Hepatobiliary Pathology

LEC 1

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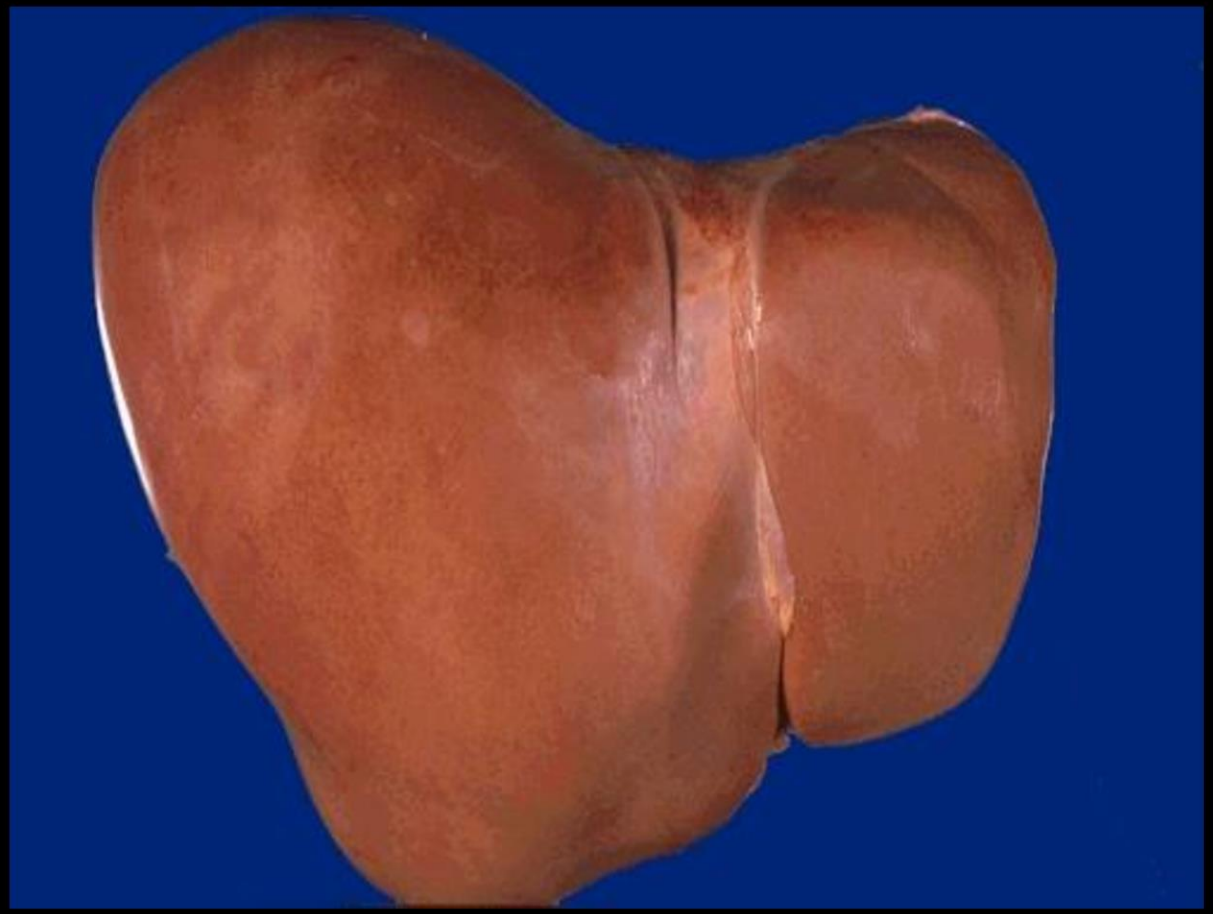
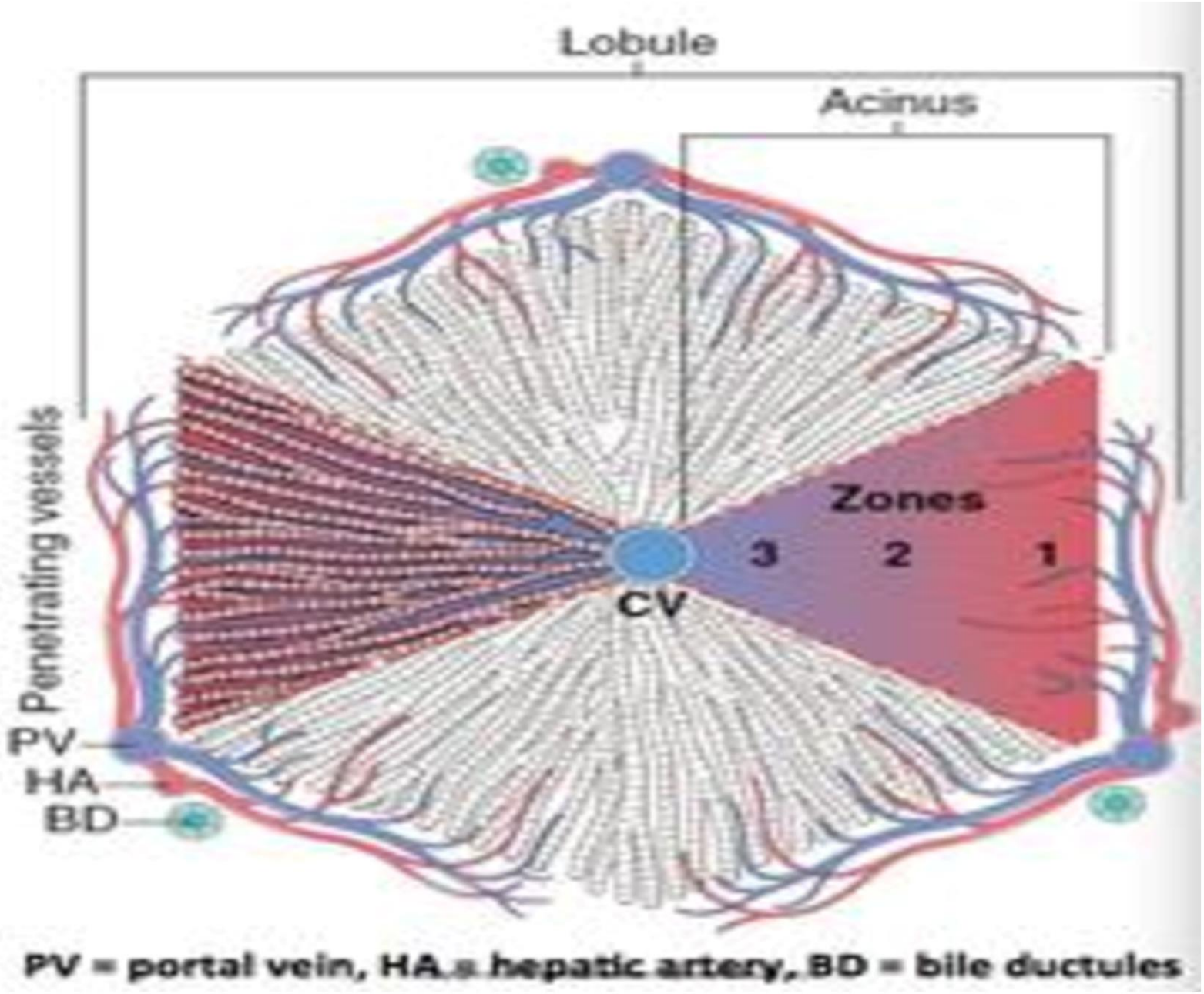
EXTERNAL SURFACE OF A NORMAL LIVER



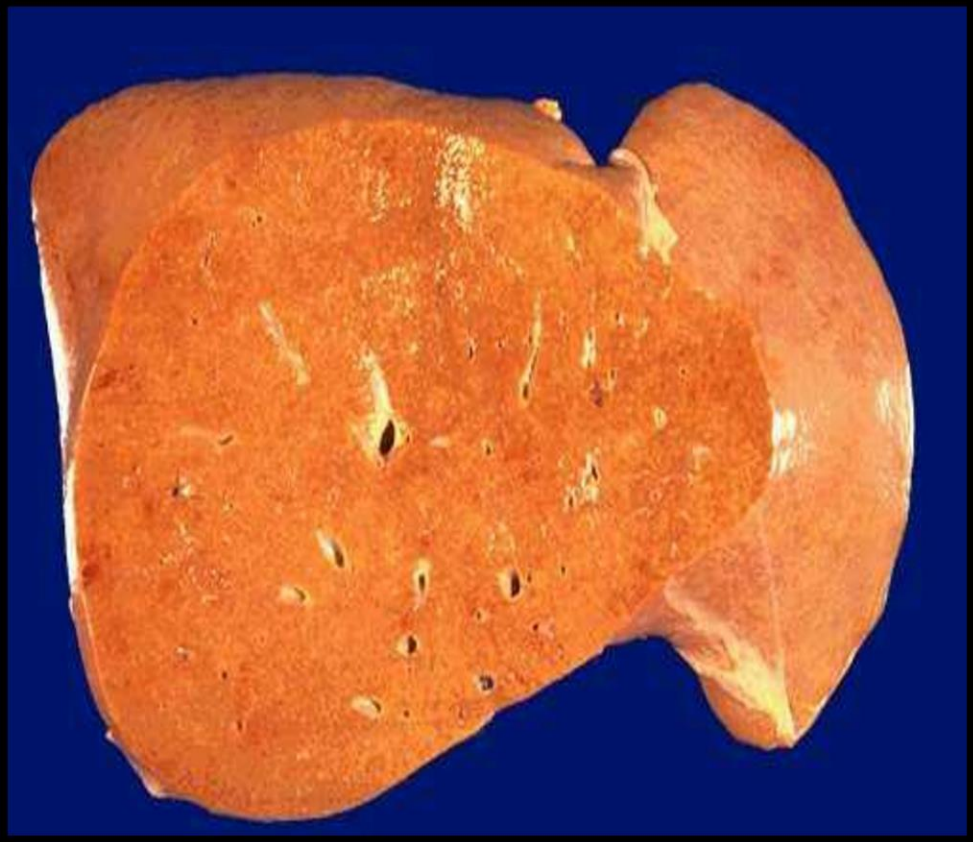
- -red - brown
- - smooth
- - soft

Normal liver: 1200 – 1600g


Lobule
Acinus
Penetrating vessels
PV
HA
BD
Zones
3
2
1
CV
PV = portal vein, HA = hepatic artery, BD = bile ductules

FATTY CHANGE: GROSS

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



General paranchymatous hepatic responses to liver injury

1- Inflammation (acute &chronic).

2- Degeneration & intracellular accumulation.

3- Necrosis and apoptosis.

4- Regeneration.

5- Fibrosis.

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 .

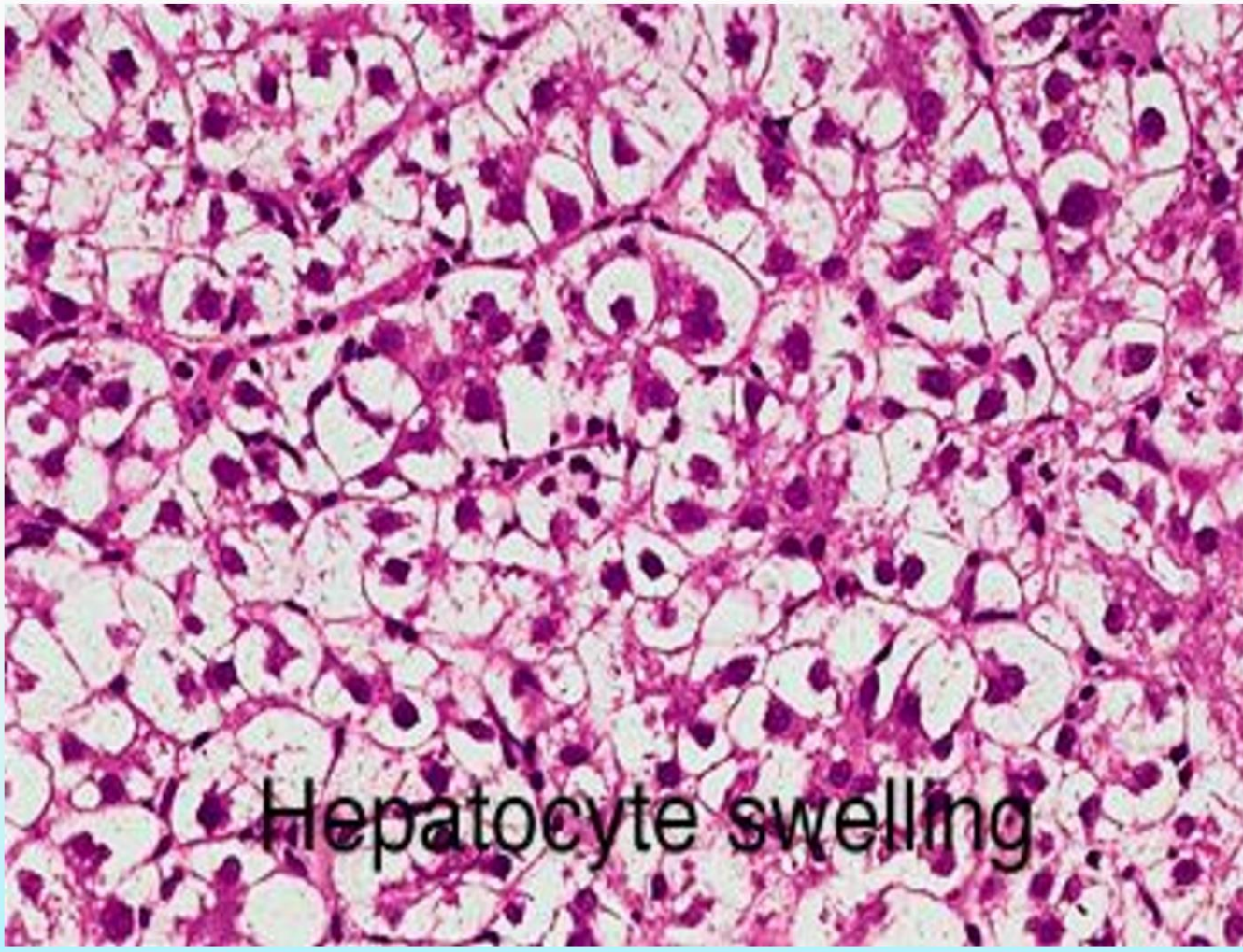
- **Foamy (feathery) degeneration**: foamy swollen hepatocytes due to retained pigments as bile, copper, iron materials

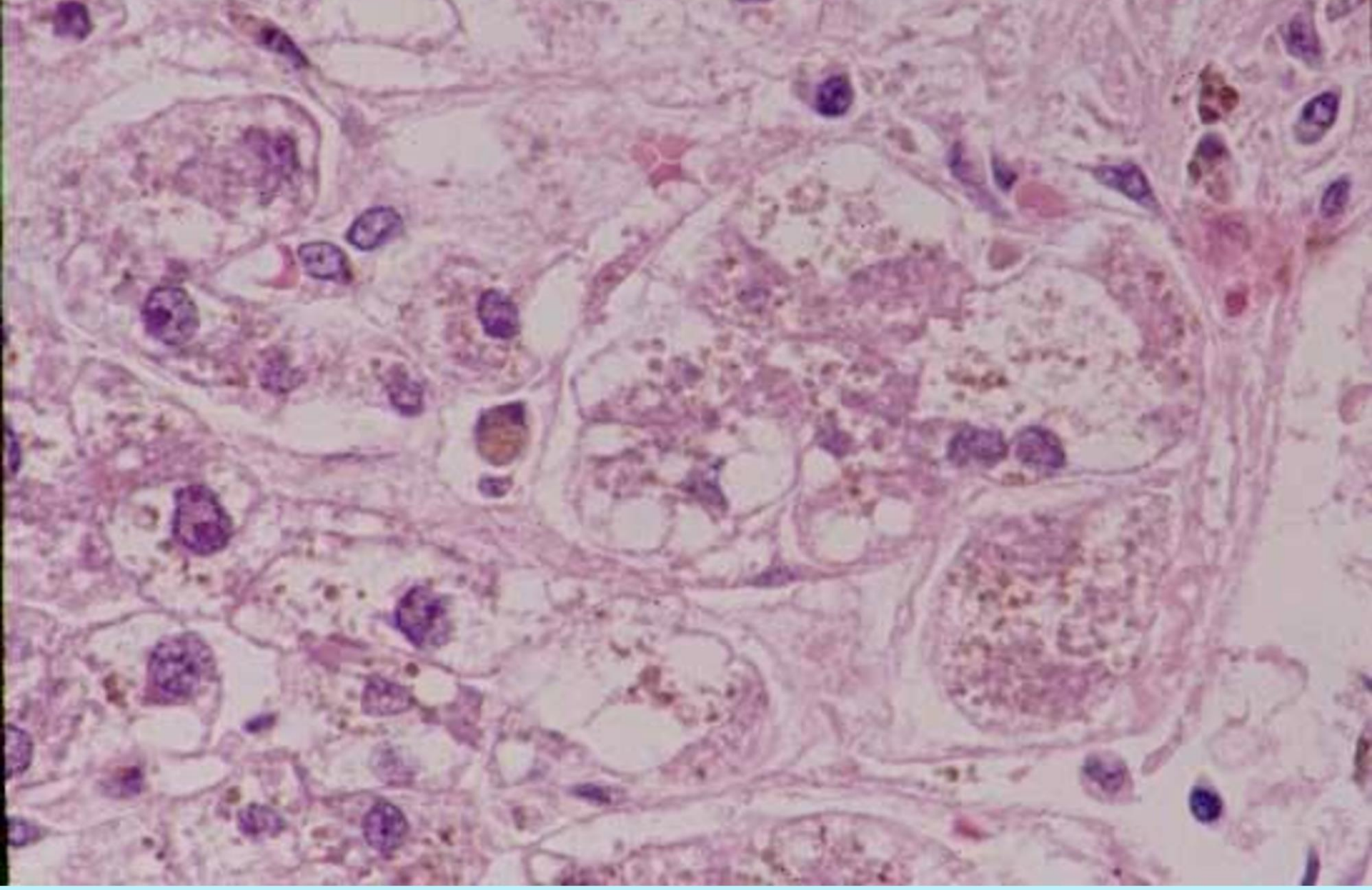
- **Steatosis** : accumulation of fat droplets in the hepatocytes (microvesicular & macrovesicular).

HISTOLOGIC PATTERNS OF HEPATIC INJURY

HEPATOCYTE SWELLING

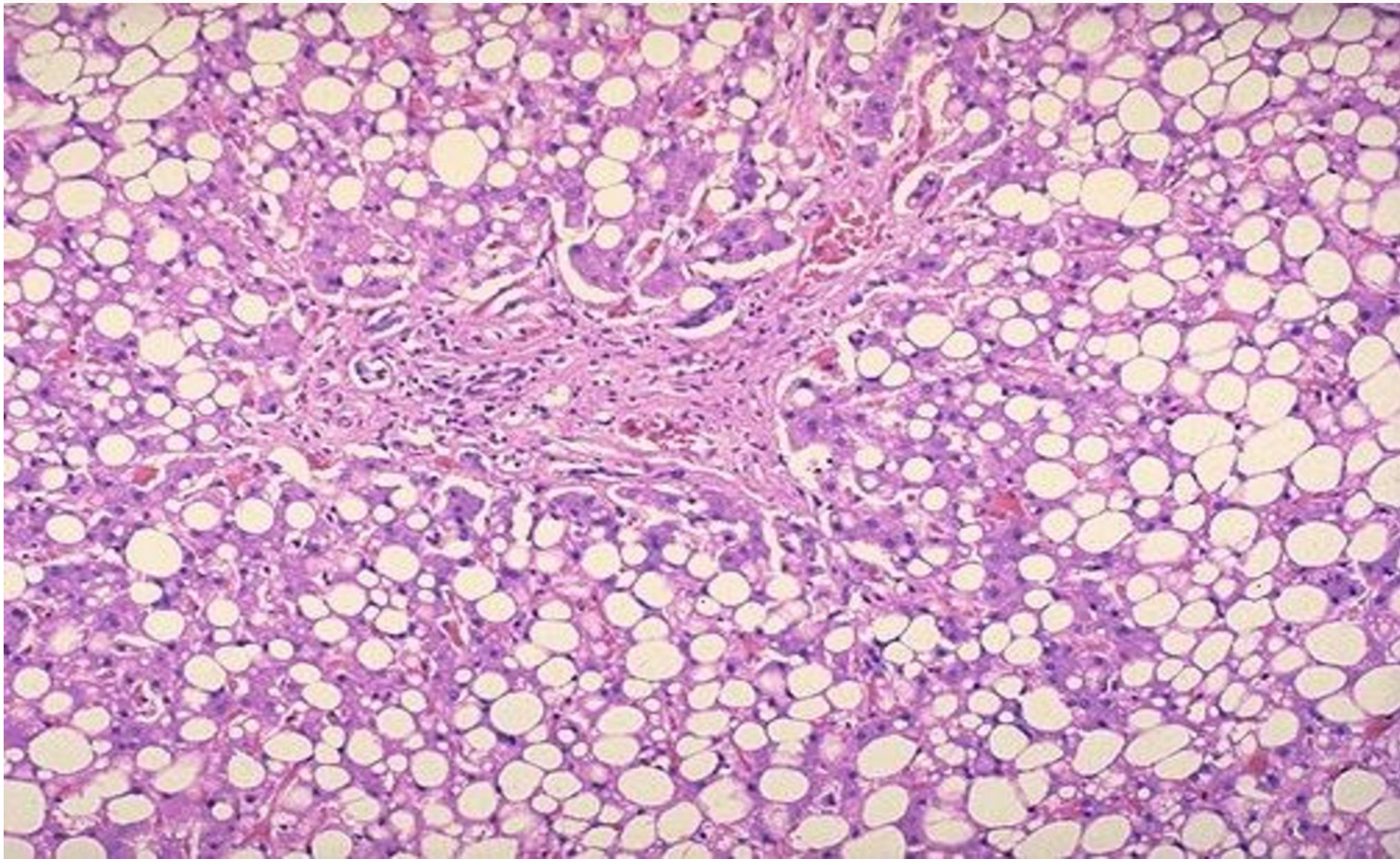
Swelling or hydropic change is a result of defects in membrane and/or mitochondrial function

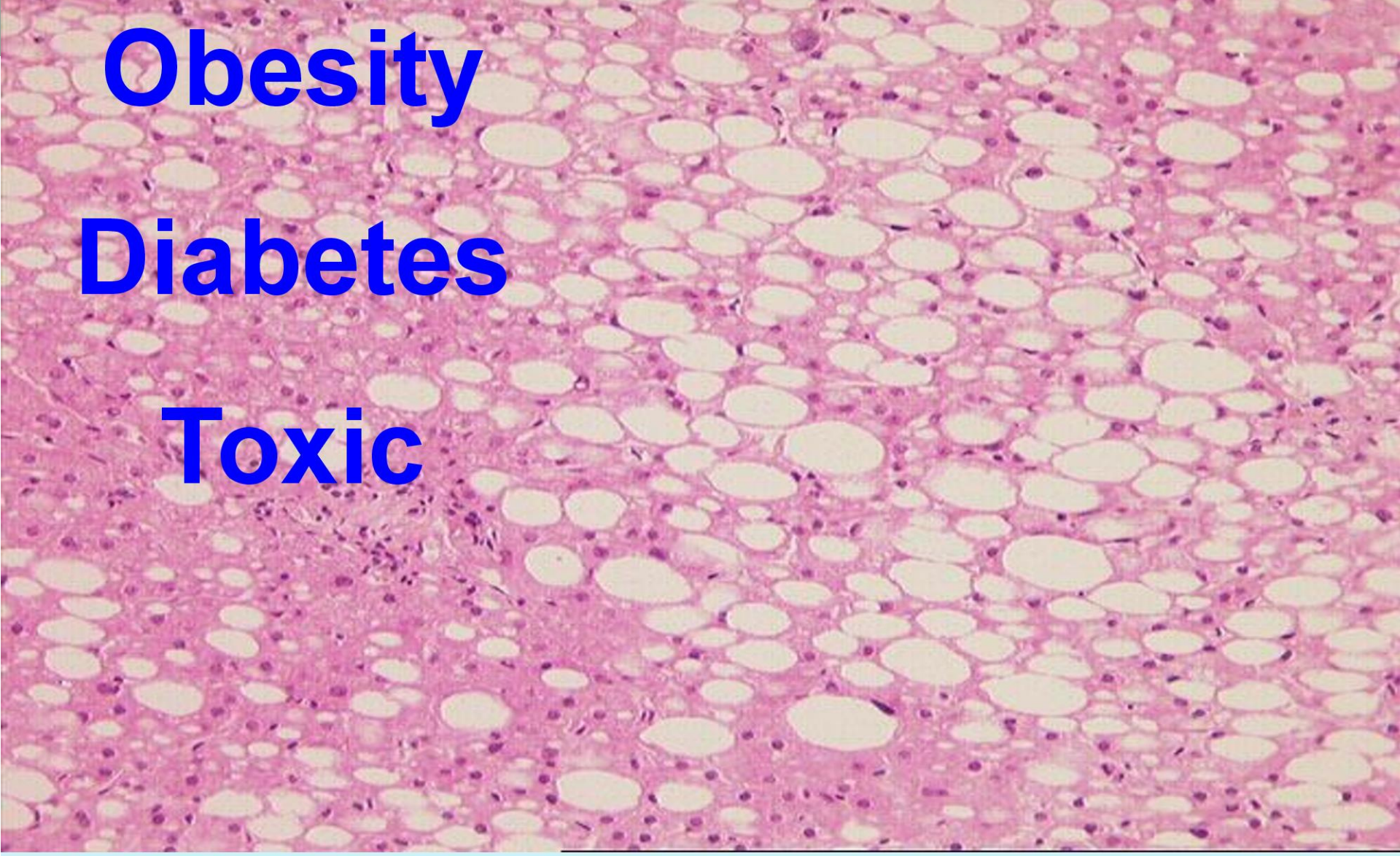




“FEATHERY” DEGENERATION

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



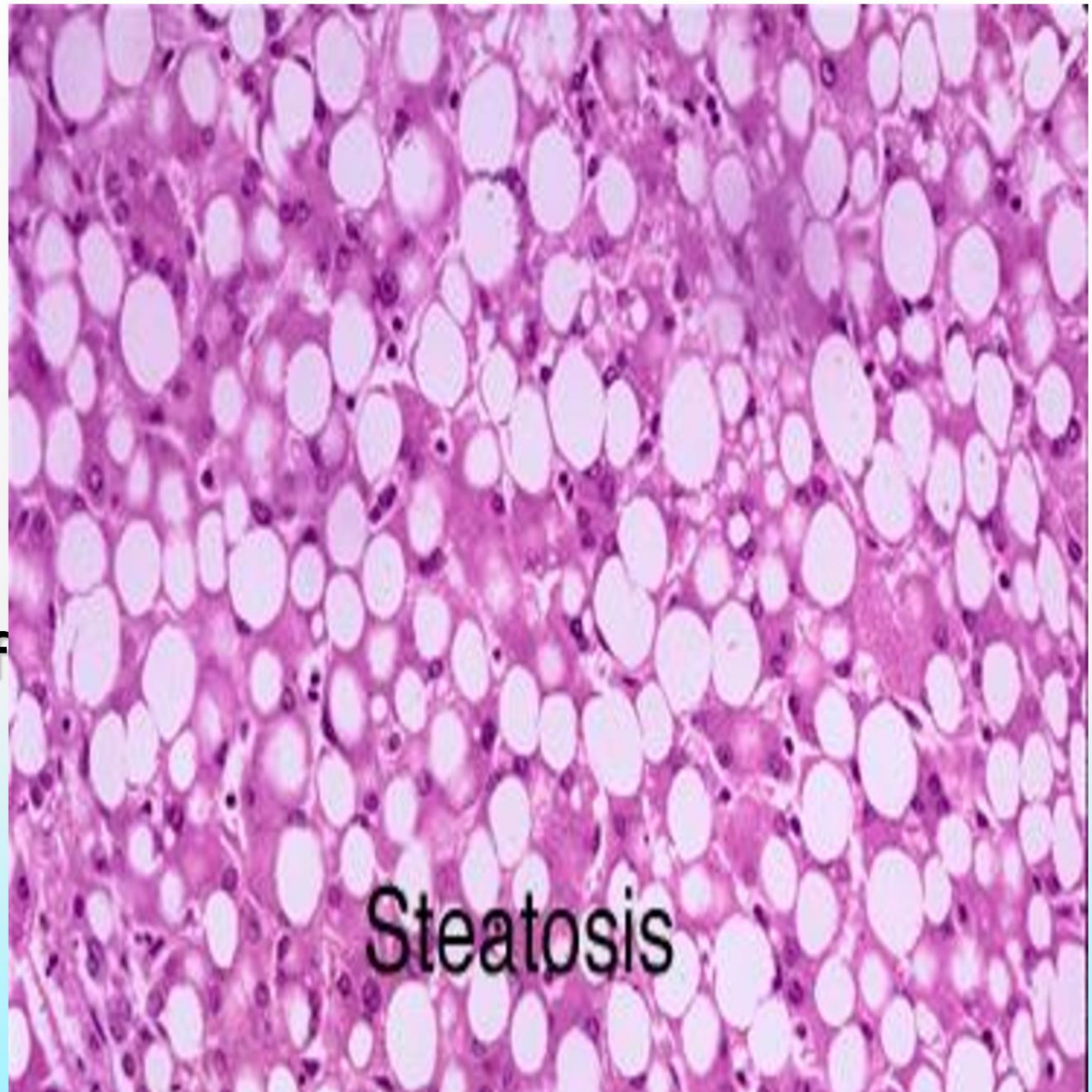


Fat vacuoles which are **LARGER** than hepatocytes is termed **MACRO**-vesicular.

HISTOLOGIC PATTERNS OF HEPATIC INJURY

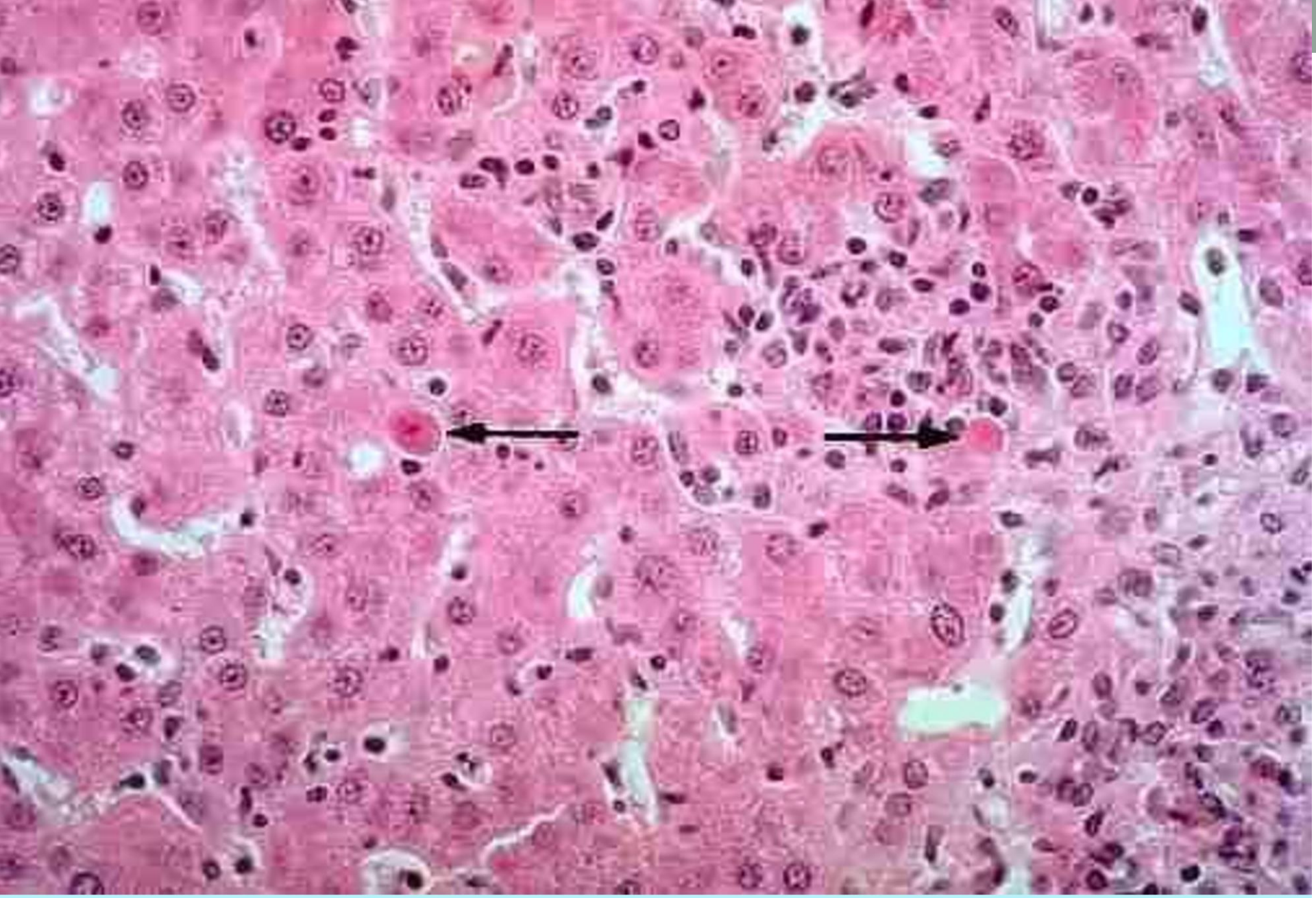
STEATOSIS

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

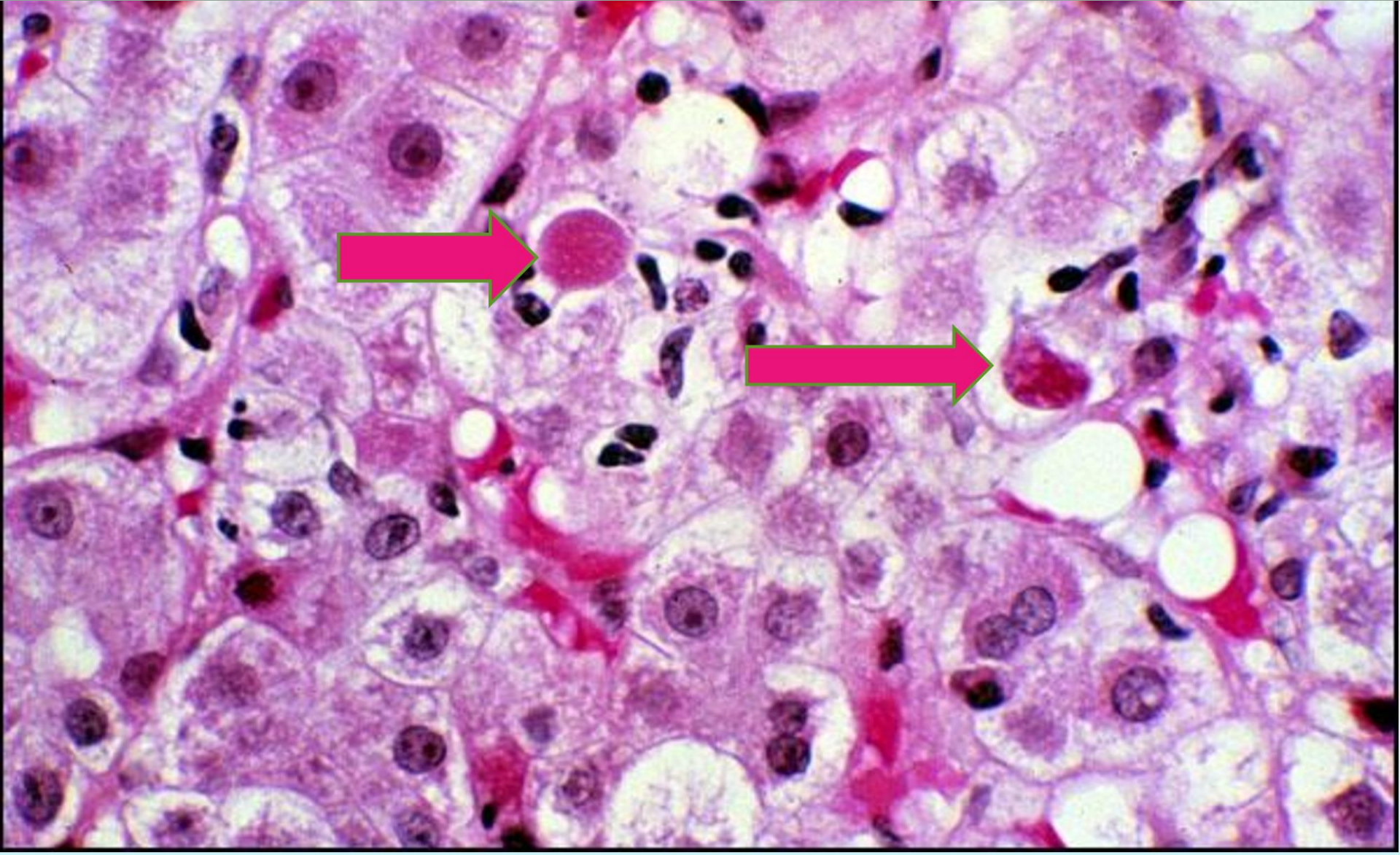


3- Necrosis and apoptosis

- 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

Histologic patterns of hepatic injury

NECROSIS

Coagulative necrosis:

preserved architecture

loss of cellular details

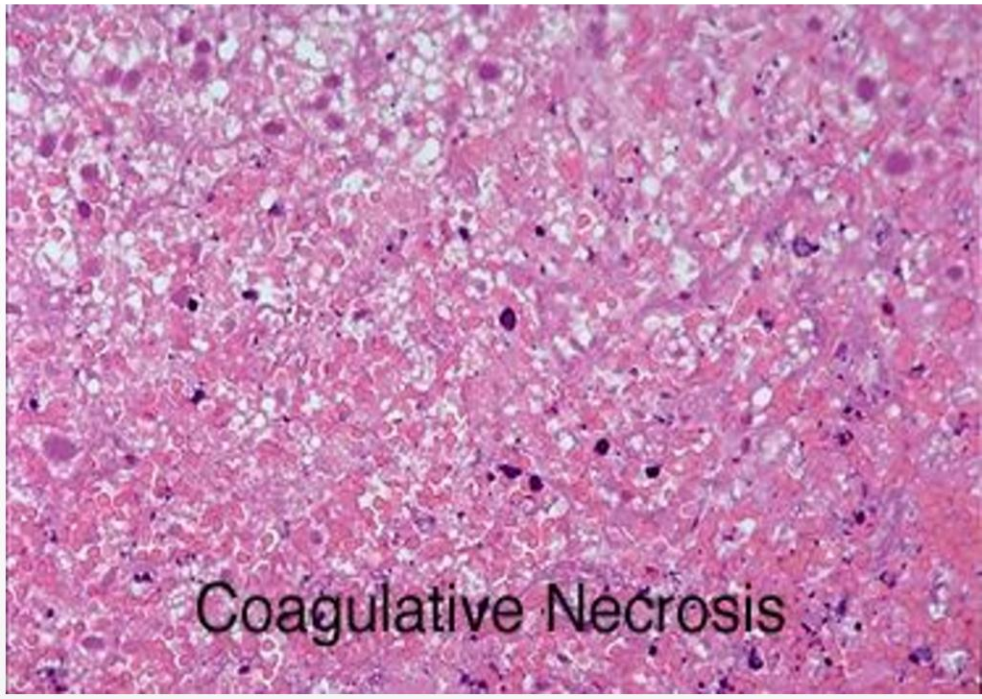
Councilman bodies:

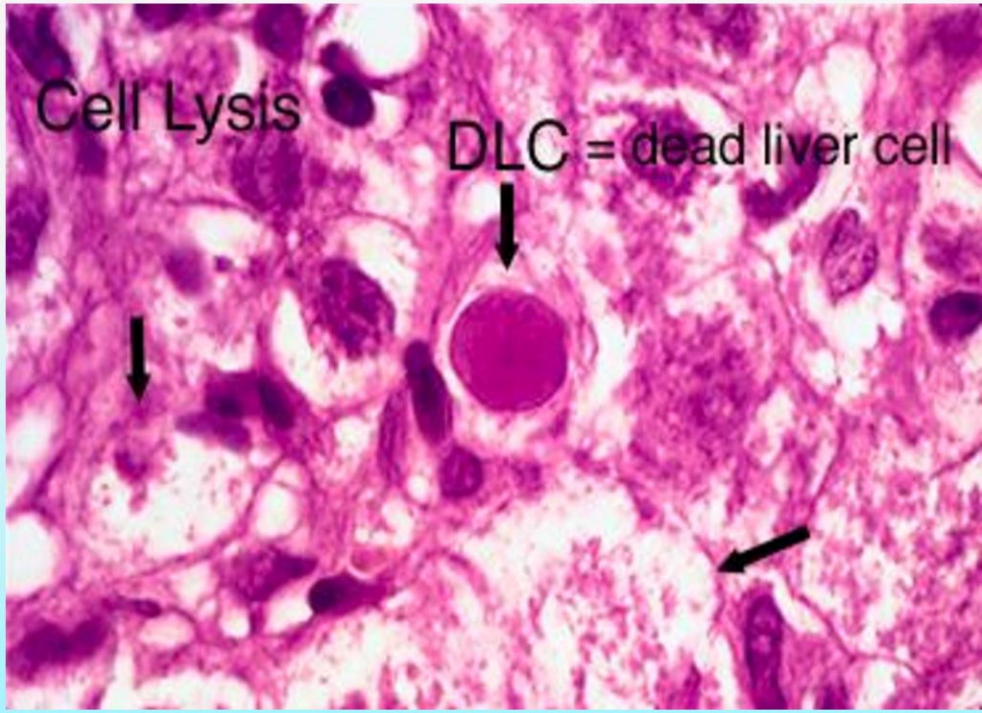
apoptotic cells

shrinkage deeply eosinophilic

Lytic necrosis:

hepatocytes swell & rupture





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

A-Focal necrosis

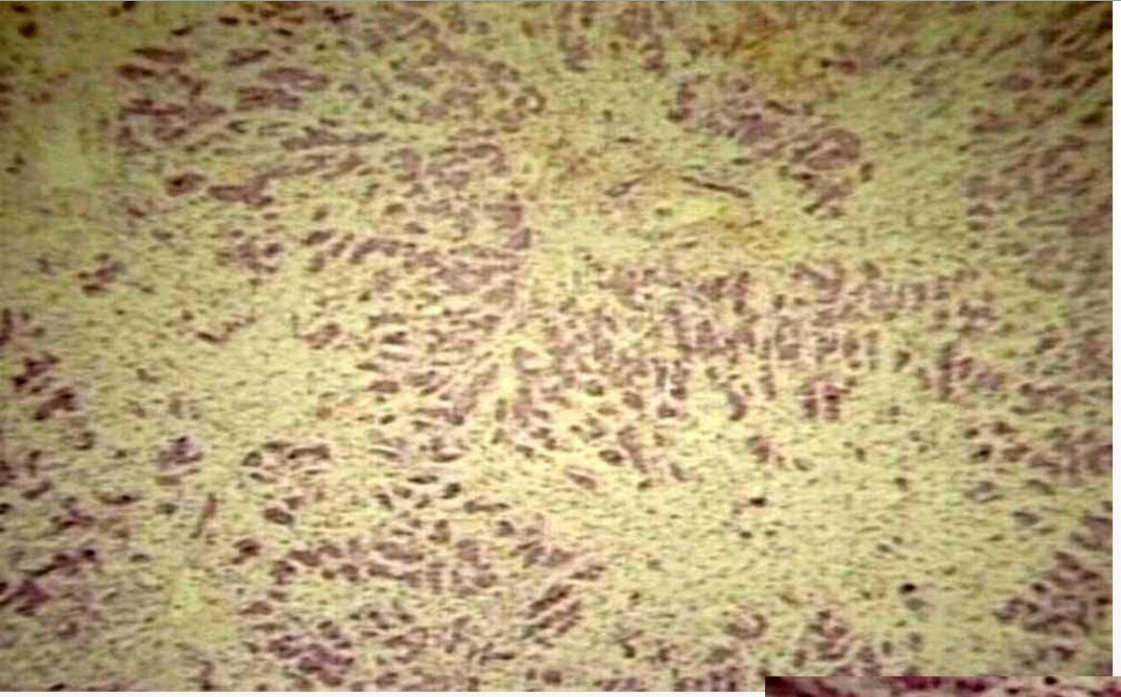
B- centrilobular necrosis. Hepatocytes necrosis around the central vein. (Due to drugs, ischemia)

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

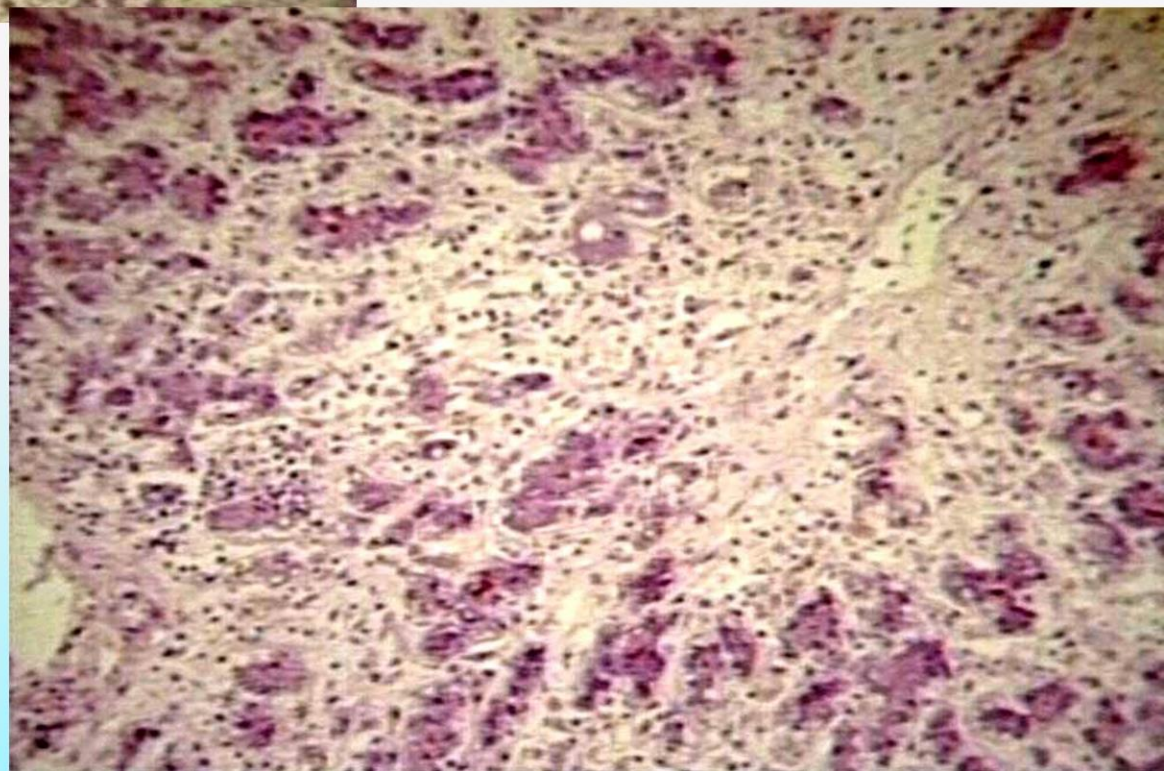
D-bridging necrosis. necrosis of hepatocytes may span the adjacent lobules in a portal – to – portal, portal –to – central, or central – to – central fashion.

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

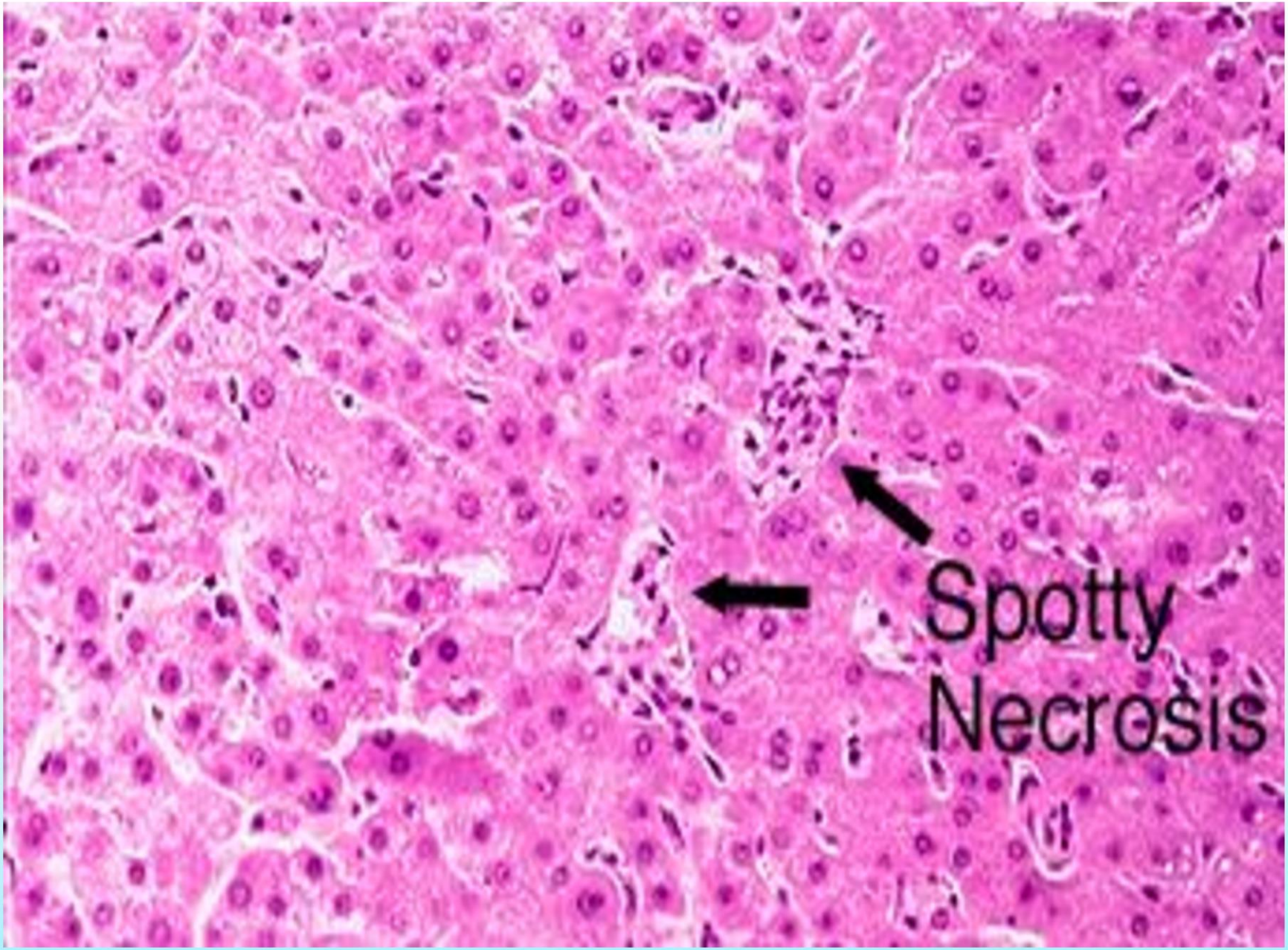
CHRONIC

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

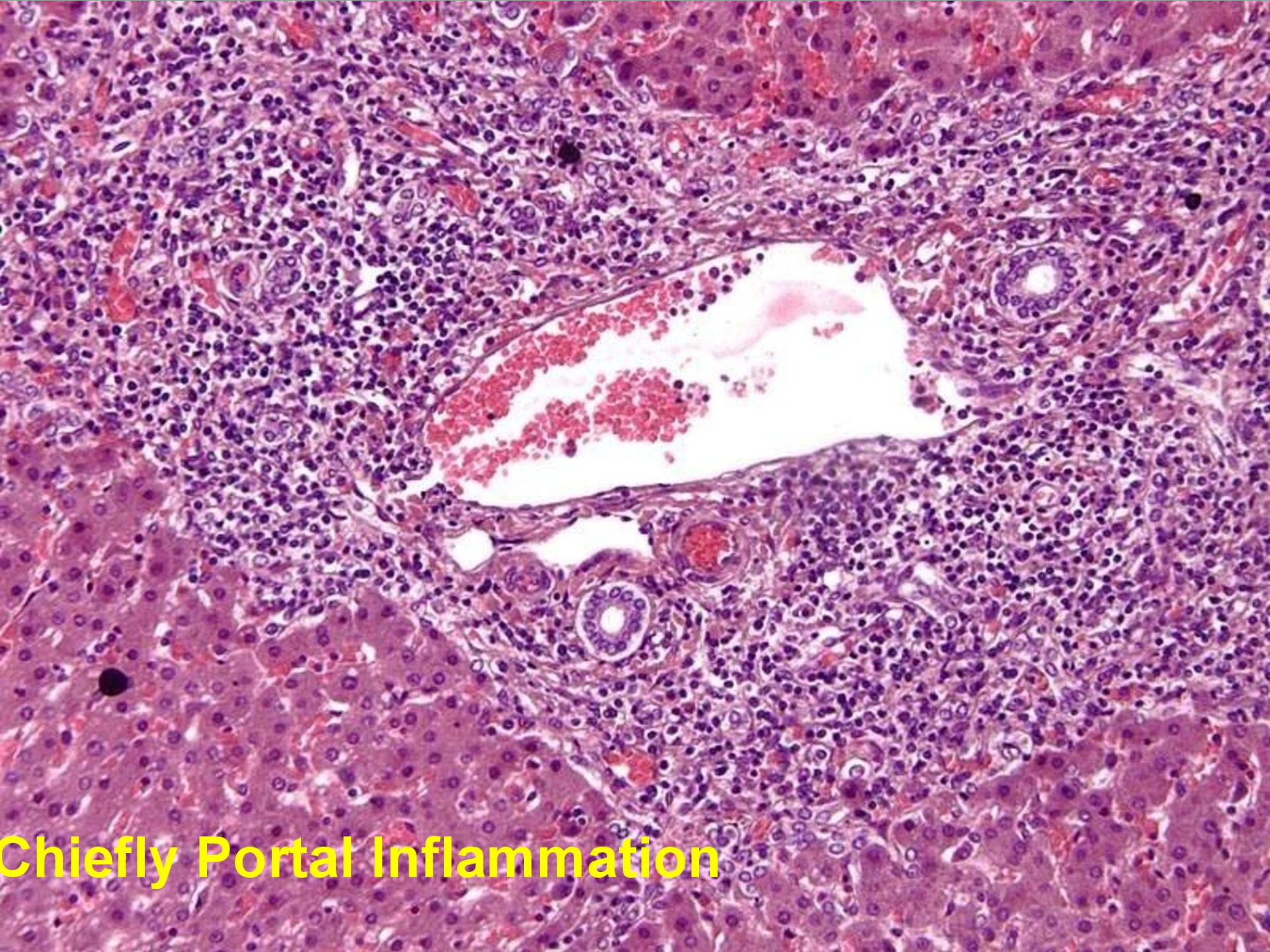
1. Hepatitis A Virus (HAV)
2. Hepatitis B Virus (HBV)
3. Hepatitis C Virus (HCV)
4. Hepatitis D Virus (HDV)
5. Hepatitis E Virus (HEV)

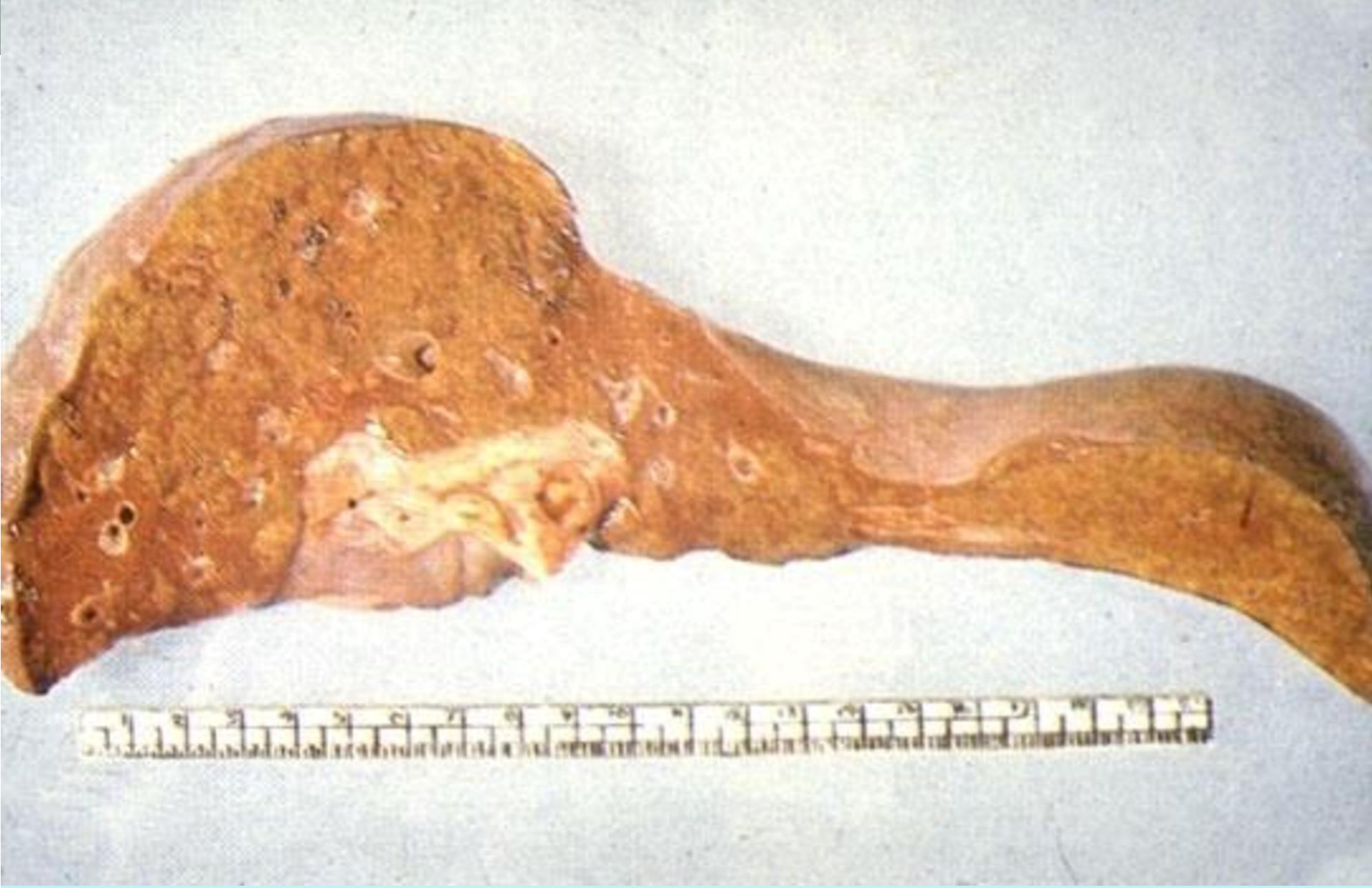
(2) Systemic viruses. Include.

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

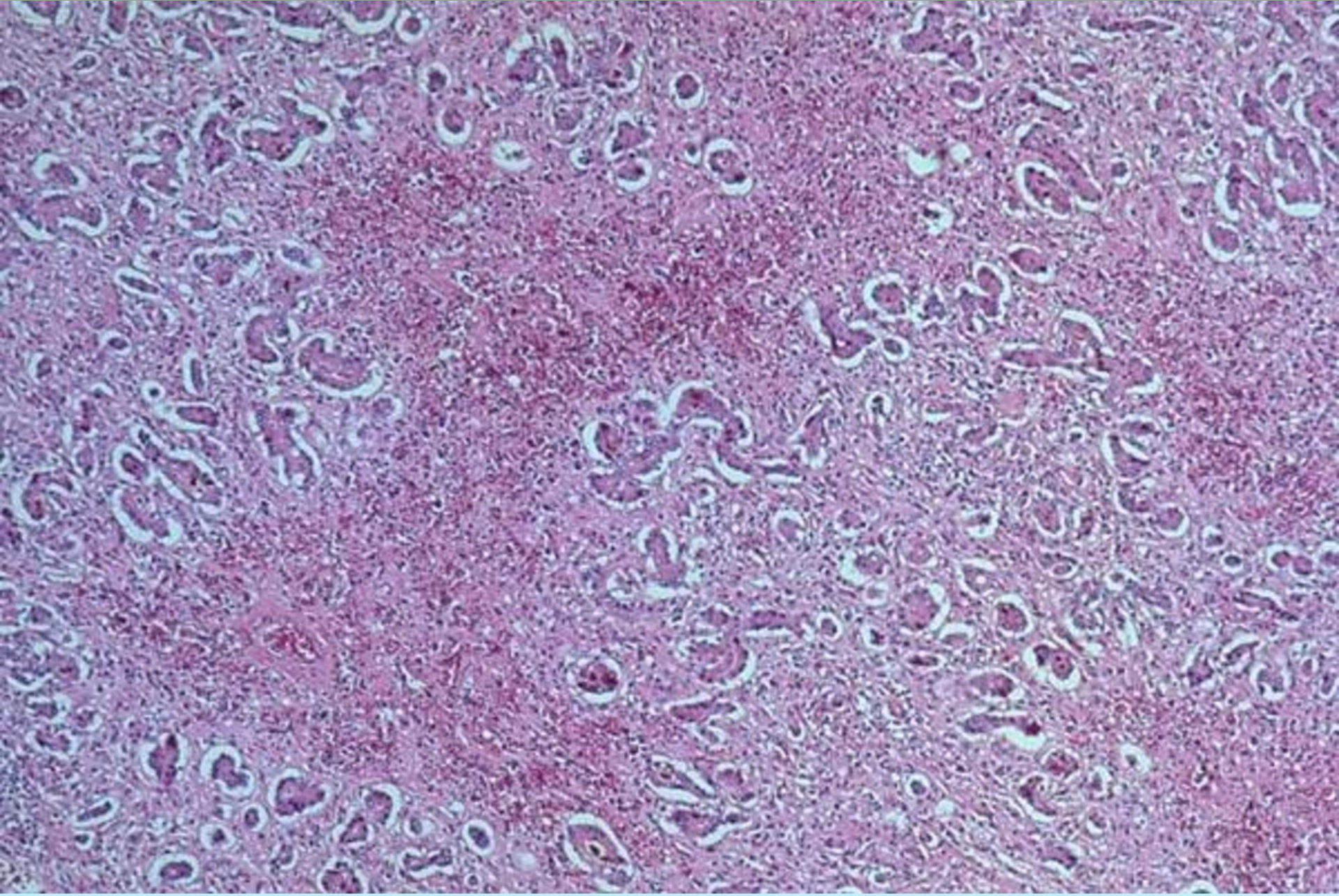
VIRAL HEPATITIS

- A, **B, C**, D, E,
- 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



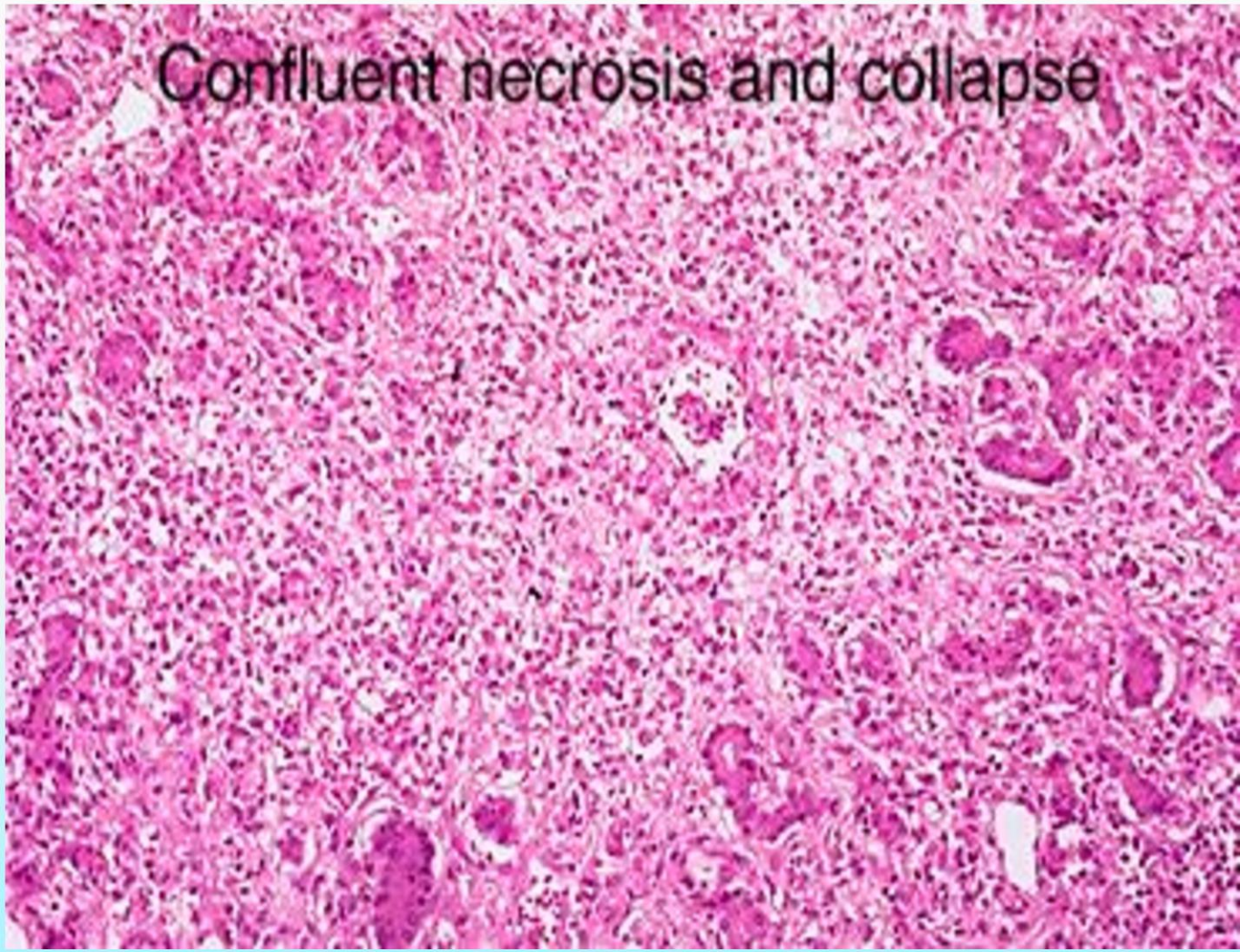
FULMINANT HEPATITIS



“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**.

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.

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.**

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*.

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.

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.