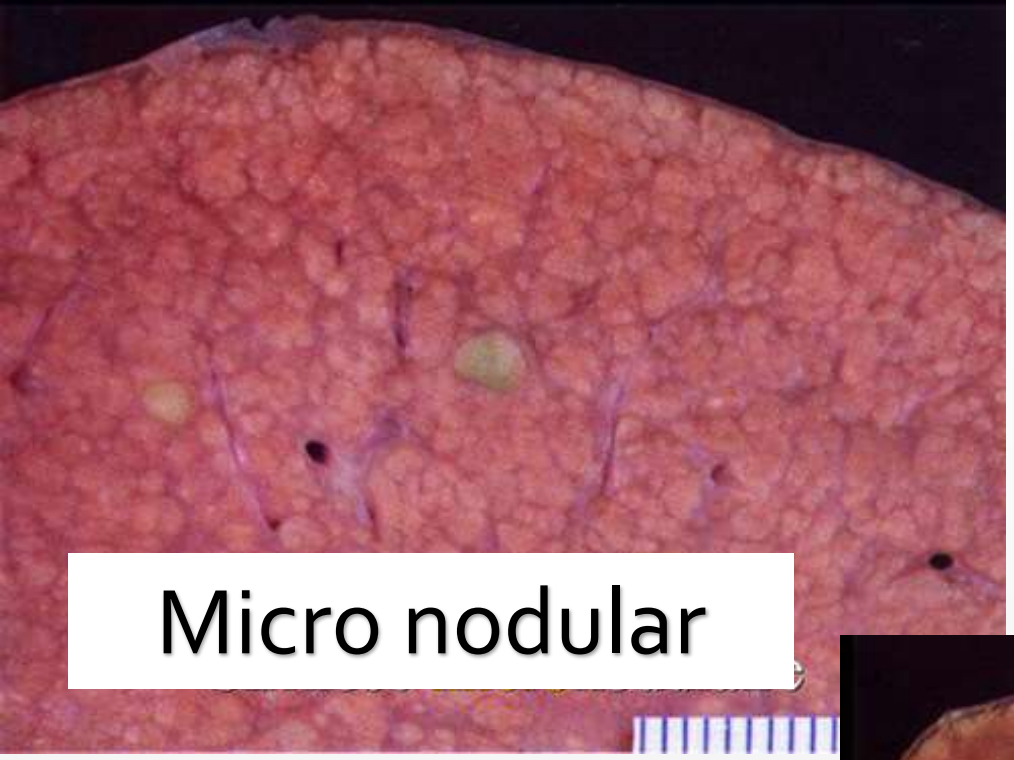
Microscopically:

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

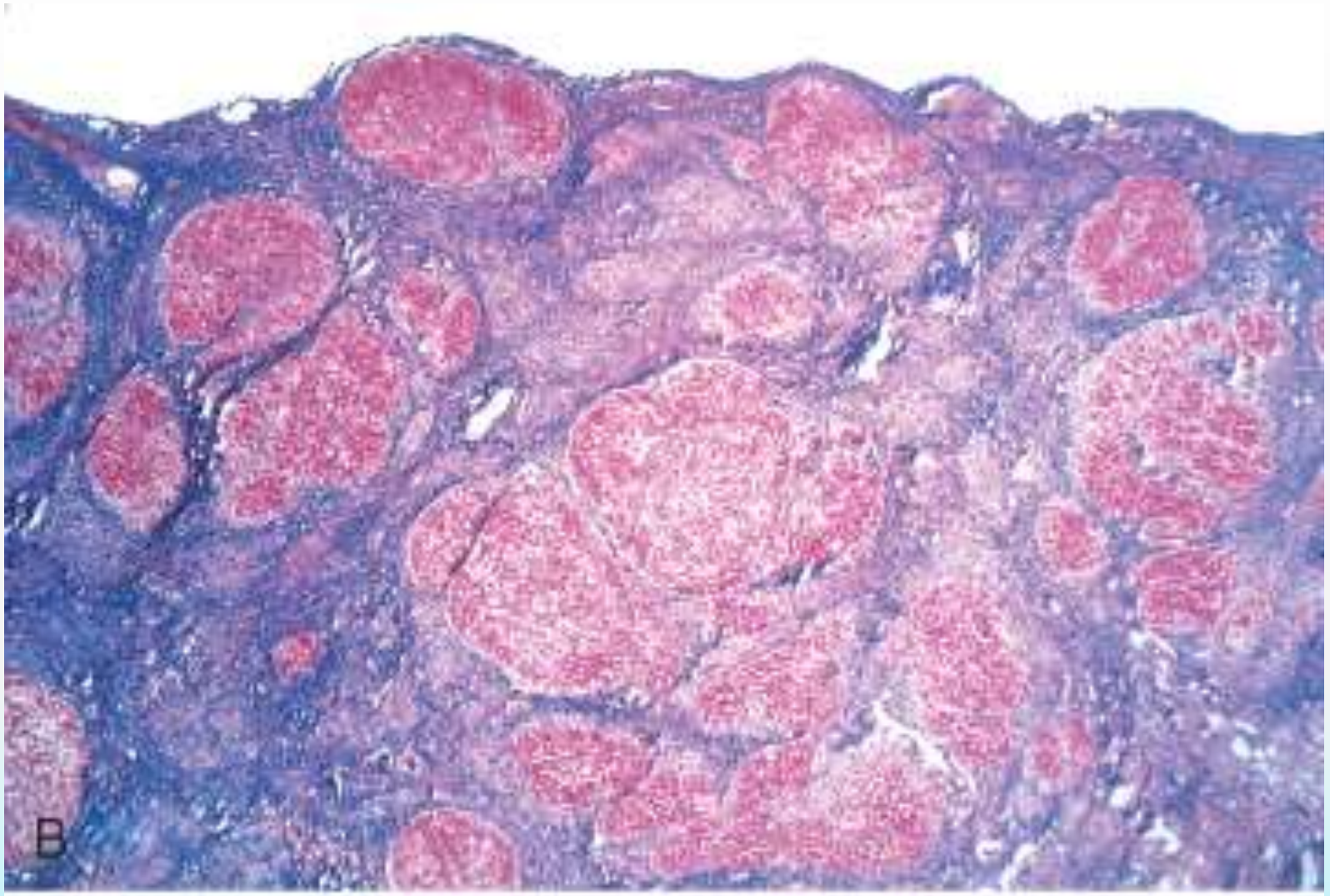
The final and irreversible form usually evolves slowly.





Micro nodular

Macro nodular



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).

METABOLIC LIVER DISEASES

NONALCOHOLIC FATTY LIVER DISEASE(NAFLD)

clinical features:

Pt. with steatosis are asymptomatic.

Patients with NASH may be asymptomatic, but some have fatigue, malaise, right upper discomfort or even symptoms of chronic liver disease.

METABOLIC LIVER DISEASES
NONALCOHOLIC FATTY LIVER DISEASE(NAFLD)

Prognosis:

The frequancy of progression from steatosis to NASH , and from NASH to cirrhosis, seems to be low.

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,

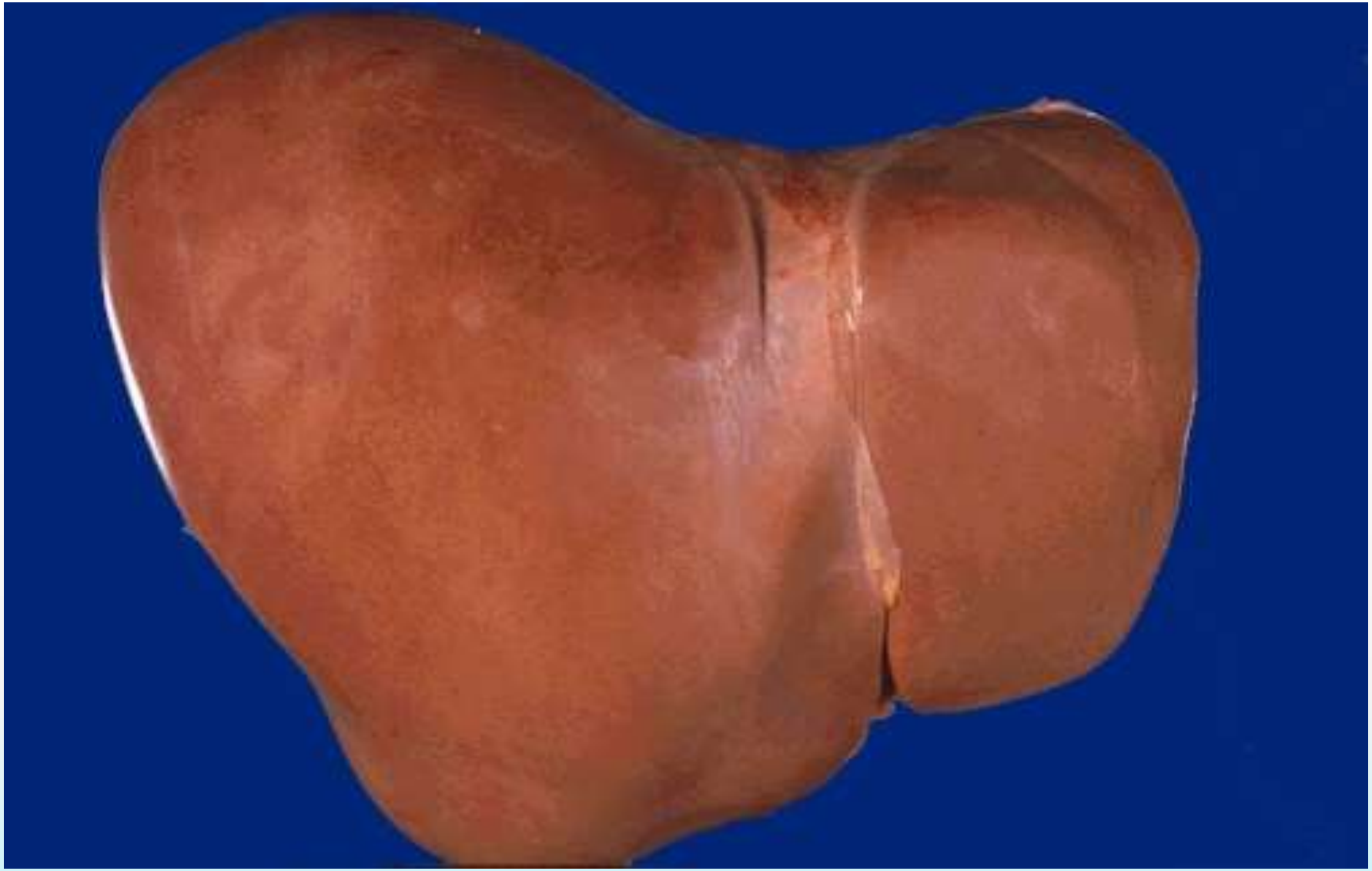
It is mainly characterized by three main histological modifications which are:

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

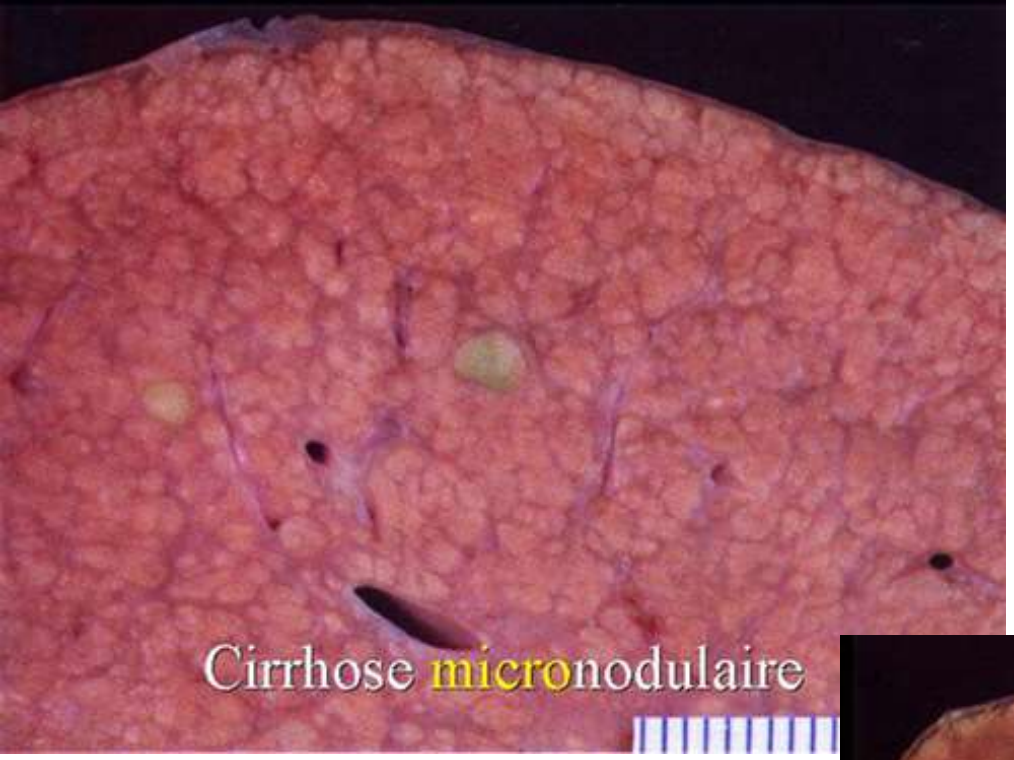
- **Classification of Cirrhosis. :**
- Many classifications of liver cirrhosis
- **A. Morphological classification**: Macronodular, Micronodular, Mixed
- **B. Histologic classification**: Portal, Post-necrotic, Post Hepatitic, Biliary, Congestive.
-

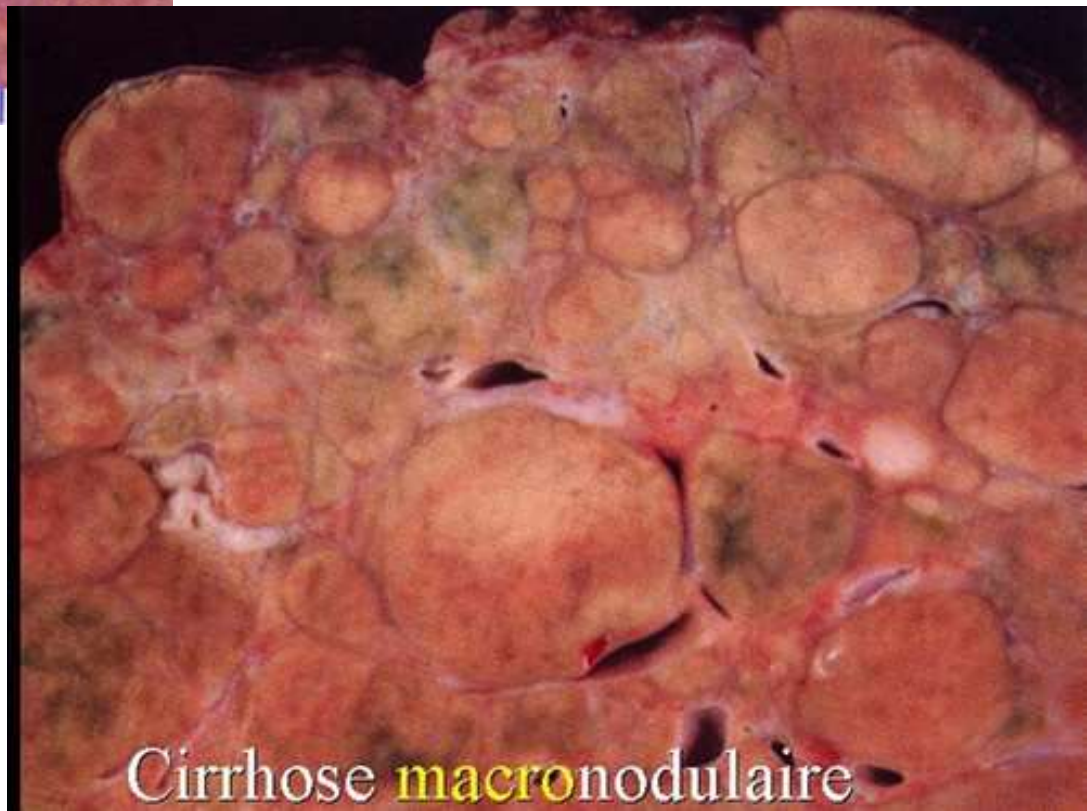
C. Etiological classification (most commonly used)

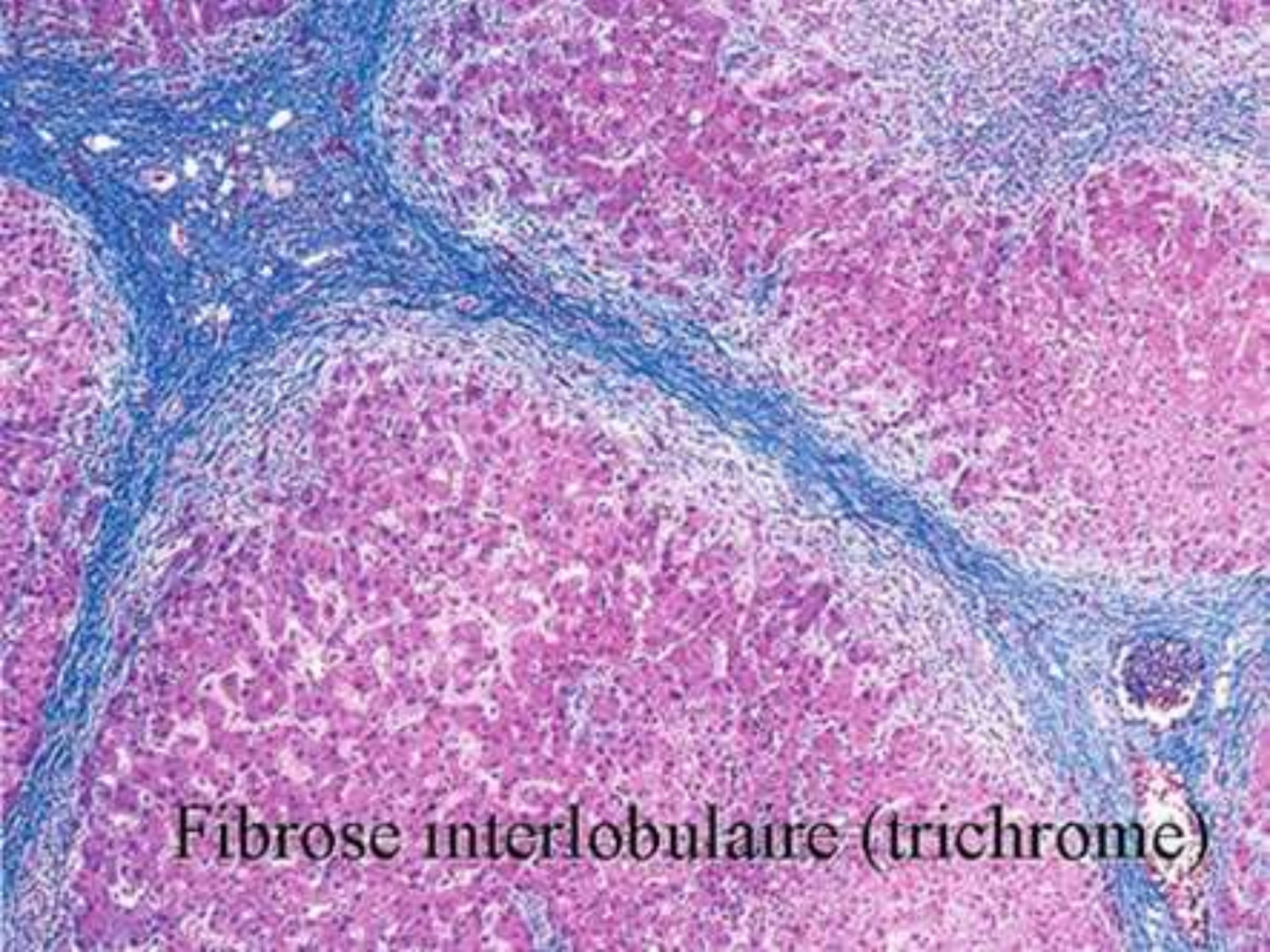
- Cirrhosis is classified according to etiology.
- 1. Alcoholic liver diseases (60% to 70%)
- 2. Viral hepatitis 10%
- 3. Biliary diseases 5% to 10%
- 4. Hereditary hemochromatosis 5%
- 5. Wilson disease rare.
- 6. Alph1- antitrypsin deficiency rare
- 7. Cryptogenic cirrhosis (idiopathic) 10% to 15%.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



Normal liver


Cirrhose micronodulaire

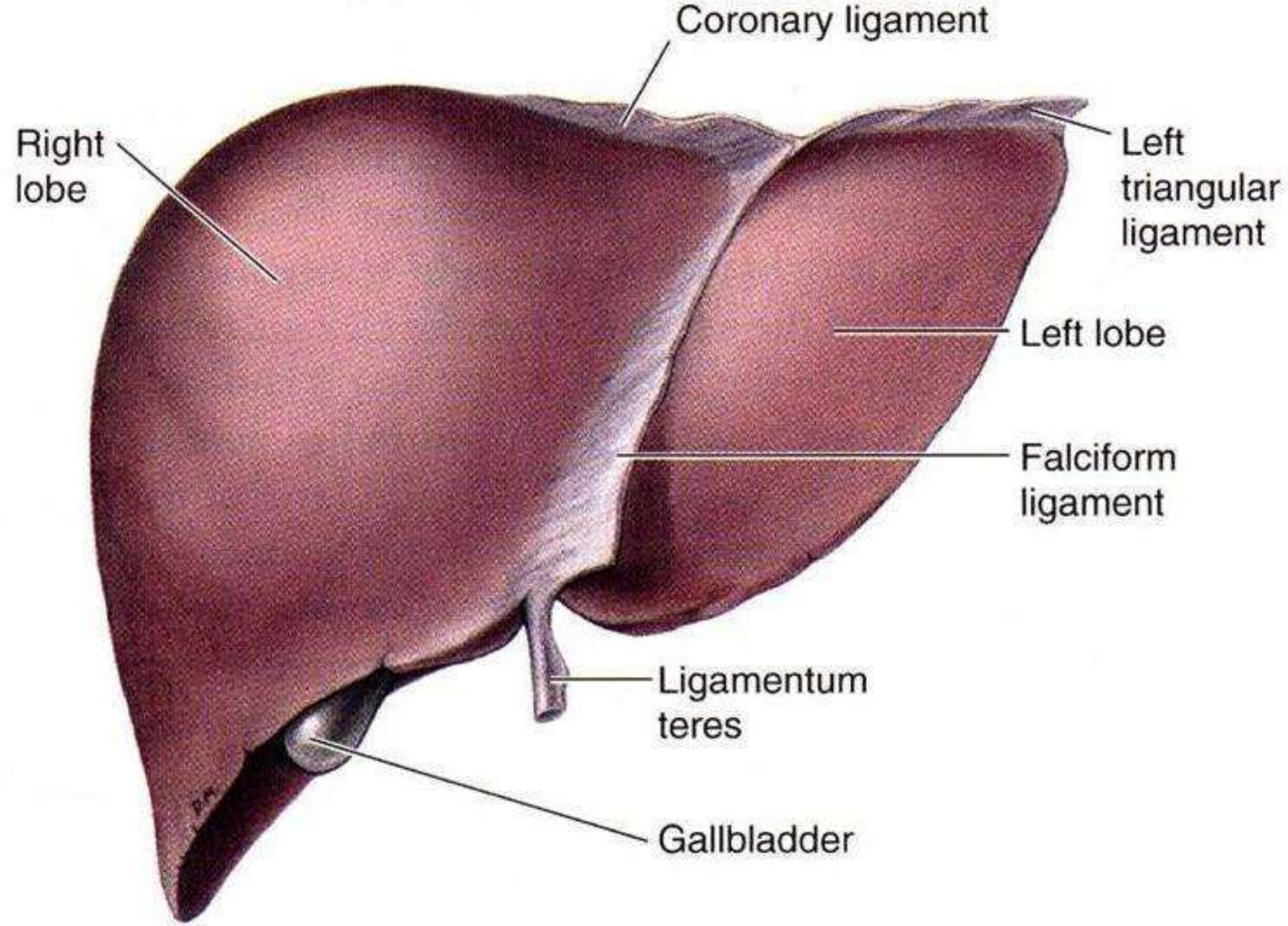

Cirrhose macronodulaire



Fibrose interlobulaire (trichrome)

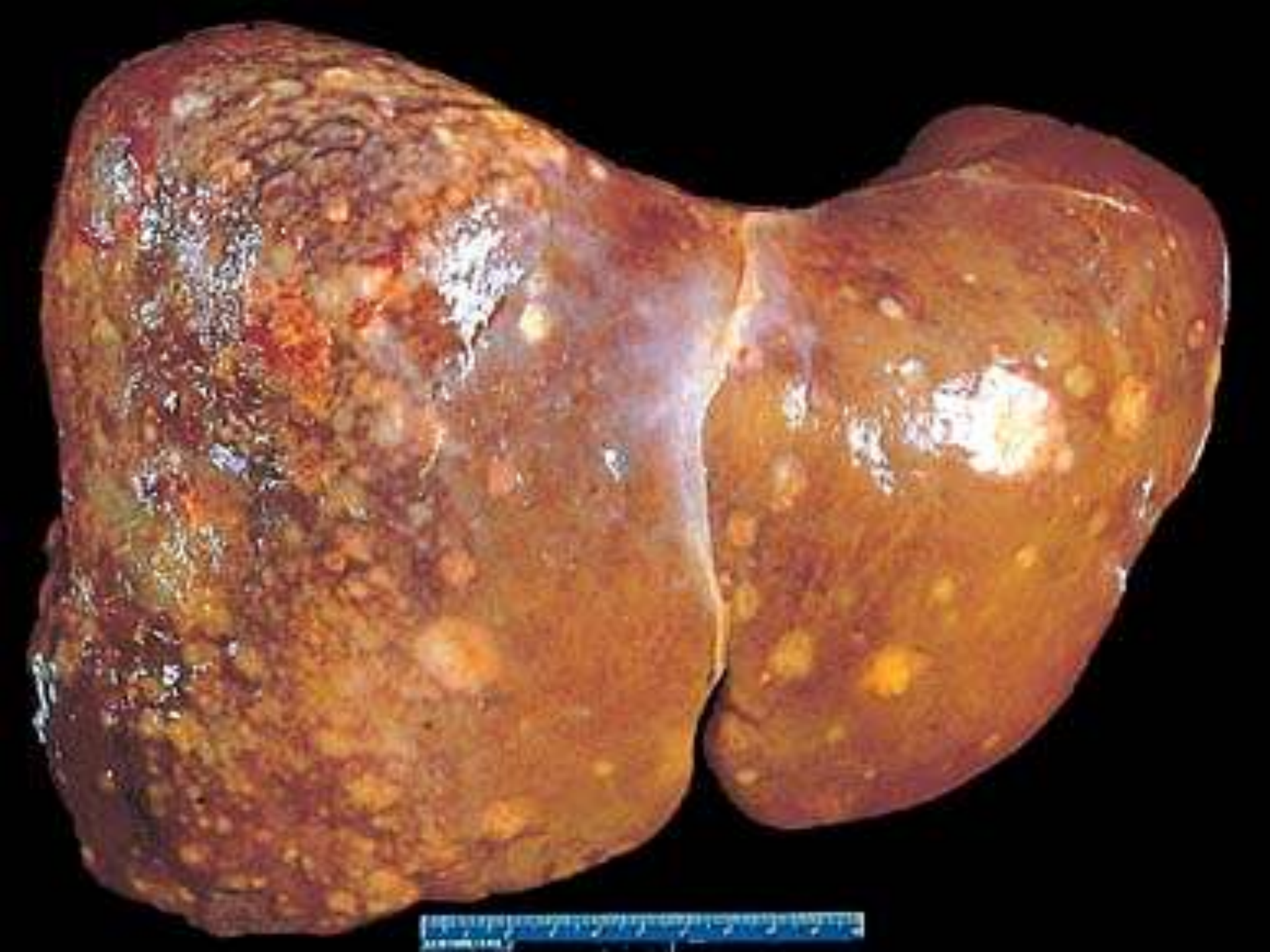
ALL CIRRHOSIS IS:

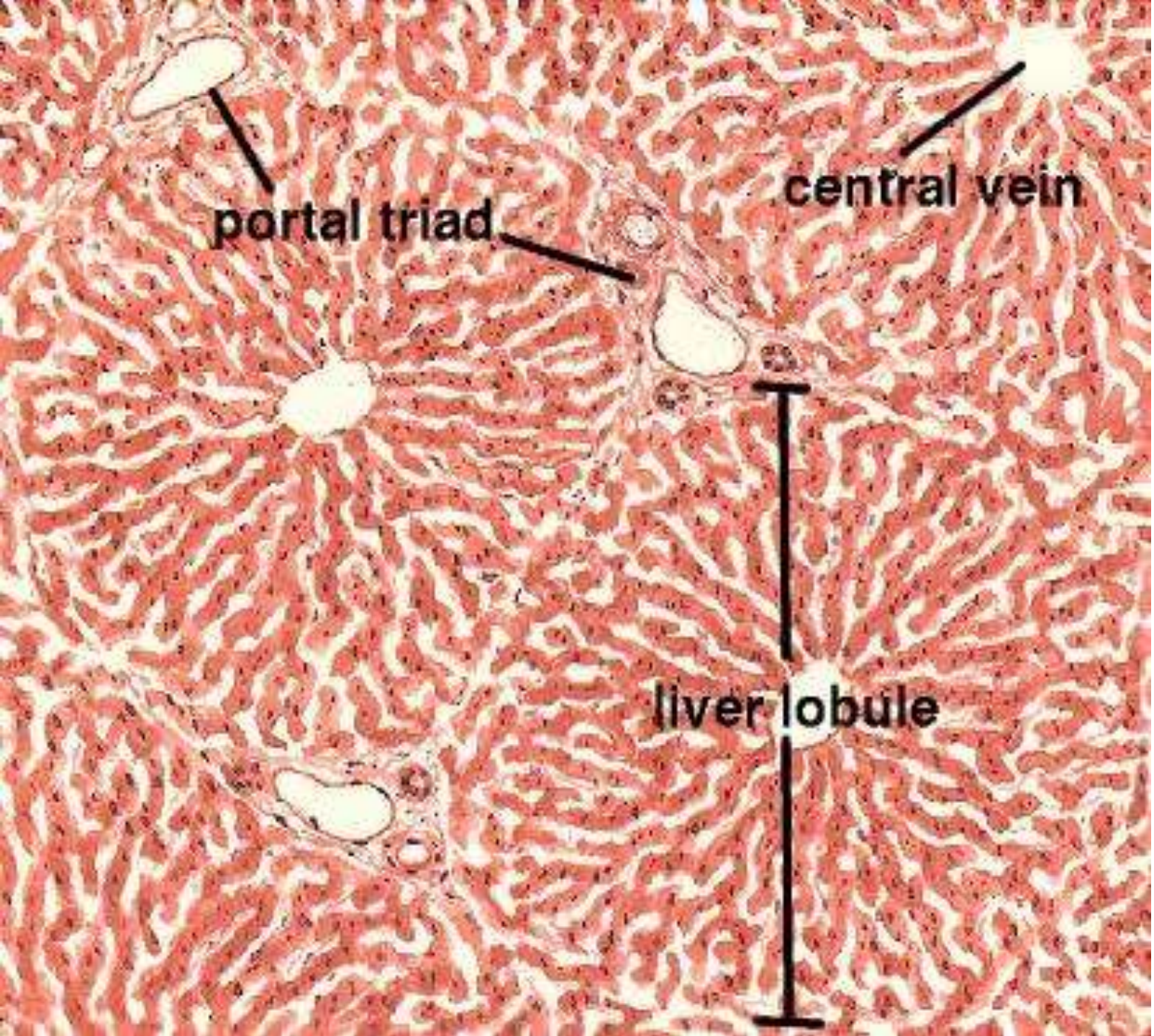
- **IRREVERSIBLE**
- The end stage of ALL chronic liver disease, often many years,
- Associated with a HUGE degree of nodular regeneration, and therefore represents a significant “risk” for primary liver neoplasm, i.e., Hepatocellular Carcinoma



BLIND MAN's LIVER

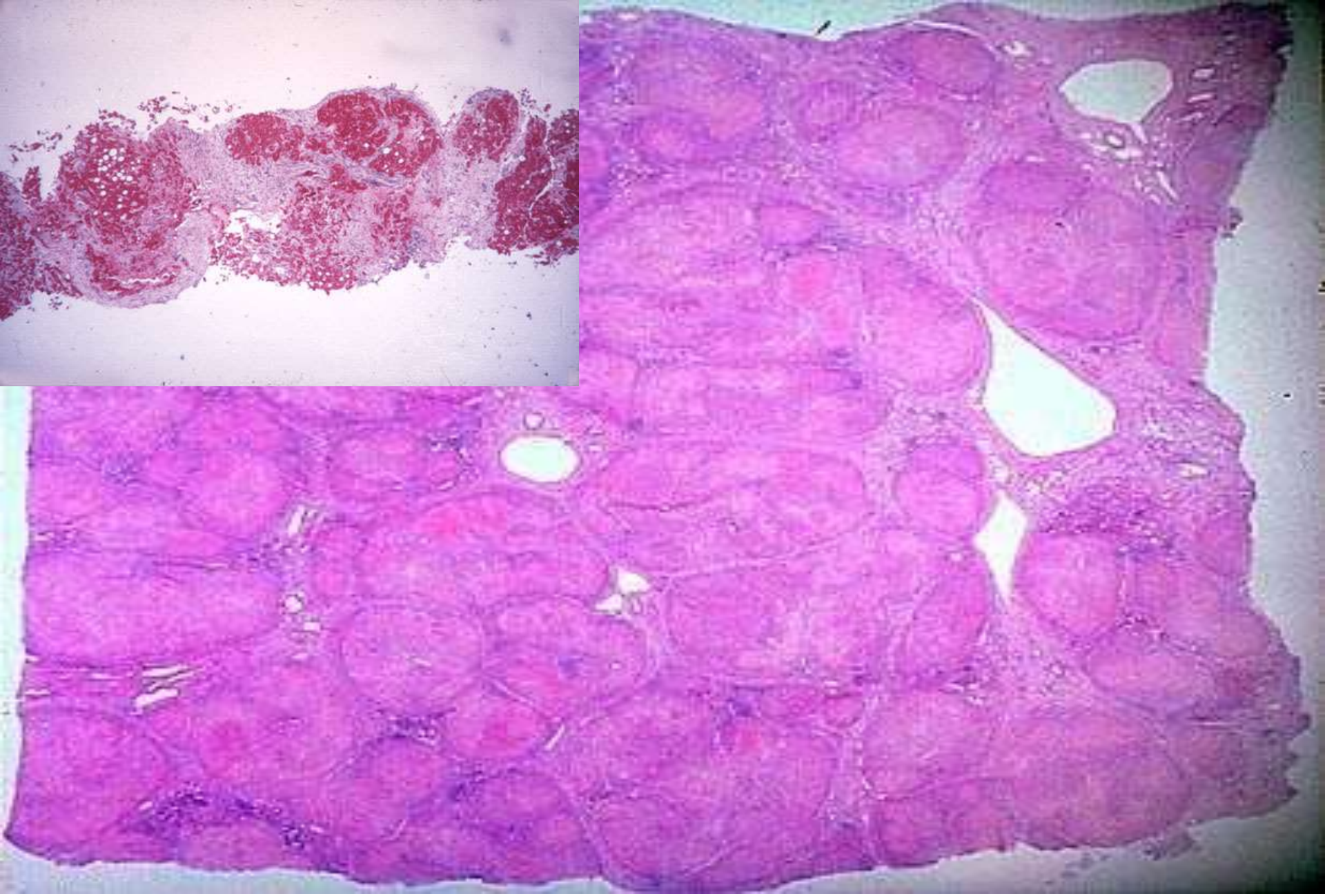
Blind Man’s Diagnosis



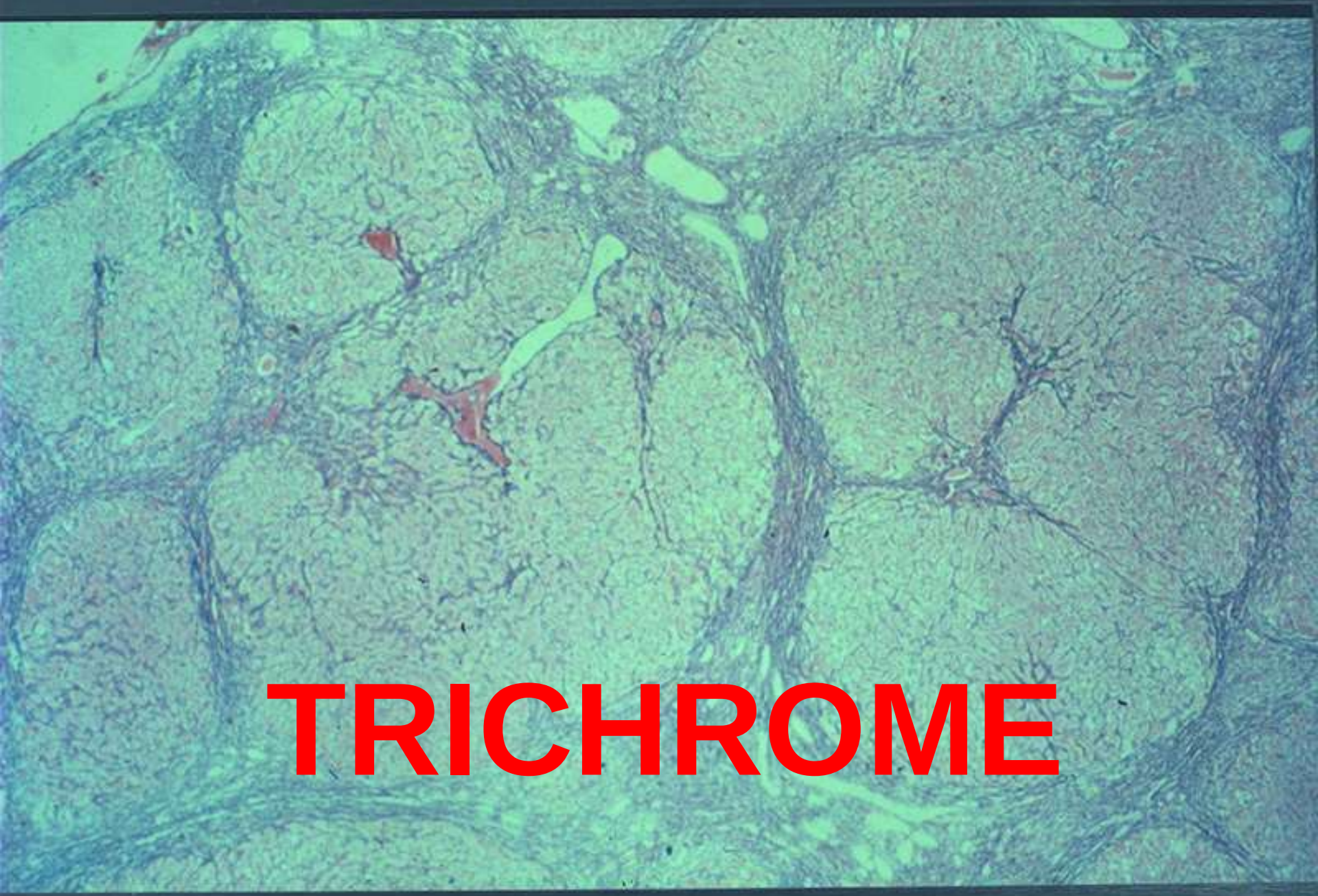


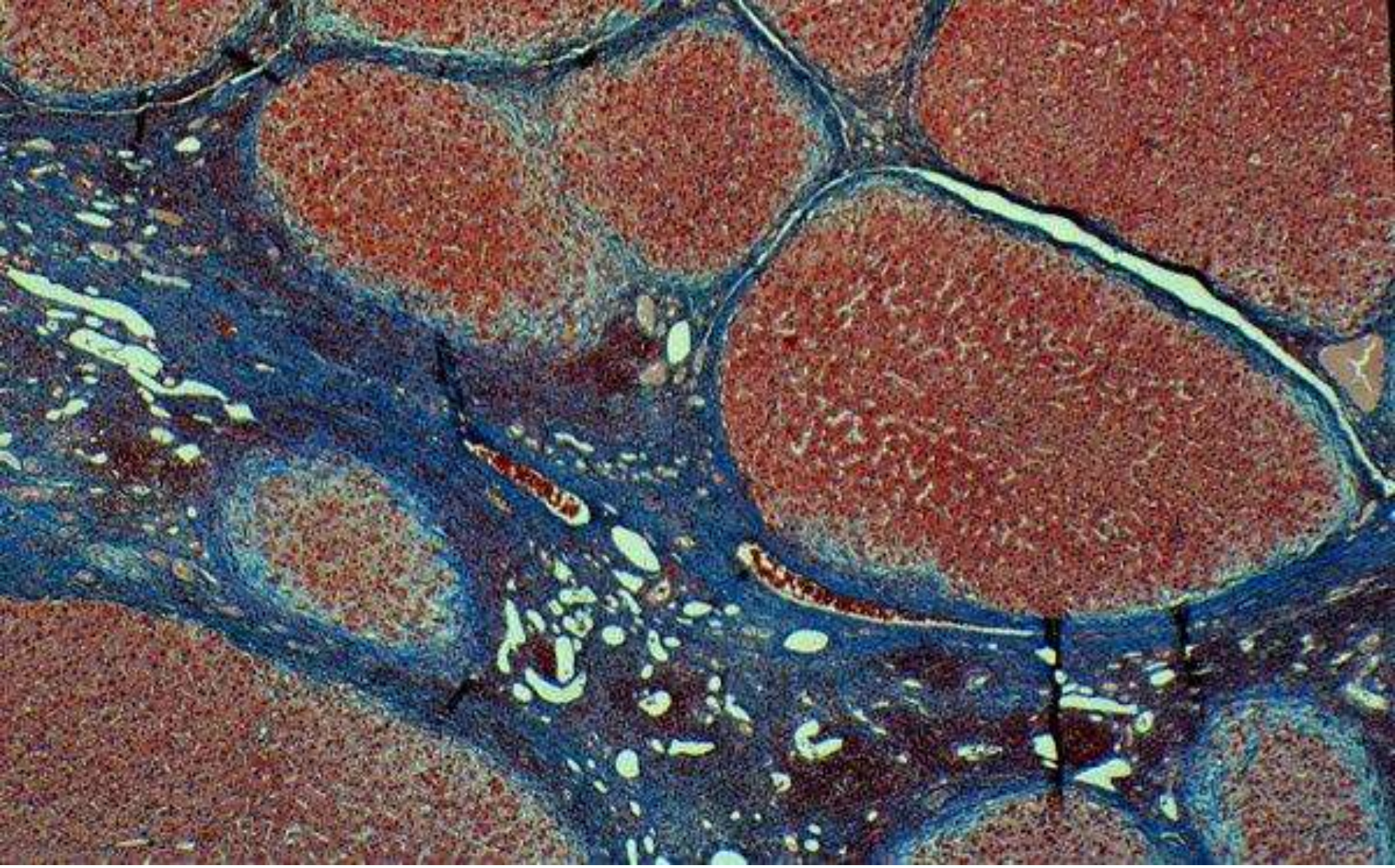
NO

FIBROUS TISSUE BETWEEN PORTAL AREAS

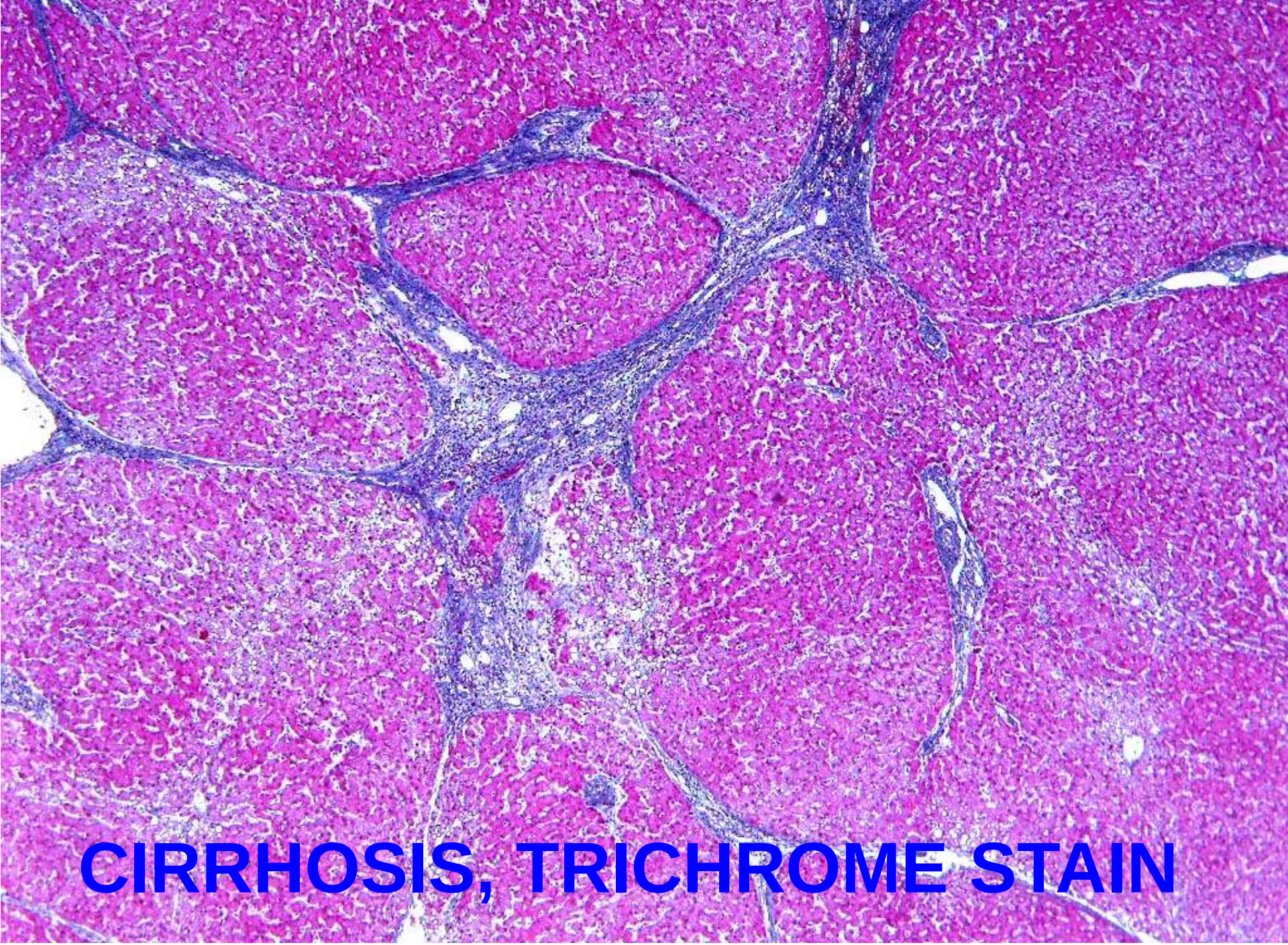


IRREGULAR NODULES SEPARATED BY PORTAL-to-PORTAL FIBROUS BANDS


TRICHROME



CIRRHOSIS, TRICHROME STAIN


CIRRHOSIS, TRICHROME STAIN

Pathogenesis of cirrhosis

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

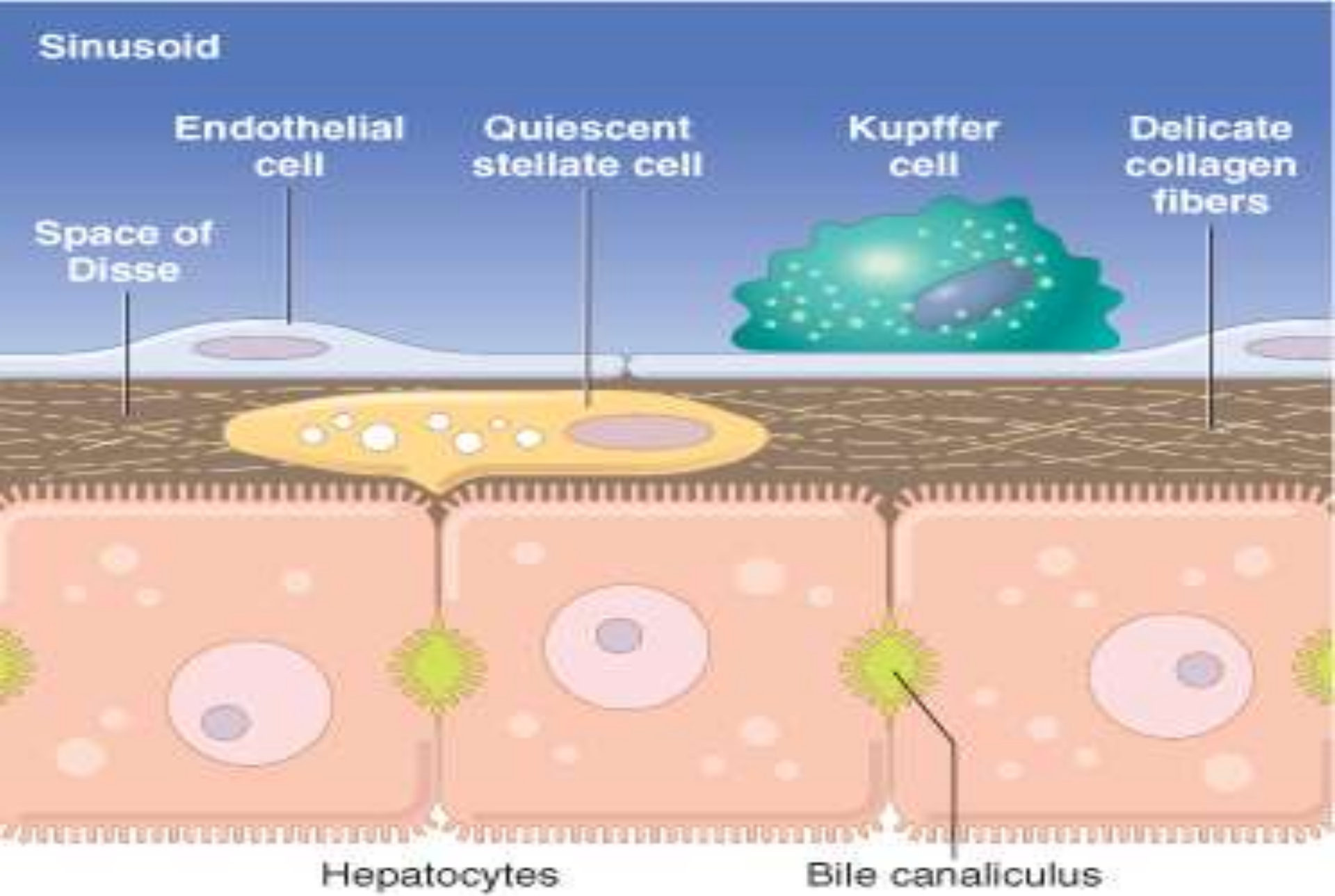
1. **Hepatocellular death.**
2. **Regeneration (normal tissue response).**
3. **Progressive fibrosis. Due to excessive collagen deposition.**

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

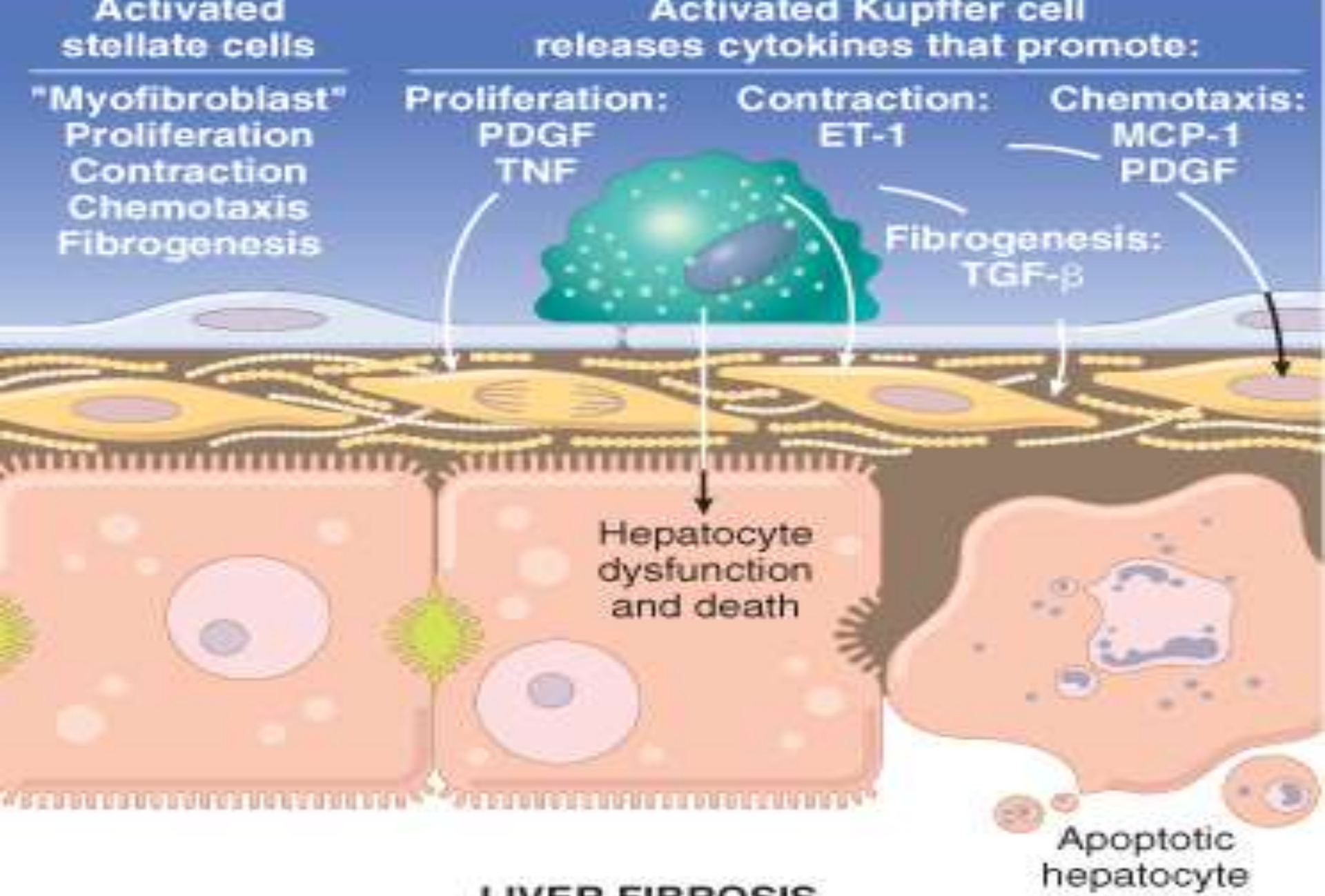
In cirrhosis, types of collagen are I & III which are deposited in the all parts of the lobule & sinusoidal.

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.
-



NORMAL LIVER



LIVER FIBROSIS

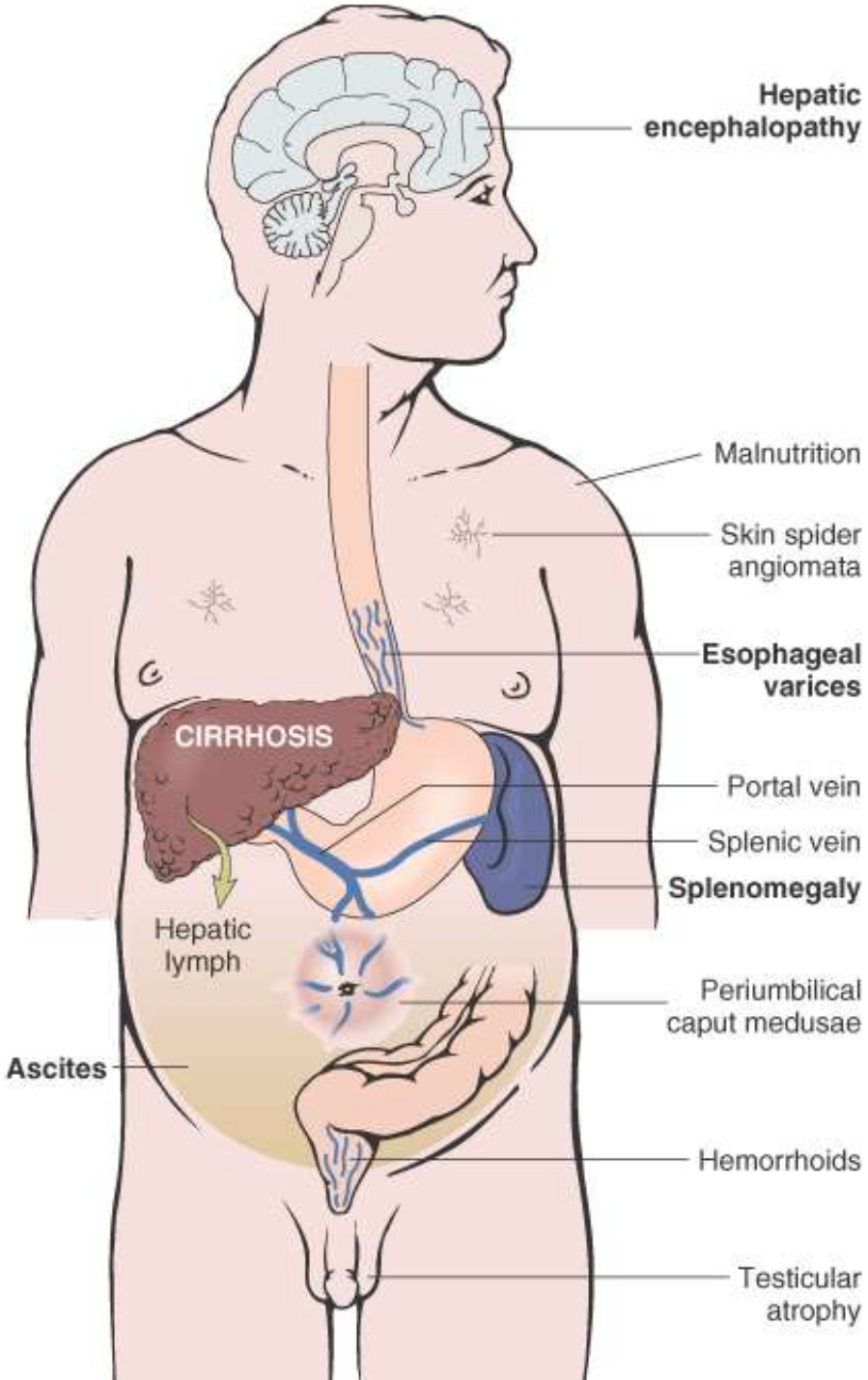
❖Clinical features of cirrhosis:

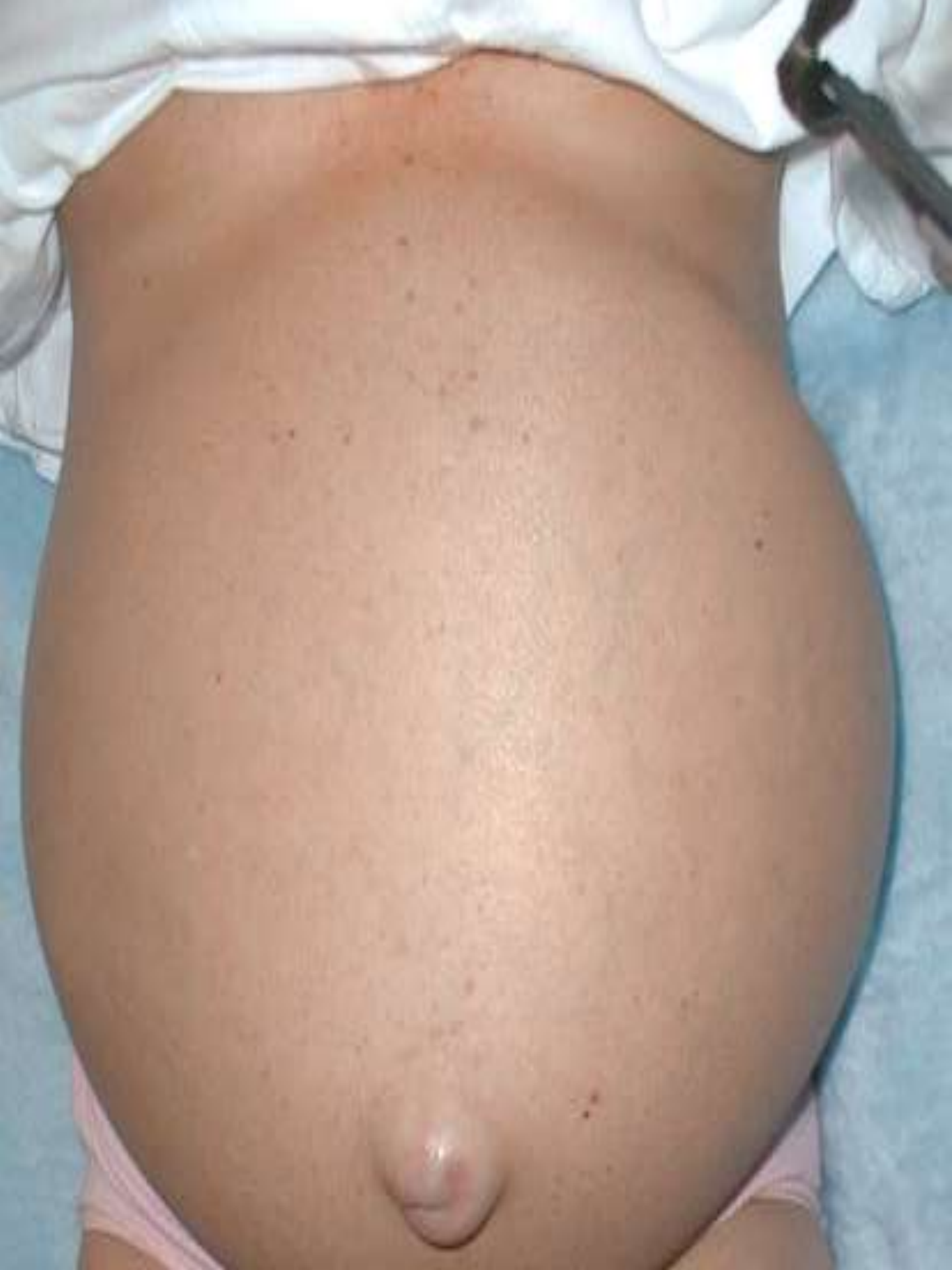
- All forms of cirrhosis may be silent, When symptomatic, they lead to non specific manifestations:

- anorexia, weight loss, weakness, and frank debilitation.

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?

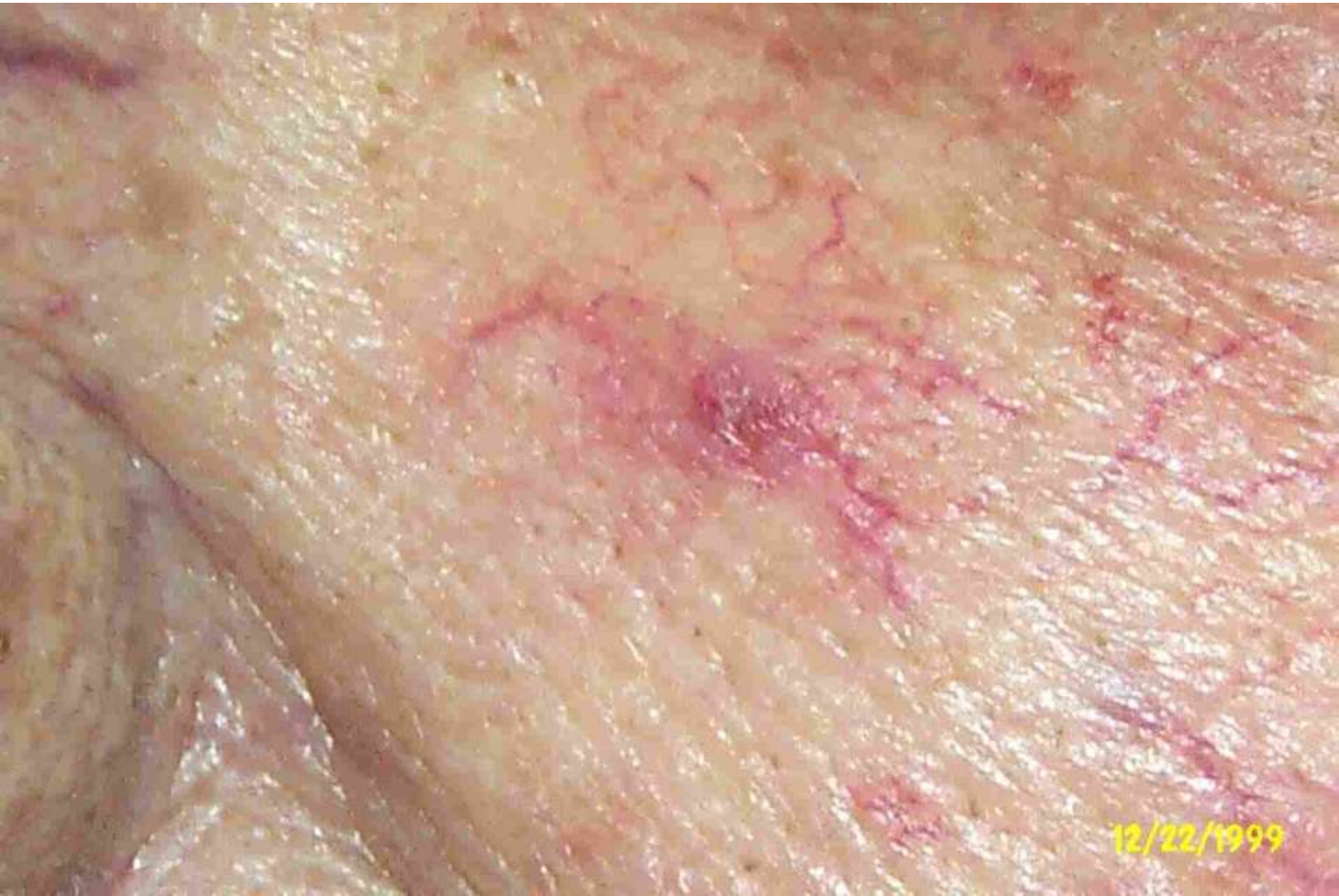

Hepatic encephalopathy
Malnutrition
Skin spider angiomata
Esophageal varices
CIRRHOSIS
Portal vein
Splenic vein
Splenomegaly
Hepatic lymph
Periumbilical caput medusae
Ascites
Hemorrhoids
Testicular atrophy



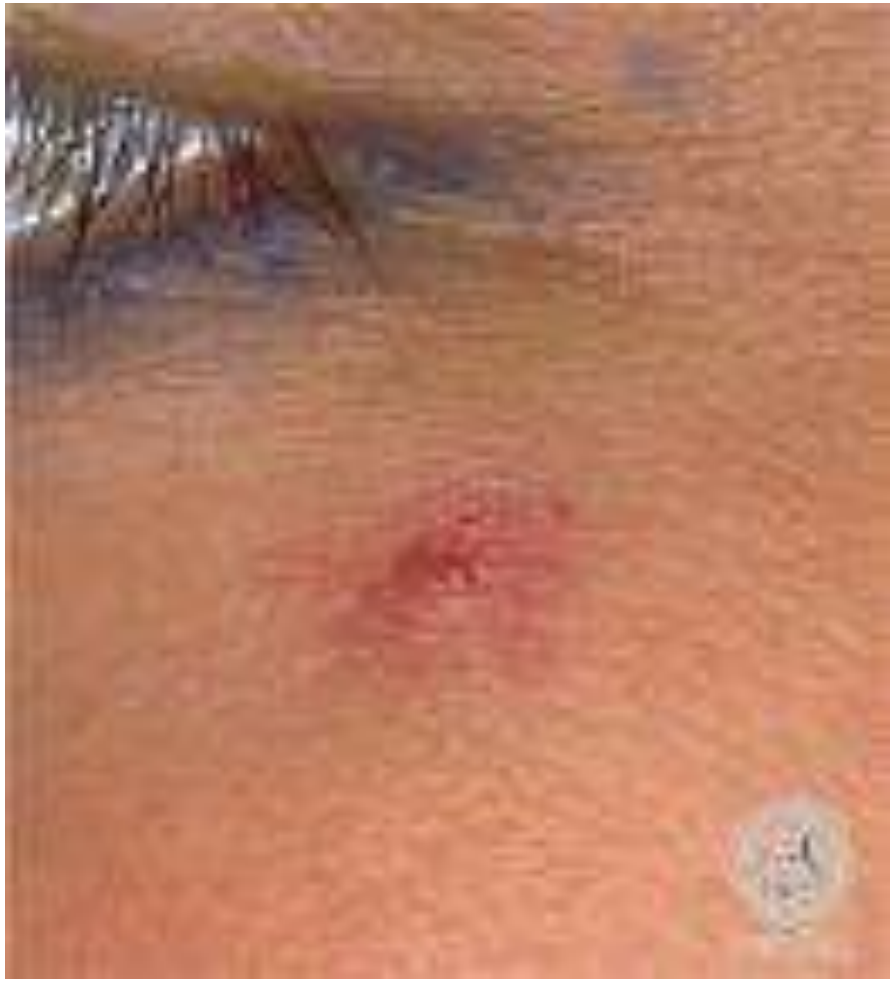
Jaundice and cholestasis

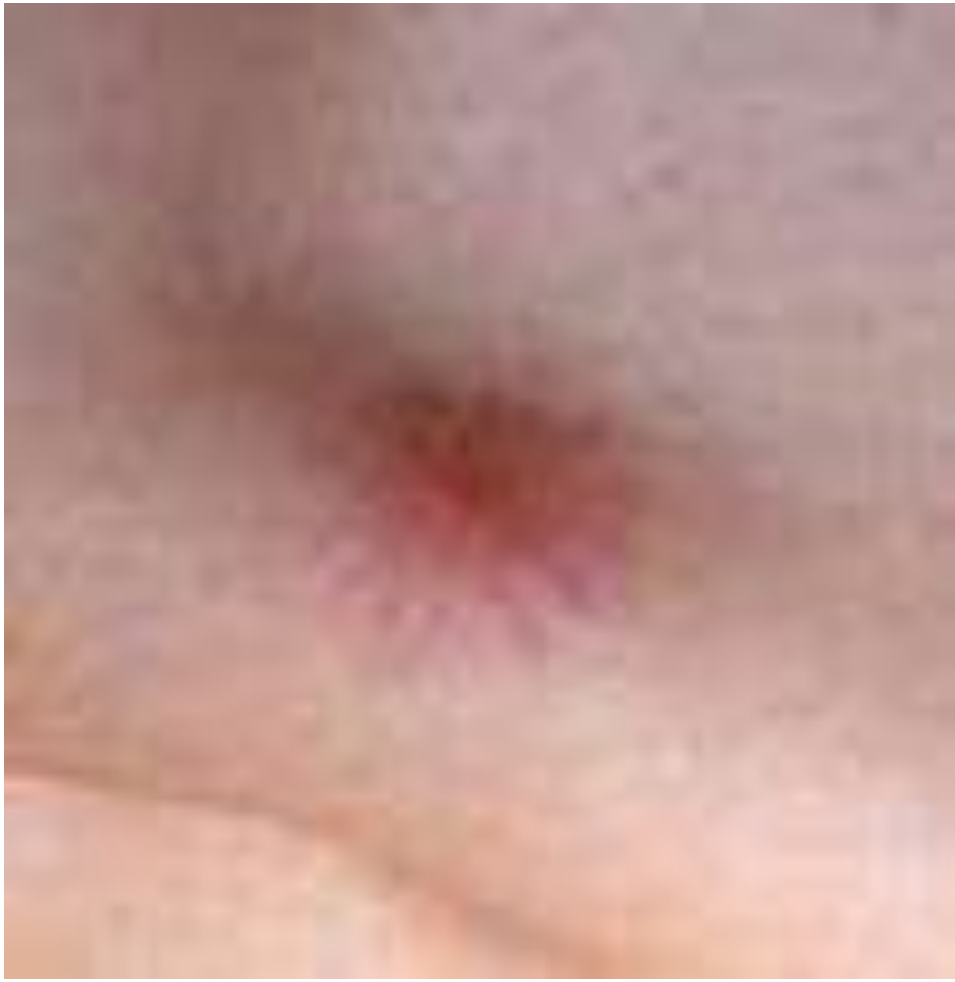
Palmer erythema

“SPIDER” ANGIOMA, CIRRHOSIS

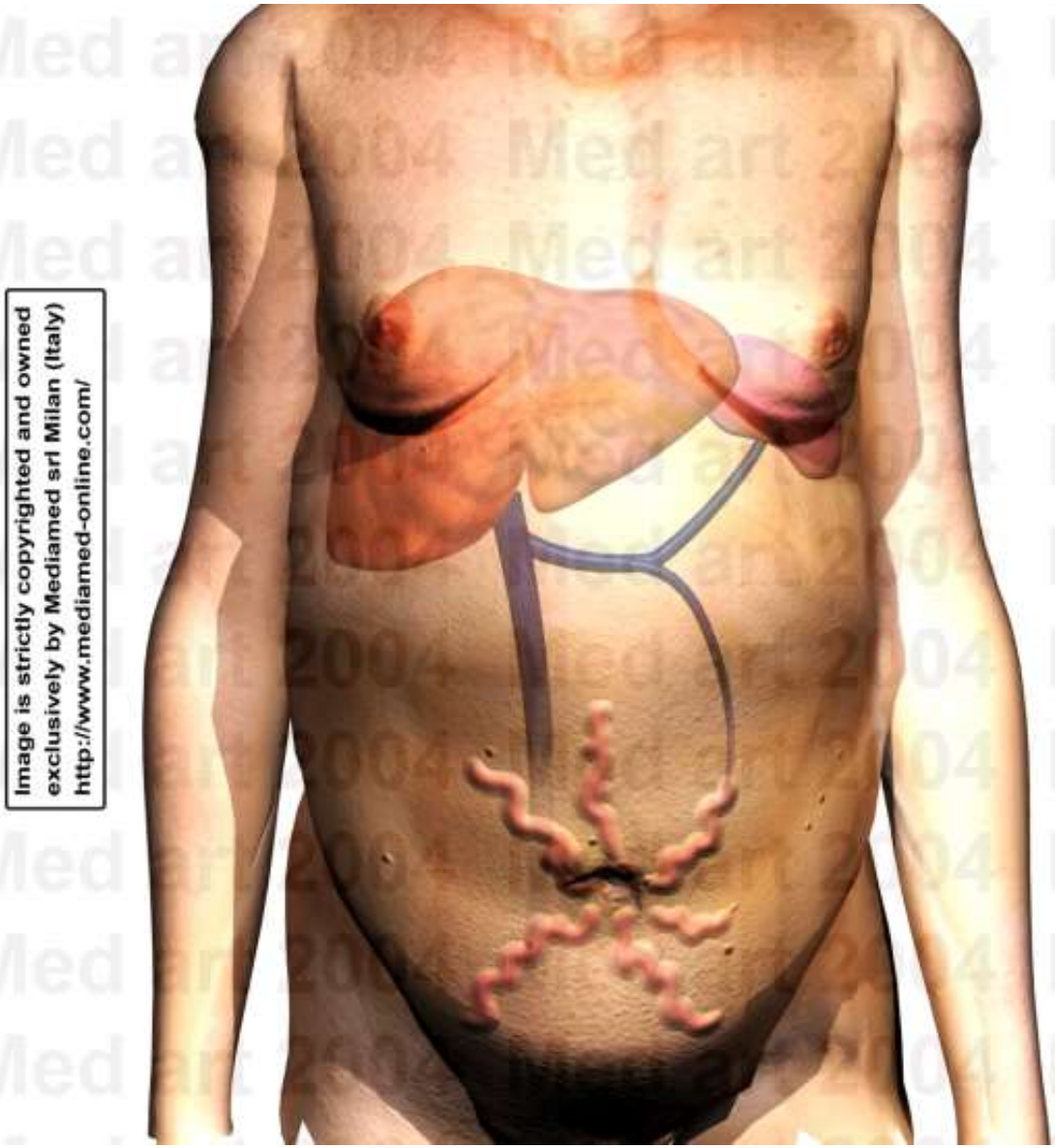


Spider angioma





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.**

Hepatic failure

- it is the end point of progressive damage to the liver, either by insidious destruction of hepatocytes or by repetitive discrete waves of parenchyma damage.
- Whatever the sequence, 80%to 90% of hepatic function capacity must be eroded before hepatic failure ensues.
- Due to sudden , progressive & massive hepatic destruction .
- 70-90% mortality rate
- Liver transplantation is the only hope for survival

Precipitating factors

- (1) Systemic infections.
- (2) Electrolytes disturbances.
- (3) Stress (major surgery, cardiac failure).
  (4)GIT bleeding.

Morphological changes of liver failure

(3 categories):

(I) Massive liver necrosis.

due to sudden and massive hepatic destruction .

It denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks.

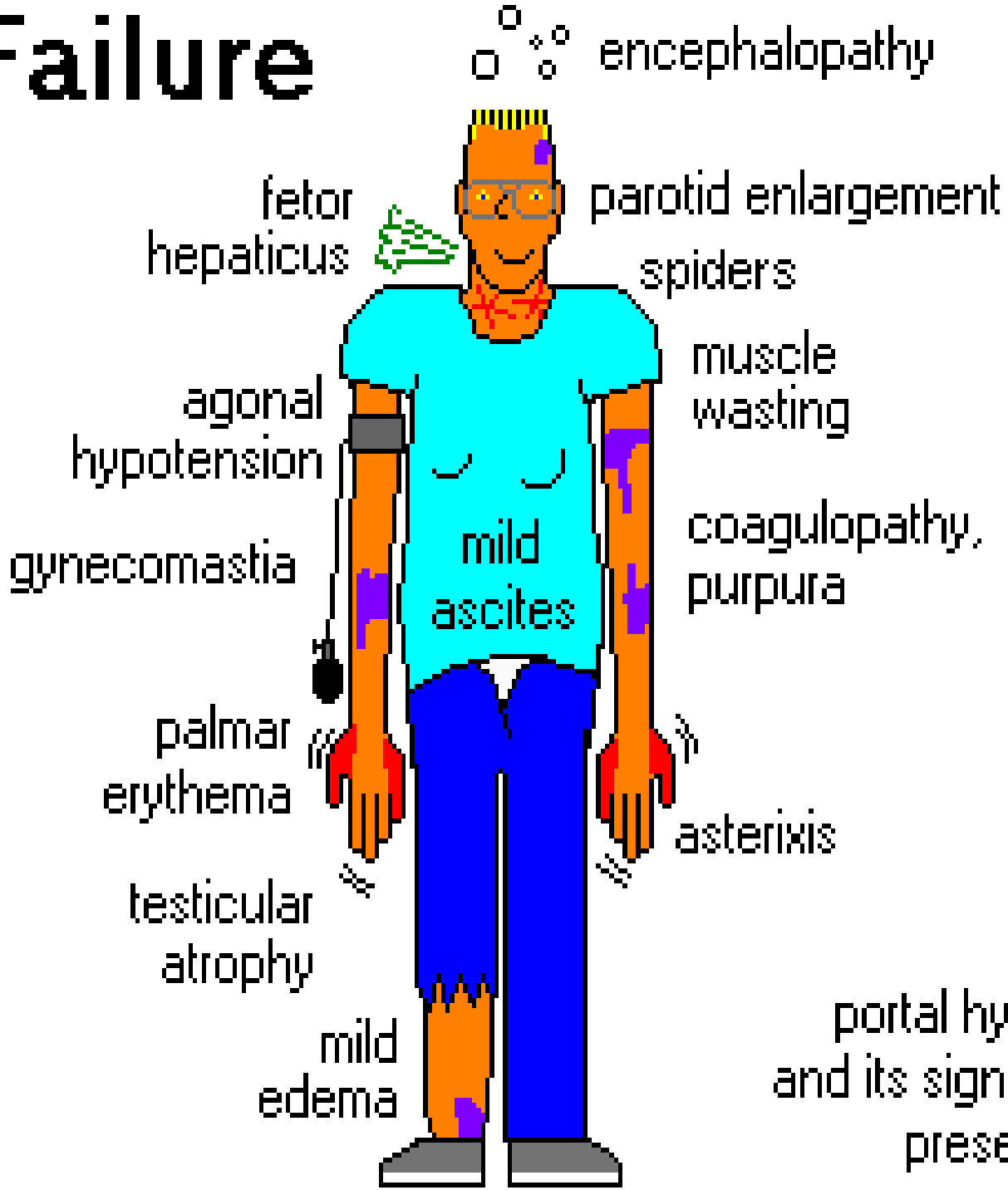
A course extending up to 3 months is called subfulminant failure.

Causes.

- 1. Fulminant Viral hepatitis (50%to 65%) by hepatotropic or non hepatotropic viruses.
- 2. Drugs & chemicals (25% to 30%) like acetaminophen, halothane anti TB drugs,CCL4
- 3. Others (obstruction of hepatic vein, massive malignant infiltration & reactivation of HBV or super infection with HDV & autoimmune hepatitis).

- Gross. Shrinkage of liver to as little as 500- 700 g.
- Mic. Main microscopic feature of massive liver necrosis is liver destruction which either involves the entire liver of only random areas are affected.
-
- **(II) Chronic liver disease**. This is the most common cause of hepatic failure.
- **(III) Hepatic dysfunction without overt cirrhosis**. Like in acute fatty liver of pregnancy, tetracycline toxicity and Reye syndrome.

Liver Failure



elevated urinary urobilinogen (why?)
elevated serum indirect bilirubin (why?)
most liver diseases also elevate direct bilirubin (why?)

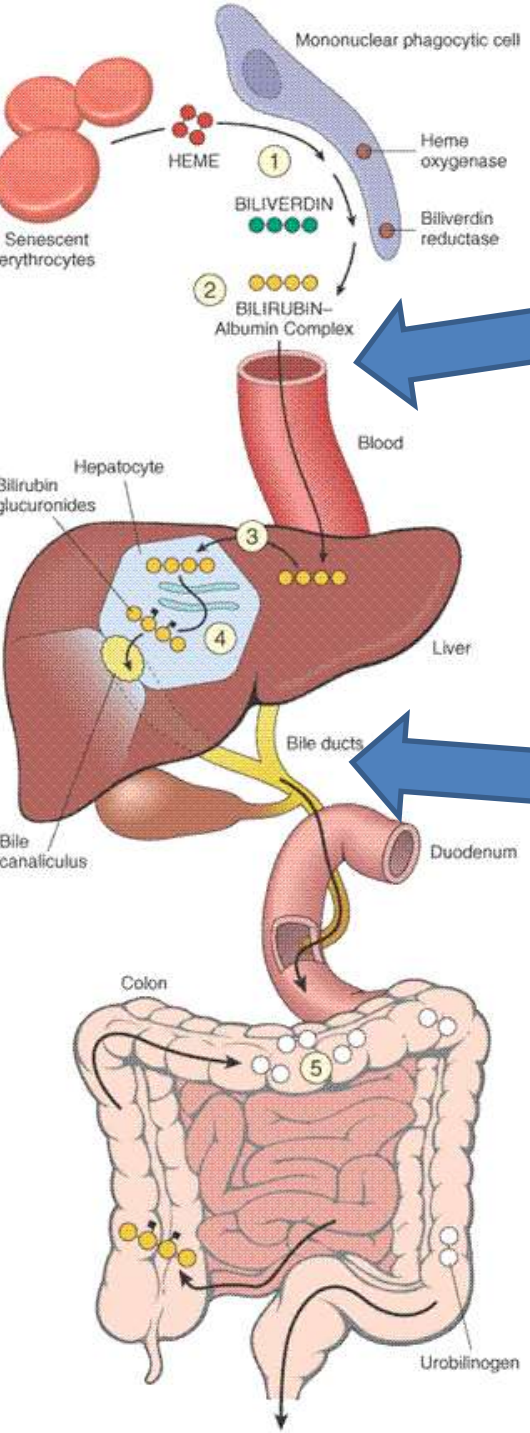
hepatorenal syndrome?
hepatopulmonary syndrome?

Of course, portal hypertension and its signs are often present as well.

Characteristic signs of severe hepatic dysfunction (fulminant hepatic failure)

- Jaundice and cholestasis
- Palmer erythema
- Spider angioma
- Gynecomastia
- Caput medusae-abdominal skin
- Weigh loss
- Ascite
- Hypogonadism

JAUNDICE



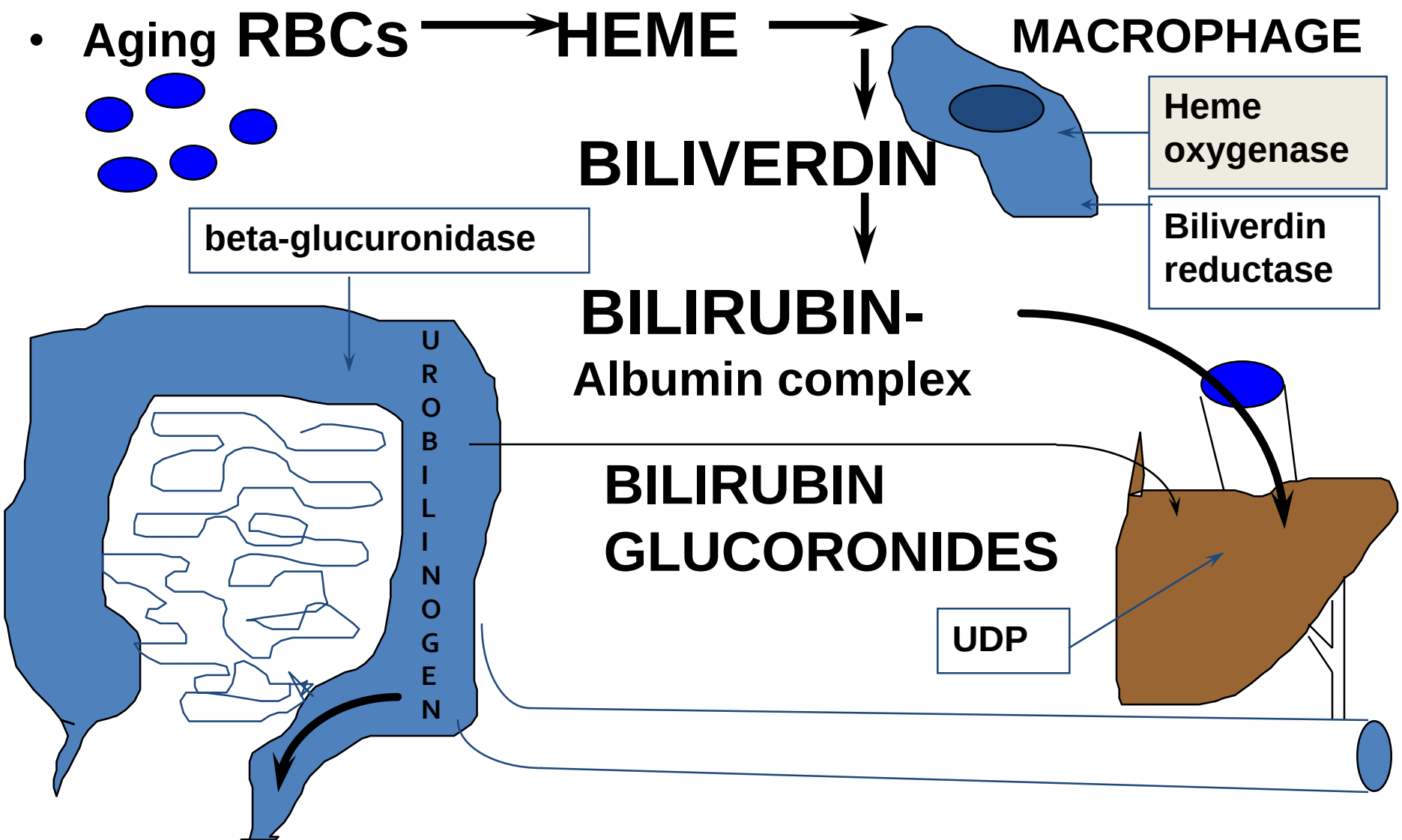
Bilirubin: (0.3-1.2 mg/dl)

UN-conjugated (IN-direct)

Conjugated (direct)

PHYSIOLOGY OF THE LIVER

BILIRUBIN METABOLISM



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)

TYPES OF
JAUNDICE

- **UNCONJUGATED BILIRUBIN**
  - Water-insoluble
  - Tightly complexed to serum albumin
  - Cannot be excreted in urine
  - Free form is toxic
  - Lab test: Total bilirubin minus direct bilirubin
- **CONJUGATED BILIRUBIN**
  - Water-soluble
  - Loosely bound to serum albumin
  - Excess amounts are excreted in urine
  - Nontoxic
  - Lab test: measured by direct bilirubin

LAB EVALUATION OF LIVER DISEASE

LIVER FUNCTION TESTS

- **Tests of hepatocyte integrity**
  - **ASL (SGOT)***
  - **ALT (SGPT)***
  - **LDH**
- **Tests of biliary excretory function**
  - **Serum Bilirubin***
  - **Alkaline phosphatase***
  - **Gamma-glutamyl transpeptidas**
- **Tests of hepatocyte function**
  - **Albumin***
  - **Prothrombine time***
  - **Ammonia**

-

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.

B. Other clinical features of hepatic failure

- 1. **Hyperammonemia**: due to impaired urea cycle in the liver
- 2. **Fetor hepaticus**. Characteristic body odor (musty, sweet & sour) due to formation of mercaptan by GIT bacteria.
- 3. **Multiple organs failure** (renal, respiratory failure).

- 4. **Bleeding tendency.** Due to loss of clotting factors synthesis by the liver.
- 5. **Hypo albuminemia**. Due to decrease synthesis of albumin by the liver.
- 6. **impaired metabolism of estrogen** by the liver: **Gynecomastia** and **hypogonadism in male**, **palmar erythema** (due to local vasodilatation). **Spider angioma of skin**(central pulsating dilated arteriole from which small vessels radiate)

Prognosis of hepatic failure

Is grave, a rapid downhill course is usual with death occur within weeks to a few months in 80% of cases.

Complications of hepatic failure.

- (**1) hepatoencephalopathy**.

Patient exhibit a spectrum of disturbance in consciousness ranging from behavioral abnormalities to marked confusion and stupor to deep coma and death.

- **2 factors appears to be important in the genesis of this disorder:**
- A-sever loss of hepatocellular function
- B-shunting of blood around the chronically diseased liver.
- The net result is exposure of the brain to an altered metabolic milieu.
- **In acute condition**: due to elevated ammonia level which impairs neuronal function and promote generalized brain edema
- **In chronic condition:** deranged neurotransmission arises as a result of a number of adverse alterations in CNS amino acid metabolism..

(2) hepatorenal syndrome.

- Renal failure in patients with severe liver diseases in spite of no intrinsic morphologic or functional causes for the renal failure.
- Kidney function improves if hepatic failure is reversed.
- The exact cause is unknown but possible explanation is: **splanchnic vasodilatation** and **systemic vasoconstriction** leading to sever **reduction of renal blood flow** particularly to the cortex. It is characterized by **decrease in urine output** and **increased blood urea nitrogen and creatinine level.**