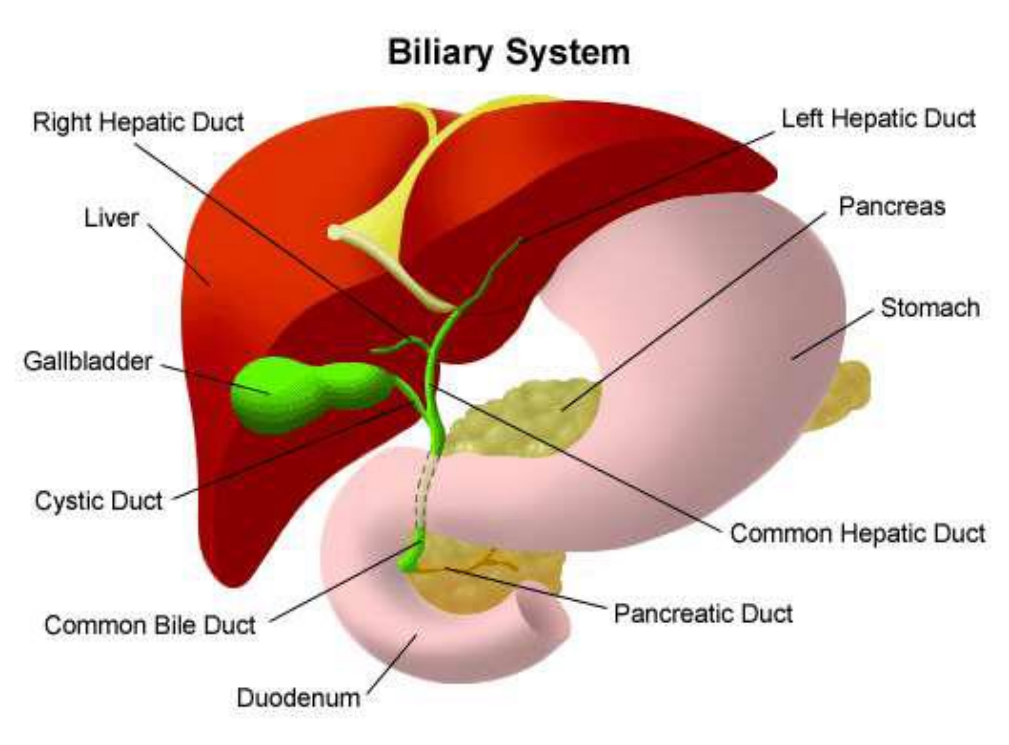
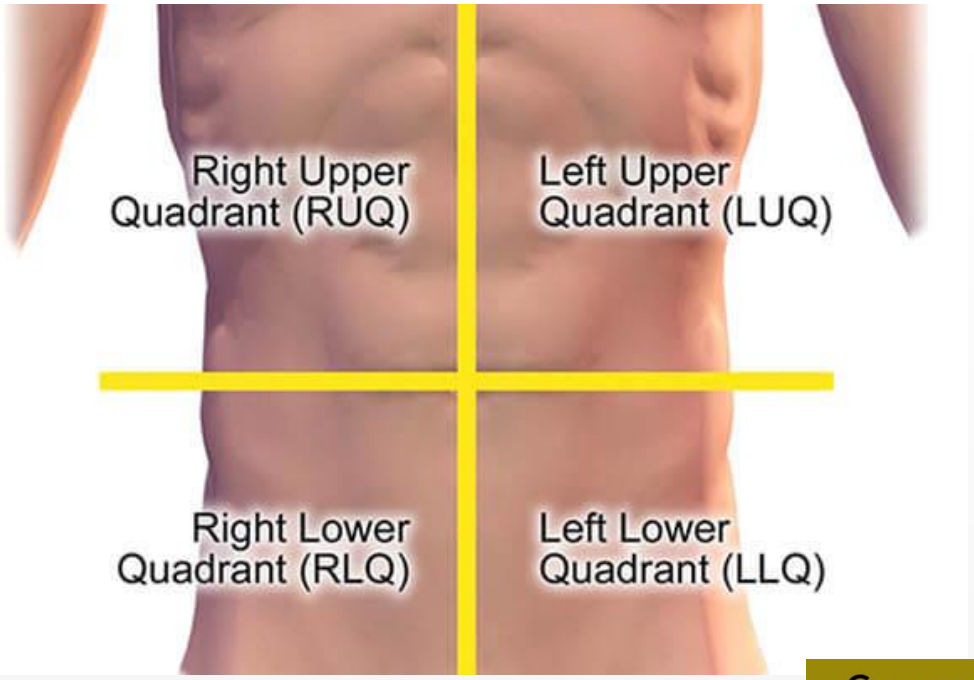
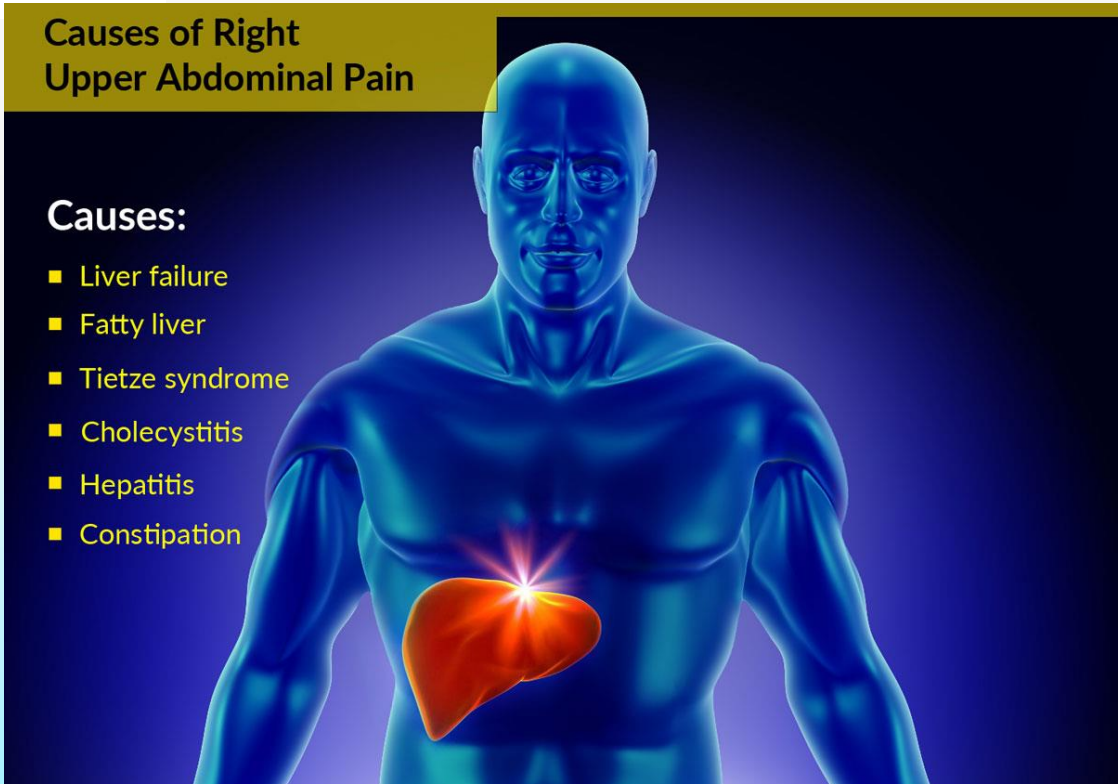
# Hepatobiliary system

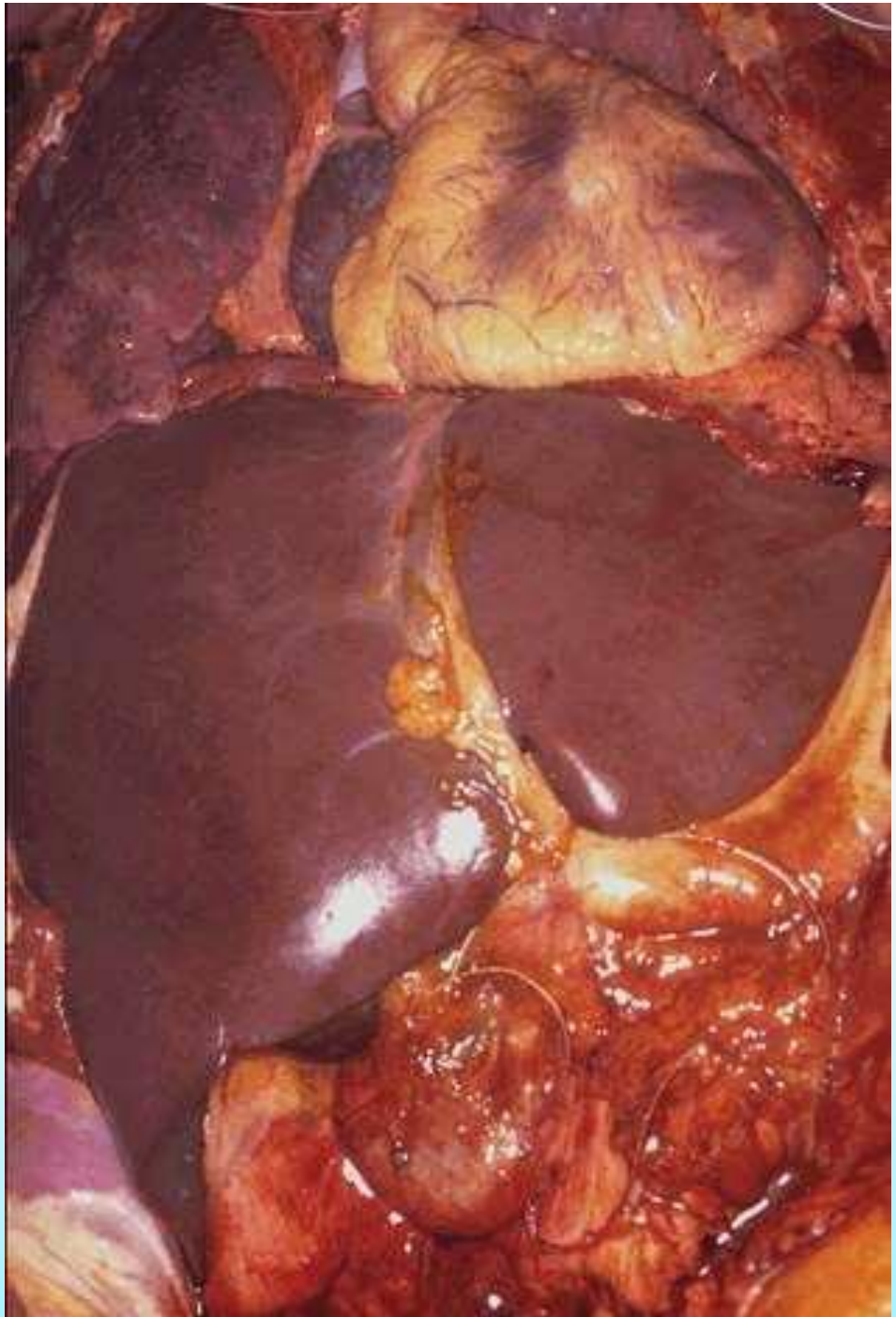
## LEC. 1

## Dr. Methaq Mueen




Right Upper Quadrant (RUQ)
Left Upper Quadrant (LUQ)
Right Lower Quadrant (RLQ)
Left Lower Quadrant (LLQ)


Causes of Right Upper Abdominal Pain
Causes:
Liver failure
Fatty liver
Tietze syndrome
Cholecystitis
Hepatitis
Constipation



# ANATOMY

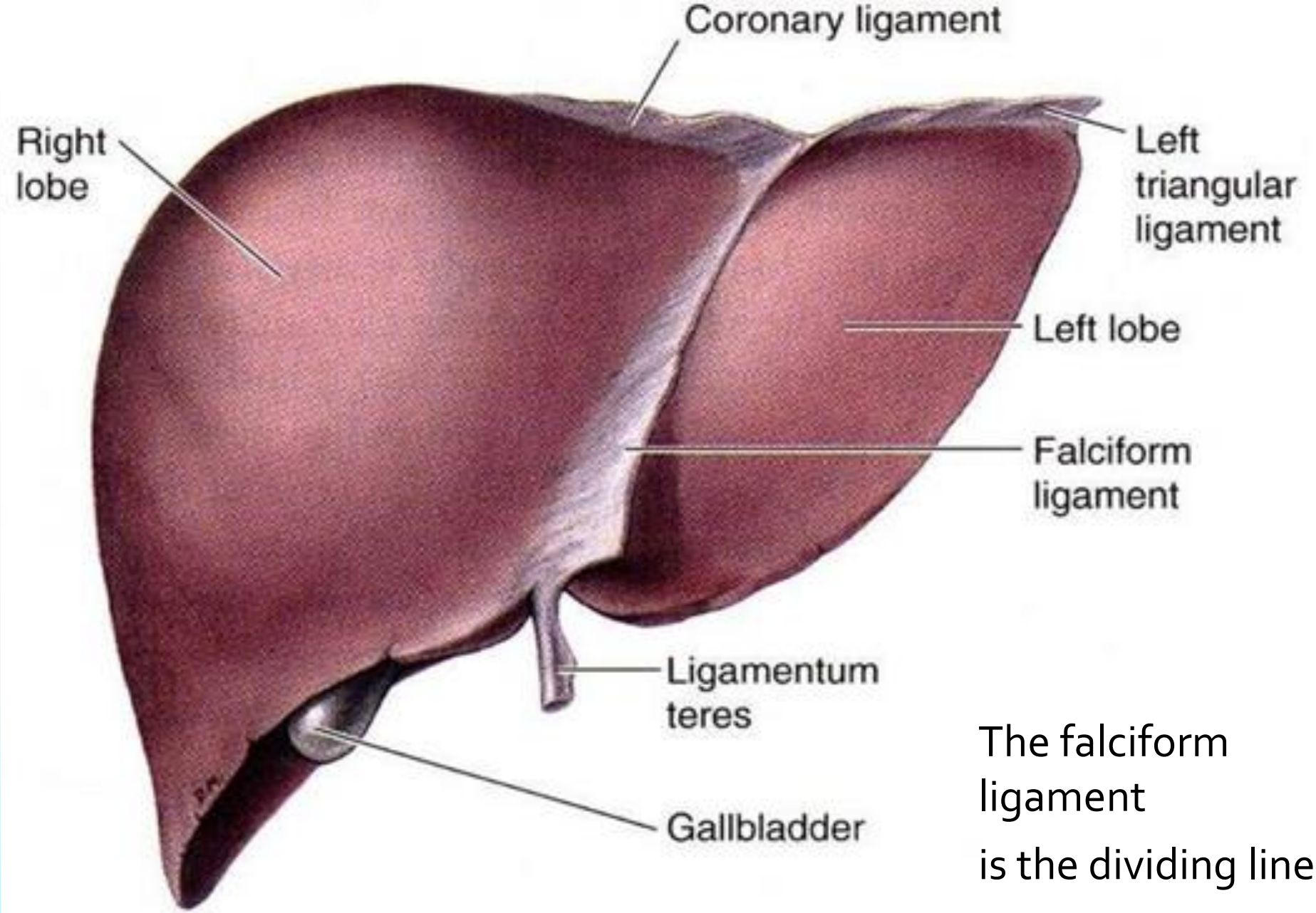
-Located in the **RUQ** of the abdominal cavity,

below the diaphragm

to the right of the stomach and overlies the GB.

-The Rt lobe is larger.

-

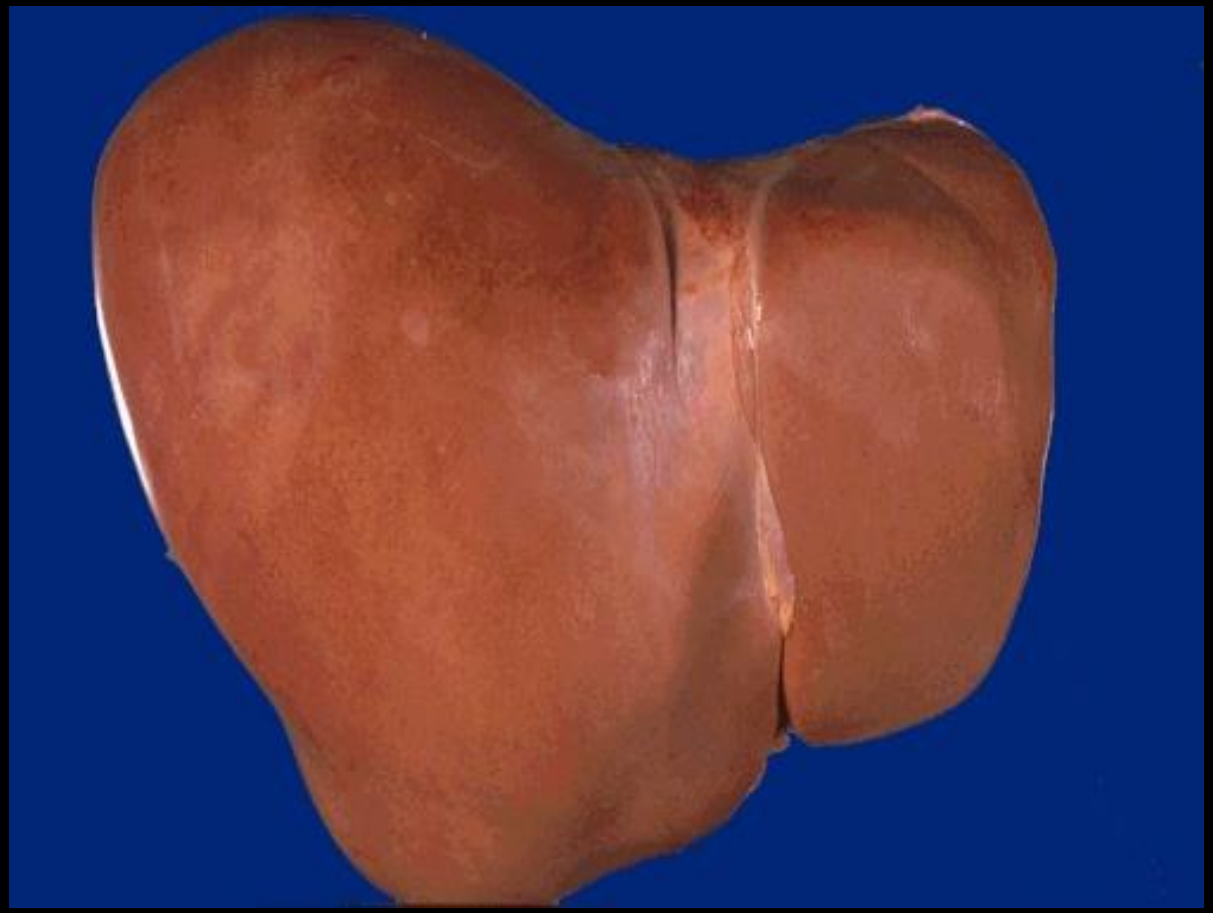



The falciform ligament

is the dividing line

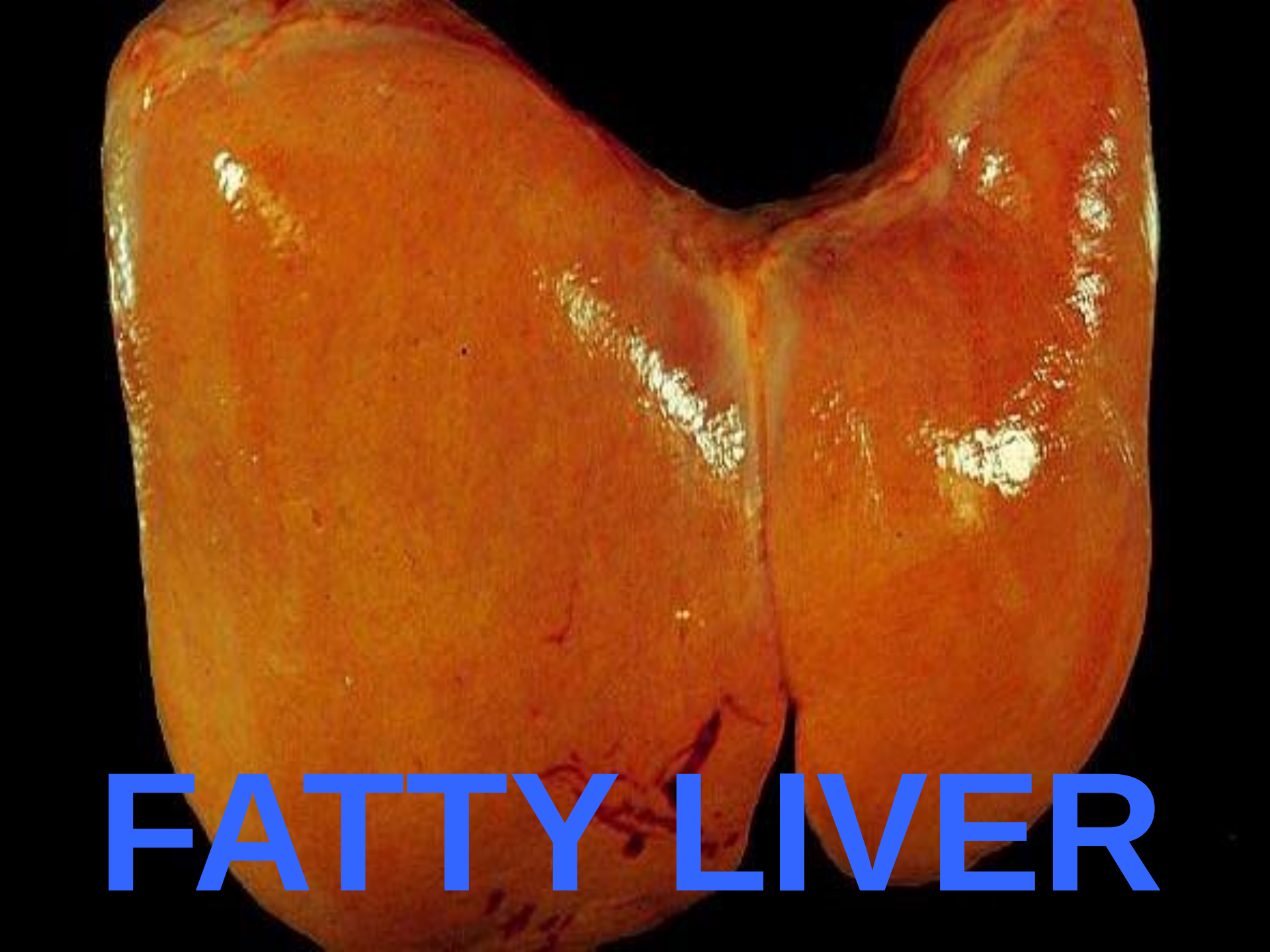
between the two lobes.

# EXTERNAL SURFACE OF A NORMAL LIVER



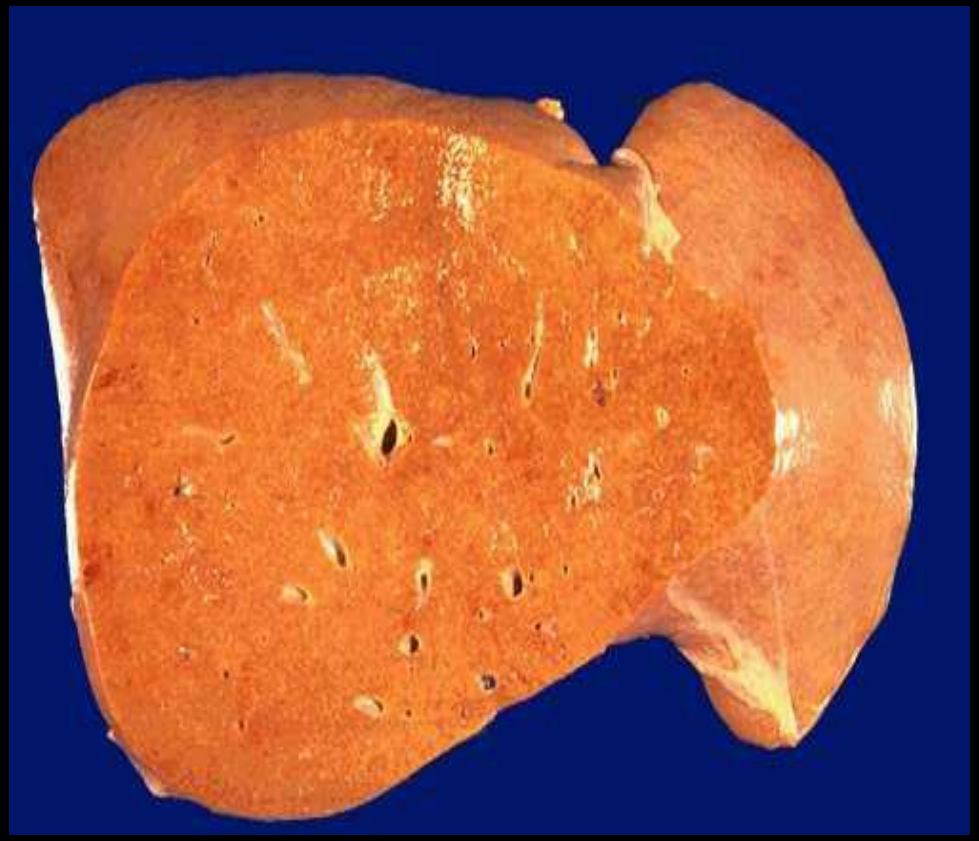
- -red - brown
- - smooth
- - soft

**Normal liver: 1200 – 1600g**


FATTY LIVER

# FATTY CHANGE: GROSS

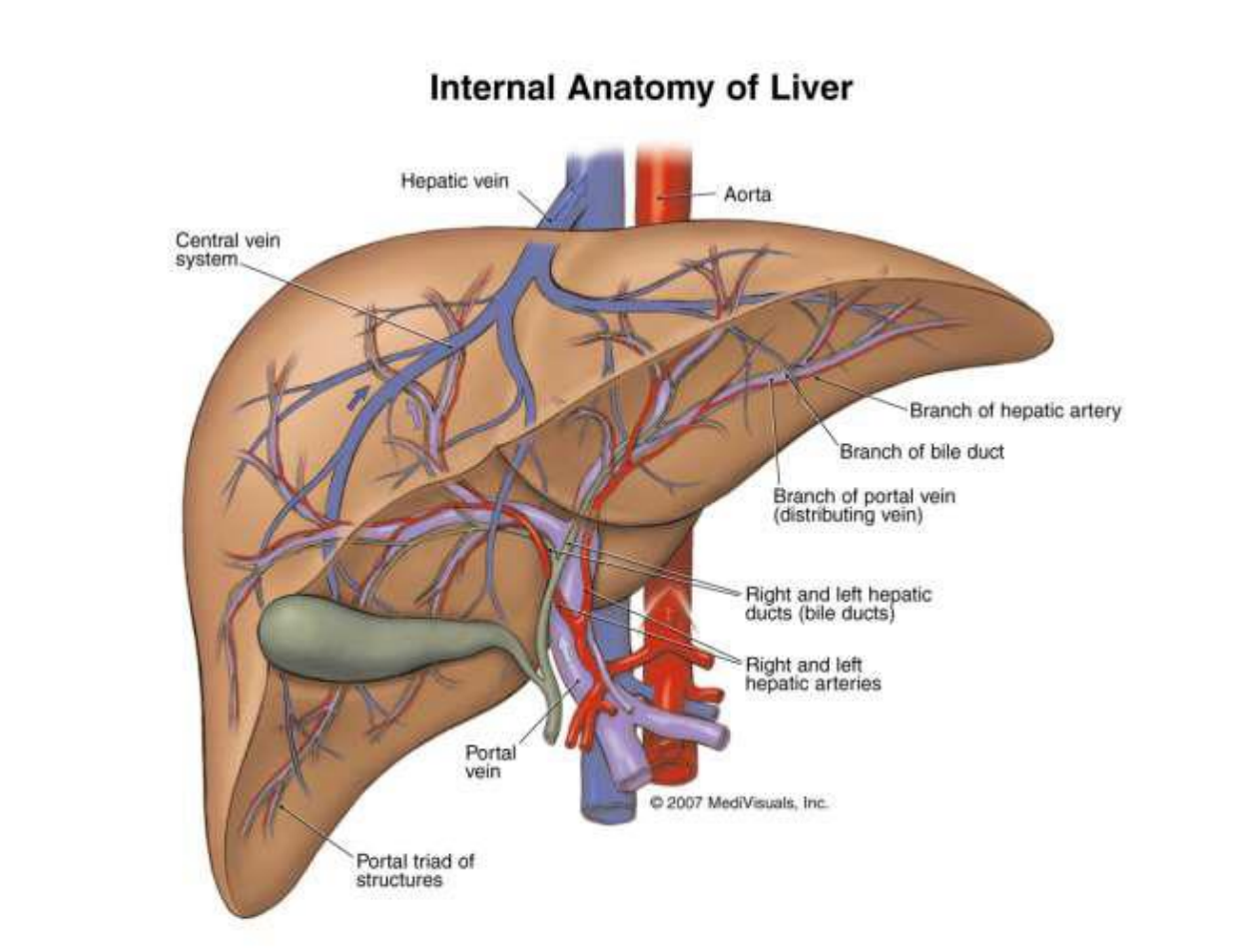
This liver is slightly enlarged and is pale yellow seen both on the capsule and cut surface



# BLOOD SUPPLY

- Two large BV, one called the HEPATIC ARTERY and one called the PORTAL VEIN.
- The HA carries blood from the aorta whereas the PVcarries blood containing digested nutrients from the small intestine and the descending colon.
- These blood vessels subdivide into capillaries which then lead to a lobule.
- Each lobule is made up of millions of hepatic cells which are the basic metabolic cells

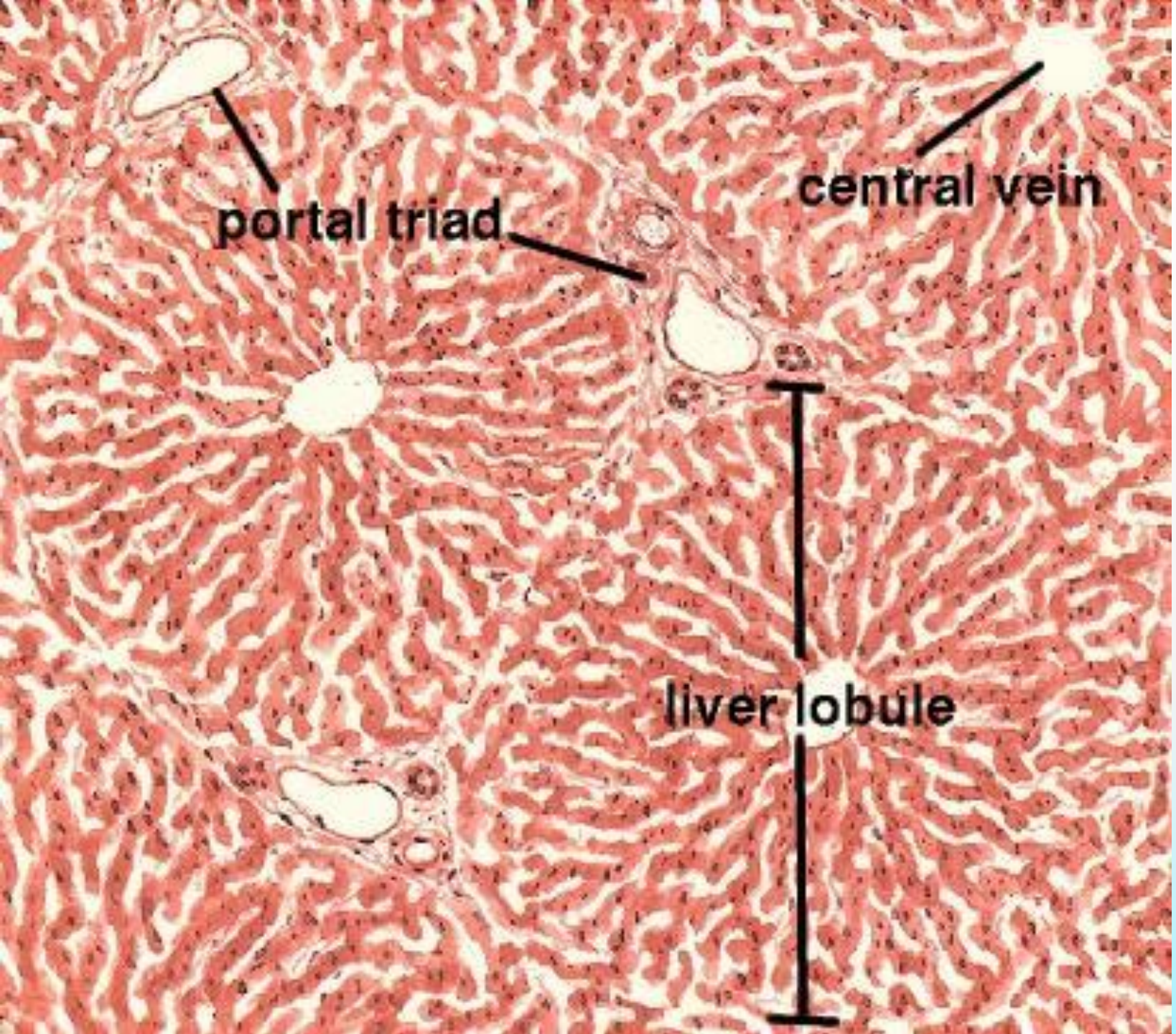
**It is one of only two organs to have two blood supplies, receiving blood from the hepatic arteries [30-40 %] portal vein [60-70%] (carrying blood from the intestines).**



# Normal Liver - Functions

- Synthesis
  - Proteins: albumin, clotting factors
  - Bile
  - Cholesterol & lipoproteins
- Storage and secretion
  - Glucose
  - Fat-soluble vitamins (vitamins A, D, E and K)
  - Folate, vitamin $B_{12}$ , copper, iron.
- Excretion
  - Ammonia, bilirubin, steroid hormones, many drugs, alcohol, toxins

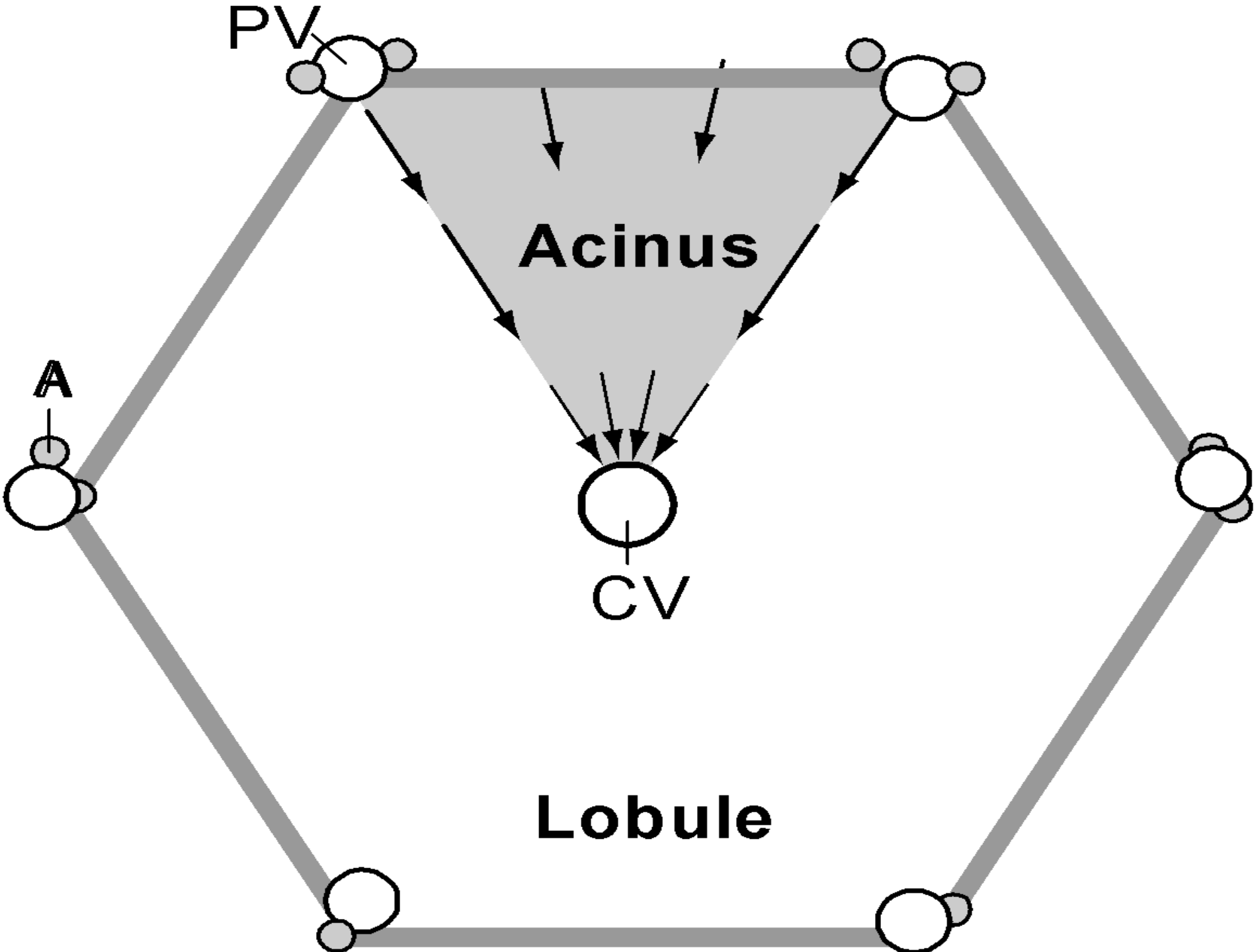
- Histologically Divided into LOBULES
- Hexagonal shape
- Center of the lobule - CV
- Periphery of the lobule - PT
- Functionally, Divided into :
- 3 ZONES, based upon oxygen supply
- Zone 1- Encircles the PT where the oxygenated blood from hepatic arteries enters.
- Zone 3 is located around CV, where oxygenation is poor.
- Zone 2 is located in between.

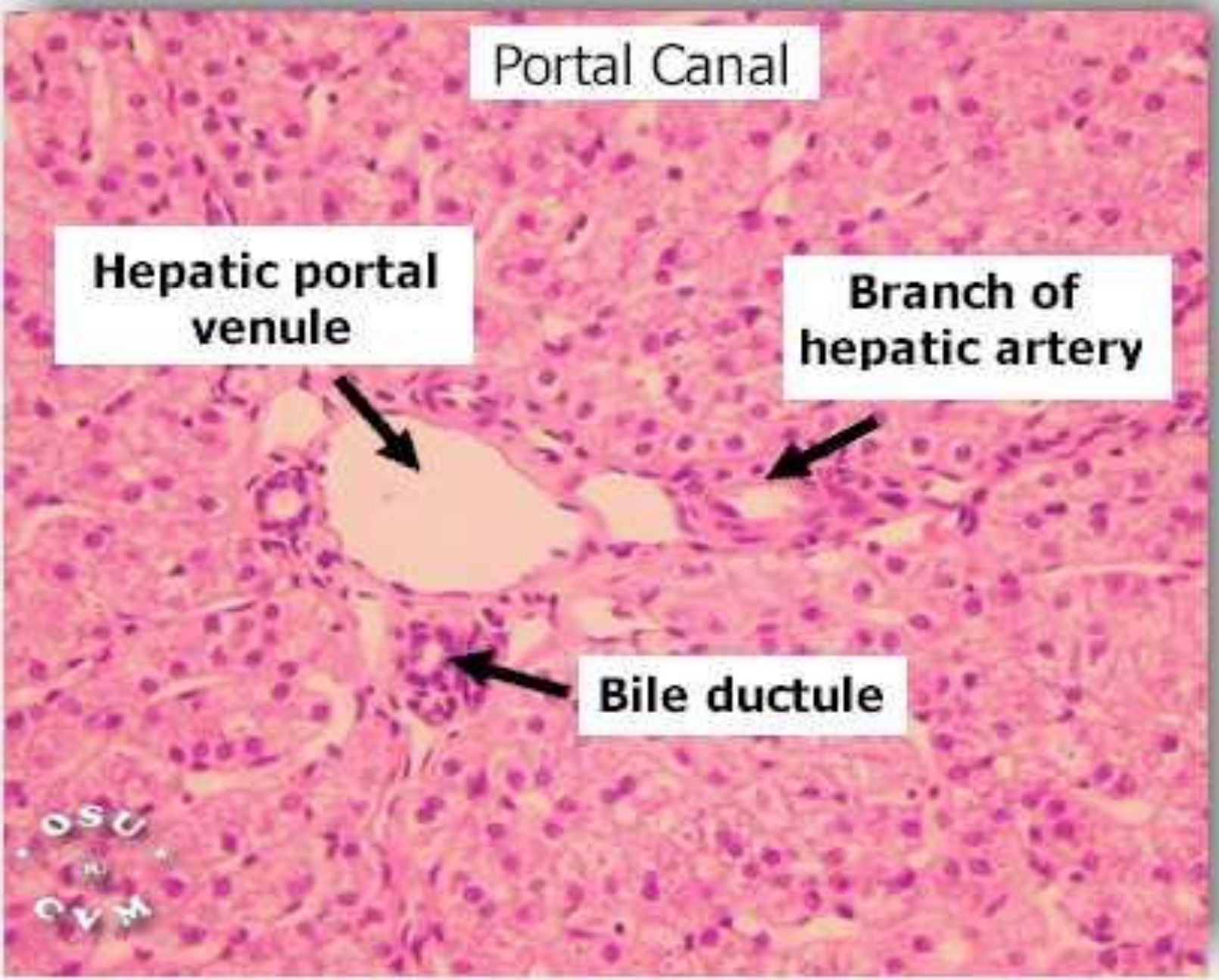


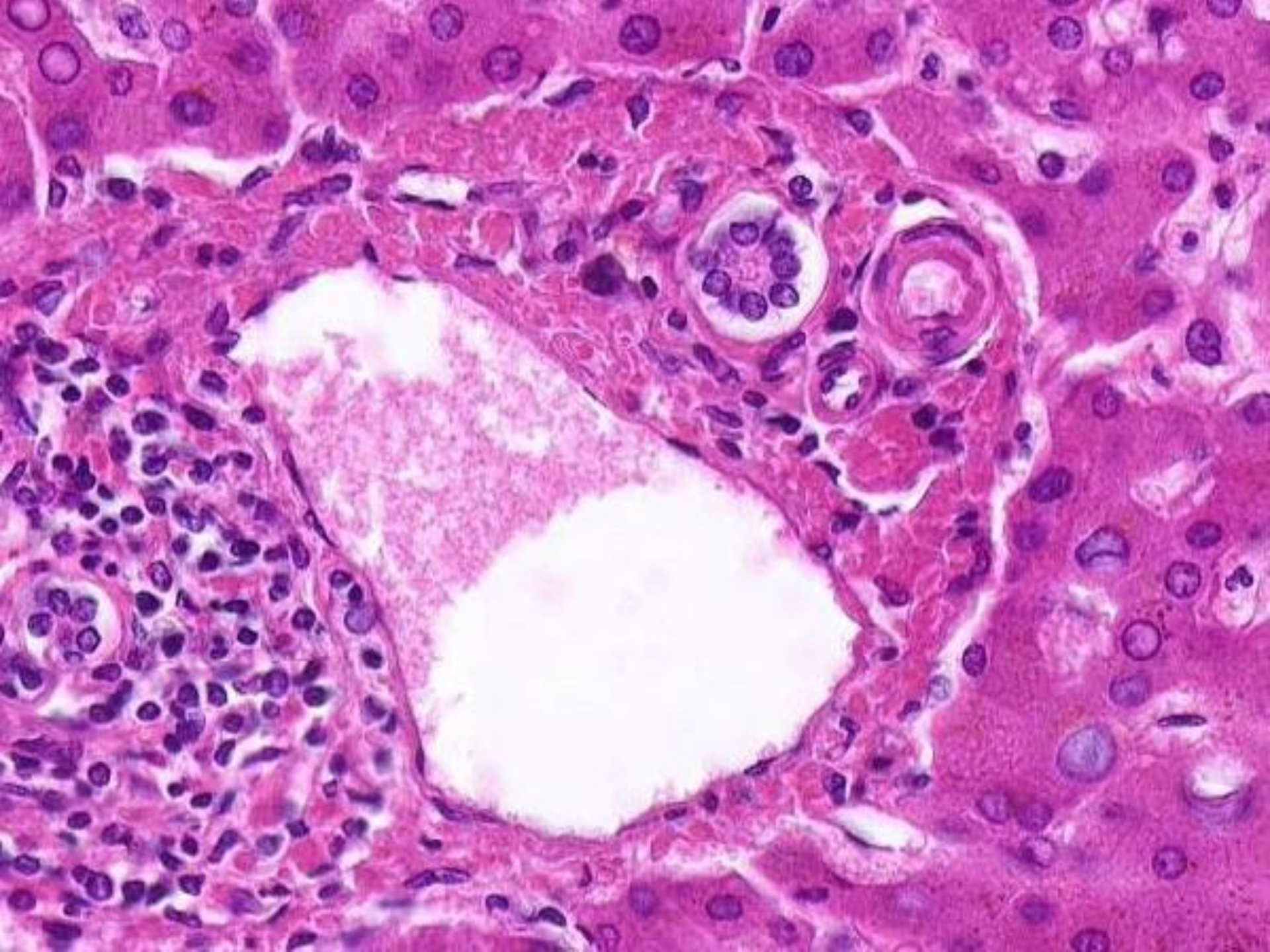

N

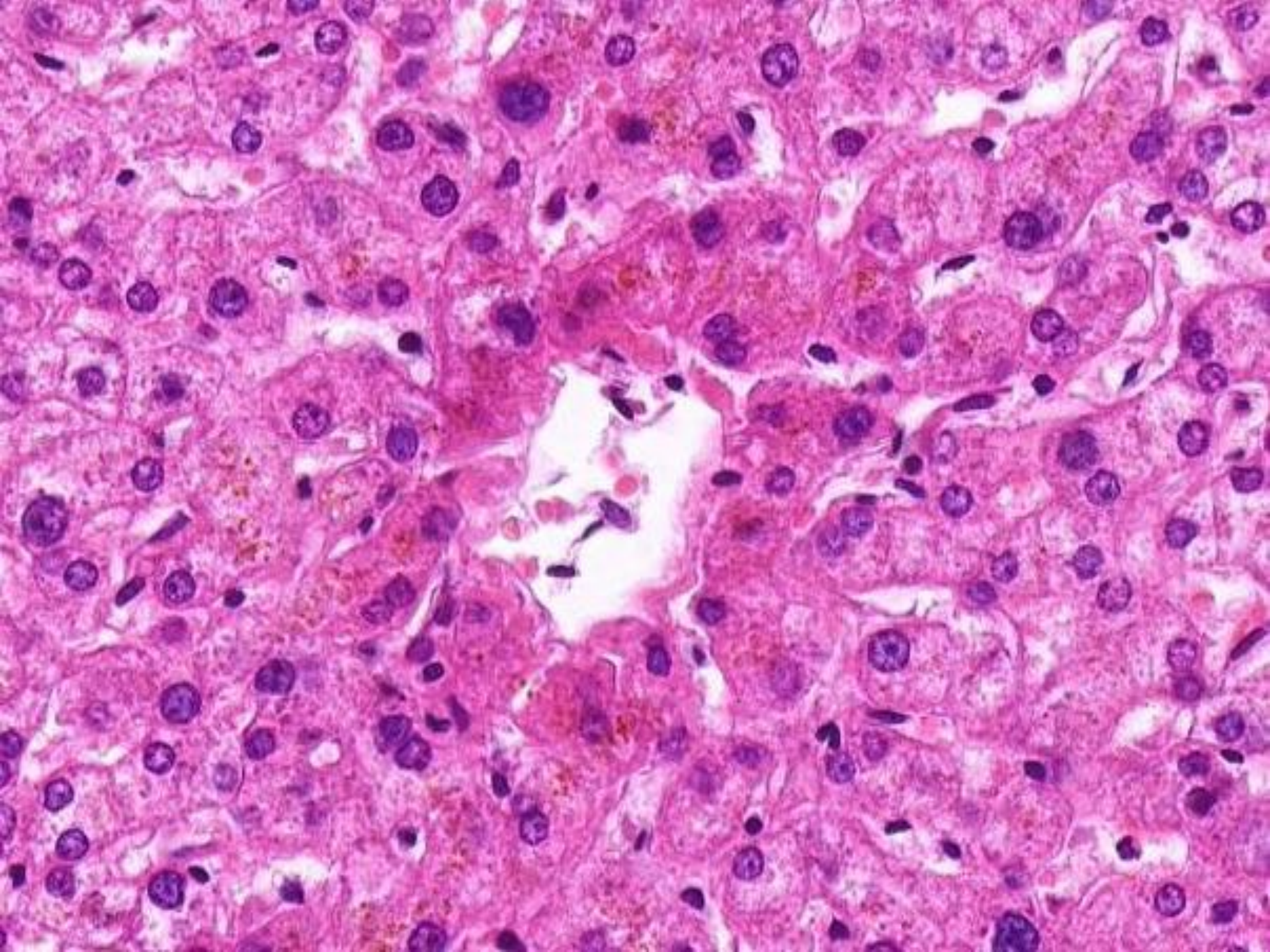
O

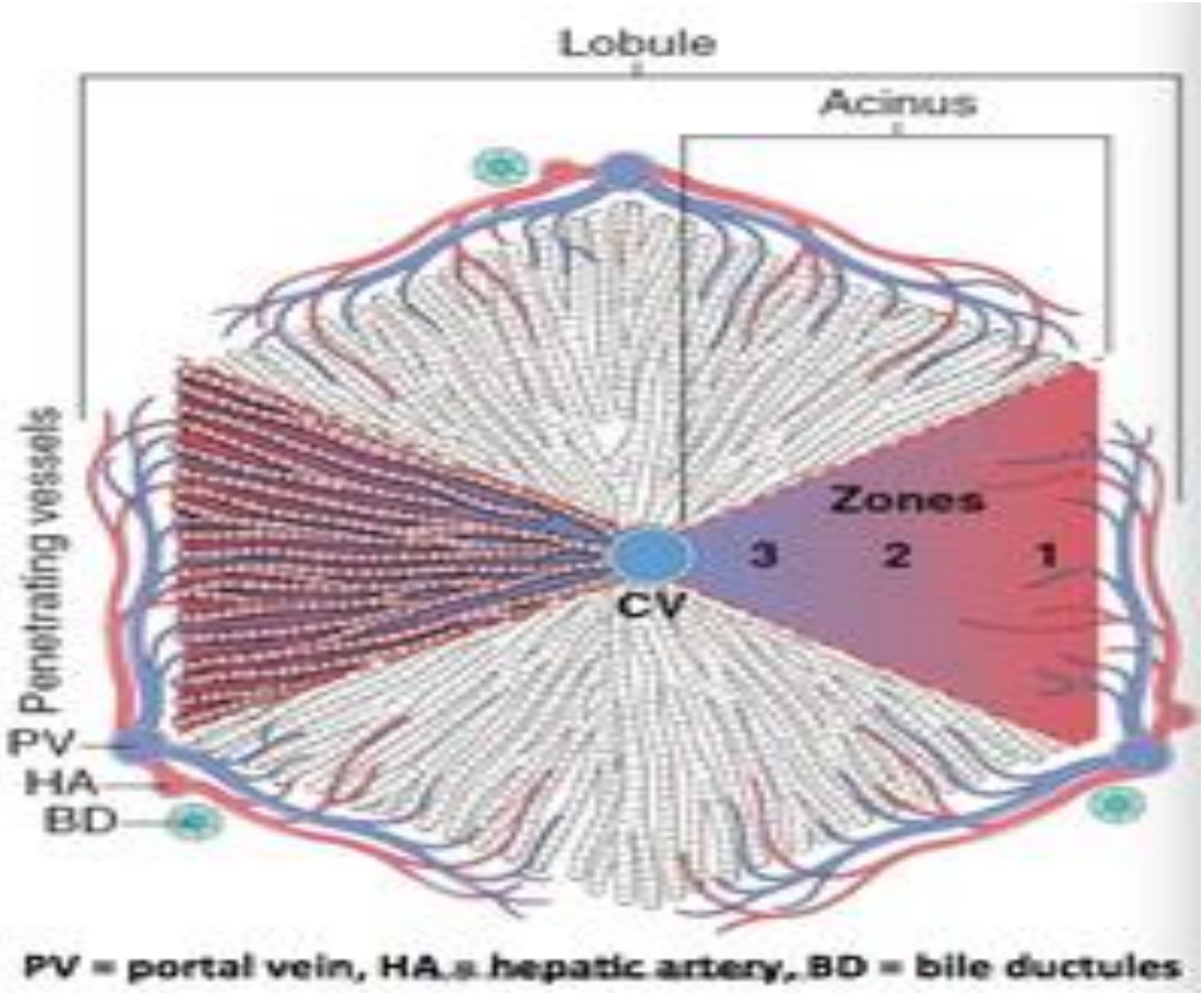
FIBROUS TISSUE


PV
Acinus
A
CV
Lobule

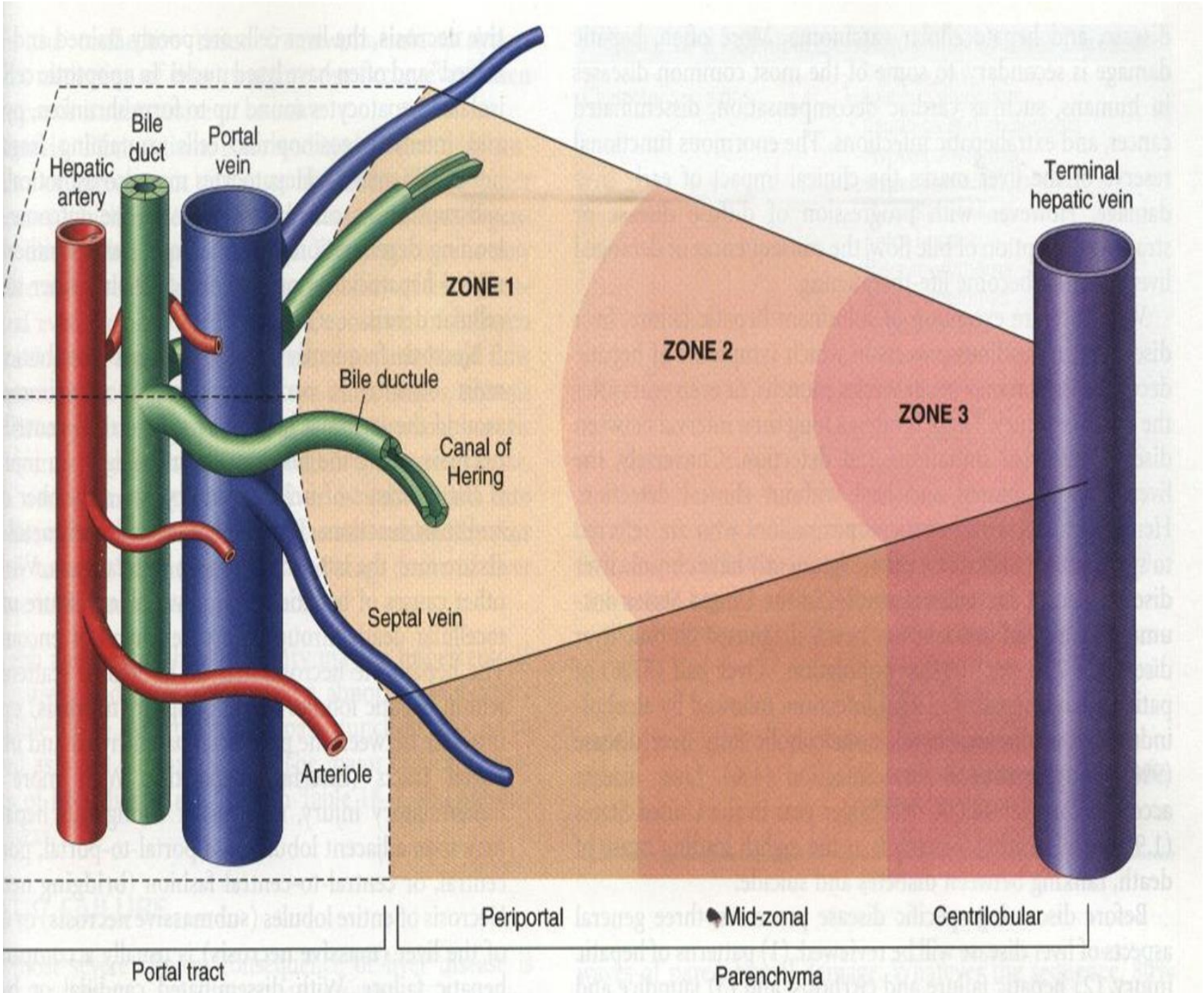

Portal Canal
Hepatic portal venule
Branch of hepatic artery
Bile ductule
OSU
CVM








PV = portal vein, HA = hepatic artery, BD = bile ductules


Hepatic artery
Bile duct
Portal vein
Terminal hepatic vein
ZONE 1
ZONE 2
ZONE 3
Bile ductule
Canal of Hering
Septal vein
Arteriole
Periportal
Mid-zonal
Centrilobular
Portal tract
Parenchyma

# Metabolic diversity within zones

| Zone 1(periportal) | Zone 3(pericentral) |
|---|---|
| Rich in oxygen and the nutrients | Relatively poor in O2 and nutrients |
| Less prone to hypoxia and drug toxicity | More prone for hypoxic & drug induced damage |
| Oxidative/phaseII reaction | Anaerobic/phaseI reaction |
| Glycogen snthesis as well as gluconeogenesis | Glycolysis |
| Bile salt formation | Lipolysis |

- Liver pathology

# The major causes of liver diseases

- **metabolic**
- **toxic,**
- **microbial**
- **circulatory insults**.
- Injury process :
- **either primary to the liver or secondary hepatic injury to systemic diseases e.g. alcoholism, heart failure.**
- **C I M T D I N**
- **Congenital , inflammatory. Infectious. Metabolic, degenerative. toxic traumatic, neoplastic**

# General paranchymatous hepatic responses to liver injury

1- Inflammation ( acute &chronic ).

2- Degeneration & intracellular accumulation.

3- Necrosis and apoptosis.

4- Regeneration.

5- Fibrosis.

# 3- Inflammation: viral or toxic

**it is injury to hepatocytes associated with.**

- **Influx of acute & chronic inflammatory cells into the liver.**
- **Hepatocytes necrosis.**
- **Inflammation may limited to portal tracts or may spill into the liver parenchyma.**
- **Scavenger macrophages engulf dead hepatocytes within hours.**
- **Attack of hepatocytes by sensitized T-cells is the common cause of the inflammation.**

# 2- Degeneration & intracellular accumulation

- **Ballooning degeneration**: swollen edematous hepatocytes (cloudy "swelling), representing some compromise of the Na-K pump due to decrease ATP .

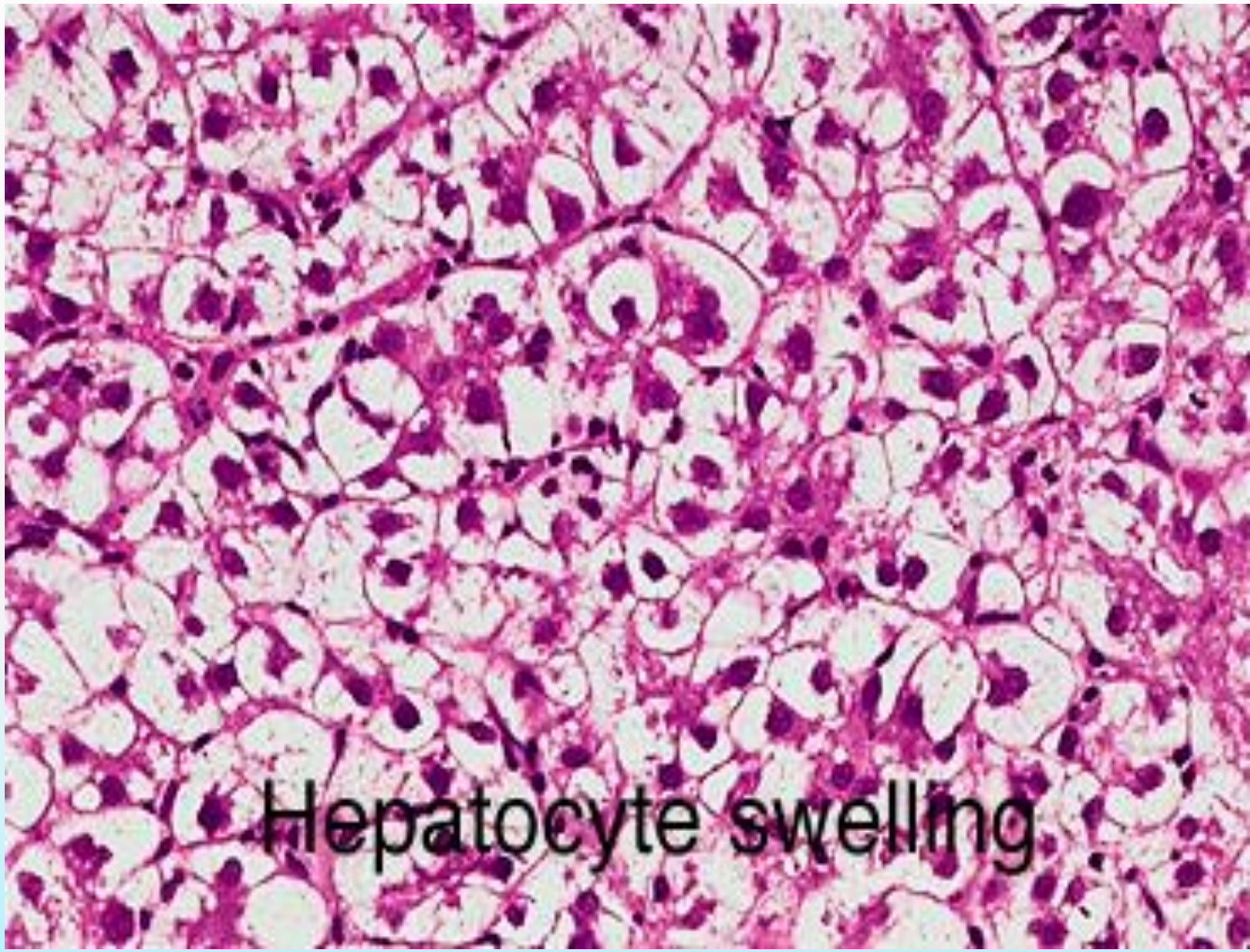
- **Foamy (feathery) degeneration**: foamy swollen hepatocytes due to retained pigments as bile, copper, iron materials

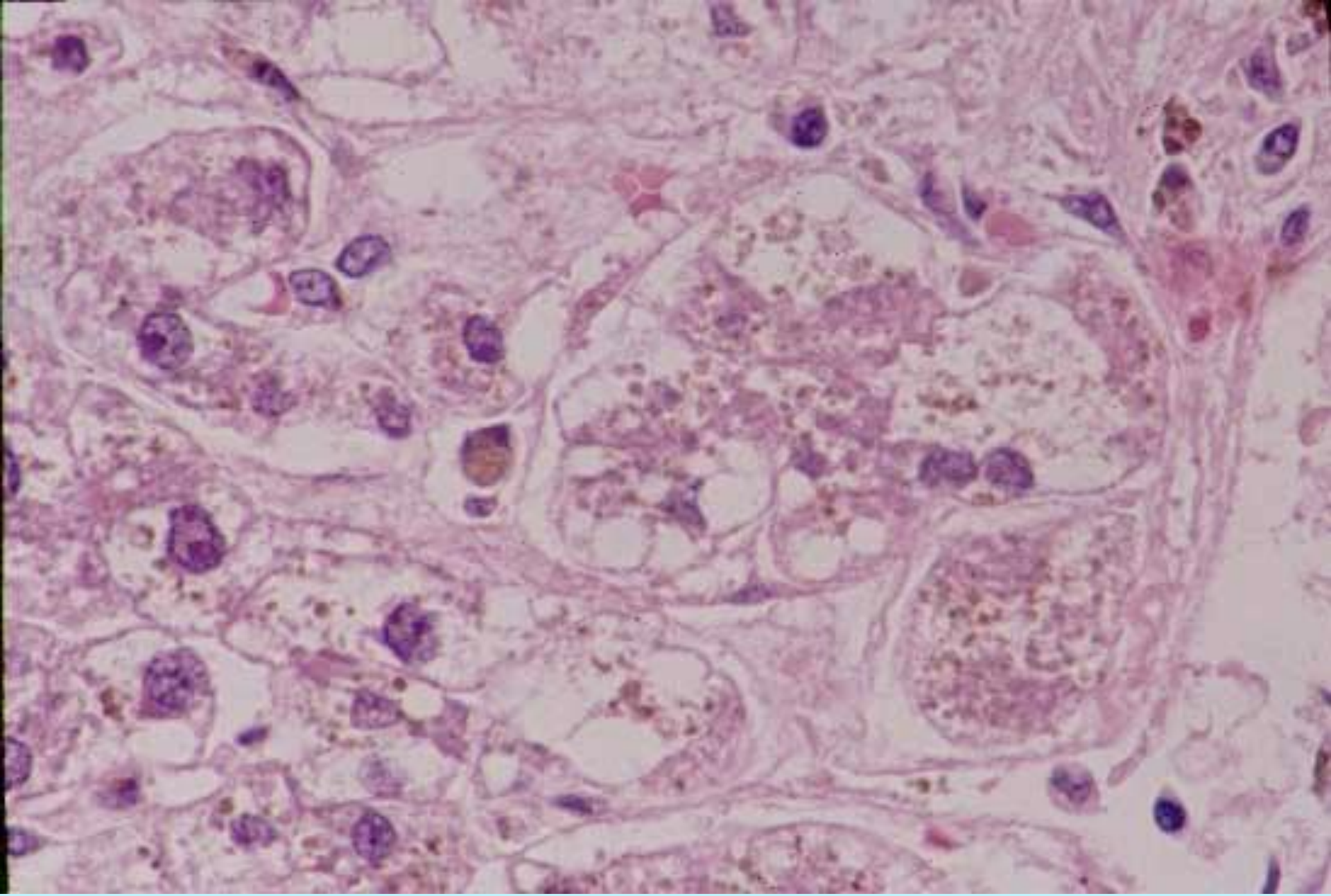
- **Steatosis** : accumulation of fat droplets in the hepatocytes ( microvesicular & macrovesicular).

## HISTOLOGIC PATTERNS OF HEPATIC INJURY

# HEPATOCYTE SWELLING

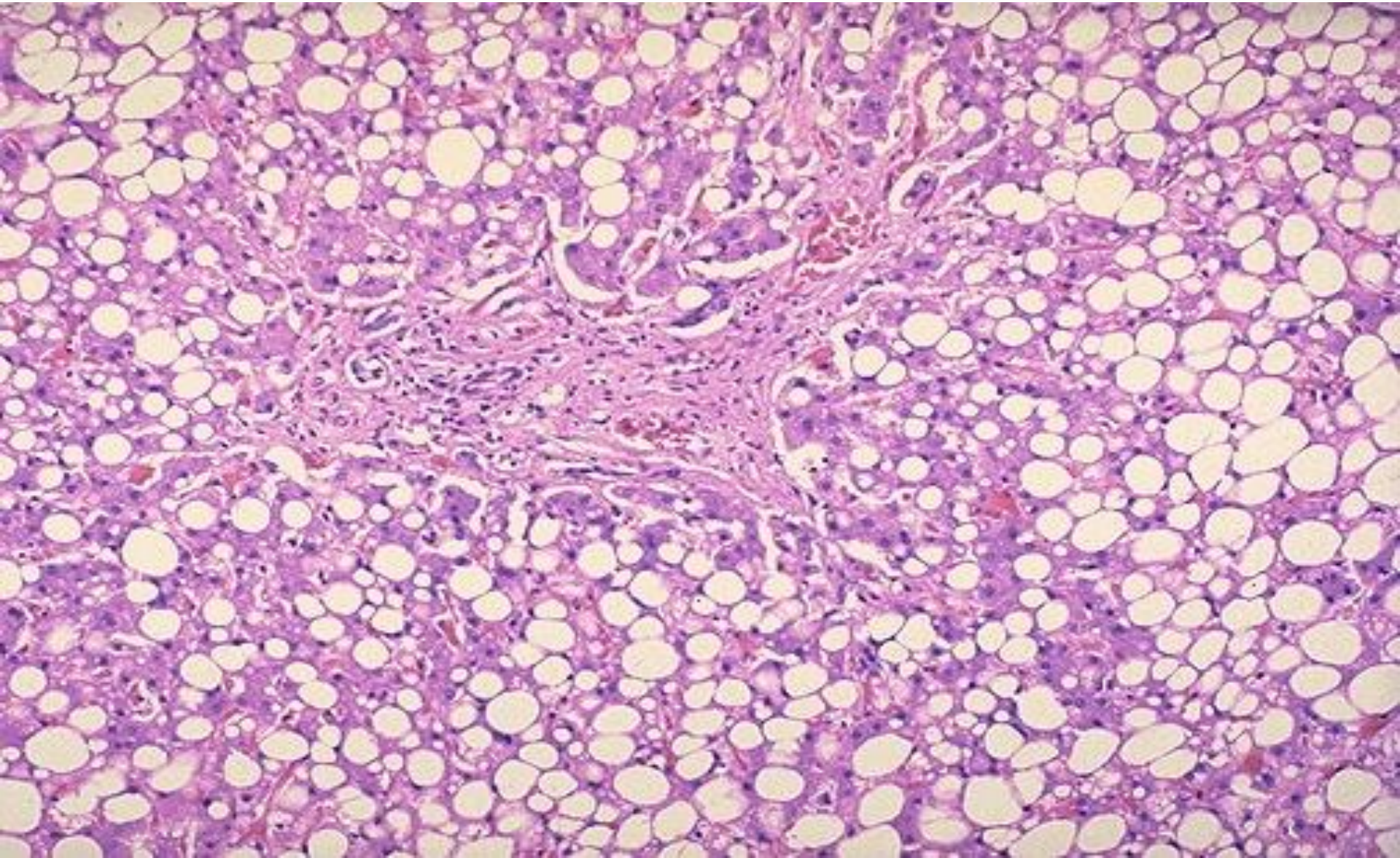
**Swelling or hydropic change is a result of defects in membrane and/or mitochondrial function**

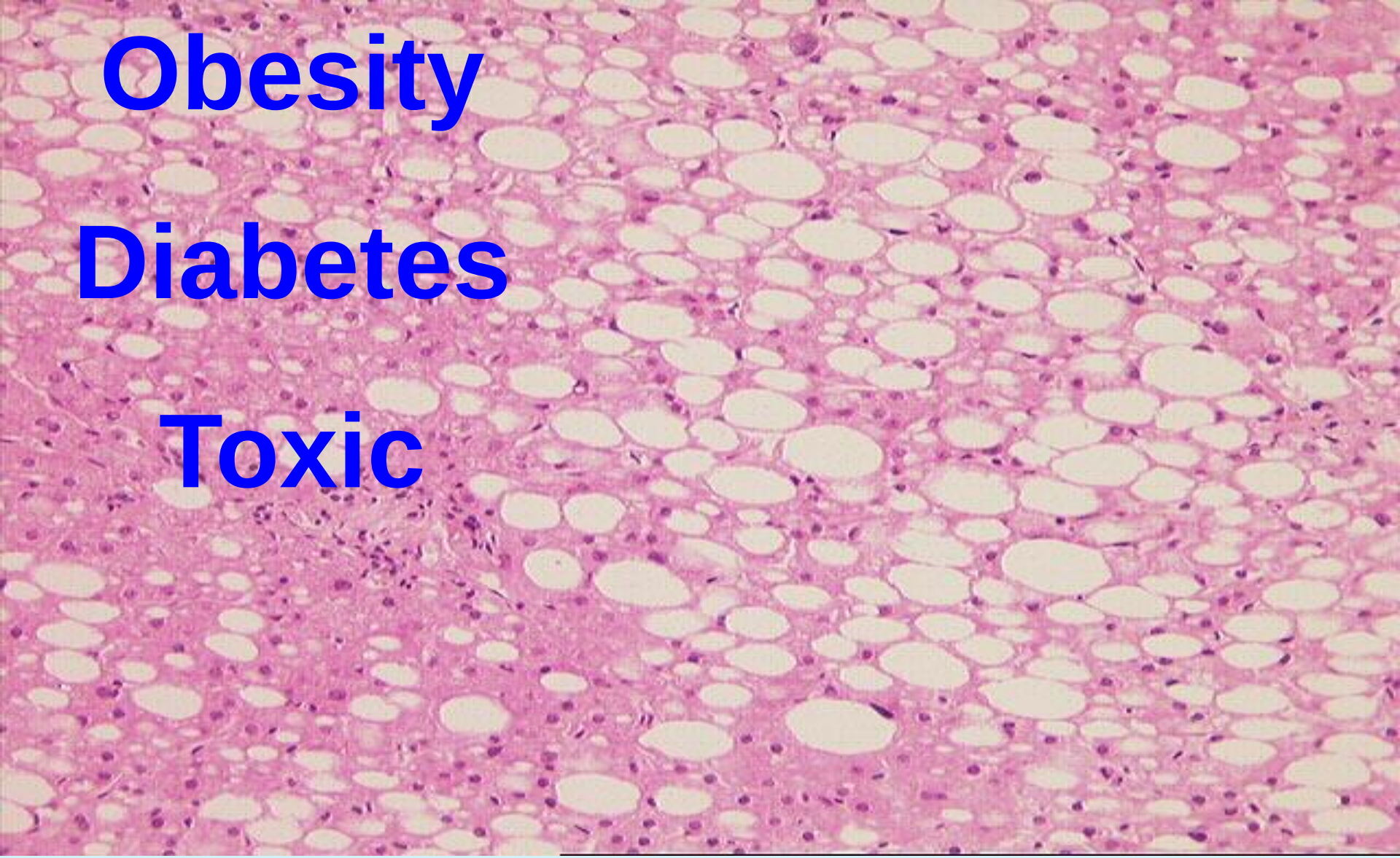




# “FEATHERY” DEGENERATION

**Steatosis:** Fat vacoules are small enough to lie completely ***WITHIN*** the hepatocte cytoplasm are termed ***MICRO-vesicular***



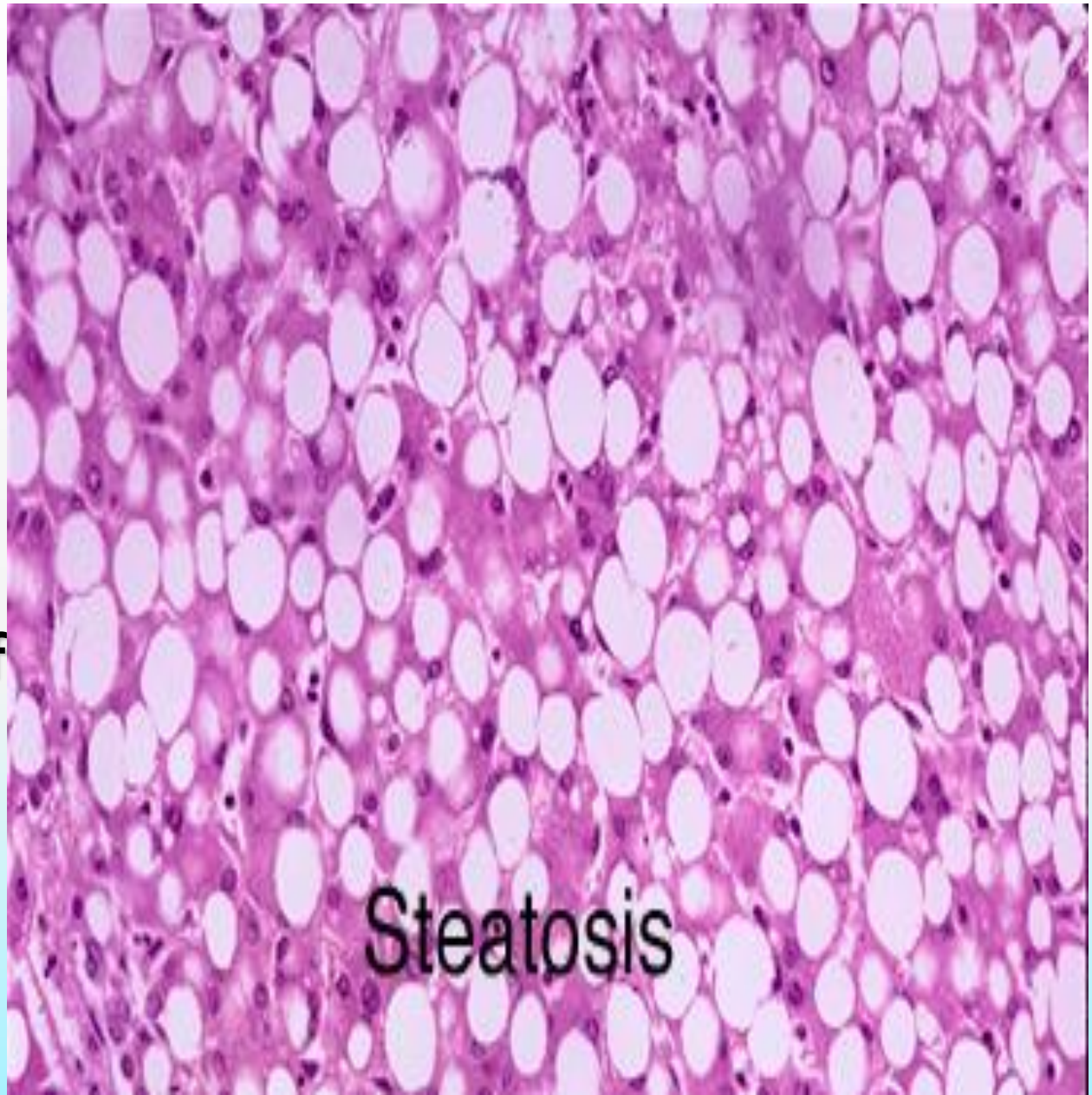



Fat vacuoles which are **LARGER** than hepatocytes is termed **MACRO**-vesicular.

# HISTOLOGIC PATTERNS OF HEPATIC INJURY

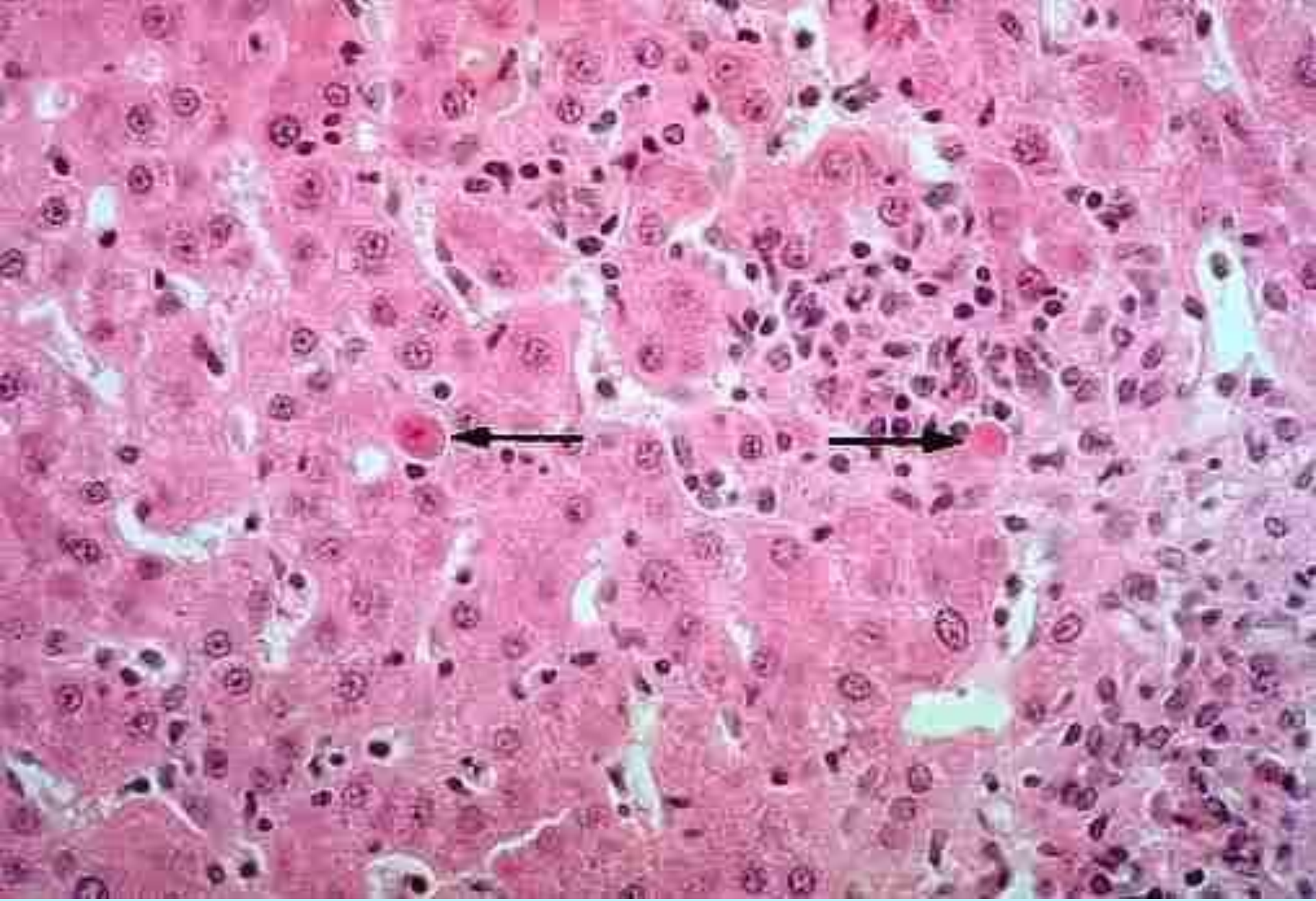
## STEATOSIS

Fat (neutral fat, triglycerides) in liver cells indicates defect in lipid metabolism or lipoprotein synthesis or unusual amounts of adipose or dietary lipids brought to liver

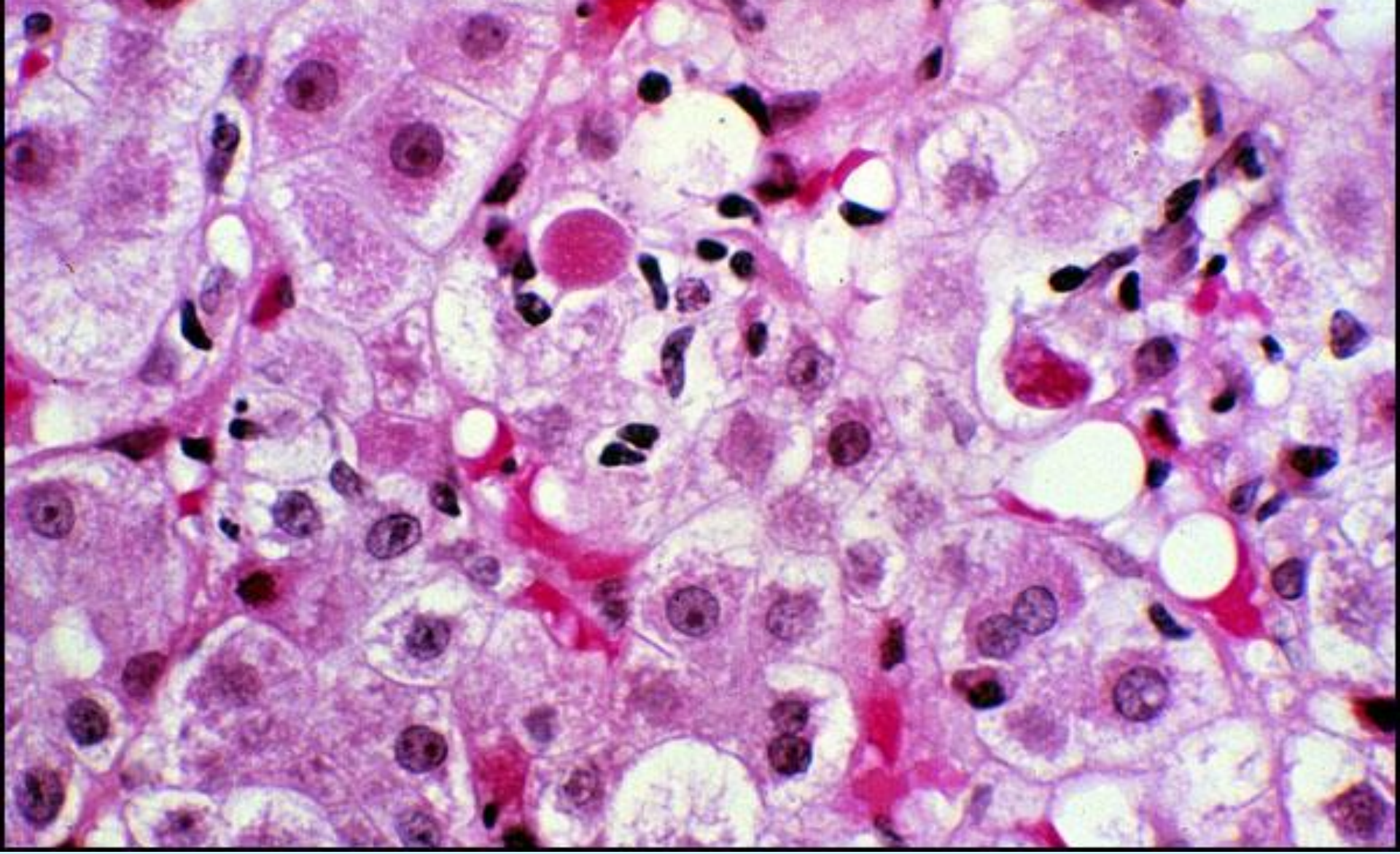


# 3- Necrosis and apoptosis

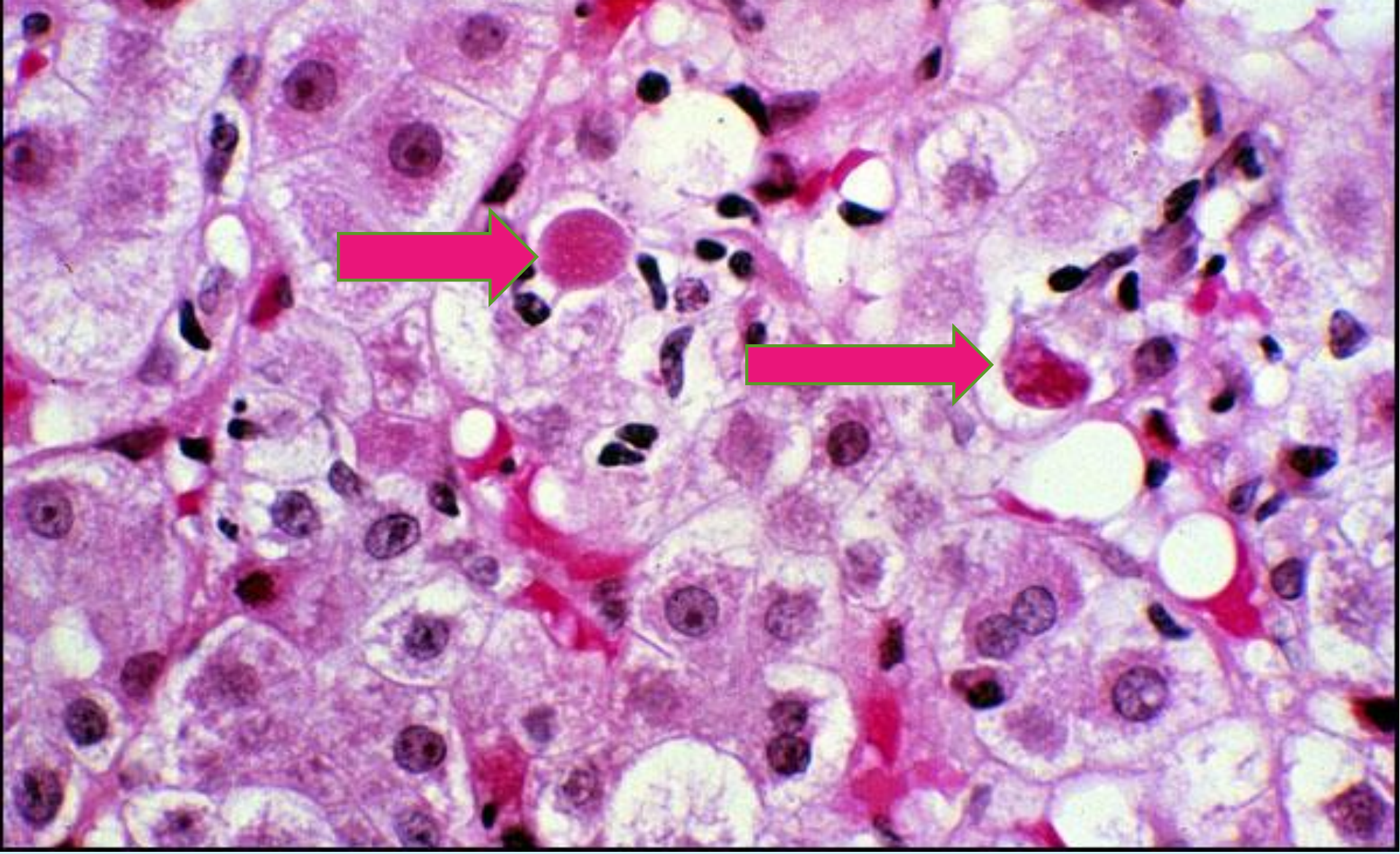
- Apoptosis: rounded , pyknotic & intensely eosinophilic hepatocytes.( Councilman bodies).
- Necrosis:
- Types of hepatocytes necrosis: (according to etiology).
- 1. Coagulative necrosis (ischemic).
- 2. Lytic necrosis (osmotic swollen hepatocytes leading to cell rupture).



# “Councilman” Bodies



# APOPTOSIS



# APOPTOSIS

# Histologic patterns of hepatic injury

## NECROSIS

**Coagulative necrosis:**

preserved architecture

loss of cellular details

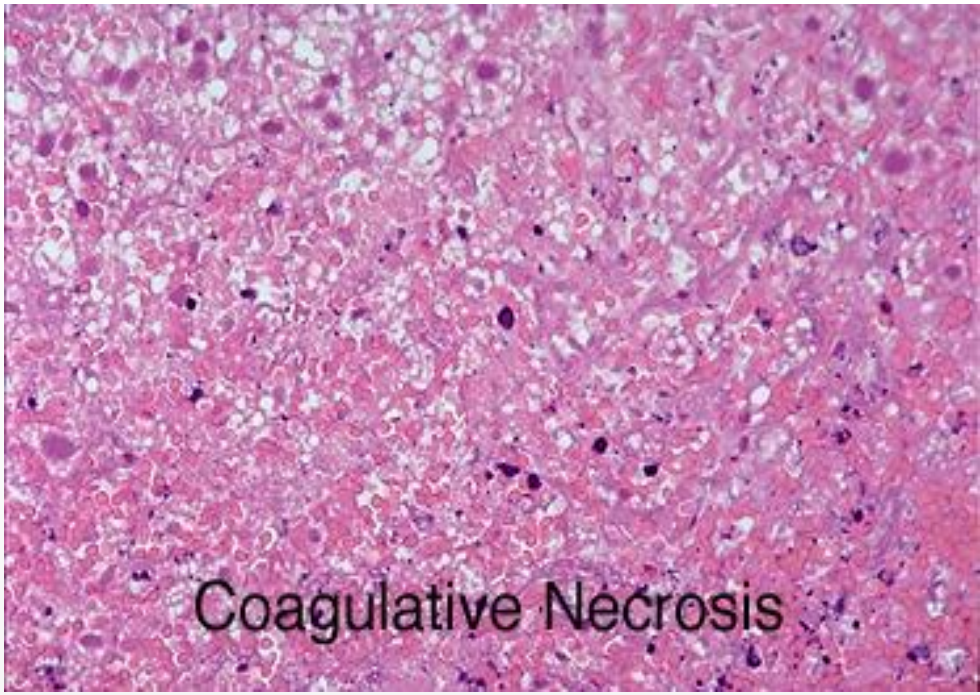
**Councilman bodies:**

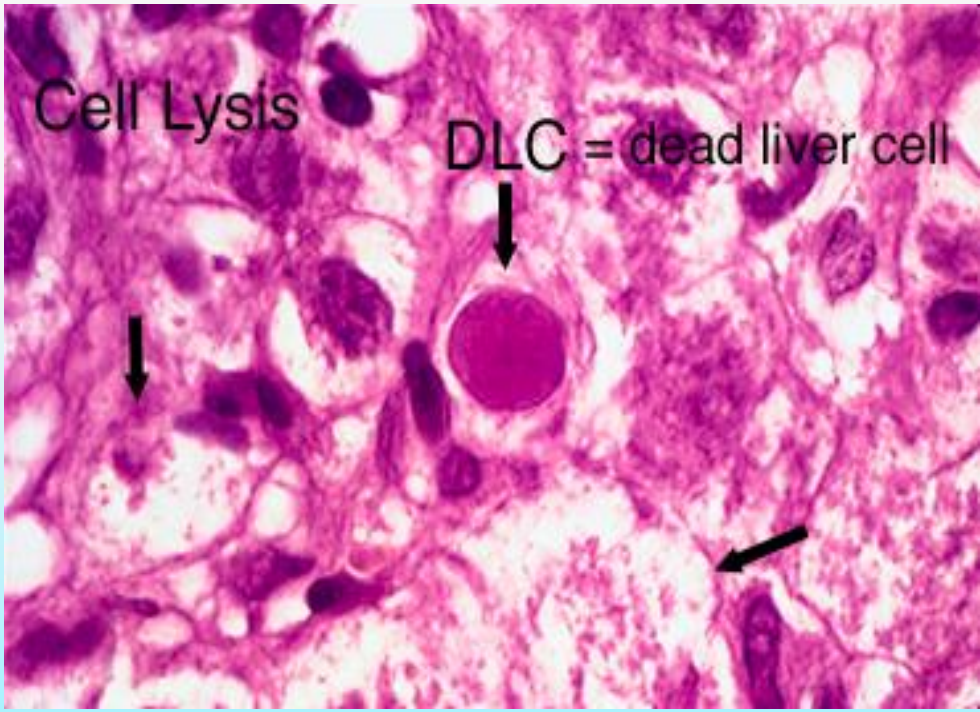
apoptotic cells

shrinkage deeply eosinophilic

**Lytic necrosis:**

hepatocytes swell & rupture



# Types of hepatocytes necrosis: (according to sites of necrosis)

**A-Focal necrosis**

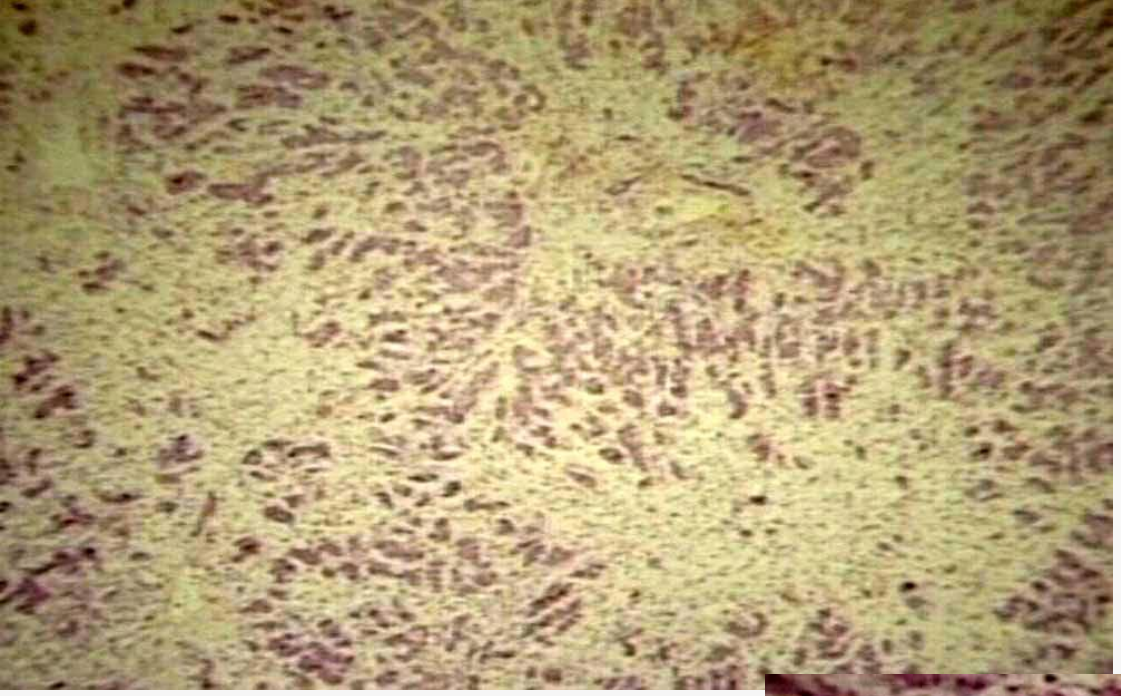
**B- centrilobular necrosis. Hepatocytes necrosis around the central vein**. (Due to drugs, ischemia)

**C-interface hepatitis. necrosis of hepatocytes interface between the periportal parenchyma & inflamed portal tract**

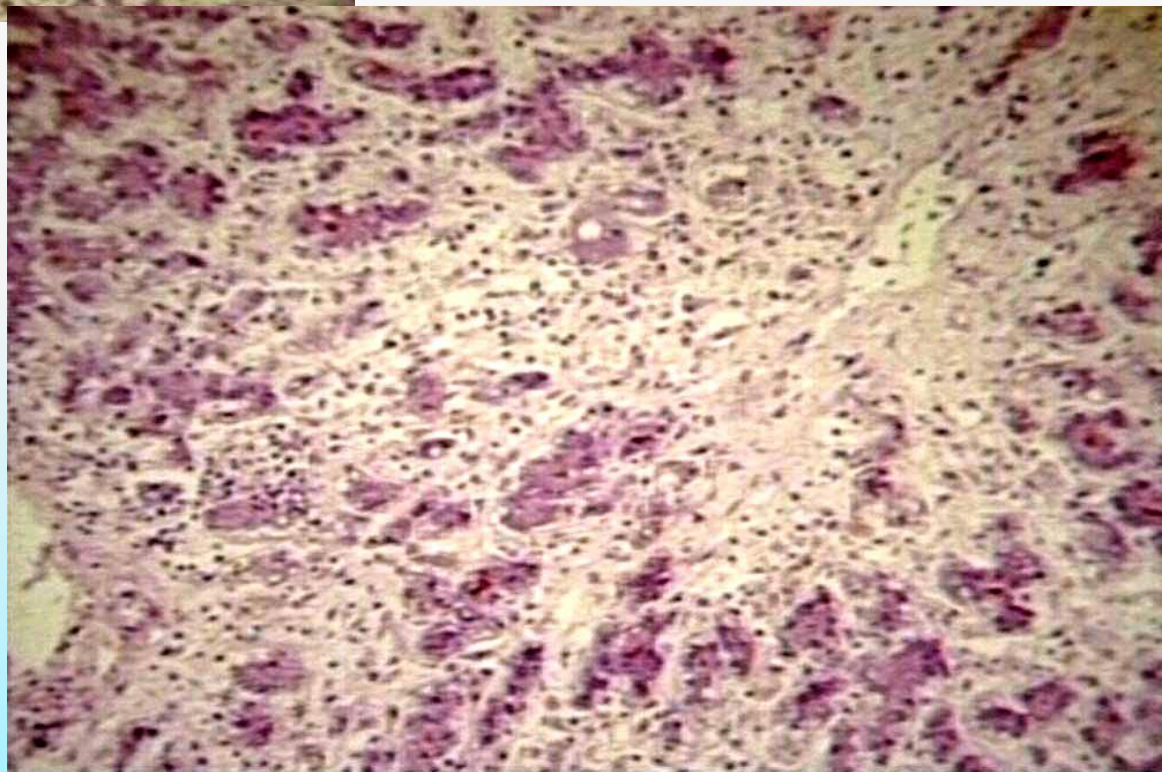
**D-bridging necrosis. necrosis of hepatocytes may span the adjacent lobules in a portal – to – portal, portal –to – central, or central – to – central fashion.**

**E-sub massive necrosis. Destruction of entire hepatic lobules.**

**F- Massive necrosis. Destruction of most of the liver parenchyma & this usually accompanied by hepatic failure.**



## Massive necrosis



## 4- Regeneration:

**Hepatocellular and bile duct proliferation. it is signified by mitosis.**

# 5- Fibrosis:

- **Is due to collagen deposition that affects the blood flow & perfusion of hepatocytes.**
- **In initial stages. Fibrosis develops within or around portal tracts or the central vein or may be directly deposited within the sinusoids.**
- **With time ……. bridging fibrosis (portal –to –portal…..etc).**
- **Fibrosis is irreversible hepatic response to injury.**

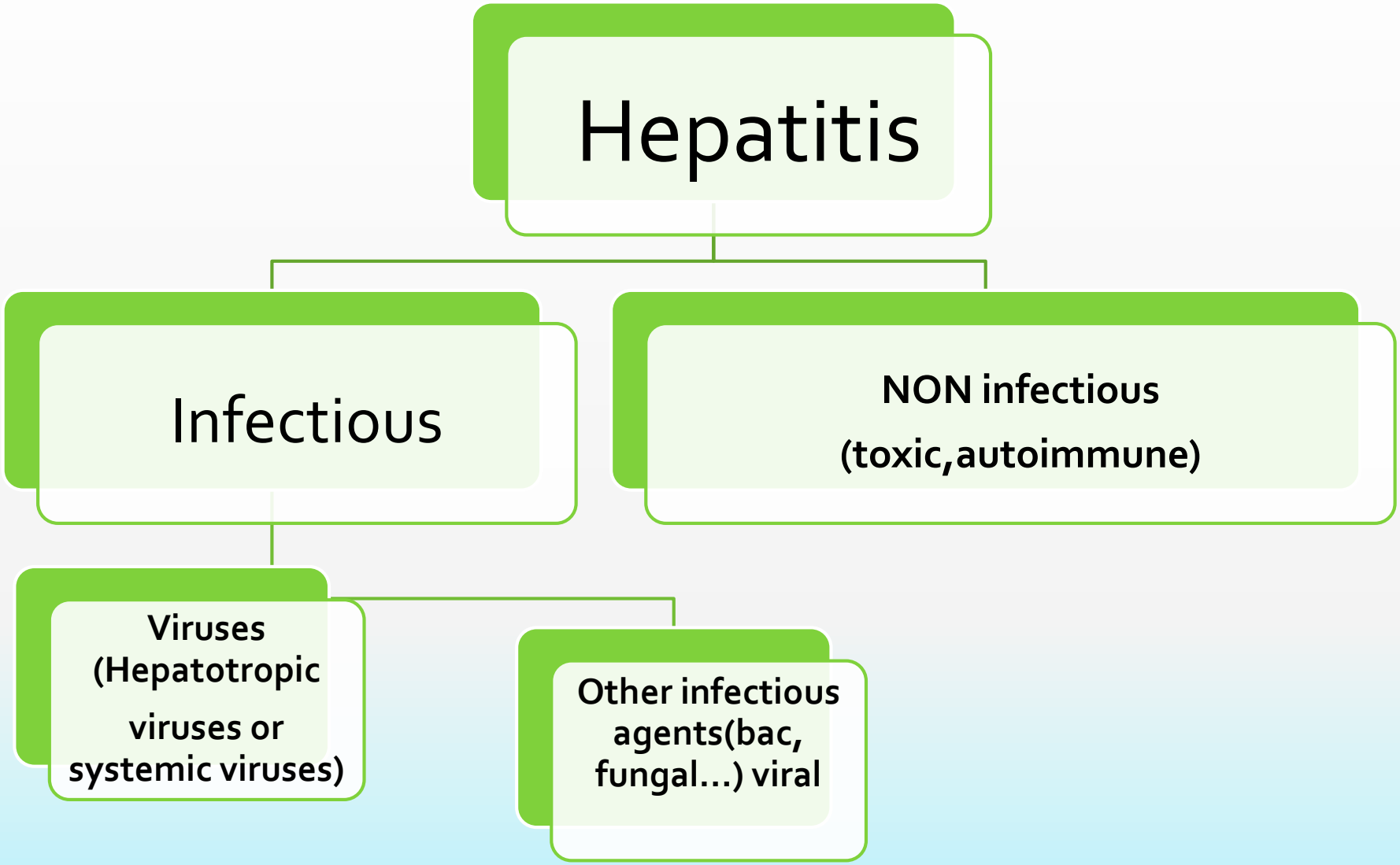
is the end stage of MOST chronic liver diseases

- **With continuing fibrosis & parenchymal injury ….subdivided the liver into nodules of regenerating hepatocytes surrounded by scar tissue….(liver cirrhosis)**

# Hepatitis

**ACUTE or**

**CHRONIC**

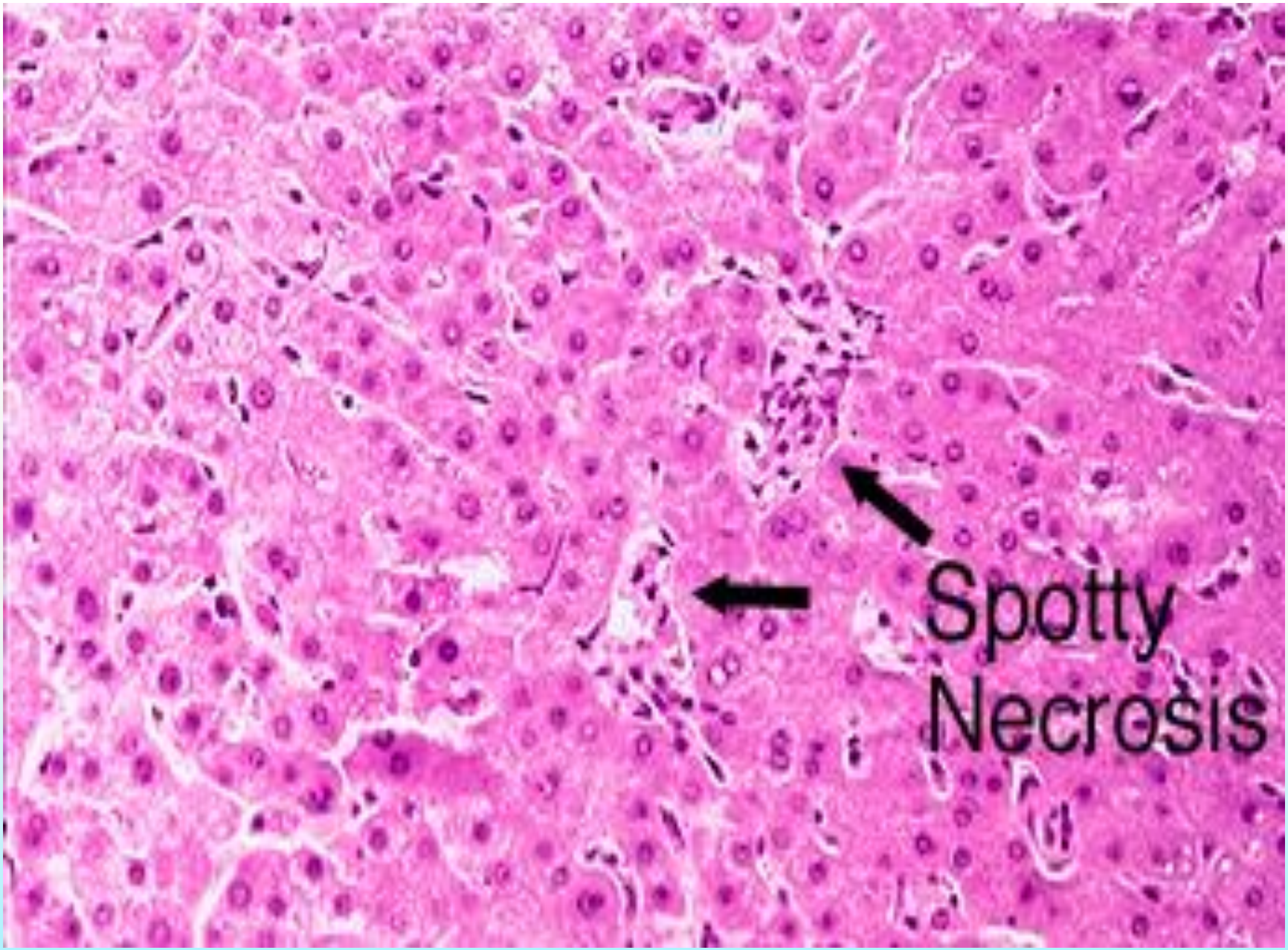

Hepatitis
Infectious
NON infectious
(toxic,autoimmune)
Viruses
(Hepatotropic
viruses or
systemic viruses)
Other infectious
agents(bac,
fungal…) viral

# Acute hepatitis

- active hepatocellular damage and necrosis, usually with a lobular inflammatory response, less than 6 months duration .

**Micro:**

- **spotty** hepatocytes **inflammation**
- **Diffuse sinusoidal and portal mononuclear inflammation**.
- **Swollen hepatocytes, apoptotic hepatocytes; (usually not biopsied).**


Spotty
Necrosis

# Chronic hepatitis:

Either with interface hepatitis **or without interface hepatitis**

a. **Chronic hepatitis with (interface hepatitis); (periportal) necrosis:**

**or formerly called piecemeal necrosis or chronic active hepatitis.**

Patients with **liver disease for 6 months or more** and **portal-based inflammation**, fibrosis with ballooned hepatocytes & collagen deposition occurs in periportal zone forming septa that extend into lobule.

**b. Chronic hepatitis without interface hepatitis :**formerly called **chronic persistent hepatitis** or **chronic lobular hepatitis** (if focal hepatocytes apoptosis).

# VIRAL HEPATITIS

- An infection of hepatocytes characterized by diffuse inflammation and widespread liver cell necrosis.
- 95% caused by hepatotropic viruses named from A to G hepatitis.
- All lead to Acute, Chronic & carrier viral hepatitis.

**(1) Hepatotropic viruses. Include**

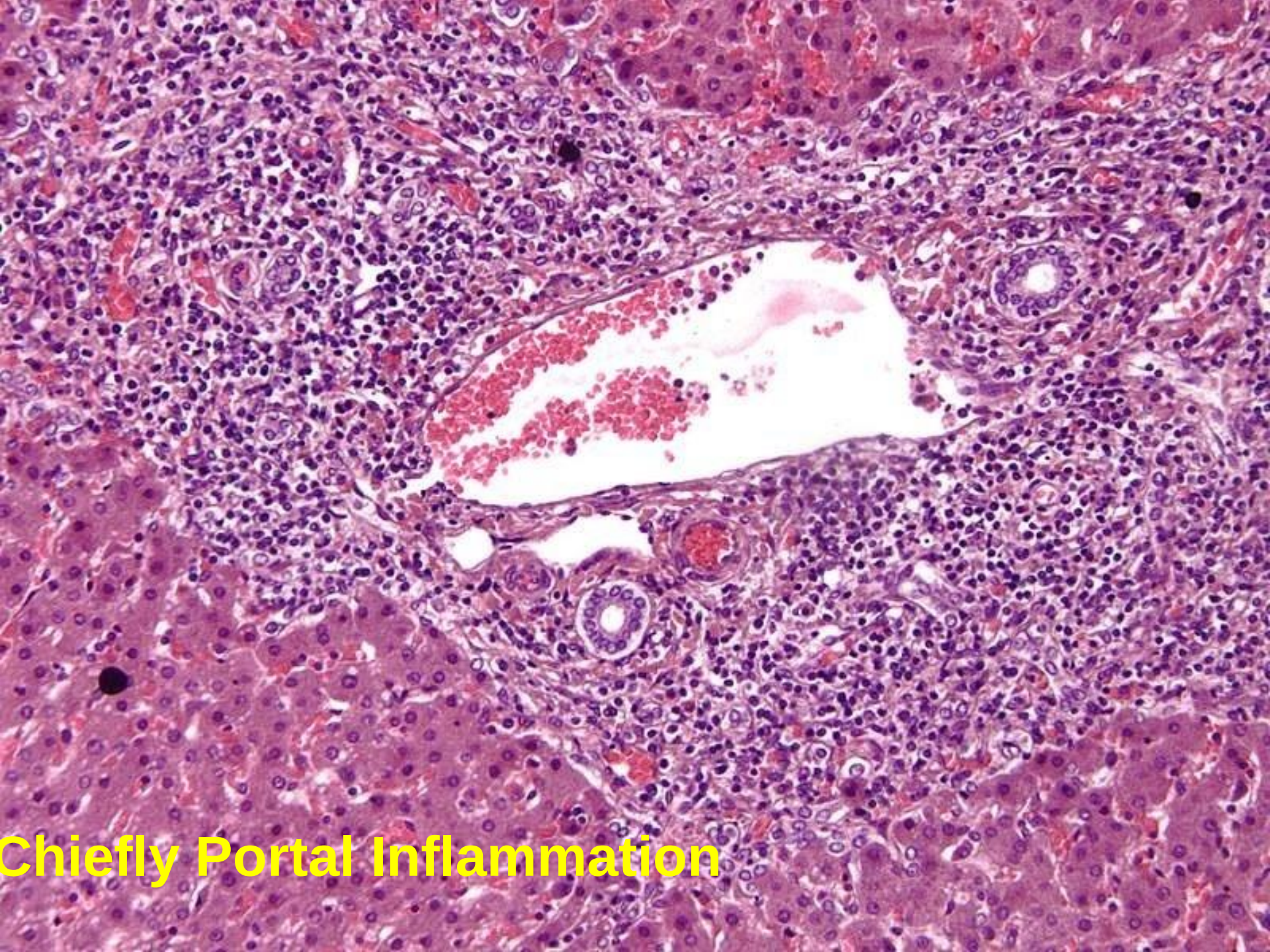
1. **Hepatitis A Virus (HAV)**
2. **Hepatitis B Virus (HBV)**
3. **Hepatitis C Virus (HCV)**
4. **Hepatitis D Virus (HDV)**
5. **Hepatitis E Virus (HEV)**
6. **Hepatitis G Virus (HGV)**

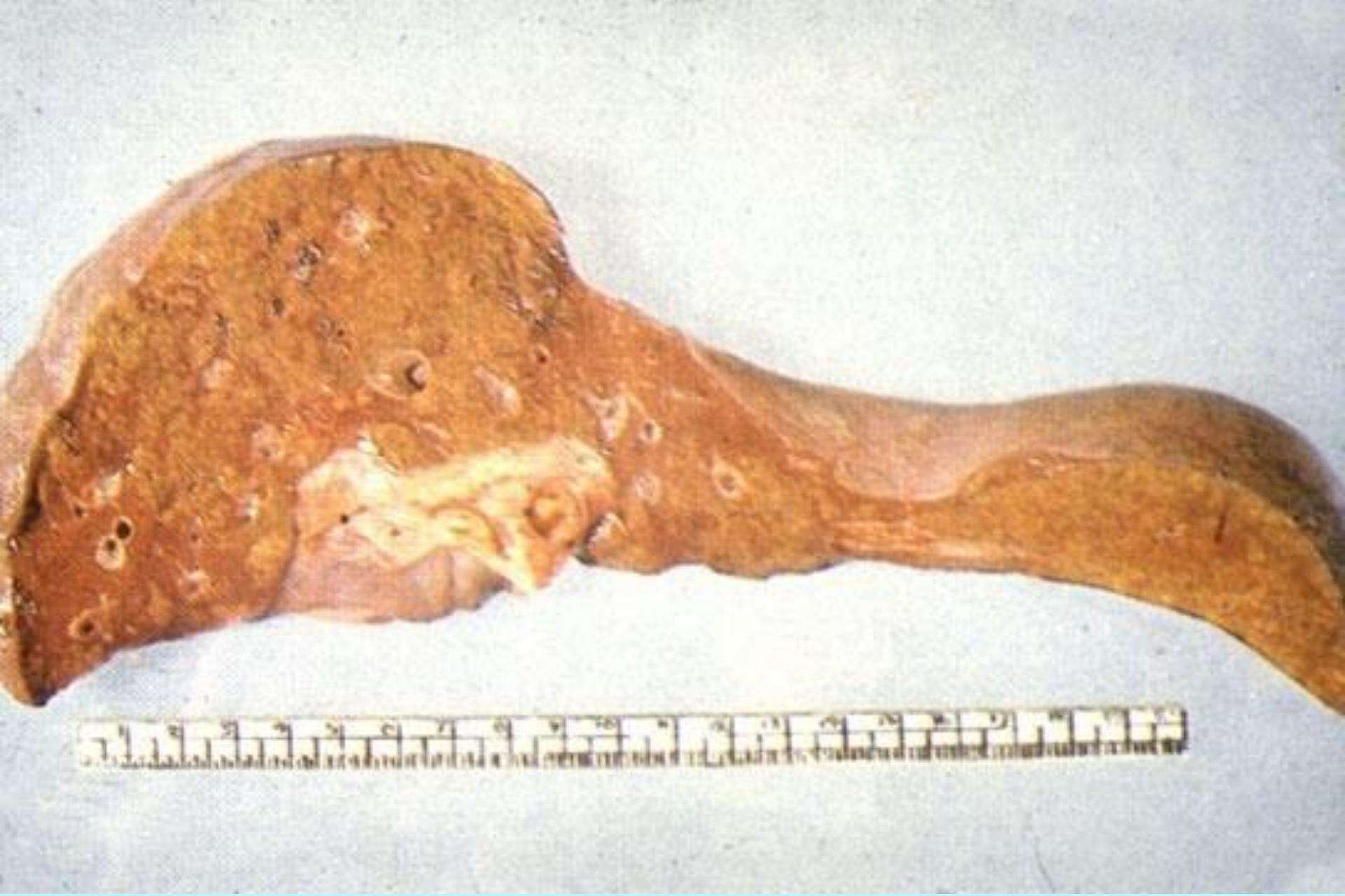
**(2) Systemic viruses. Include.**

1. **infectious mononucleosis (EBV)**
2. **Cytomegalovirus virus (CMV)**
3. **Yellow fever virus**
4. **Others (Rubella, adenovirus…….etc)**

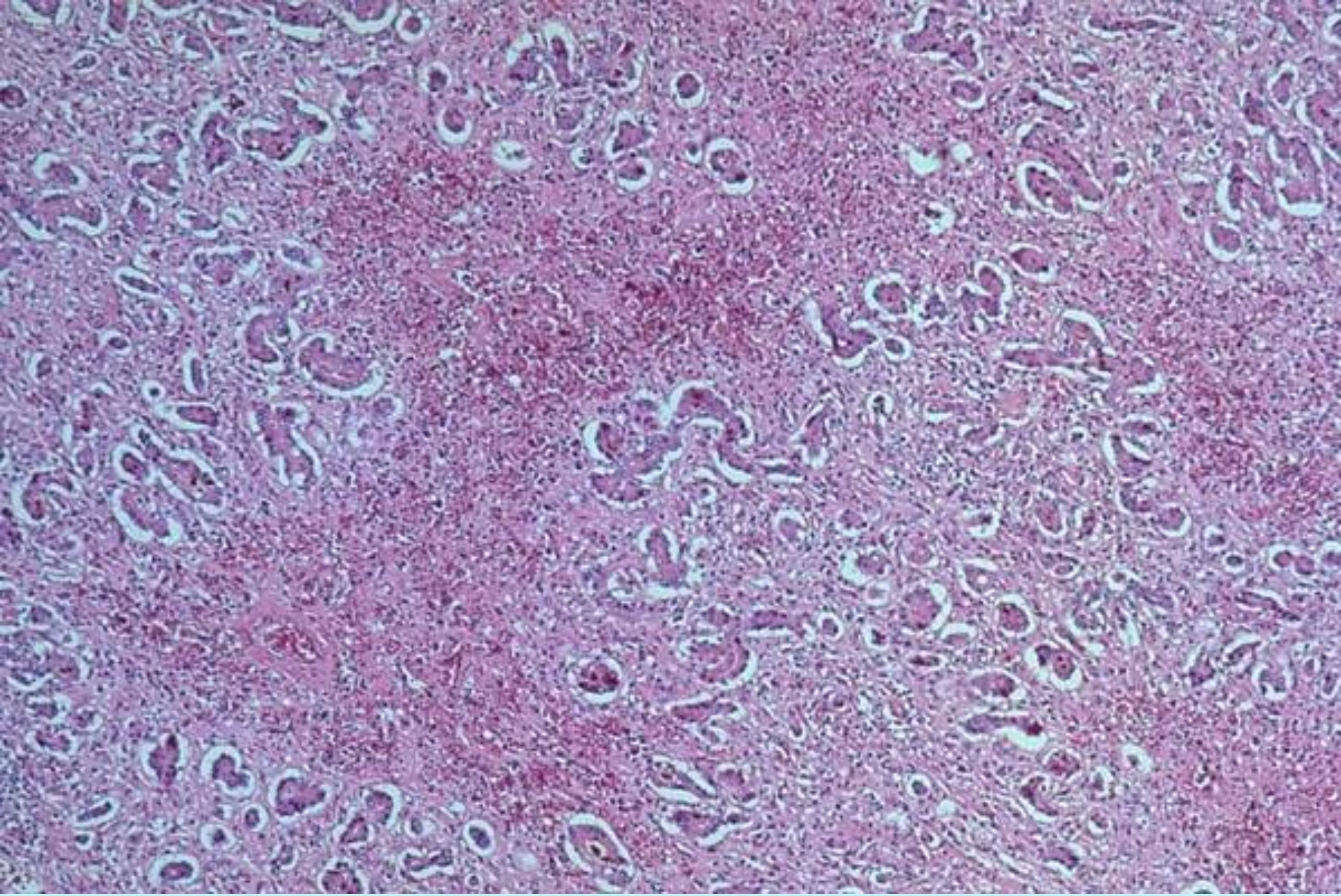
# VIRAL HEPATITIS

- A, **B, C**, D, E, G.
- mic: They all look similar, ranging from a few extra portal triad lymphocytes, to "FULMINANT" hepatitis with total collapse of lobules
- Associated with **full recovery** (usual), **chronic progression** over years leading to cirrhosis (not rare), risk of **hepatocelular carcinoma** (uncmmon), or **death** (uncommon).


Chiefly Portal Inflammation



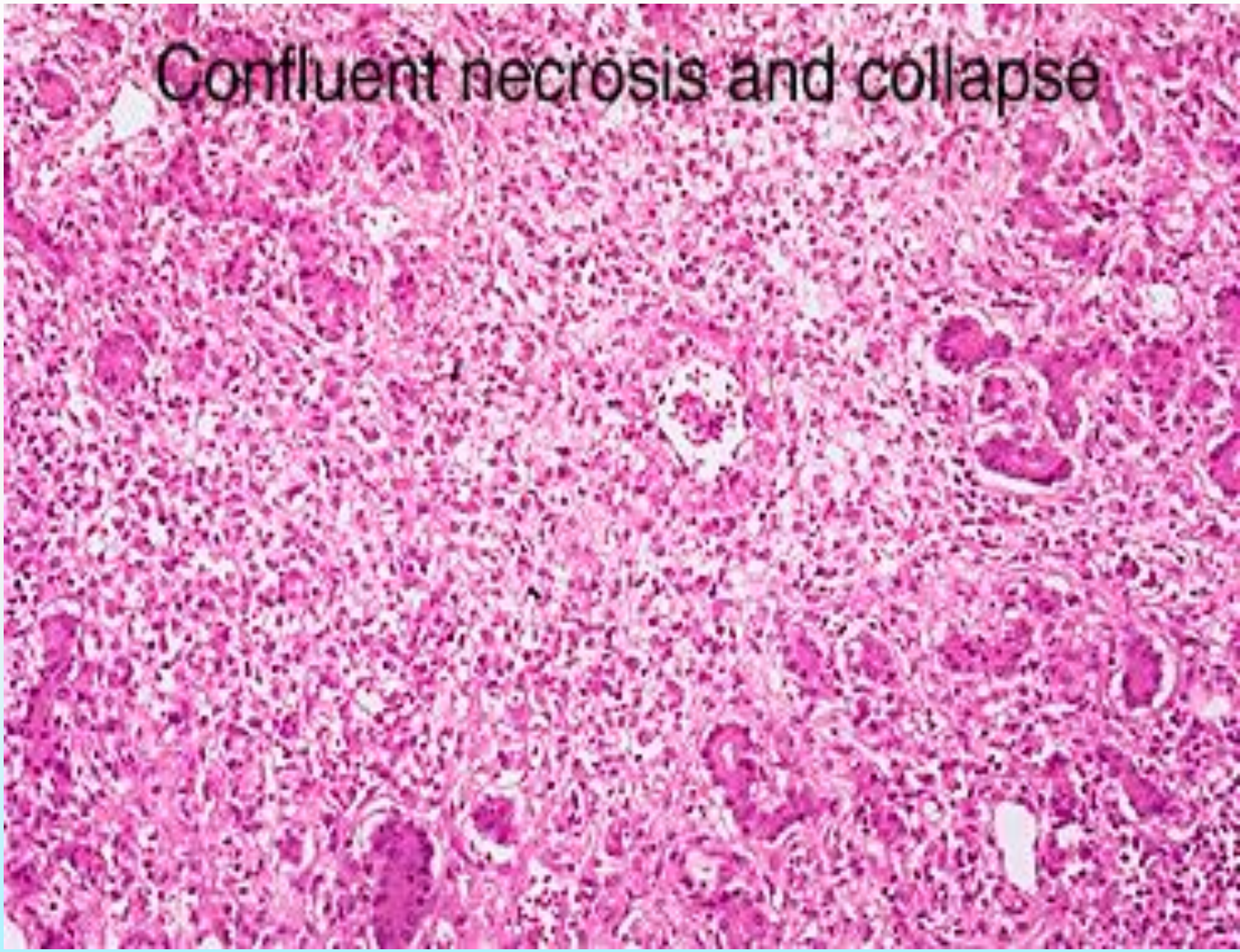
# FULMINANT HEPATITIS



# “FULMINANT” Acute Viral Hepatitis

# HISTOLOGY OF FULMINANT HEPATITIS

Extensive liver destruction with collapse of normal architecture, presence of residual hepatocytes & inflammatory cells



# *I- Acute viral hepatitis*

**1-Hepatitis A virus:** (benign self limited disease).

- **Is single stranded RNA virus**
- Incubation period of **2-6 weeks.**
- HAV does **NOT cause chronic hepatitis or a carrier state & rarely cause fulminant hepatitis**.
- HAV is **more common in developing countries** & **more in children** but it causes more morbidity in older age.
- Mode of transmission is by **feco-oral route** via contaminated water.
- HAV has **no role in etiology of hepatocellular carcinoma**.

# 2- Hepatitis B virus

- Is a DNA virus, a member of the **hepadna** group viruses.
- The complete (mature) infective virion is a spherical double layered (**Dane particle**) consisting of the following antigens:

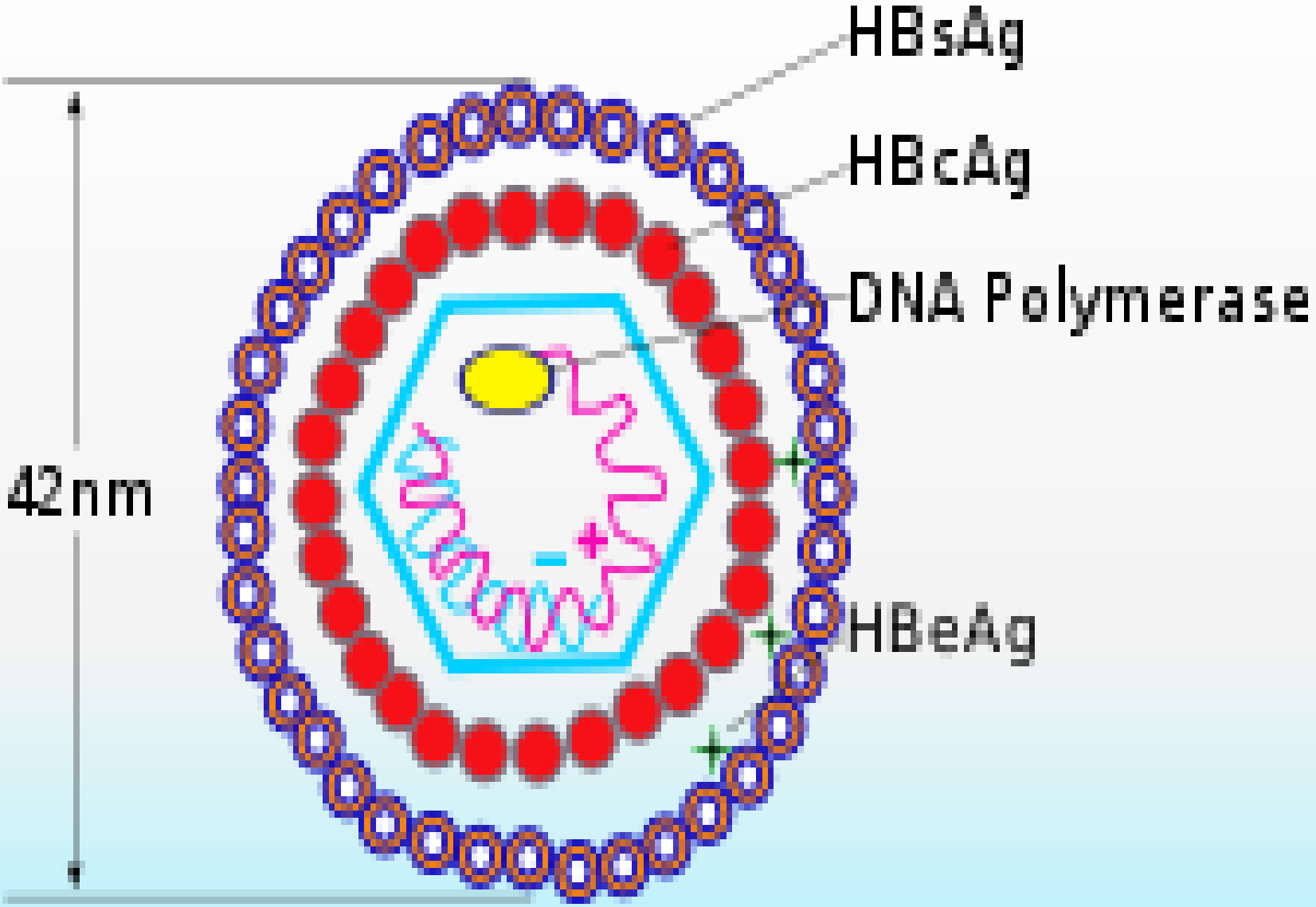
(1) **HBcAg** (hepatitis **B core antigen**) this Ag is retained in the infected hepatocytes. & this Ag has its antibodies (antiHBc).

(2) **HBeAg** (hepatitis **B e antigen**) this Ag is **secreted into the blood & its antiHBe**.

(3) **HBsAg** (hepatitis **B surface antigen**) also present **in the blood & its antiHBs**.

(4) A protein of **X region** (**HBV X-protein**) which affect the host genes & may play a role in the causation of **hepatocellular carcinoma.**

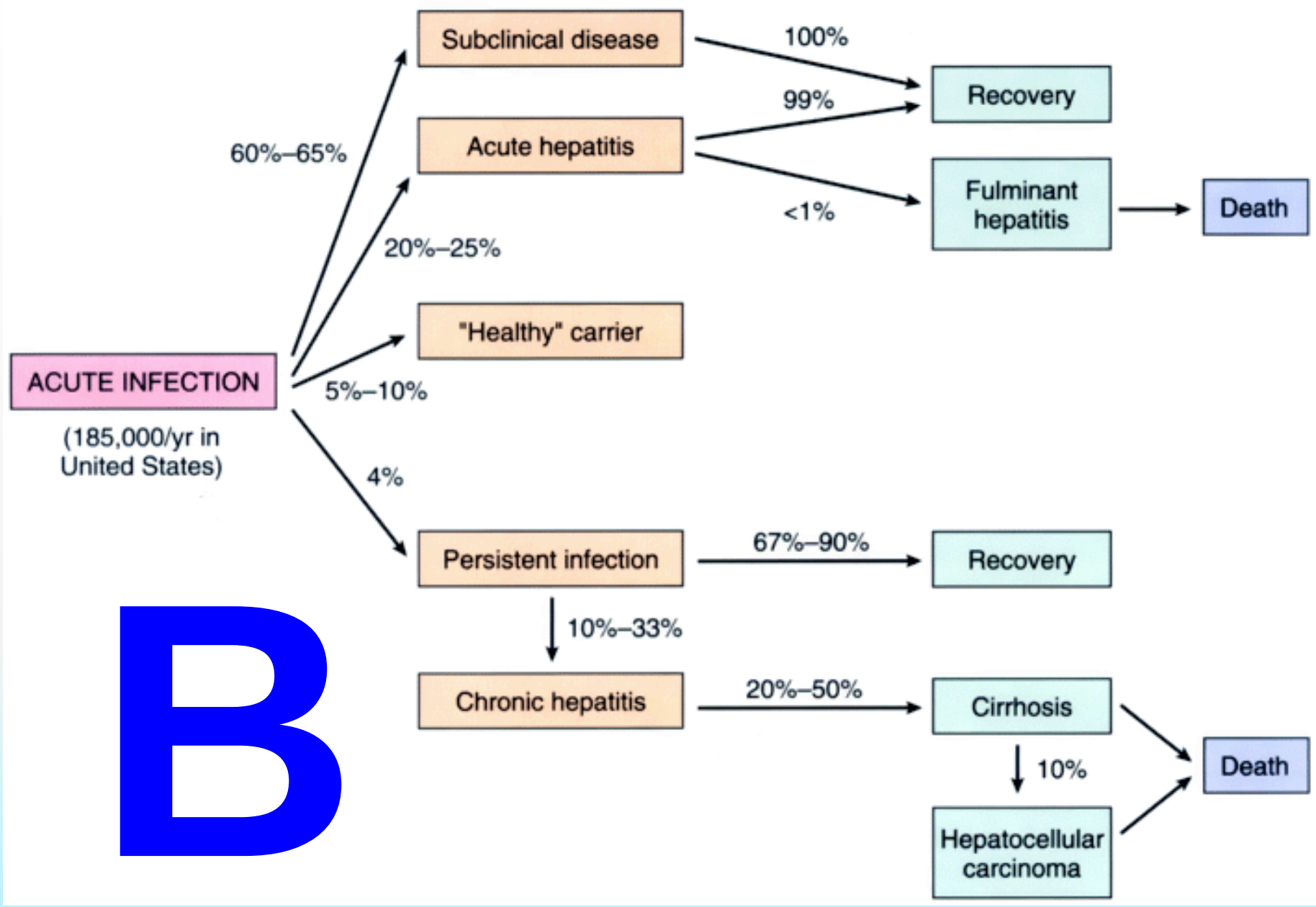
(5) **DNA polymerase**.


HBsAg
HBcAg
DNA Polymerase
HBeAg
42nm

# HBV Epidemiology:

- **Incubation period ( 4 – 26 weeks).**
- It is present in the blood & in all physiological & pathological body fluids (effusions) except the stool.
- Transmission frequently through blood & body secretions:

  ( semen, saliva, sweat, tears & breast milk) by transfusions, blood products, dialysis, needles, i.v. drug abuse & homosexual activity.
- Vertical transmission from mother to fetus during birth
- Occurs in any age group, it is more severe than hepatitis A with a higher mortality, & infection may result in the development of a carrier state or in progression to chronic liver disease.
- Synthetic **vaccines** for HBV composed of recombinant HBsAg which is highly effective & confers a life - long immunity.


ACUTE INFECTION
(185,000/yr in United States)
60%–65%
20%–25%
5%–10%
4%
Subclinical disease
Acute hepatitis
"Healthy" carrier
Persistent infection
Chronic hepatitis
100%
99%
<1%
Recovery
Fulminant hepatitis
Death
67%–90%
Recovery
10%–33%
20%–50%
Cirrhosis
10%
Hepatocellular carcinoma
Death

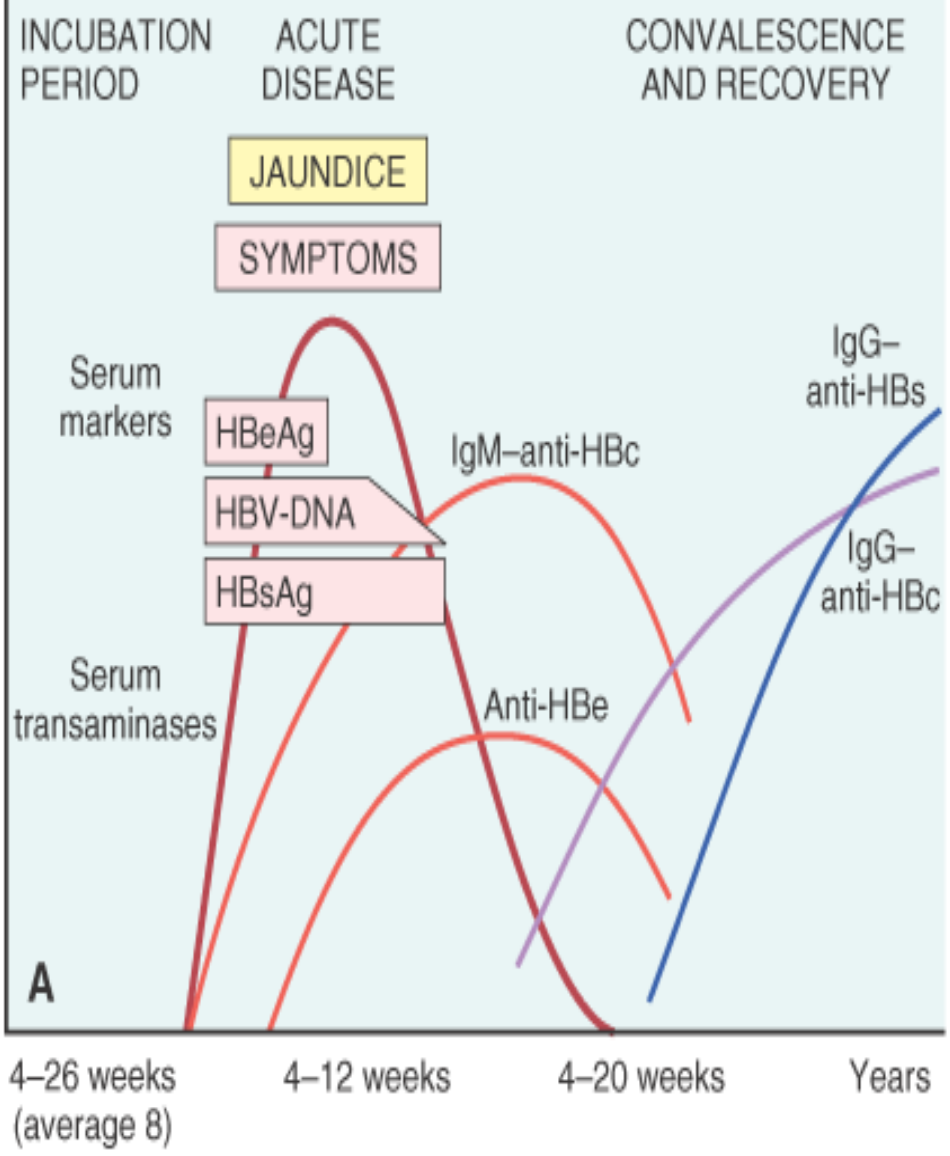
B

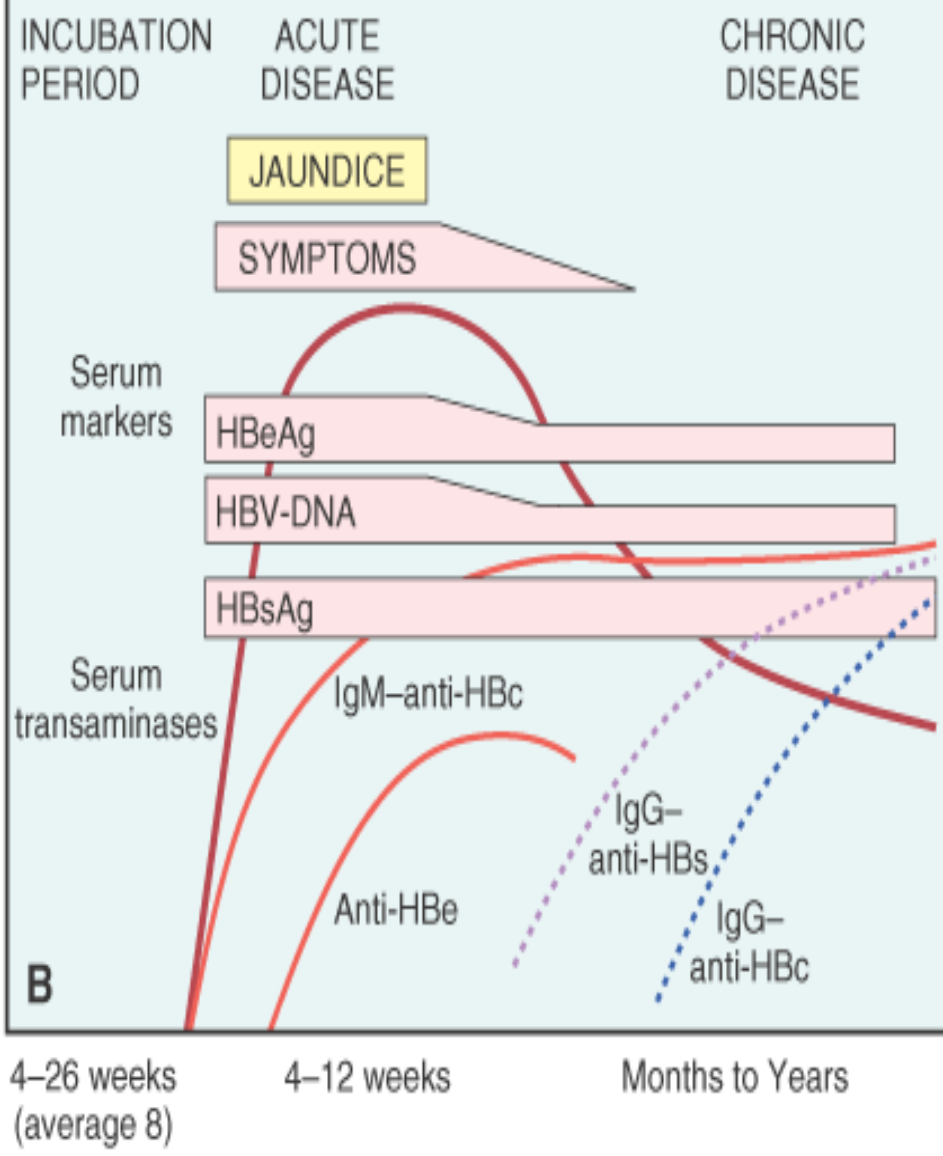
# Pathogenesis:

- HBV is **not directly cytopathic**,.
- but cytotoxic CD8+ T lymphocytes directed against HBV are the major mediators of the destruction of hepatocytes,
- as CD8+ recognized the infected hepatocytes that express the viral Ag conjugated with HLA - class I ( Human Leukocyte Ag) on their surfaces & kill them directly.

# Serological diagnosis:

- **HBsAg appears before the onset of symptoms, peaks during** active disease & declines to undetectable levels in 3-6 months **., Anti-HBs antibody does not rise until the acute disease is over & may persist for life, conferring protection;**
- The presence of **HBeAg, HBV-DNA & viral DNA polymerase** in the serum indicates **active viral replication & infectivity of the blood**.
- **Persistence of HBeAg** is an important indicator of continued **viral replication, infectivity, and probable progression to chronic hepatitis.**
- The appearance of **anti-HBe antibodies** implies that an **acute infection has peaked.**
- **IgM anti-HBc** (**indicative of hepatocyte destruction**).
- **Over a period of months the IgM anti-HBc antibody is replaced by IgG anti-HBc.**



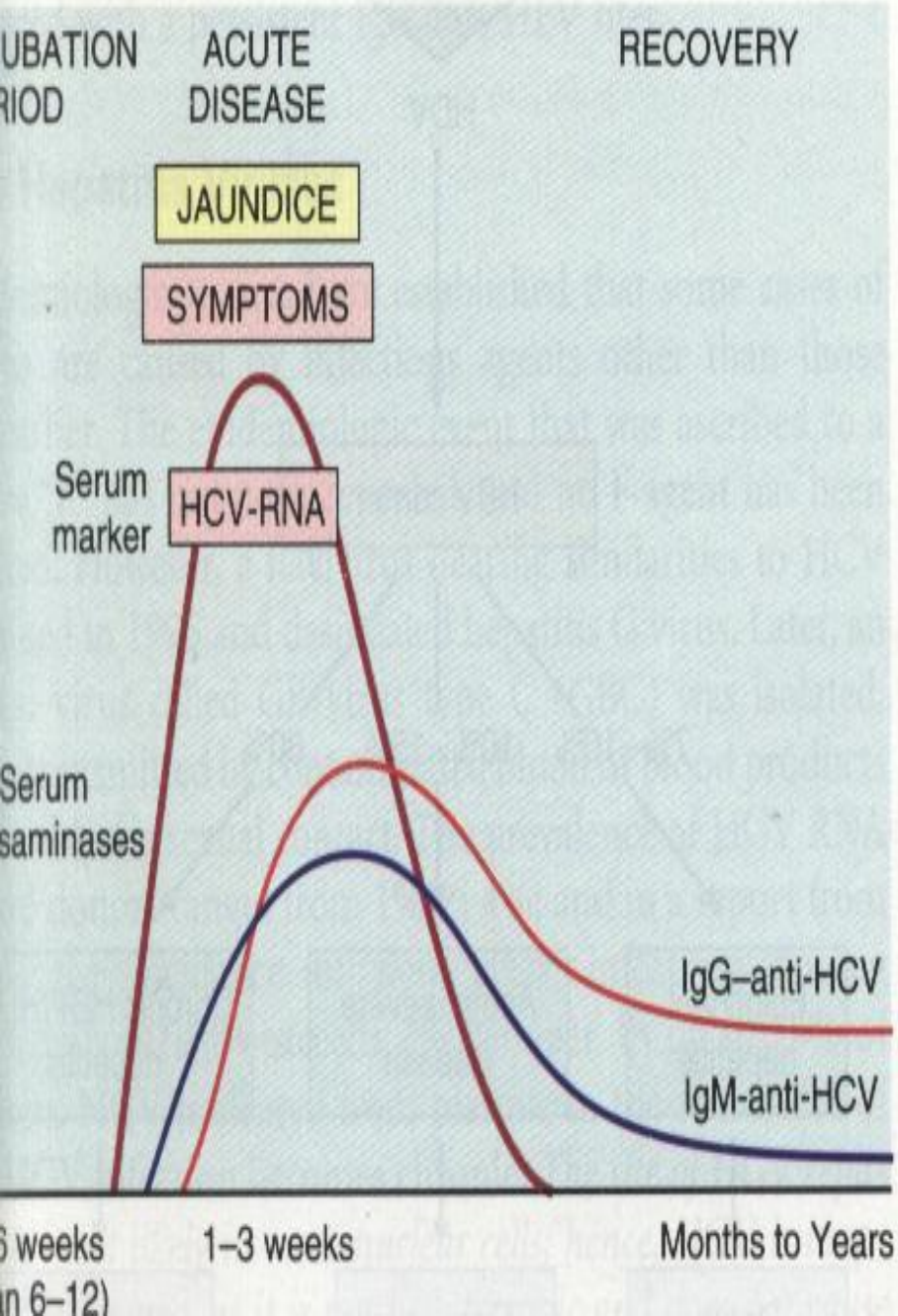

**Comple recovery**

**Chronic disease**

# 3- hepatitis C virus(HCV)

- **SS RNA virus**, with IP of **2 to 26 weeks**.
- The clinical course of HCV hepatitis is usually milder than HBV hepatitis & is asymptomatic in 75% of individual.
- The major **routes of transmission** : inoculations & blood transfusions, & IV drugs.
- HCV has a higher rate of progression to chronic disease & eventual cirrhosis in 20% of cases.
- Persistent infection with HCV is the hallmark of the disease & the level of anti-HCV antibodies are not significant to prevent persistent infection.
- HCV may also play important role in etiology of hepatocellular carcinoma (HCC).

- HCV RNA is detectable in blood for 1 to 3 weeks and is accompanied by elevations in serum aminotransferase.
- Although neutralizing anti-HCV antibodies develop within weeks to a few months, they *do not confer effective immunity*.


UBATION
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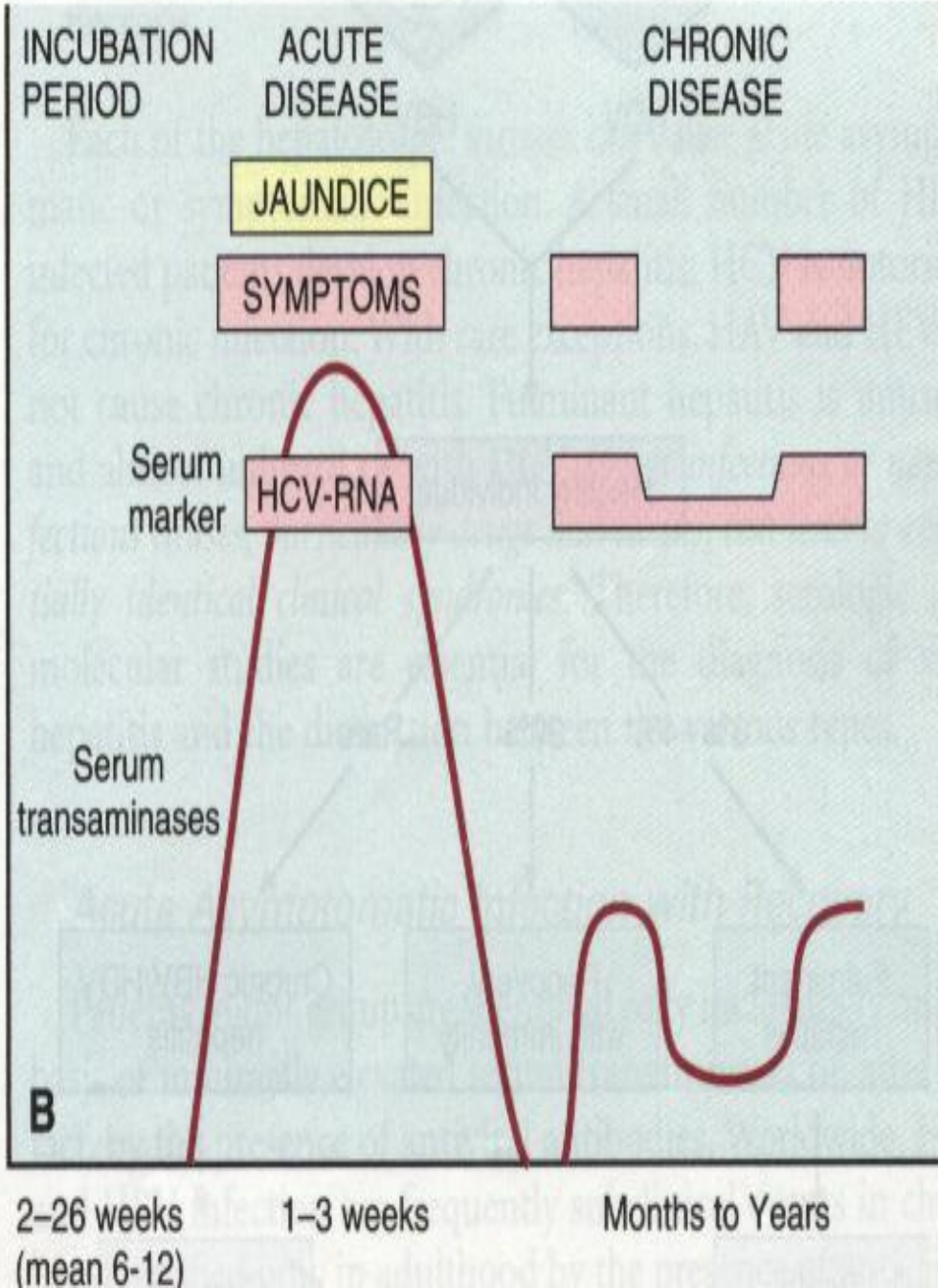
IgM-anti-HCV
6 weeks
n 6–12)
1–3 weeks
Months to Years


INCUBATION
PERIOD
ACUTE
DISEASE
CHRONIC
DISEASE
JAUNDICE
SYMPTOMS
Serum
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HCV-RNA
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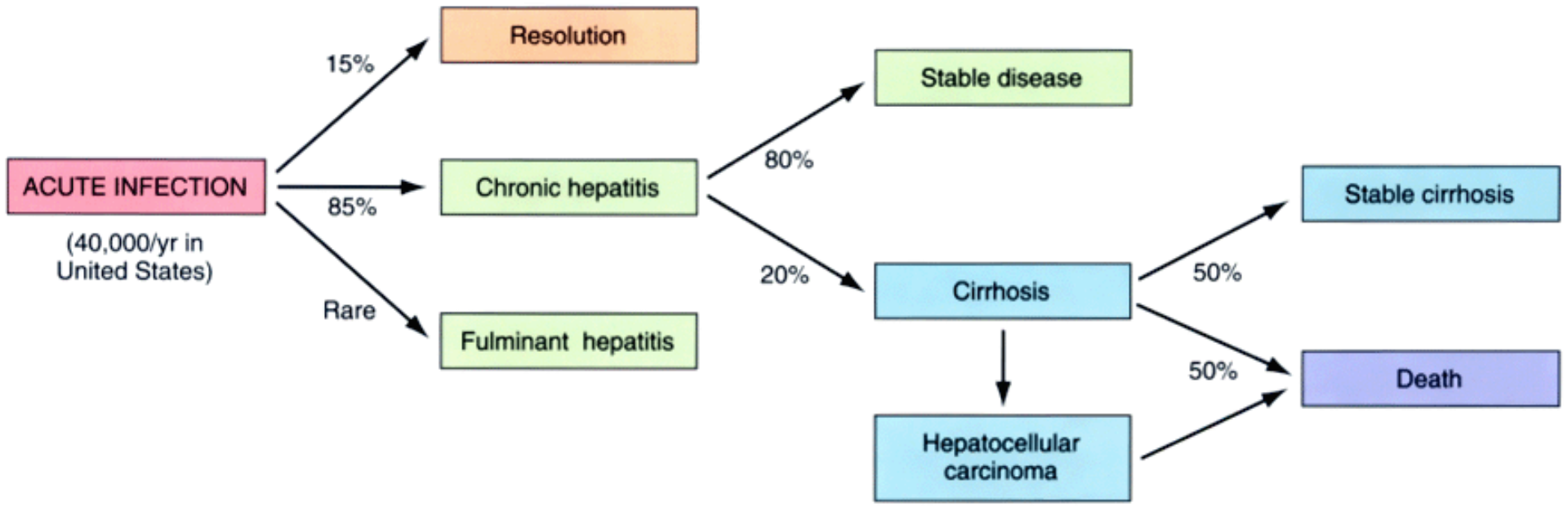
(mean 6-12)
1–3 weeks
Months to Years




# C

**LESS common than B (one fourth)**

**LESS dangerous than B in the acute phase**

**MORE likely to go chronic than B**

**MORE closely linked with HCC than B**

**C= Chronic, Carrier , Cirrhosis, Ca**

# HCV

- In **persistent infection**, circulating **HCV-RNA** is detectable, and aminotransferases show episodic elevations.
- ***Persistent infection*** *is the hallmark of HCV infection, occurring in 80% to 85% of individuals with subclinical or asymptomatic acute infection*.
- Cirrhosis develops in 20% of persistently infected individuals.
- Fulminant hepatitis is rare.

# 4- Hepatitis D Virus (HDV):

- Also called hepatitis delta virus, HDV is a unique RNA virus that is replication defective, causing infection only when it is encapsulated by HBsAg,
- *HDV is absolutely dependent on HBV coinfection for multiplication.*
- **Mode of transmission** is via blood transfusion & drug addiction.

# HDV

- **Two types of infection with HDV + HBV:**

(1) **Coinfection.** This type of infection occurs after exposure to serum containing HDV & HBV. This type of infection is rarely progress to fulminant hepatitis & chronic hepatitis.

(2) **Superinfection.** This type of infection occurs in chronic carrier of HBV with new inoculum of HDV. **This type of infection can progress to chronic hepatitis** within 4 to 7 weeks.

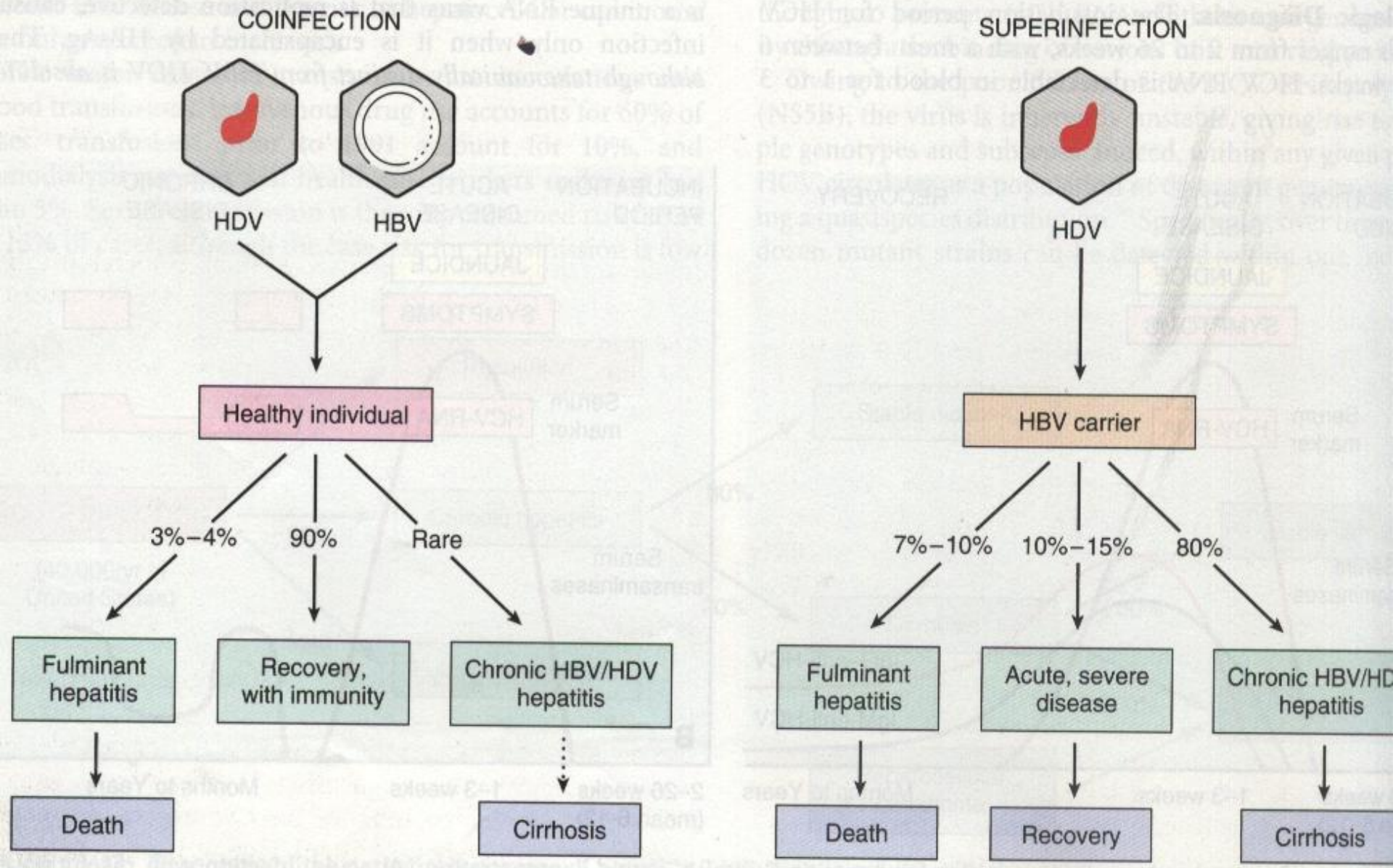



**FIGURE 18–15** Differing clinical consequences of two patterns of combined hepatitis D virus and hepatitis B virus infectio

# 5- Hepatitis E Virus (HEV):

- HEV is a **single-stranded RNA virus.**
- HEV hepatitis is an **enterically transmitted, waterborne infection** HEV is **endemic in India** (where it was first documented as caused by fecal contamination of drinking water).
- In most cases, the disease is **self-limited;** HEV is not associated with chronic liver disease or persistent viremia.
- *A characteristic feature of the infection is **the high mortality rate among pregnant women, approaching 20%.***
- The average incubation period after exposure is 6 weeks (range, 2-8 weeks).
- A specific antigen (HEV Ag) can be identified in the cytoplasm of hepatocytes during active infection.
- Virus can be detected in stools, and **anti-HEV IgG and IgM antibodies are detectable in serum.**

**Table 18-3** The Hepatitis Viruses

| Virus | Hepatitis A | Hepatitis B | Hepatitis C | Hepatitis D | Hepatitis E |
|---|---|---|---|---|---|
| Type of virus | ssRNA | partially dsDNA | ssRNA | Circular defective ssRNA | ssRNA |
| Viral family | Hepatovirus; related to picornavirus | Hepadnavirus | Flaviviridae | Subviral particle in Deltaviridae family | Hepevirus |
| Route of transmission | Fecal-oral (contaminated food or water) | Parenteral, sexual contact, perinatal | Parenteral; intranasal cocaine use is a risk factor | Parenteral | Fecal-oral |
| Mean incubation period | 2 to 6 weeks | 2 to 26 weeks (mean 8 weeks) | 4 to 26 weeks (mean 9 weeks) | Same as HBV | 4 to 5 weeks |
| Frequency of chronic liver disease | Never | 5%-10% | >80% | 10% (co-infection); 90%-100% for superinfection | In immunocompromised hosts only |
| Diagnosis | Detection of serum IgM antibodies | Detection of HBsAg or antibody to HBcAg; PCR for HBV DNA | 3rd-generation ELISA for antibody detection; PCR for HCV RNA | Detection of IgM and IgG antibodies; HDV RNA serum; HDAg in liver | Detection of serum IgM and IgG antibodies; PCR for HEV RNA |

dsDNA, Double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDAg, hepatitis D antigen; HDV, hepatitis D virus; HEV, hepatitis E virus; IV, intravenous; PCR, polymerase chain reaction; ssRNA, single stranded RNA.

From Washington K: Inflammatory and infectious diseases of the liver. In Iacobuzio-Donahue CA, Montgomery EA (eds): Gastrointestinal and Liver Pathology. Philadelphia, Churchill Livingstone; 2005.

# Morphologic features of viral hepatitis:

The morphologic changes in acute & chronic hepatitis are shared among the hepatotropic viruses & can mimic by drug reactions **or autoimmune hepatitis**.

**(1) In acute hepatitis.**

**Morphological changes include.**

**Gross:**

mild acute hepatitis appear normal or slightly mottled.

At the other end of the spectrum, in massive hepatic necrosis the liver may shrink greatly

# Microscopically

both acute and chronic hepatitis evoke a lymphoplasmacytic (mononuclear) infiltrate.

Portal inflammation in acute hepatitis is minimal or absent.

Most parenchymal injury is scattered throughout the hepatic lobule as "spotty necrosis" or **lobular hepatitis**

# Hepatocyte injury

**1-reversible :**

**A-(ballooning degeneration),** so that the cytoplasm looks empty and contains only scattered wisps of cytoplasmic reminants

**B-feathery degeneration**

**C. Cholestasis:** This means bile plugs in canaliculi & brown pigment of the hepatocytes.

**D. Fatty changes:** is mild; **except with HCV infection which produces fulminant fatty changes.**

**Irreversible changes (hepatocyte death) : Two patterns of are seen**

A-Apoptosis (councilman bodies ) Hepatocytes become intensely eosinophilic, & have fragmented nuclei

B-Necrosis(lytic rupture of cell membrane)

Near dead cells there is T cells with scavenger macrophages

In severe cases there is confluent necrosis of hepatocytes may lead to **bridging necrosis** connecting portal-to-portal, central-to-central, or portal-to-central regions of adjacent lobules & lobular disarray.