Digestive System

University of Jordan

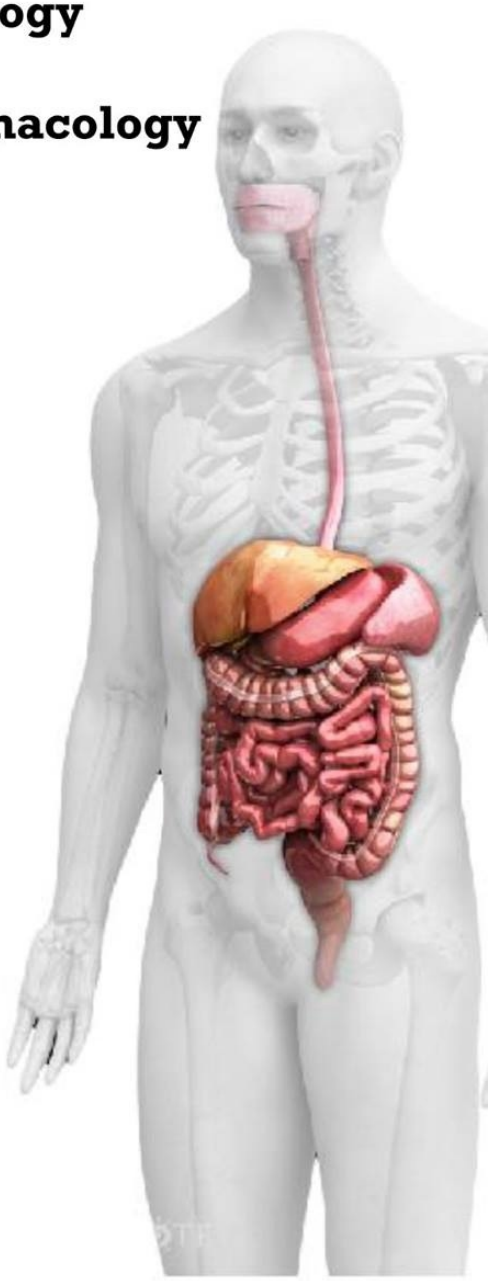
Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

(●) Slide ( ) Sheet ( ) Handout ( ) Other

- [ ] Anatomy
- [ ] Embryology
- [ ] Physiology
- [ ] Histology
- [x] Pathology
- [ ] Pharmacology
- [ ] Microbiology
- [ ] PBL



Slide #: 7 (1- Dr. Maha)

Doctor: Dr. Maha

Date:

Price:

DESIGNED BY: TAMER ALTAMIMI "SMILE"

Liver

- **Function:**

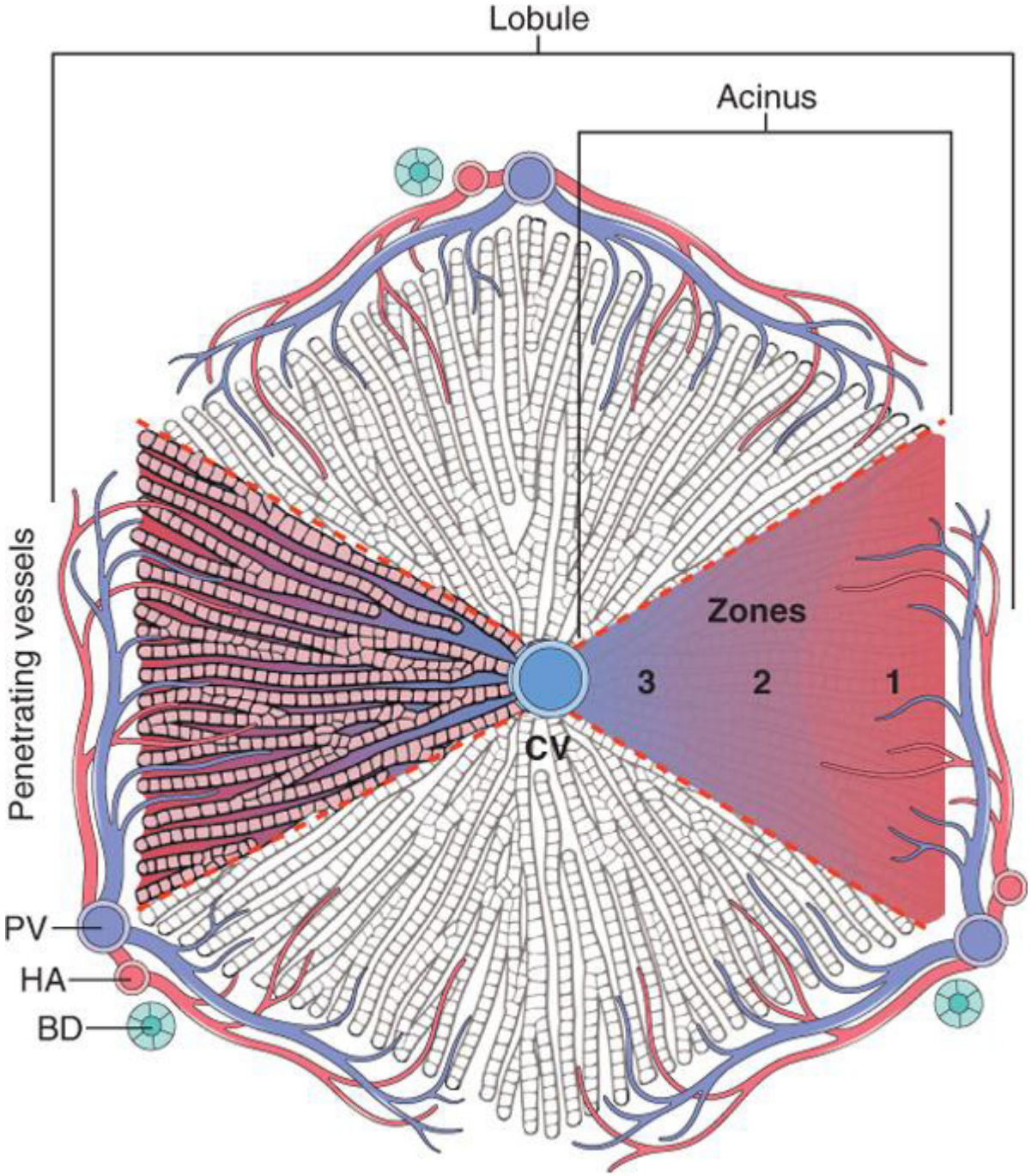
1-Metabolic : Glucose
2-Synthetic : Albumin, clotting factors …..
3-Detoxification : Drugs, hormones , NH3
4-Storage : Glycogen, TG, Fe, Cu, vit
5-Excretory : Bile

- **Net wt. 1400 – 1600gm (2.5% of body wt)**
- **Blood supply:**

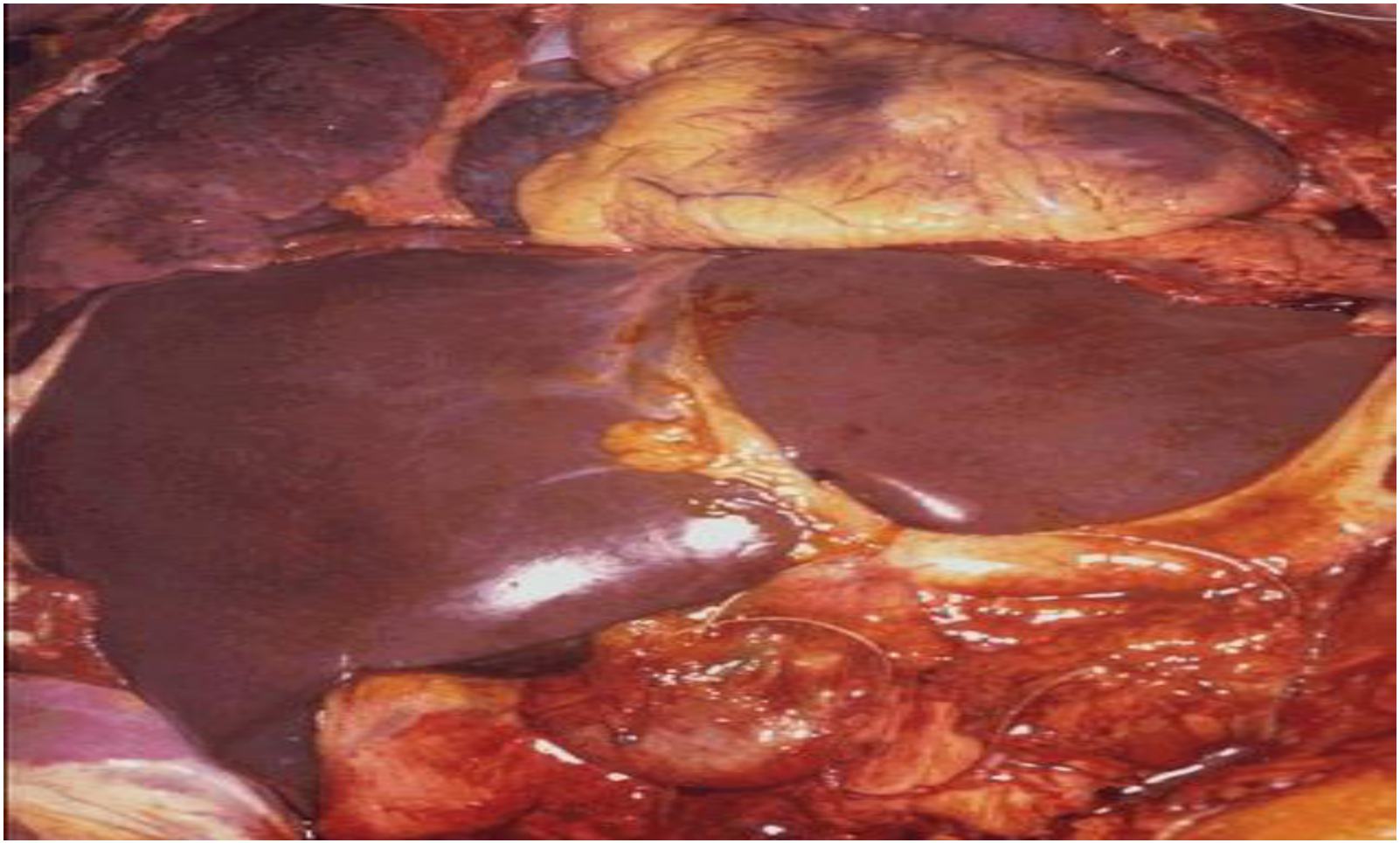
Portal v : 60 - 70%
Hepatic a : 30 - 40%

- **Microstructure**
- **Hexagonal lobules →6 acini**
- **Acinus is divided into 3 zones:**

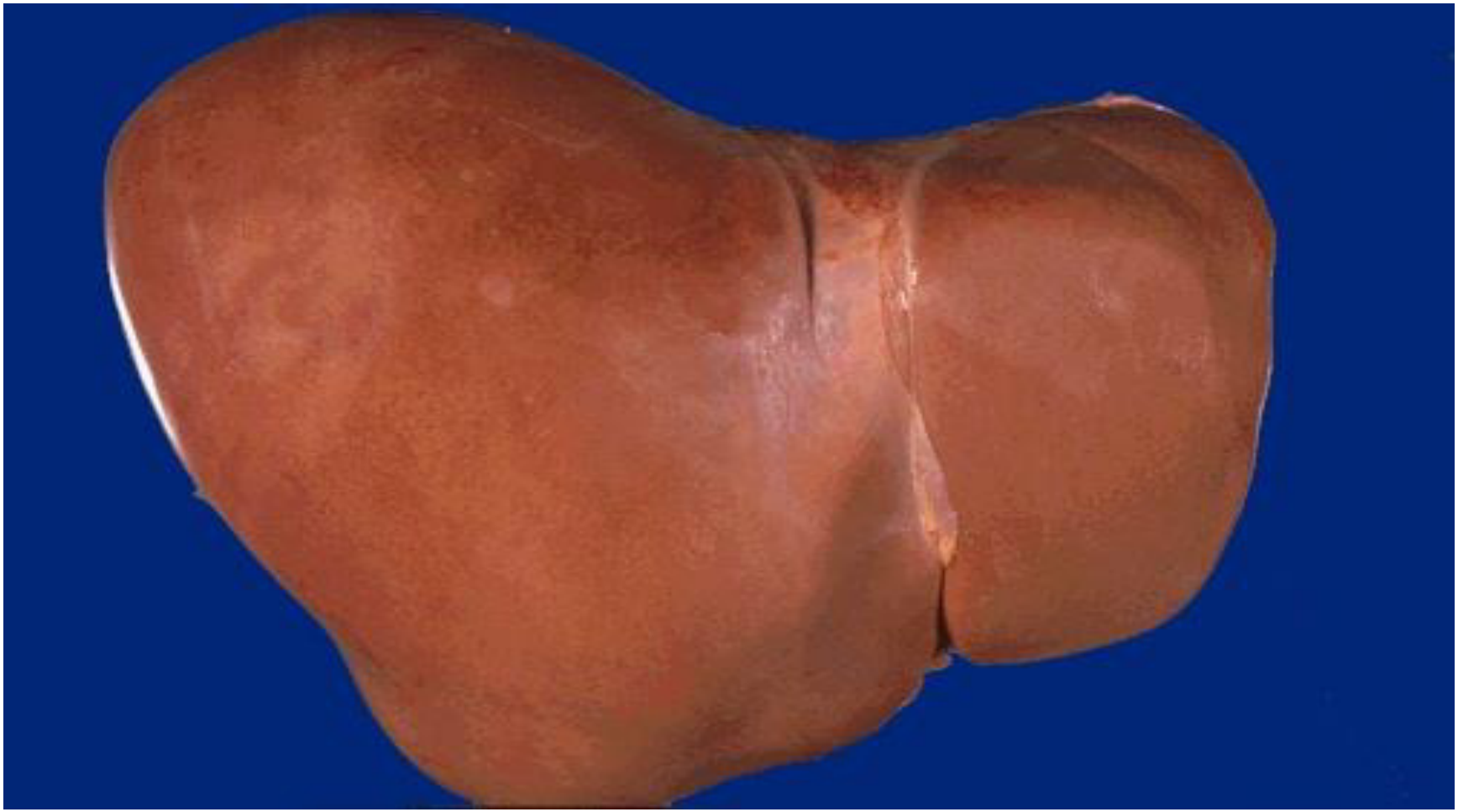
1-Zone 1
Periportal areas – closet to the vascular supply
2-Zone 3
Pericentral area
3-Zone 2
Inrermediate bet. Zone 1&2



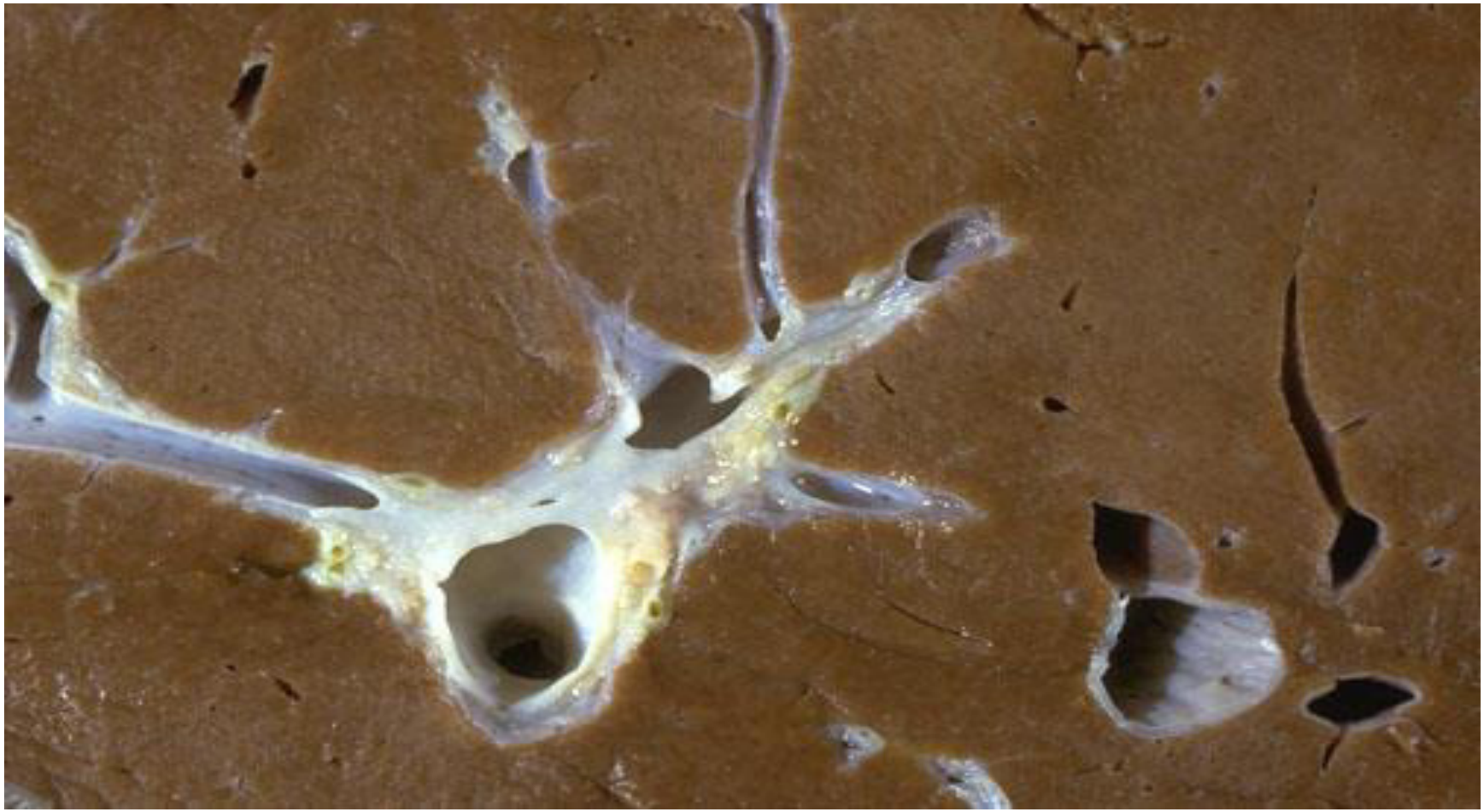
Normal liver



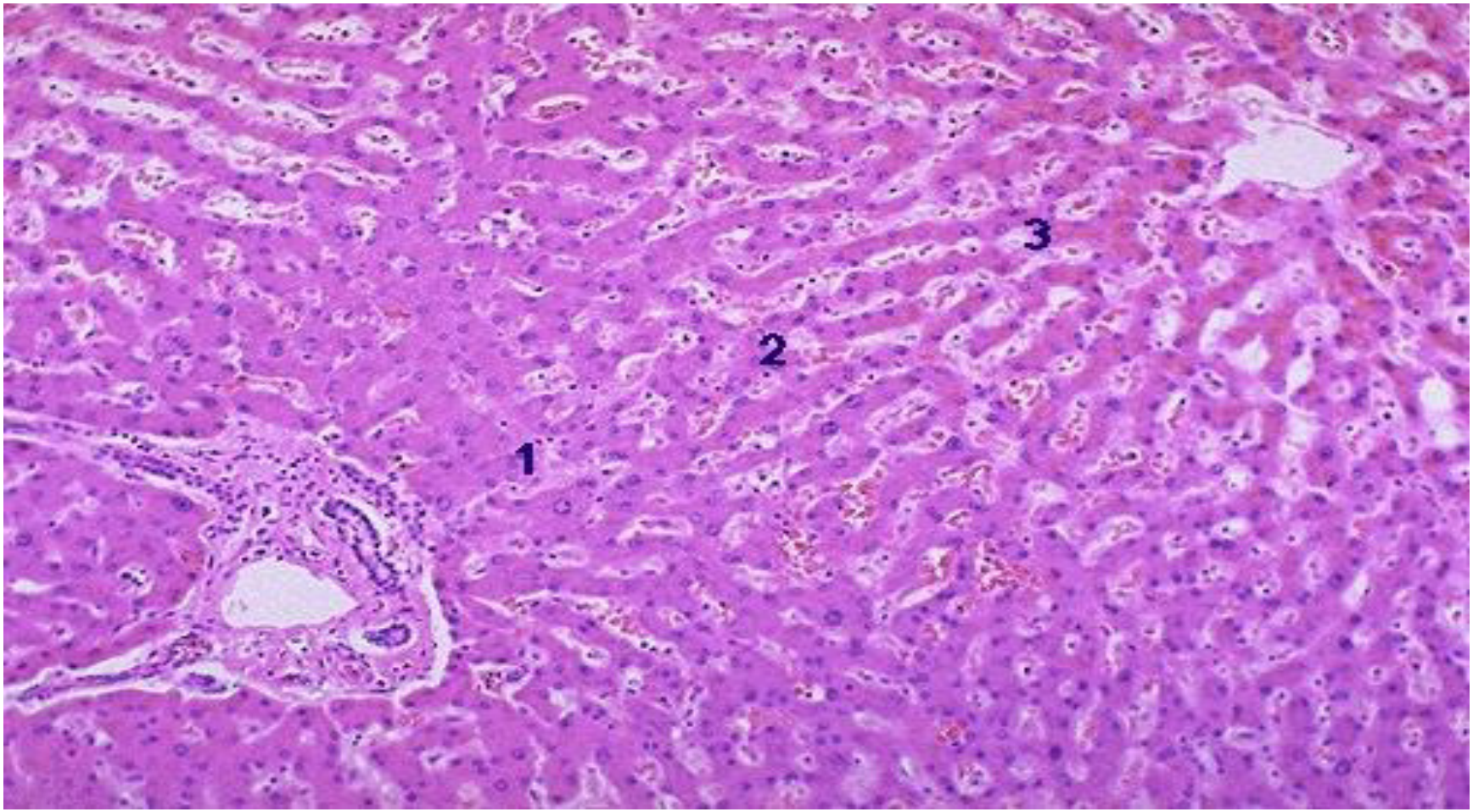
Normal liver



Cross section of normal liver



Liver zones



The parenbchyma is organized into plates of hepatocytes

Hepatocytes are radially oriented around terminal hepatic vein (central v.)

-Hepatocytes show only minimal variation in the overall size but nuclei may vary in size , number & ploidy esp. with advancing age

-Vascular sinusoids present bet. cords of hepatocytes

Hepatic injury

1-Inflammation (Hepatitis)

2-Degeneration :

ballooning degeneration

feathery degeneration:retained biliary material

accumulation of iron ,copper

3-Steatosis (fatty change)

<u>microvesicular:</u>

ALD

Reye syndrome

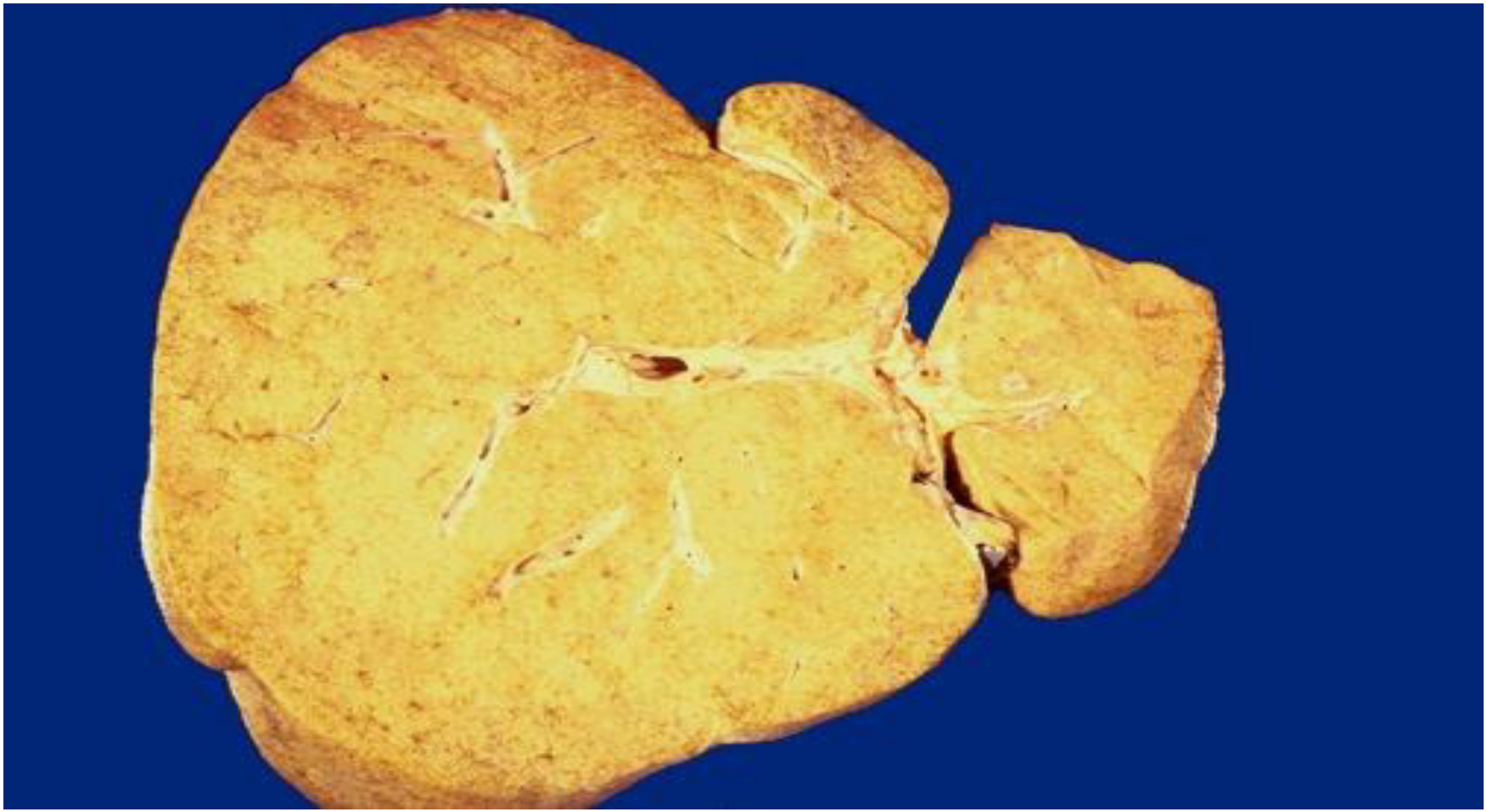
acute fatty change of pregnancy

<u>macrovesicular:</u>

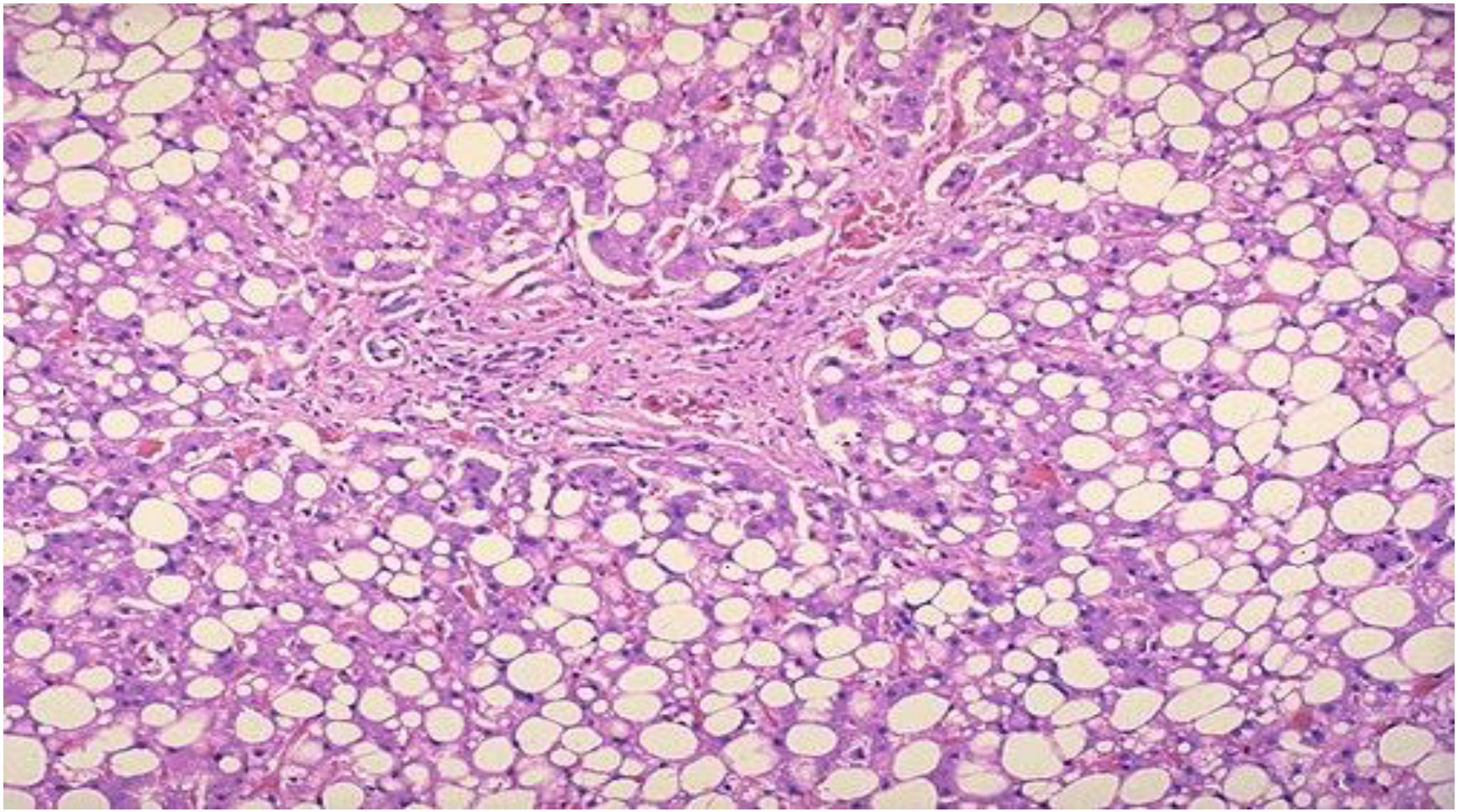
DM

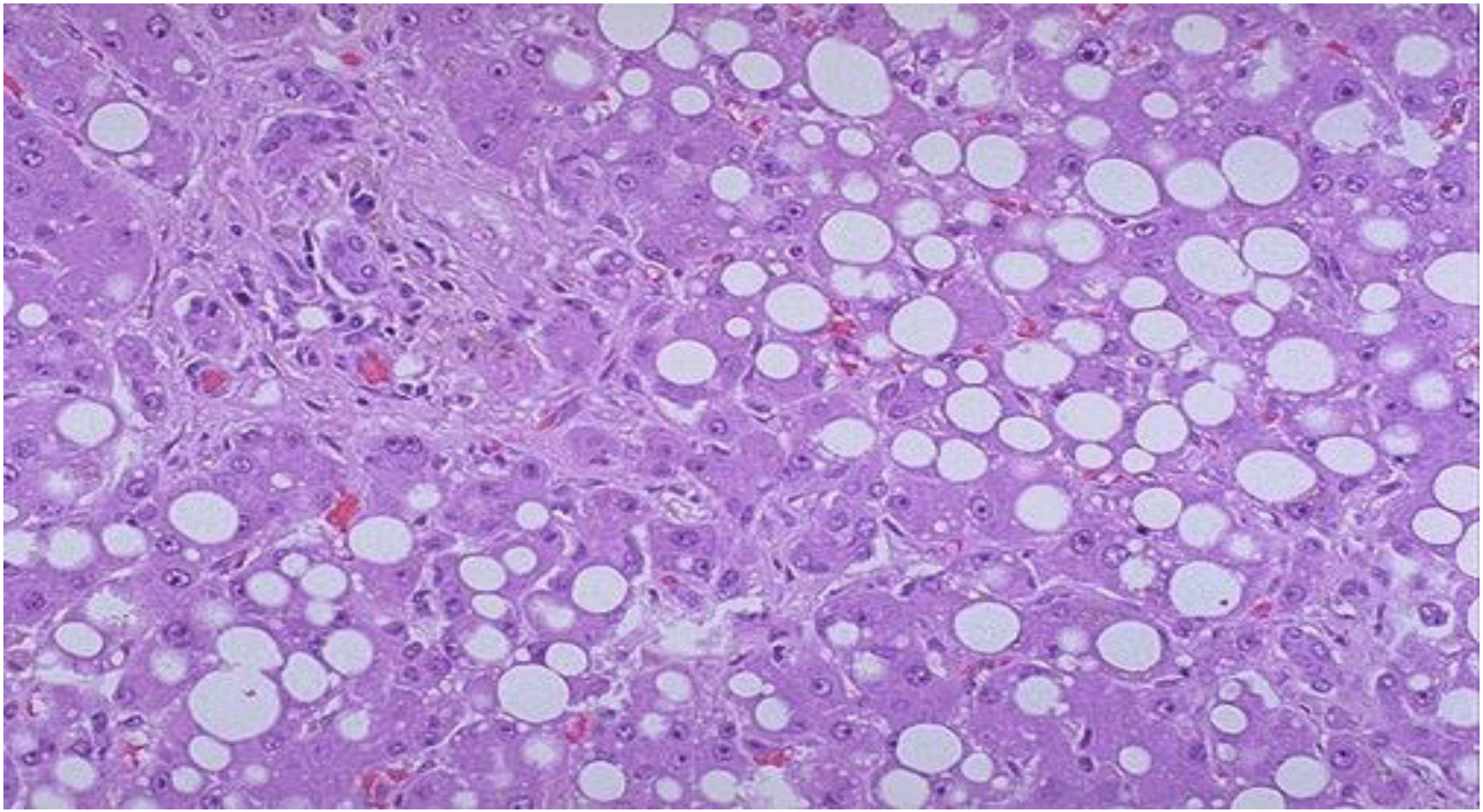
obesity

Fatty change



fatty change





4-Necrosis

- Depending on the type:

Coagulative necrosis

Councilman bodies

Lytic necrosis

- Depending on the cause

Ischemic

Toxic

- Depending on location

Centrilobular necrosis:

Mid zonal :

Periportal : interface hepatitis

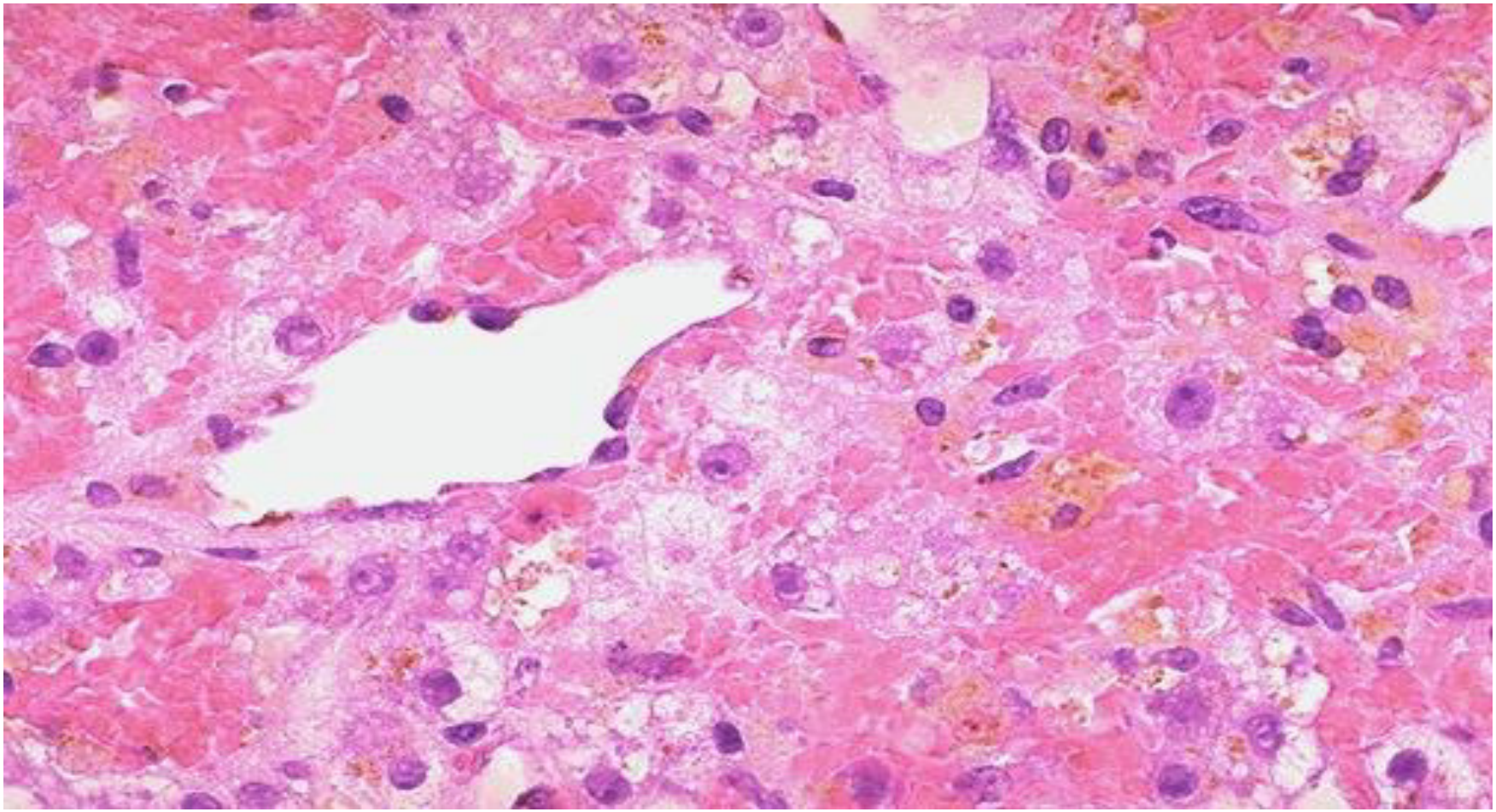
Focal:

- Piece meal necrosis
- bridging necrosis

Diffuse:

- massive & submassive necrosis

Necrosis of liver



5-Regeneration

-evidenced by increased mitosis or cell cycle markers.

-the cells of the canal of Hering are the progenitor for hepatocytes & bile duct cells (oval cells).

6-Fibrosis

bridging fibrosis

7-Cirrhosis

micronodular

Macronodular

8-Ductular proliferation

CLINICAL SYNDROMES

- **The major clinical syndromes of liver disease are:**
- **1-hepatic failure**
- **2-cirrhosis**
- **3-portal hypertension**
- **4-cholestasis.**

liver failure

- **The alterations that cause liver failure fall into 3 categories:**
- **1-** ***Acute liver failure with massive hepatic necrosis***
- ***2- Chronic liver disease***
- ***3- Hepatic dysfunction without overt necrosis.***

1-Acute liver failure.

- **This is most often caused by *drugs* or *fulminant viral hepatitis*.**
- **Acute liver failure denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks.**
- **A course extending as long as 3 months is called subacute failure.**

- ***The histologic correlate of acute liver failure is massive hepatic necrosis.***
- **It is an uncommon but life-threatening condition that often requires liver transplantation.**

2-Chronic liver disease

- **This is the most common route to hepatic failure and is the end point of relentless chronic liver damage ending in cirrhosis.**

3-Hepatic dysfunction without overt necrosis.

- **Hepatocytes may be viable but unable to perform normal metabolic function:**
- **1- Acute fatty liver of pregnancy (which can lead to acute liver failure a few days after onset)**
- **2- Tetracycline toxicity**
- **3- Reye syndrome**

Clinical features

1-Jaundice

2-Hypoalbuminemia →edema

3-Hyperammonemia

4-hyperestrogenemia

5-Spider angiomas

6-Hypogonadism & gynecomastia

Complications:

1-Multiple organ failure e.g lung

2-Coagulopathy → bleeding

def. factors II, VII, IX, X

3-Hepatic encephalopathy

4-Hepatorenal Syndrome

Alcoholic liver disease

-Alcohol is most widely abused agent

-Excessive ethanol consumption causes more than 60% of chronic liver disease in most Western countries and accounts for 40-50% of deaths due to cirrhosis.

-It is the 5th leading cause of death in USA due to :

1. Accident
2. Cirrhosis

Pathogenesis

- Short-term ingestion of as much as 80 gm of ethanol/d (8 beers or 7 ounces of 80-proof liquor) generally produces mild reversible hepatic changes.
- Chronic intake of 50 to 60 gm/day is considered a borderline risk for severe injury.
- Women seem to be more susceptible to hepatic injury than are men because of low gastric metabolism of ethanol and differences in body composition.

-80–100 mg/dl is the legal definition for driving under the influence of alcohol

-44 ml of ethanol is required to produce this level in 70kg person

-In occasional drinkers, bl. Level of 200 mg/dl produces coma & death & resp. failure at 300-400 mg/dl

- **Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance explained by**

  5-10X induction of cytochrome P-450 system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetominophen .

Forms of alcoholic liver disease

1-Hepatic steatosis (90-100% of drinkers)

2-Alcoholic hepatitis (1- 35% of drinkers)

3-Cirrhosis (14% of drinkers)

- **Steatosis & hepatitis may develop independently**

Hepatic steatosis

-Can occur following even moderate intake of alcohol in form of microvesicular steatosis

- initially centrilobular but in severe cases it may involve the entire lobule .

-Chronic intake → diffuse steatosis

-Liver is large (4 – 6 kg) soft yellow & greasy

-Continued intake →fibrosis

-Fatty change is reversible with complete absention from further intake of alcohol

Alcoholic hepatitis

Characteristic findings :

1-Hepatocyte swelling & necrosis

-Accumulation of fat & water & proteins

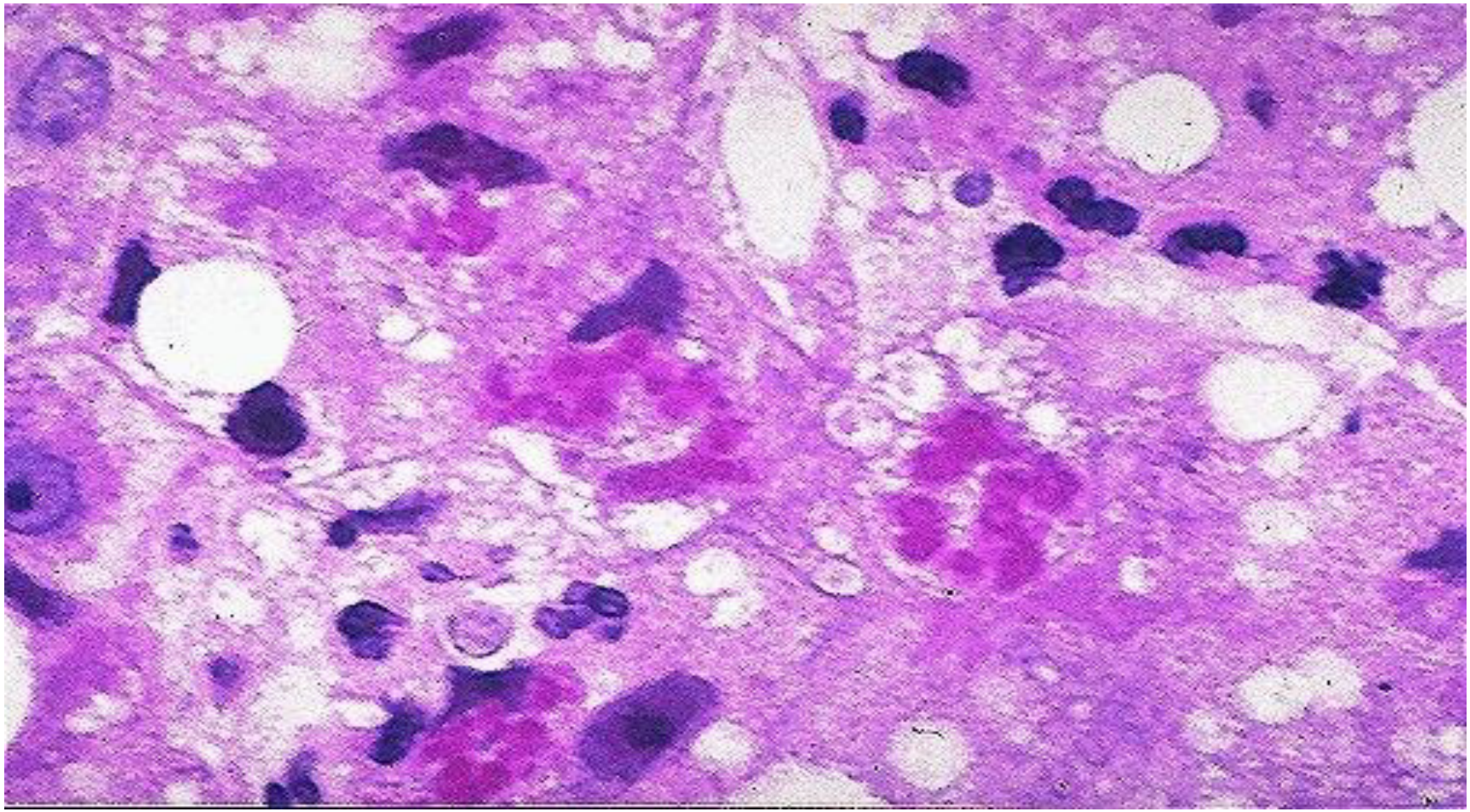
-Cholestasis

-Hemosiderin deposition in hepatocytocytes & kupffer cells

2-Mallory-hayline bodies

-eosinoplilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin infermediate filaments & other proteins

Mallory-hayline bodies



- Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease, they are also seen in :

  1-Primary biliary cirrhosis

  2-Wilson disease

  3-Chronic cholestatic syndromes

  4-Hepatocellular carcinoma

3-Neutrophilic reaction

4-Fibrosis

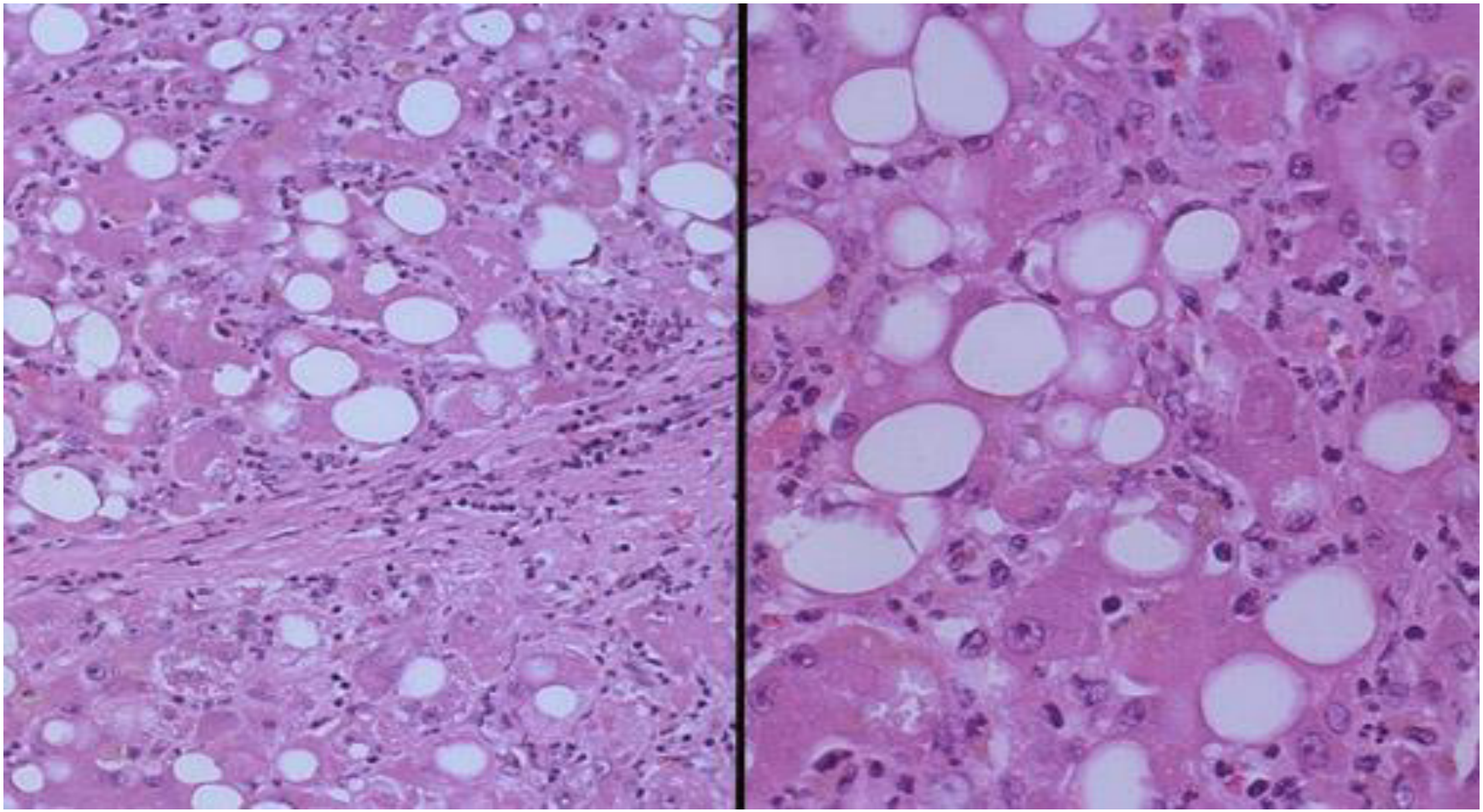
-Sinusoidal & perivenular fibrosis

-Periportal fibrosis

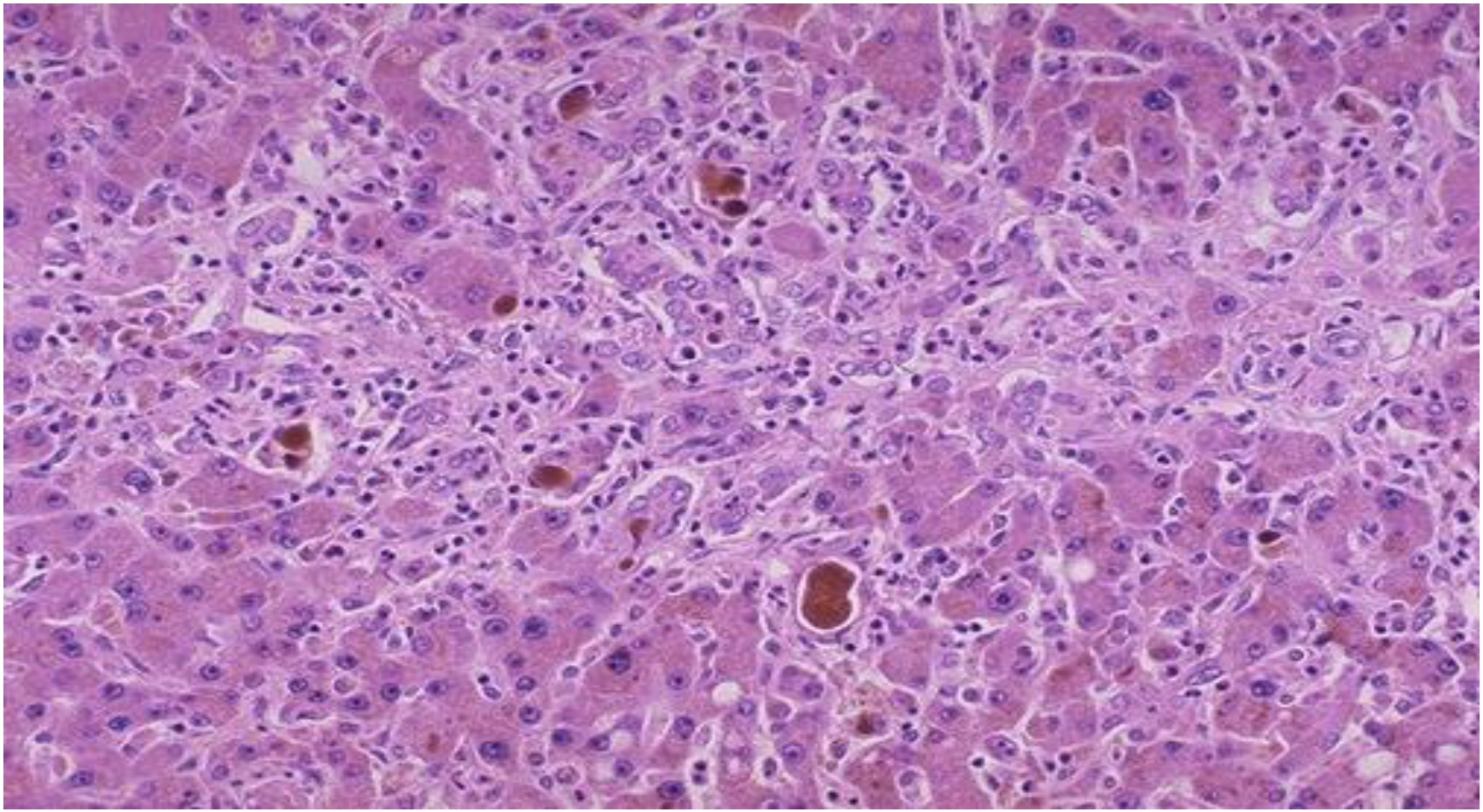
5-Cholestasis

6-Mild deposition of hemosiderin in hepatocytes & kupffer cells

Alcoholic hepatitis



Cholestasis



Alcoholic cirrhosis

-Usually it develops slowly

-Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ

s.t < l kg in wt.

-Micronodular → mixed micro & macronodular

-Laennec cirrhosis = scar tissue

-Bile stasis

-Mallory bodies are only rarely evident at this stage

-Irreversible

-It can develop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).

Liver cirrhosis

Ethanol metabolism

Ethanol → acetaldehyde

CH3 CH2OH CH3 C=O

H

↑

-Alcohol dehydrogenase
(stomach + liver)

-Cytochrome P-450

-Catalase (liver)

-

Acetaldehyde → Acetic acid

↑

Aldehyde dehydrogenase

- After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level

- Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol.

- Less than 10% of absorbed ethanol is excreted unchanged in urine , sweat & breathe

-There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism

e.g 50% of chinese , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme. → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation.

Mechanism of ethanol toxicity

1-Fatty change

a-Shunting of lipid catabolism toward lipid bio-synthesis due to excess production of NADH over NAD in cystol & mitochondria

b-Acetaldehyde forms adducts with tubulin & ↓ function of microtubules → ↓ in lipoprotein transport from liver

c- ↑ peripheral catabolism of fat → ↑ FFA delivery to the liver

d- ↓ sec. of lipoproteins from hepatocytes

e. ↓ oxidation of FFA by mitochondria

2-Induction of cytochrome P-450 enhances the metabolism of drugs to toxic metabolites (e.g acetominophen)

3. ↑free radicals production due to activation of cytochrome P-4so leads to membrane & protein damage
4. Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
5. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack
6. Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)

7. Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver
8. Alcohol → regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion
9. Alteration of cytokine regulation

   TNF is a major effector of injury

   IL6 IL8 IL18

Clinical features

-Hepatic steatosis (reversible)

- ↑ liver
- ↑ liver enz.
- Severe hepatic dysfunction is unusual

-Alcoholic hepatitis

- 15-20 yr. of excessive drinking
- Non-specific symptoms, malaise, anorexia, wt. loss
- Hepatosplenomegaly
- ↑ LFT

Each bout of hepatitis →10-20% risk of death

→ cirrhosis in 1/3 in few yrs.

-Cirrhosis

Portal hypertension

- **Causes of death in alcoholic liver disease:**

1-hepatic failure

2-Massive GI bleeding

3-Infections

4-Hepatorenal syndrome

5-HCC in 3-6% of cases

Cirrhosis

- **It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules**

- **Main characteristics**

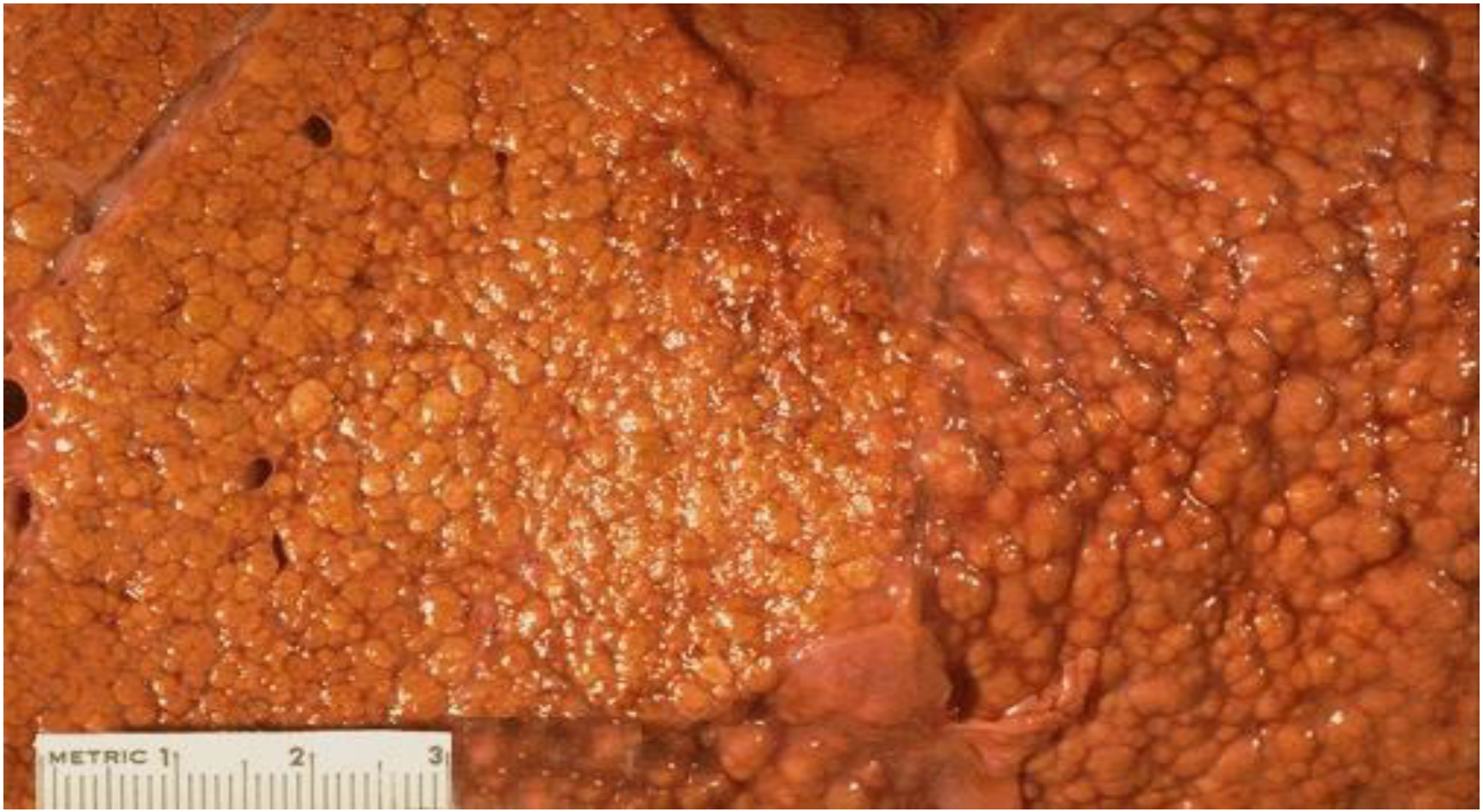
1. Bridging fibrous septae
2. Parenchymal nodules encircled by fibrotic bands
3. Diffuse architecture disruption

- **Types :**

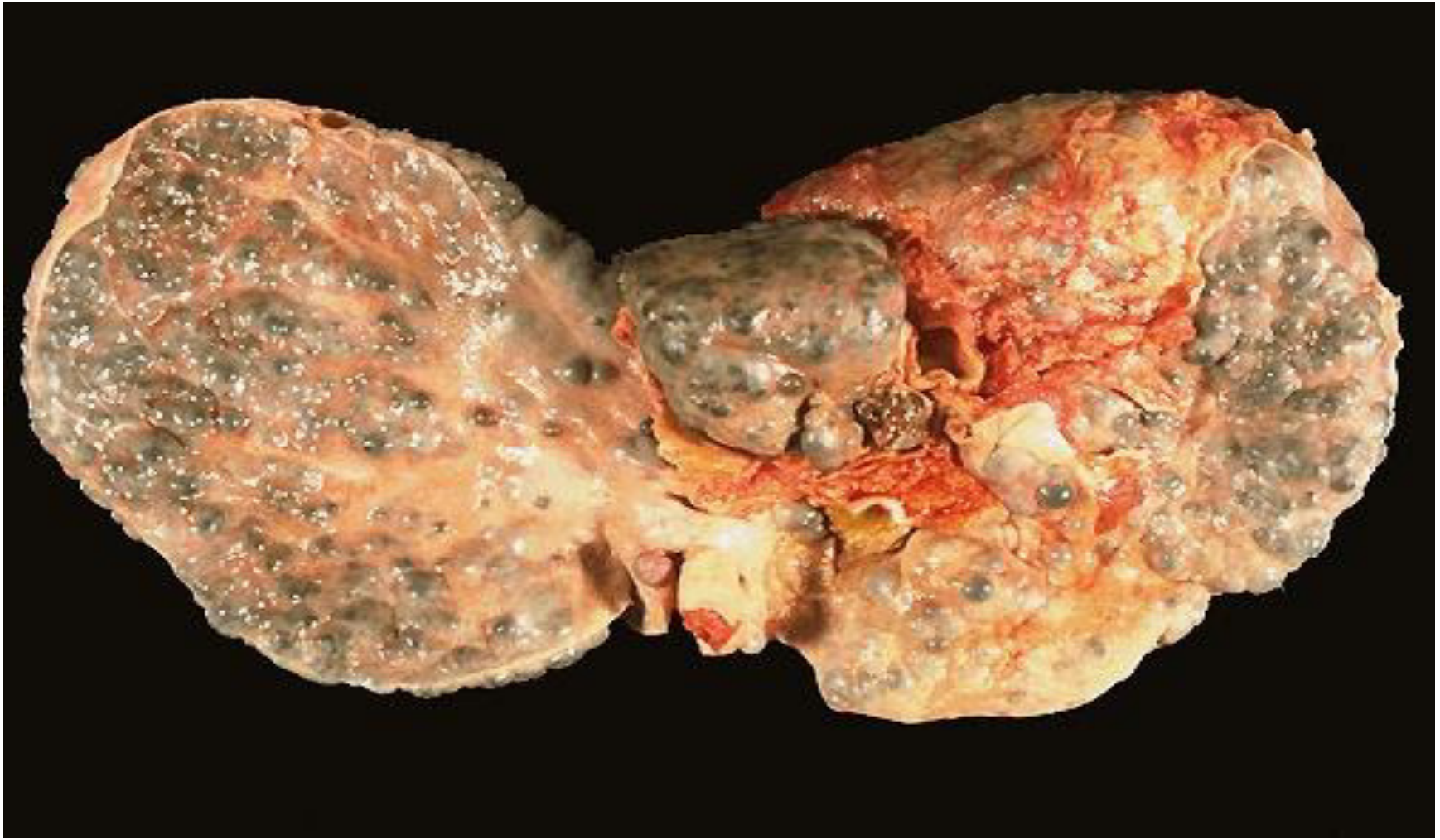
Micronodules < 3mm in diameter

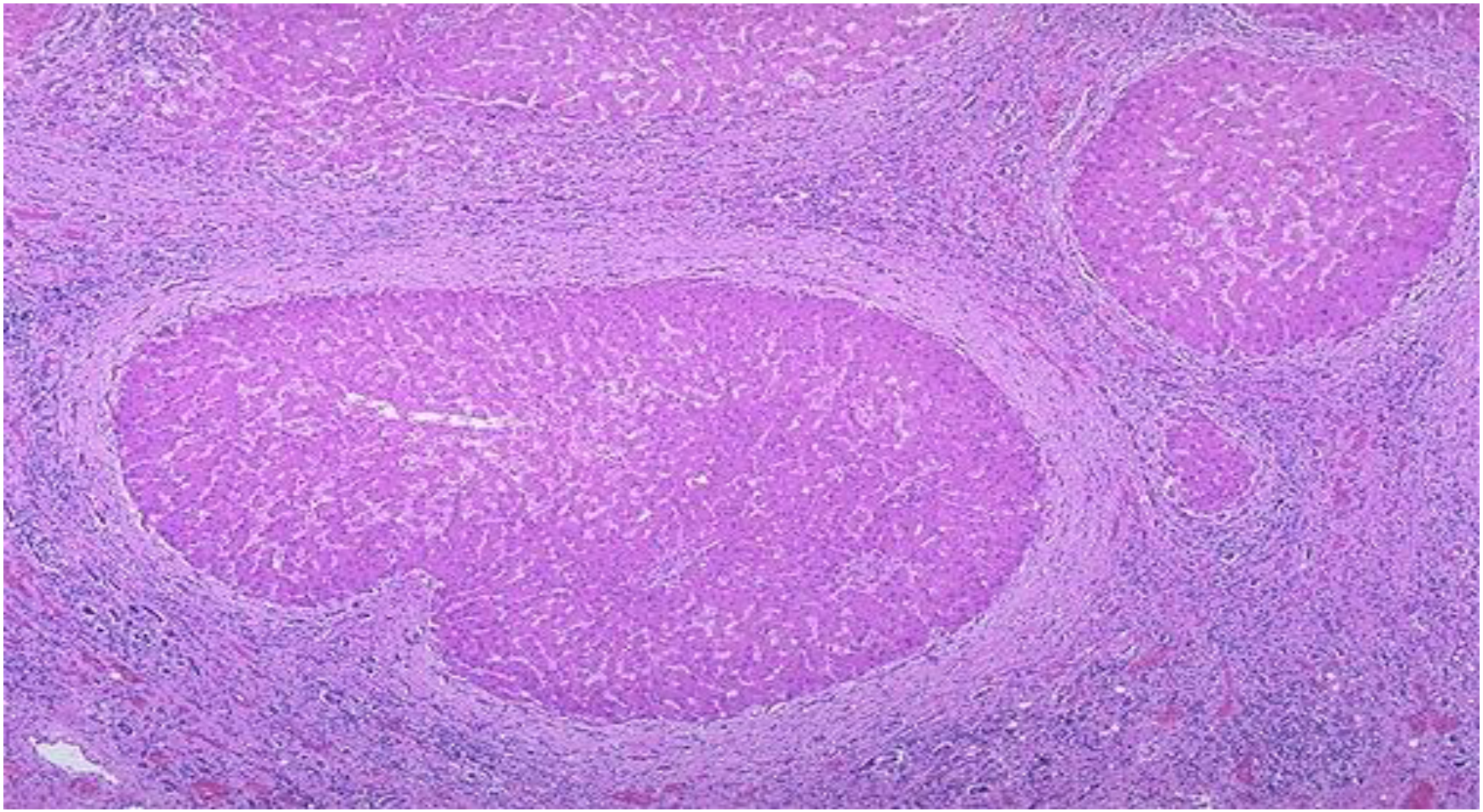
Macronodules > 3 mm in diameter

Micronodular cirrhosis



Macronodular cirrhosis





Causes of cirrhosis

1.Chronic alcoholism

2.Chronic viral infection HBV & HCV

3.Biliary disease

4.Hemochromatosis

5.Autoimmune hepatitis

6.Wilson disease

7.α-1- antitrypsin deficiency

8. Rare causes
   Galactosemia
   Tyrosinosis
   Glycogen storage disease III &IV
   Lipid storage disease
   Hereditary fructose intolerance
   Drug induced e.g methyldopa
9. Cryptogenic cirrhosis 10%

Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

1-Hepatocellular death

2-Regeneration

3-Progressive fibrosis

4-Vascular changes

- **The development of cirrhosis requires that cell death occur over long periods of time and be accompanied by fibrosis.**
- **Fibrosis progresses to scar formation when the injury involves not only the parenchyma but also the supporting connective tissue.**

-In normal liver the ECM collagen (types I, III,V & XI) is present only in :

Liver capsule

Portal tracts

Around central vein

-delicate framework of type IV collagen & other proteins lies in space of Disse.

-In cirrhosis types I & III collagen & others are deposited in the space of Disse.

- **Vascular changes consisting of the loss of sinusoidal endothelial cell fenestrations and the development of portal vein-hepatic vein and hepatic artery-portal vein vascular shunts contribute to defects in liver function.**

- **Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure fast-flowing vascular channels without such solute exchange.**

- **The movement of proteins (e.g., albumin, clotting factors, lipoproteins between hepatocytes and the plasma is markedly impaired.**
- **These functional changes are aggravated by the loss of microvilli from the hepatocyte surface which diminishes the transport capacity of the cell.**

- The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of Disse
- Ito cells are perisinusoidal stellate cells act normally as storage cells for vit A & fat .

- **Activated stellate cells produce growth factors, cytokines, and chemokines that cause their further proliferation and collagen synthesis.**
- **TGF-β is the main fibrogenic agent for stellate cells.**

-**The stimuli for the activation of stellate cells & production of collagen are :**

1-reactive oxygen species

2-Growth factors

3-cytokines TNF, IL-I, lymphotoxins

-Clinical features of cirrhosis :

-Silent

-Anorexia, wt loss, weakness

-Complications :

1-Progressive hepatic failure

2-Portal hypertension

3-Hepatocellular carcinoma

Portal hypertension

- ↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules
- Arterial – portal anastomosis develops in the fibrous bands →increase the blood pressure in portal venous system

Causes of portal hypertension

I.Prehepatic

1-Portal vein thrombosis
2-Massive splenomegaly

II. Post hepatic

1-Severe Rt.- sided heart failure
2-Constrictive pericarditis
3-Hepatic vein out flow obstruction

III. Hepatic

1-Cirrhosis
2-Schistosomiasis
3-Massive fatty change
4-Diffuse granulomatosis as sarcoidosis, TB
5-Disease of portal microcirculation as nodular regenerative hyperplasia

Clinical consequence of portal hypertension

1-Ascites

2-Portosystemic shunts

3-Hepatic encephalopathy

4-Splenomegaly

Ascites

-Collection of excess fluid in peritoneal cavity

-It becomes clinically detectable when at least 500 ml have accumulated

-**Features**

1-Serous fluid

2-Contains as much as 3g/ml of protein (albumin)

3-It has the same concentration as blood of glucose, Na+, & K+

4-Mesothelial cells & lymphocytes

5-Neutrophils = infection

6-RBCs = DISSEMINATED CANCR

-Pathogenesis

1-Sinusoidal ↑ Bp

2-Hypoalbuminemia

3-Leakage of hepatic lymph into the peritoneal cavity

N- thoracic duct lymph flow is 800-1000 ml/d

in cirrhosis it may approach 20L /day

4-Renal retention of Na+ & water due to 2ry hyperaldosteronism

Portosystemic shunt

-Because of ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds.

-Sites:

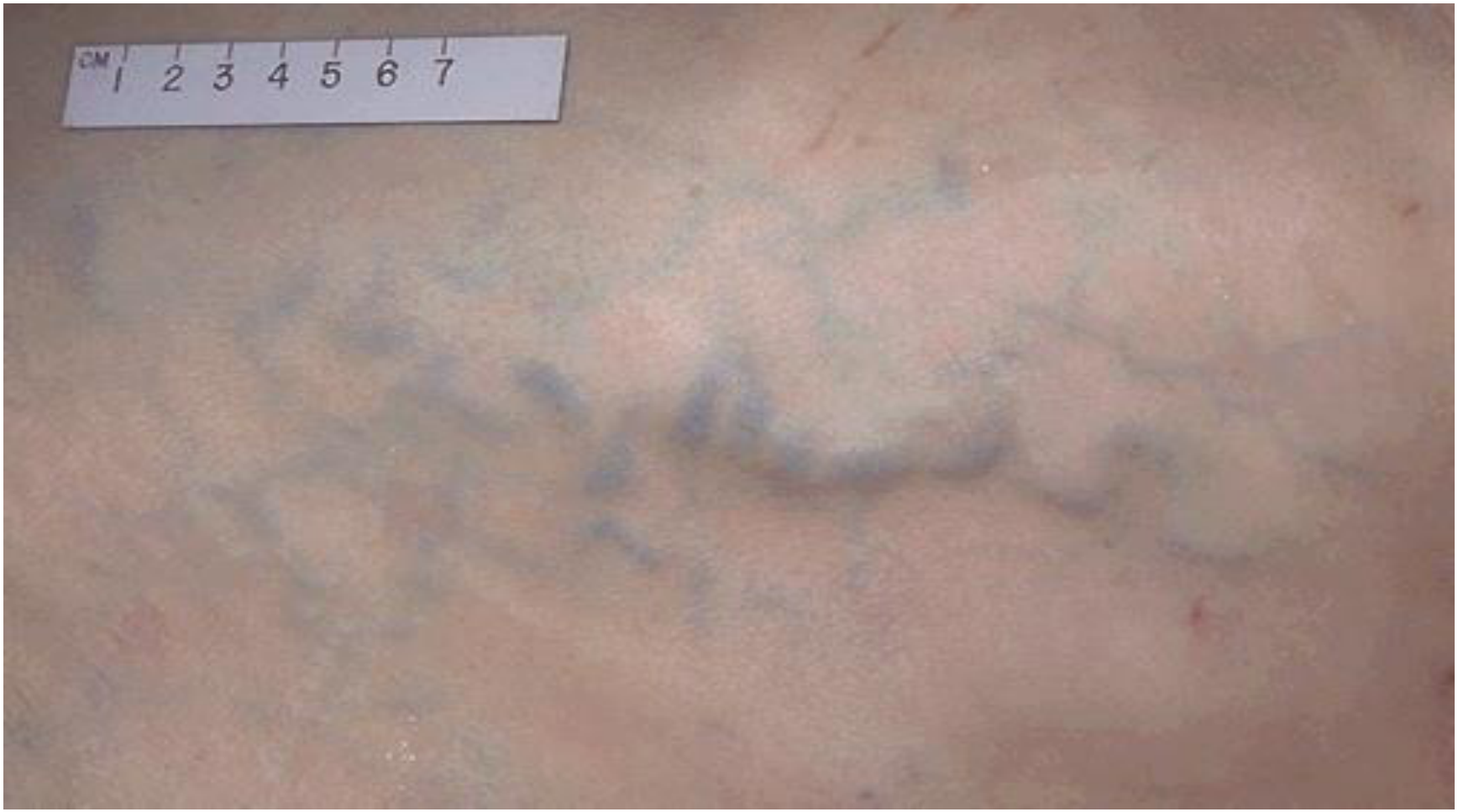
1-Around & within the rectum (Hemorrhoids)

2-Gastroesophageal junction (varicies)

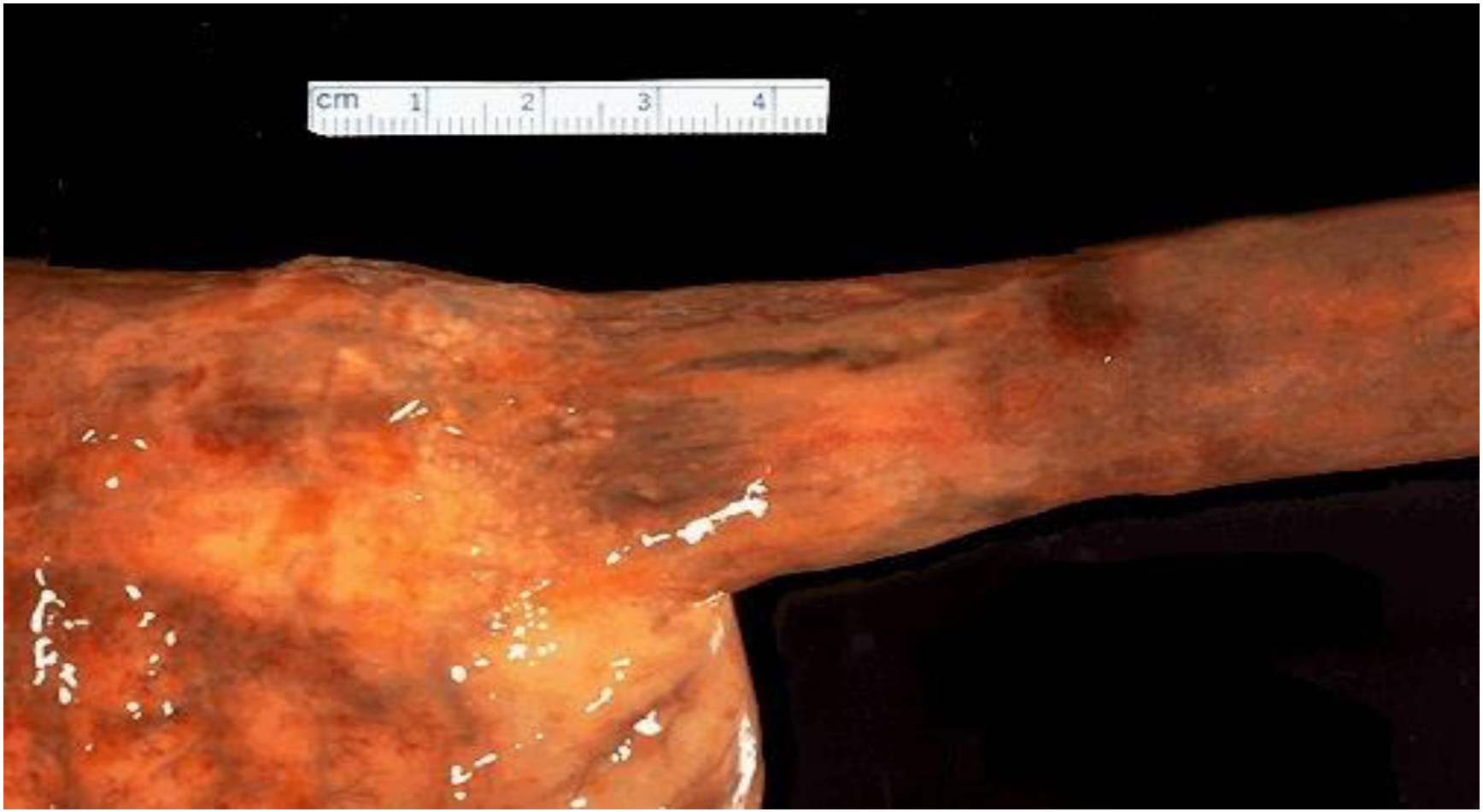
3-Retroperitoneum

4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

Caput medusae-abdominal skin



Esophageal varicies



- Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UGI bleeding.

Splenomegaly

-Usu. 500-1000 gms (N <300gms)

-Not necessarily correlated with other features of portal ↑Bp

-May result in hypersplenism

Splenomegaly

Hepatic encephalopthy

-It is a complication of acute & chronic hepatic failure

-Disturbance in brain function ranging from behavioural changes to

marked confusion & sutpor to deep coma & death

-The changes may progress over hrs. or days

-<u>Neurological signs:</u>

Rigidity

Hyper-reflexia

Non – specific EEG

Seizures

Asterixis (non-rhythmic rapid extension flexion movements of head & extremities) .

-Brain shows edema & astrocytic reaction

Pathogenesis

-Physiologic factors important in development of hepatic encephalopathy :-

1-Severe loss of hepatocellular function

2-Shunting of blood around damaged liver

↓↓

-Exposure of Brain to toxic metabolic products

-Acute insult : ↑ NH3 level in blood → generalized brain edema impaired neuronal function

-Chronic insult: alteration in central nervous system aminoacid metabolism

Hepatorenal Syndrome

- appears in individuals with severe liver disease.
- consists of the development of renal failure without primary abnormalities of the kidneys themselves.

- Excluded by this definition are concomitant damage to both liver and kidney, as may occur with exposure to CCL_4 and certain mycotoxins and the copper toxicity of Wilson disease.
- Also excluded are instances of advanced hepatic failure in which circulatory collapse leads to acute tubular necrosis & acute renal failure.

- Kidney function promptly improves if hepatic failure is reversed.
- The exact cause is unknown.
- Systemic vasoconstriction leading to severe reduction of renal blood flow particularly to the cortex.

- Onset of this syndrome is typically by a drop in urine output associated with rising BUN and creatinine values.
- The renal failure may increase the risk of death in the patient with acute fulminant or advanced chronic hepatic disease.

Drug – Induced liver disease

-Drug reactions:

1-Predictable (intrinsic)

2-Unpredictable (idiosyncratic)

- **Predictable drug reactions may occur in anyone who accumulates a sufficient dose (dose-dependent).**
- **Unpredictable reactions depend on idiosyncrasies of the host:**
- **1-the host's propensity to mount an immune response to the antigenic stimulus.**
- **2-the rate at which the host metabolizes the agent.**

- **The injury may be immediate or take weeks to months to develop.**
- ***drug-induced chronic hepatitis is clinically and histologically indistinguishable from chronic viral hepatitis or autoimmune hepatitis and hence serologic markers of viral infection are critical for making the distinction.***

Predictable drugs:

Acetaminophen
Tetracycline
Antineoplastic agents
CCL4
Alcohol

Unpredictable drugs

Chlorpromazine
Halothane
Sulfonamides
Methyldopa
Allopurinol

-Mechanism of drug injury :

1-Direct toxic damage

e.g acetaminophen
CCl_4
mushroom toxins

2-Immune-mediated damage

-Patterns of injury

1-Hepatocellular necrosis

2-Cholestasis

3-Steatosis

4-Steatohepatitis

5-Fibrosis

6-Vascular lesions

7-Granuloma

8-Neoplasms benign & malignant

Pattern of Injury	Morphology	Examples
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive Anabolic steroids
Cholestatic hepatitis	Cholestasis with lobular necroinflammatory activity	Antibiotics; Phenothiazines
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldoya, Phenytoin
	Submassive necrosis, zone 3	Acetaminophen Halothane
	Massive necrosis	Isoniazid, Phenytoin
Steatosis	Macrovesicular	Ethanol, Methotrexate Corticosteroids Total parenteral nutrition

• Steatohepatitis	Microvesicular Mallory bodies	Amiodarone, Ethanol
• Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Methotrexate, Isoniazid Enalapril
• Granulomas	non-caseating	Sulfonamides
• Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusivedisease)	High-dose chemotherapy Bush teas
	Budd-Chiari syndrome	Oral contraceptives(OCP)
	Sinusoidal dilatation	Oral contraceptives (OCP)
	Peliosis hepatis (blood-filled cavities)	Anabolic steroids Tamoxifen

- Neoplasms

Hepatic adenoma	OCP
	Anabolic steroids
HCC	Thorotrast
Cholangiocarcinoma	Thorotrast
Angiosarcoma	Thorotrast,
	Vinyl chloride

Drugs that may cause acute liver failure

1-Acetaminophen

2-Halothane

3-Antituberculosis drugs (rifampin, isoniazid)

4-Antidepressant monoamine oxidase inhibitors

5-Toxins as CCL_4 & mushroom poisoning

- The most common cause (46% of cases of acute liver failure) is acetaminophen intoxication.
- 60% of these are a consequence of accidental overdosage.

Morphology:

Massive necrosis → 500 – 700 gm liver

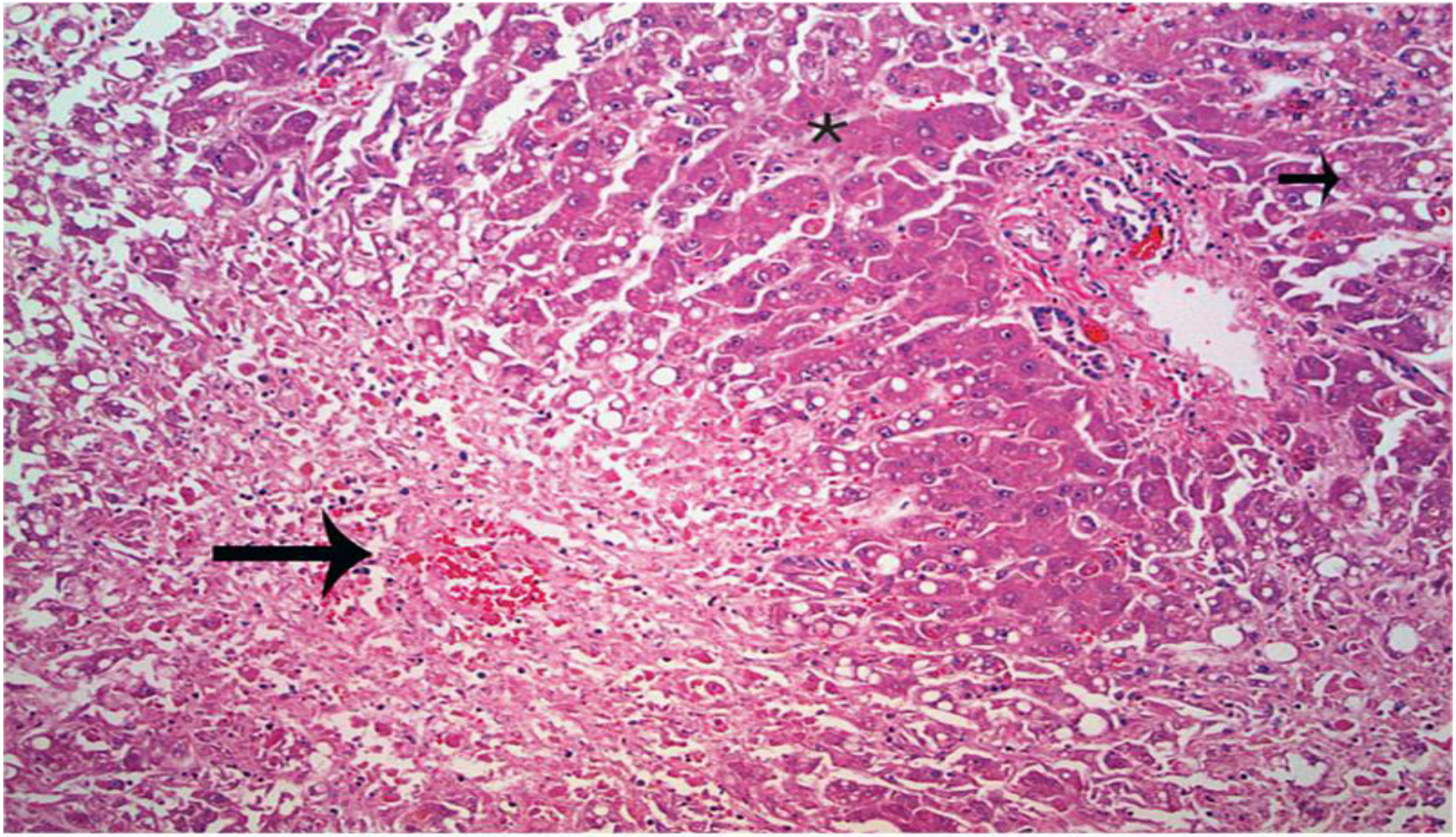
Submassive necrosis

Patchy necrosis

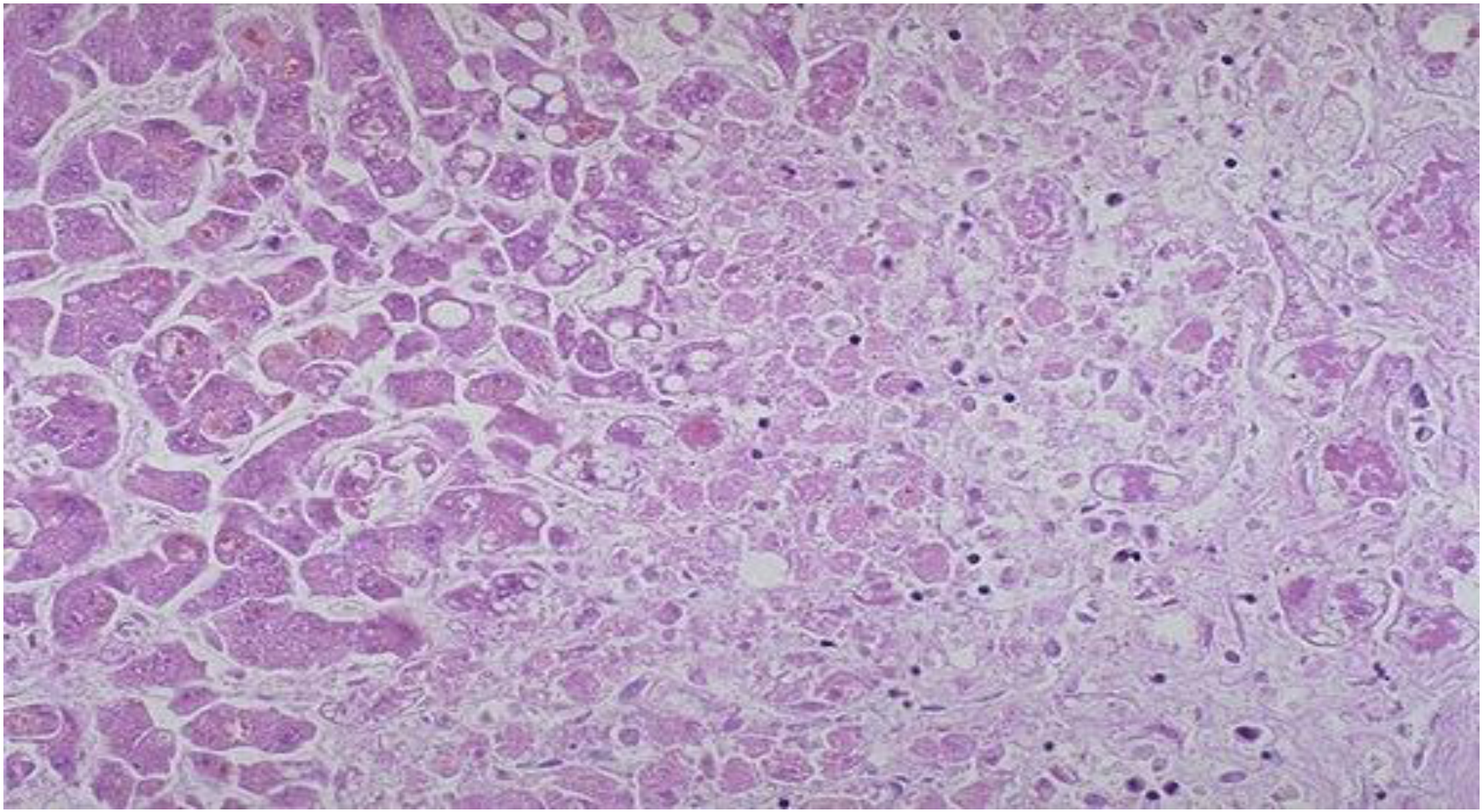
- Patient survival for more than a week permits regeneration of surviving hepatocytes.
- Regeneration is initially in the form of strings of ductular structures which mature into hepatocytes.
- If the parenchymal framework is preserved liver architecture is restored.
- With massive destruction of lobules leads to formation of nodular masses of liver cells.
- Scarring may occur in patients with a protracted course of submassive or patchy necrosis representing a route for developing so-called macronodular cirrhosis

Hepatocellular necrosis caused by acetaminophen overdose. Confluent necrosis is seen in the perivenular region (*large arrow)* There is little inflammation.

The residual normal tissue is indicated by the *asterisk*



Necrosis of hepatocytes



Infections of Liver

1-Viral infections

a-I.M EBV
b-CMV
c-Yellow fever
d-Rubella , herpesvirus
e-Adenoviruses enterovirus
f-Hepatitis viruses A B C D E G

2-Miliary tuberculosis

3-Malaria

4-Staphylococcal bacteremia

5-Salmonelloses

6-Candida

7-Amebiasis

Hepatitis A virus

- **Hepatitis A ("infectious hepatitis") is a *benign, self-limited disease.***
- **incubation period of 15 to 50 days (average 28 days).**
- ***HAV does not cause chronic hepatitis or a carrier state and only rarely causes fulminant hepatitis.***
- **Fatality rate is 0.1%**

-Transmission : Feco-oral rout

-Endemic in developing countries with low hygiene & sanitation → anti-HAV Abs by the age of 10yrs. →50% by the age of 50yrs.

-Clinically the disease is mild to asymptomatic affecting children of school age & rare thereafter

-The virus is shed in bile & feces

-The virus is shed is the stool 2-3 wks before & 1wk after the onset of jaundice

-HAV is not shed in saliva, urine, or semen

-HAV viremia is transient & bl. Donors are not screened for the virus

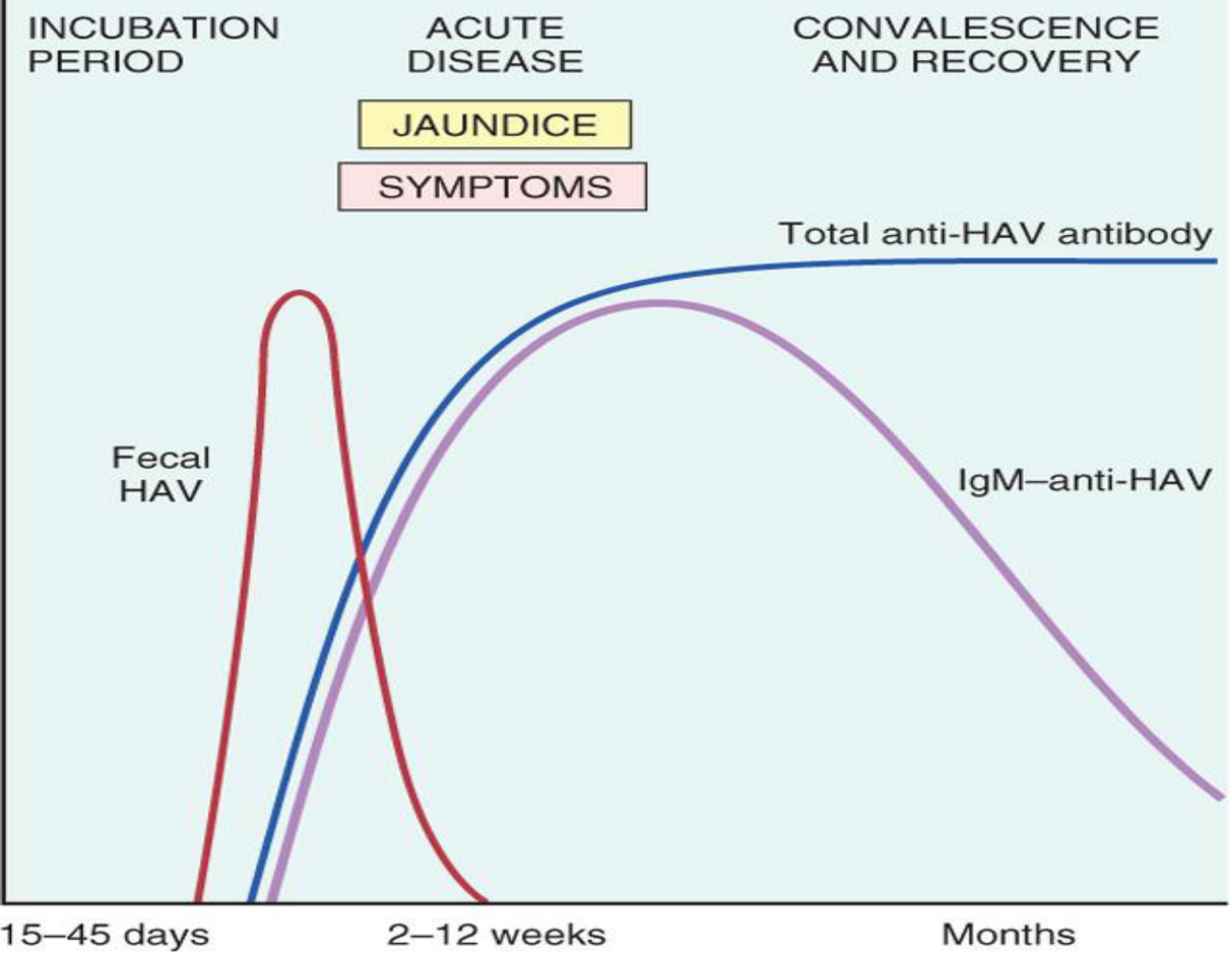
- Waterborne epidemics may occur in developing countries where people live in overcrowded, unsanitary conditions.
- Among developed countries, sporadic infections may be contracted by the consumption of raw or steamed shellfish (oysters, mussels, clams), which concentrate the virus from seawater contaminated with human sewage.
- Ingestion of raw green onions contaminated with HAV caused outbreaks of the disease in the United States in 2003

Serelogic dx

Anti HAV IgM: at the onset of symptoms
→ ↓ in few months

Anti HAV IgG:appears later & persists for life

-HAV vaccine is effective



Hepatitis B Virus

- carrier rate of approximately 400 million.
- About 80% of all chronic carriers live in Asia and the Western Pacific rim, where prevalence of chronic hepatitis B is more than 10%.
- In the United States there are approximately 185,000 new infections per year.

-**HBV is a hardy virus can withstand extremes of temperature & humidity**

-Prolonged IP 4-26 wks

-Prolonged viremia HBV remains in blood during the last stages of incubation period and during active episodes of acute and chronic hepatitis

-Present in all body fluids as tears, saliva, sweat, breast milk, vaginal sec., semen & pathological body fluids except stool

- **vertical transmission** from mother to child during birth constitutes the main mode of transmission.
- **horizontal transmission** via:
- 1- transfusion
- 2- blood products
- 3- dialysis
- 4- needle-stick accidents among health care workers
- 5-IV drug abuse
- 6-sexual transmission (homosexual or heterosexual)
- 7-In 1/3 of patients the source of infection is unknown.

- HBV infection in adults is mostly cleared, but vertical transmission produces a high rate of chronic infection.

-Phases of infection :

1. Proliferative phase
2. Integrative phase

HBV antigens :

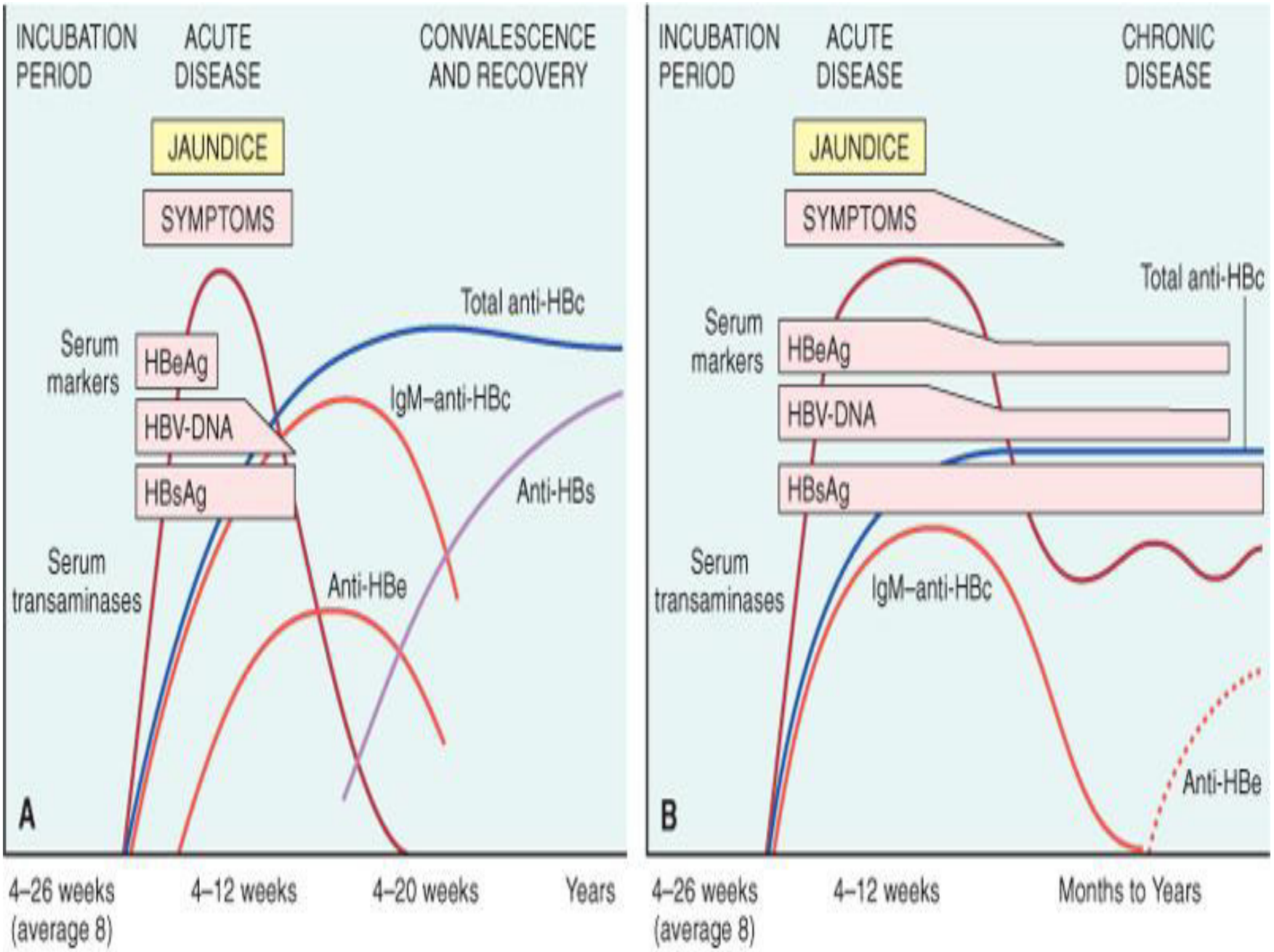
1. HBc Ag(hepatitis B core antigen) - hepatocytes
2. HBe Ag(pre-core protein) -blood
3. HBs Ag -blood
   -hepatocytes
4. DNA polymerase (HBV-DNA) (reverse transcriptase activity)
5. HBx protein (transcriptional transactivator)

required for viral infectivity and may have a role in the causation of hepatocellular carcinoma by regulating p53 degradation and expression

- HBsAg appears before the onset of symptoms, peaks during overt disease, and then declines to undetectable levels in 3 to 6 months.
- Anti-HBs antibody does not rise until the acute disease is over and is usually not detectable for a few weeks to several months after the disappearance of HBsAg.
- Anti-HBs may persist for life conferring protection
- HBV-DNA, and DNA polymerase appear in serum soon after HBsAg, and all signify active viral replication

- **Persistence of HBeAg** is an important indicator of continued viral replication, infectivity, and probable progression to chronic hepatitis.
- The appearance of **anti-HBe Abs** shortly after the disappearance of HBeAg indicates the end of the infection.
- **IgM anti-HBc** becomes detectable in serum shortly before the onset of symptoms
- Over a period of months the IgM anti-HBc antibody is replaced by IgG anti-HBc.

- **Anti – HBs IgG:** rise after the acute phase is over & remains detectable after wks or months after disappearance of HBsAg
- Hepatitis B can be prevented by vaccination and by the screening of donor blood, organs, and tissues



Clinical syndromes associated with HBV infection

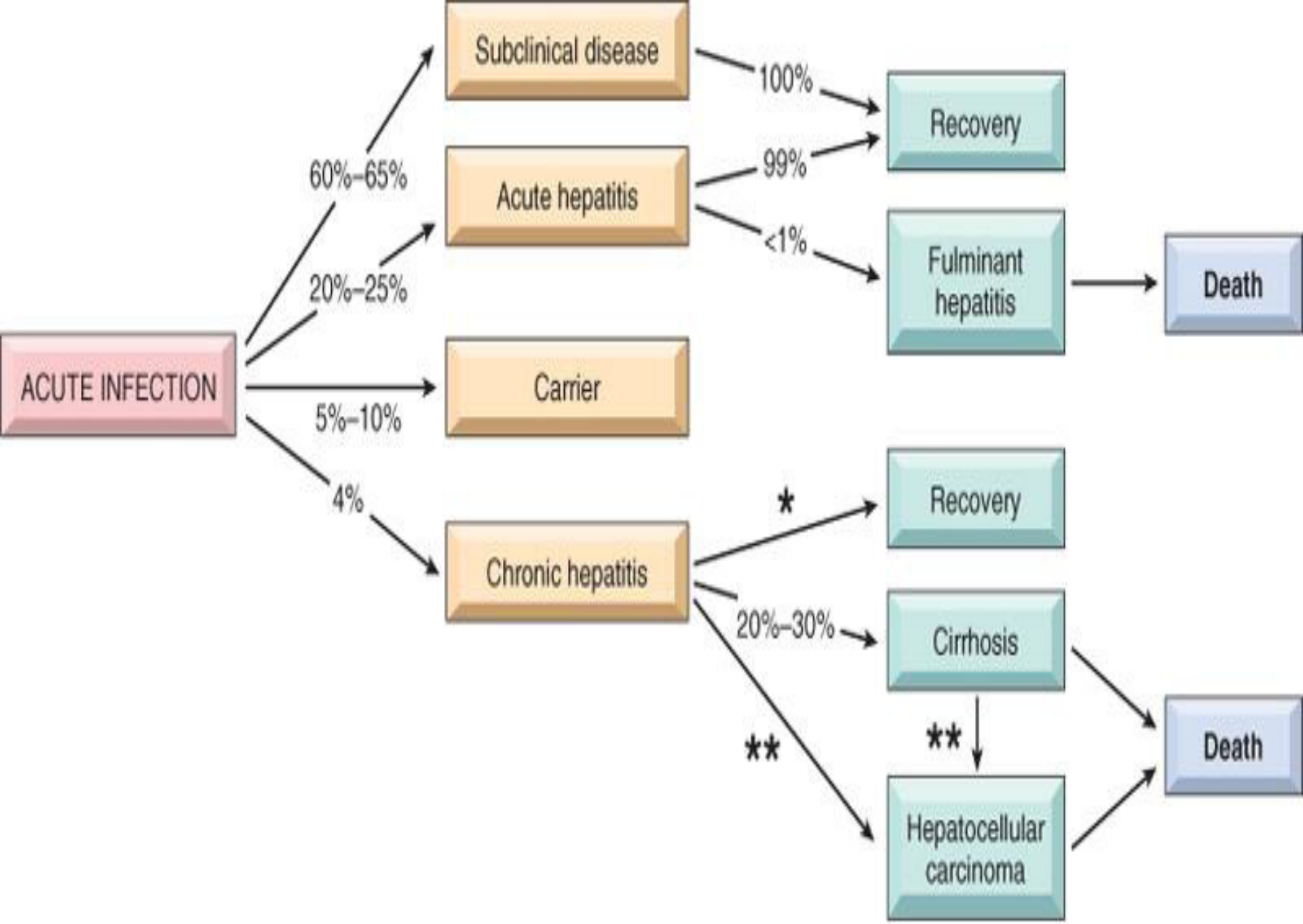
1-Acute hepatitis with recovery

2-Nonprogressive chronic hepatitis

3-Progressive chronic hepatitis ending in cirrhosis

4-Fulminant hepatitis with massive liver necrosis

5-Asymptomatic carrier state

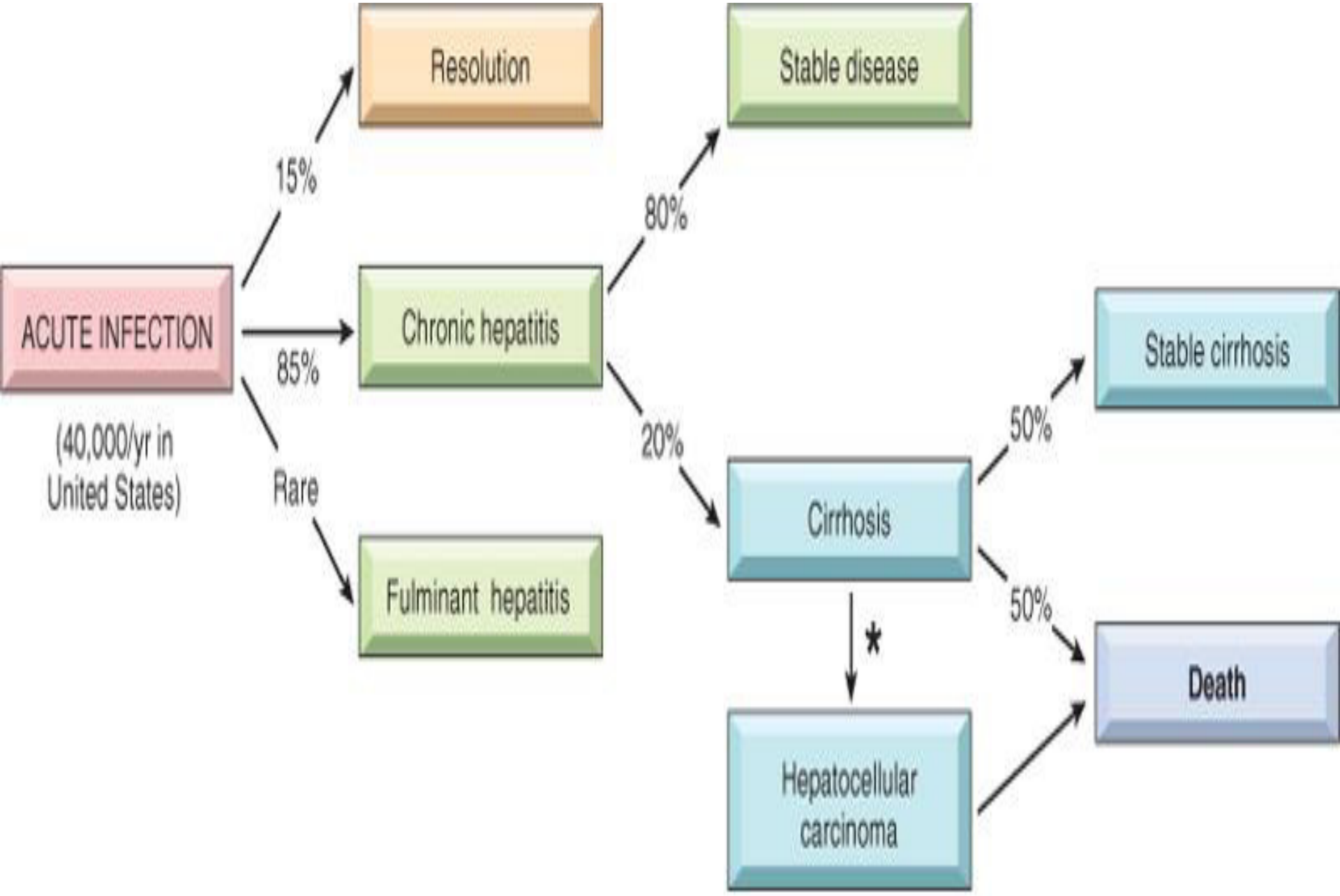


Hepatitis C Virus (HCV)

- 3% (0.1-12%, depending on the country).
- Persistent chronic infection exists in 3 to 4 million persons in the United States.
- The number of newly acquired HCV infections per year dropped from 180,000 in the mid-1980s to about 28,000 in the mid-1990s due to the marked reduction in transfusion-associated HCV as a result of screening procedures and a decline of infections in intravenous drug abusers.

- ***<u>The major route of transmission is:</u>***
- *1- through blood inoculation*
- *2- with intravenous drug use accounting for over 40% of cases in the United States.*
- 3-via blood products is now fortunately rare, accounting for only 4% of all acute HCV infections.
- 4-Occupational exposure among health care workers accounts for 4% of cases.
- 5-The rates of sexual transmission and vertical transmission are low.
- 6- Sporadic hepatitis of unknown source accounts for 40% of cases.

- ***HCV infection has a much higher rate than HBV of progression*** **to** ***chronic disease and eventual cirrhosis*****.**



Epidemiology

-40000 new cases/yr in USA

-1.8% of the population (4 millions) are seropositive 70% of which have chronic liver disease

-Anti HCV IgG occuring after active infection do not confer effective

immunity due to genomic instability of the virus & antigenic variability

-Anti HCV vaccine is not effective

-Repeatd bouts of HCV infection are common causing hepatic damage is characteristic due to reactivation of a pre existing infection or emergence of newly mutated strains

- The IP 2-26 weeks (mean of 6-12 weeks).
- The clinical course of acute hepatitis C is **asymptomatic in 75% of** individuals and is easily missed.
- HCV RNA is detectable in blood for 1-3 weeks and is accompanied by elevations in serum aminotransferase.

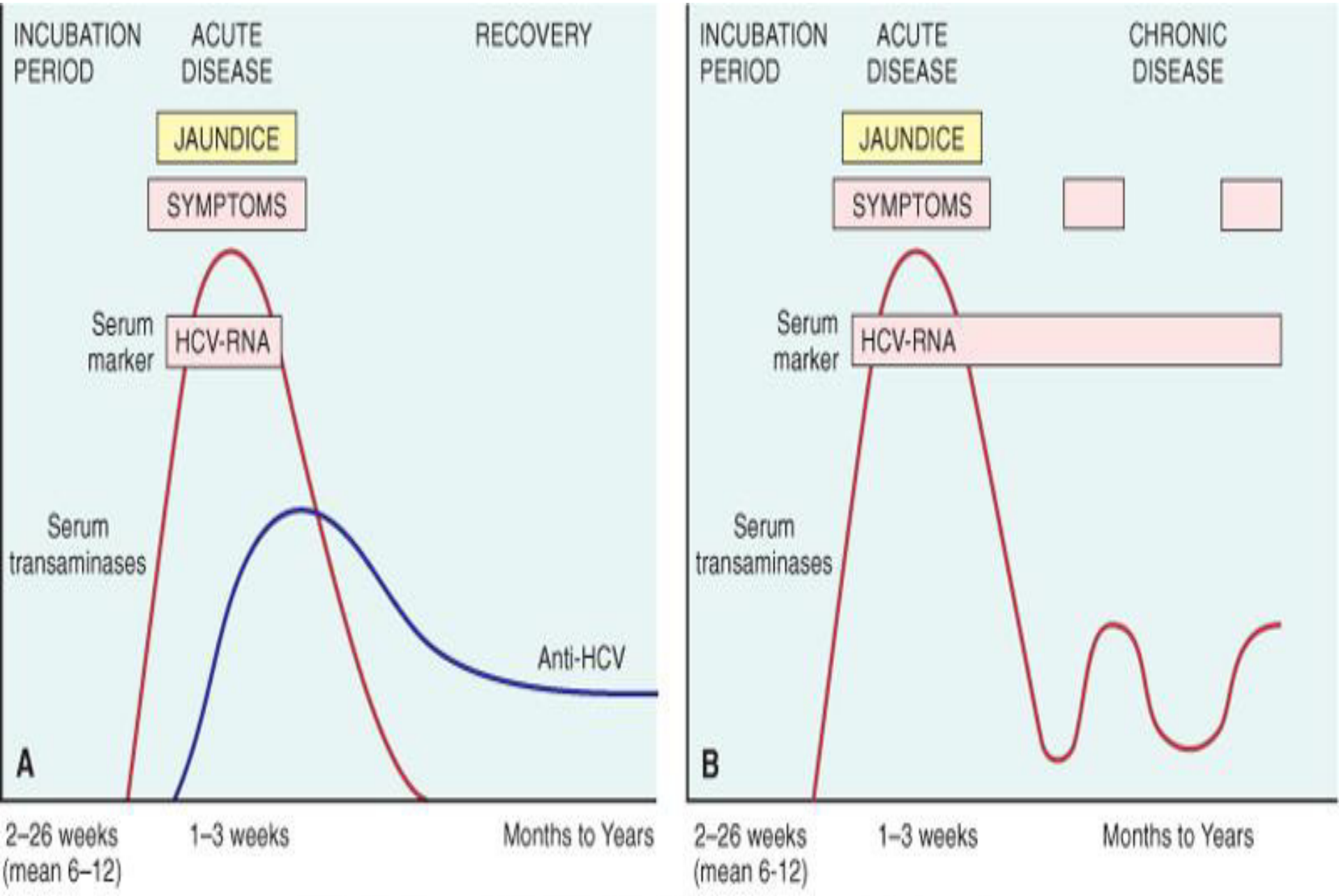
- **Clinical syndromes associated with HCV:**

- **1.Persistent infection with subclinical or asymptomatic acute infection**
- **2.Chronic hepatitis**
- **3.Fulminant hepatitis rare**
- **4.Cirrhosis 20%**
- **5.Hepatocellular carcinoma**

Serological diagnosis

- **HCV RNA is detectable in bl. For 1 – 3 wks**

  peak coincides with ↑ in serum transaminases
- **Anti HCV Abs detected in 50 – 70% of patients during symptomatic acute infection**
- **In 30 – 50% of patients the anti HCV Abs emerge after 3 – 6 wks**
- **In chronic HCV infection circulating HCV-RNA persists despite the presence of Abs in many patients (> 90%)**



Hepatitis D Virus

-Hepatitis delta virus

-Replication defective virus

-Causes infection only when it is encapsulated by HBsAg

-I.P 4 – 7 wks in superinfection

- 8% among HBsAg carriers in southern Italy to as high as 40% in Africa and the Middle East.
- HDV infection is uncommon in Southeast Asia and China, areas in which HBV infection is endemic.
- In the United States HDV infection is largely restricted to drug addicts and individuals receiving multiple transfusions (e.g.hemophiliacs who have prevalence rates of 1% to 10%).

- Delta hepatitis arises in two settings:
- (1) acute coinfection after exposure to serum containing both HDV and HBV
- (2) superinfection of a chronic carrier of HBV with a new inoculum of HDV.
- Most coinfected individuals can clear the viruses and recover completely.
- in superinfected individuals there is an acceleration of hepatitis, progressing to more severe chronic hepatitis 4 to 7 weeks later.

- **Routes of transmission:**
- Parenteral (close personal contact)

- HDV Ag are detectable in the blood and liver just before and in the early days of acute symptomatic disease.
- *IgM anti-HDV antibody is the most reliable indicator of recent HDV exposure,* but its appearance is transient.
- acute coinfection by HDV and HBV is best indicated by detection of IgM against both HDV Ag and HBcAg
- With HDV superinfection, HBsAg is present in serum; and anti-HDV antibodies (IgM and IgG) persist in low titer for months or longer.

Serologic diagnosis

.HDV-RNA is detectable in blood & liver just prior to & in early days of acute symptomatic disease

.Anti HDV IgM = recent HDV infection

.Anti HDV IgM appears late & freq. short-lived

.**Coinfection :** IgM against HDV Ag & HBV Ag

.**Superimposed infection:** anti HDV IgM & HBsAg

Hepatitis E virus

- HEV hepatitis is an enterically transmitted, waterborne infection occurring primarily beyond the years of infancy.
- HEV is endemic in India
- Prevalence rates of anti-HEV IgG antibodies approach 40% in the Indian population.
- Sporadic infection seems to be uncommon & occurs mainly in travelers and accounts for more than 50% of cases of sporadic acute viral hepatitis in India.

- Water-borne infection
- Young – middle – aged adults
- Rare in children
- Endemic infection in India, Africa, Mexico……
- Sporadic infection is uncommon & occurs mainly in travelers
- Self-limiting mild disease except in pregnant women with high mortality rate (20%)
- I.P: 6 wks (range 2-8wks)
- No chronic liver disease or carrier state

Serelogy

-HEV-RNA can be detected in stool & liver before the onset of clinical symptoms

-Anti HEV-IgM appears during acute illness & replaced by IgG when symptoms resolve (ie in 2 – 4 wks)

Clinicopathologic Syndromes

1-**Acute asymptomatic : serologic evidence only**

A B C D E

2-Acute symptomatic hepatitis icteric or anicteric

A B C D E

3-Chronic hepatitis with or without progression to cirrhosis

B & C

4-Fulminant hepatitis with massive or submassive hepatic necrosis B, D

A & C very rare

5-Chronic carrier state B,C

Acute asymptomatic infection with recovery

-Minimally ↑ serum tranaminases

-HAV & HBV infections are freq. subclinical in childhood period

-HCV infection is subclinical in 75% of the cases

Acute symptomatic infection with recovery

-Can be caused by any hepatotropic viruses although it is uncommon in HCV infection

-Phases:

1-Incubation period

2-Symptomatic preicteric phase

.Malaise

.General fatigability

.Nausea

.Loss of appetite

.Fever, headaches, muscle pain, diarrhea

.10% of pts. Develop serum sickness-like synd. esp. with HBV infection (fever, rash, arthralgia) due to circulating immune complexes

3-Symptomatic icteric phase

.Usual in adults but not children with HAV

.Absent in 50% of cases of HBV & the majority of HCV

.Conj.hyperbilirubinemia, dark colored urine ,dark stool, pruritus

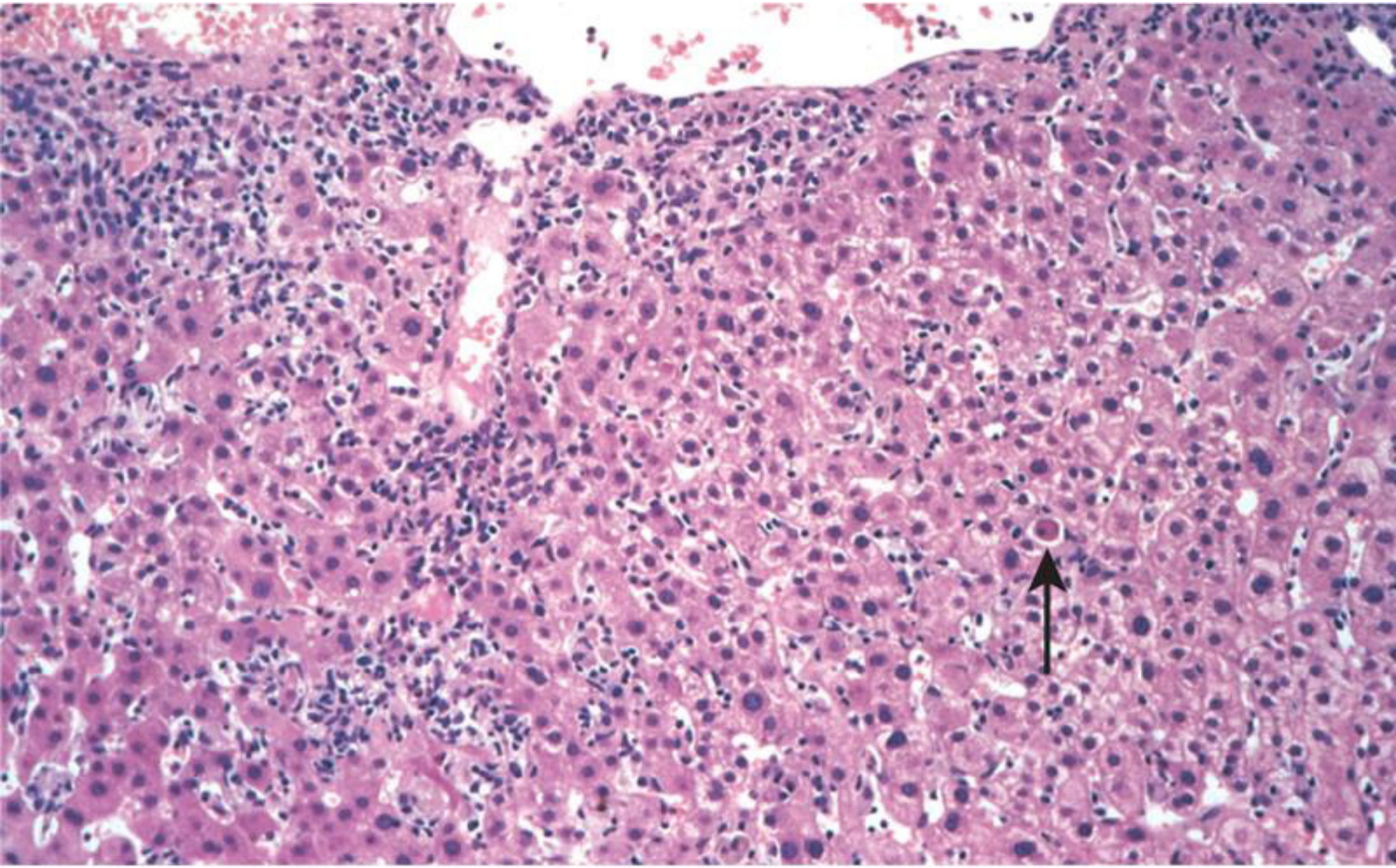
.Prolonged PT, hyperglobulinemia, ↑ serum alkaline phosphatase

- **1- diffuse swelling (ballooning degeneration)**
- **2- cholestasis, with bile plugs in canaliculi and brown pigmentation of hepatocytes.**
- **3-Fatty change is mild and is unusual except with HCV infection.**
- **4- HBV infection may generate "ground-glass" hepatocytes**
- **a finely granular, eosinophilic cytoplasm shown by electron microscopy to contain massive quantities of HBsAg in the form of spheres and tubules.**
- **Other HBV-infected hepatocytes may have "sanded" nuclei, resulting from abundant intranuclear HBcAg.**

- **5- patterns of hepatocyte death are seen.**
- **6-confluent necrosis of hepatocytes may lead to bridging necrosis**
- **7-lobular disarray**
- **8-Inflammation.**

- **9- Kupffer cells undergo hypertrophy and hyperplasia and are often laden with lipofuscin pigment caused by phagocytosis of hepatocellular debris.**
- **10-The portal tracts are usually infiltrated with a mixture of inflammatory cells.**
- **11-interface hepatitis) .**
- **12-bile duct proliferation**

Acute viral hepatitis showing disruption of lobular architecture, inflammatory cells in sinusoids, and apoptotic cells *(arrow).*



Fulminant hepatitis

- **Hepatic insufficiency that progresses from onset of symptoms to hepatic escepholopathy in 2-3 wks**
- **Subfulminant (up to 3 mon)**

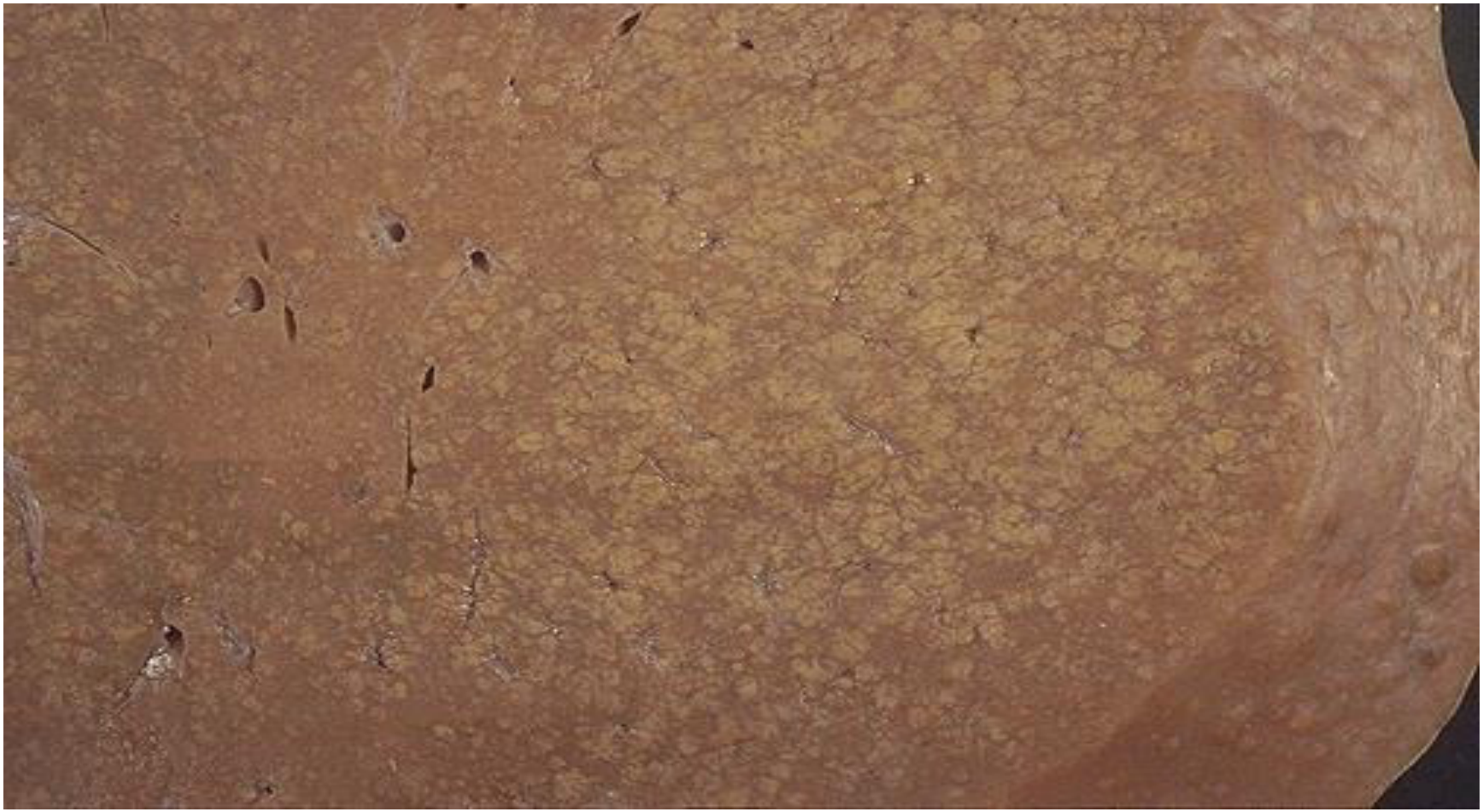
Causes :

1-Viral hepatitis 50 – 65% B,C,E
HBV 2x > HCV
2-Drugs & chemical 25- 50%
e.g Isoniazid , halothane , methyldopa & acetominophen
3-Obstruction of hepatic vein
4-Wilson's disease
5-Acute fatty change of pregnancy.
6-Massive tumor infiltration
7-Reactivation of chronic hepatitis B
8-Acute immune hepatitis

- **Morphology**

-↓ liver size (500 – 700 gm)
-Necrosis of hepatocytes
-Collapsed reticulin tissue
-Inflammatory infillrate
-Regenerative activity of hepatocytes
-Fibrosis

Fulminant hepatitis



Chronic Hepatitis

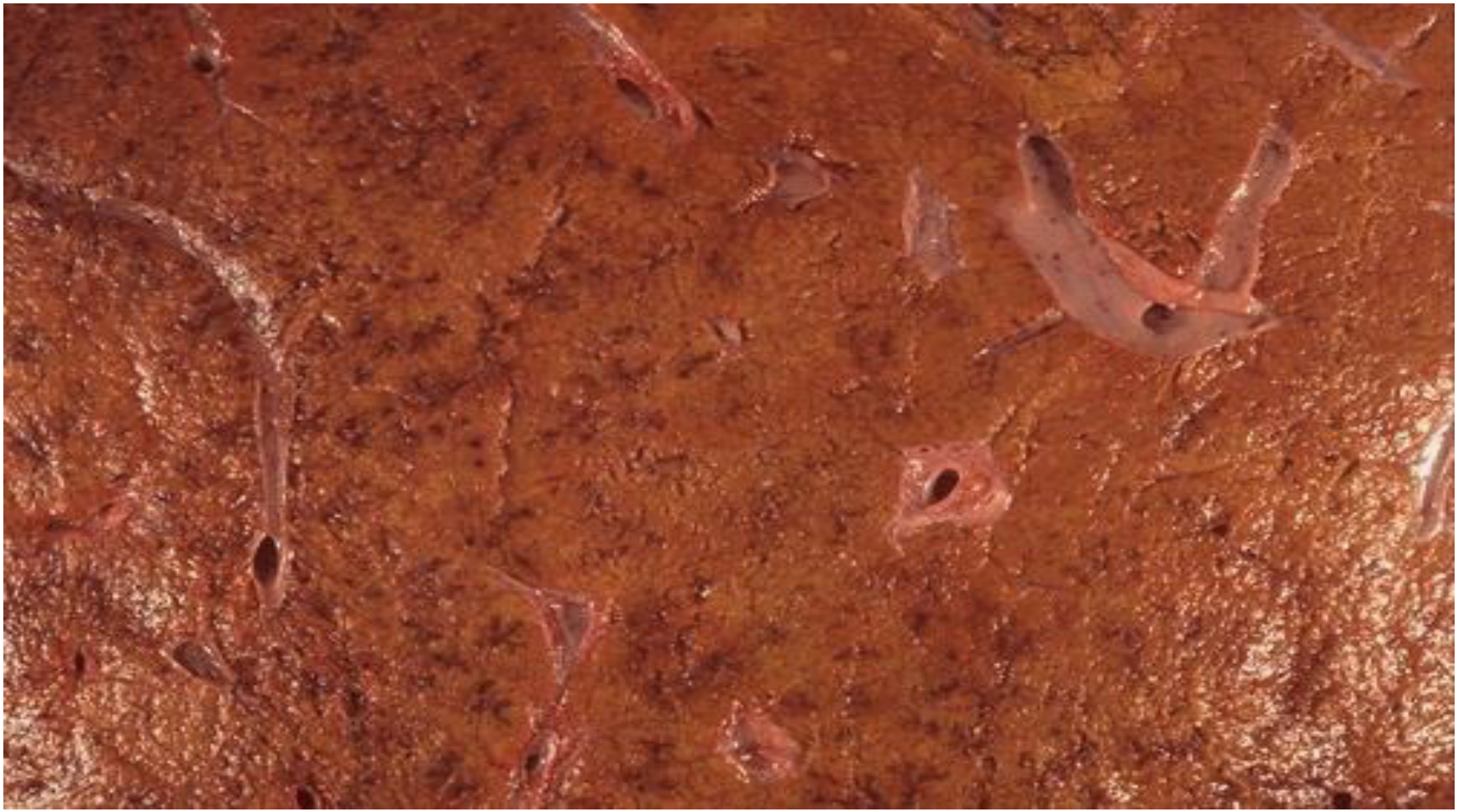
- **Symptomatic, biochemical or serelogic evidence of continuing or relapsing hepatic disease for more than 6months with histologically documented inflammation and necrosis.**
- **Progressive or non progressive**
- **HBV , HCV, HBV-HDV.**

Morphology of chronic hepatitis

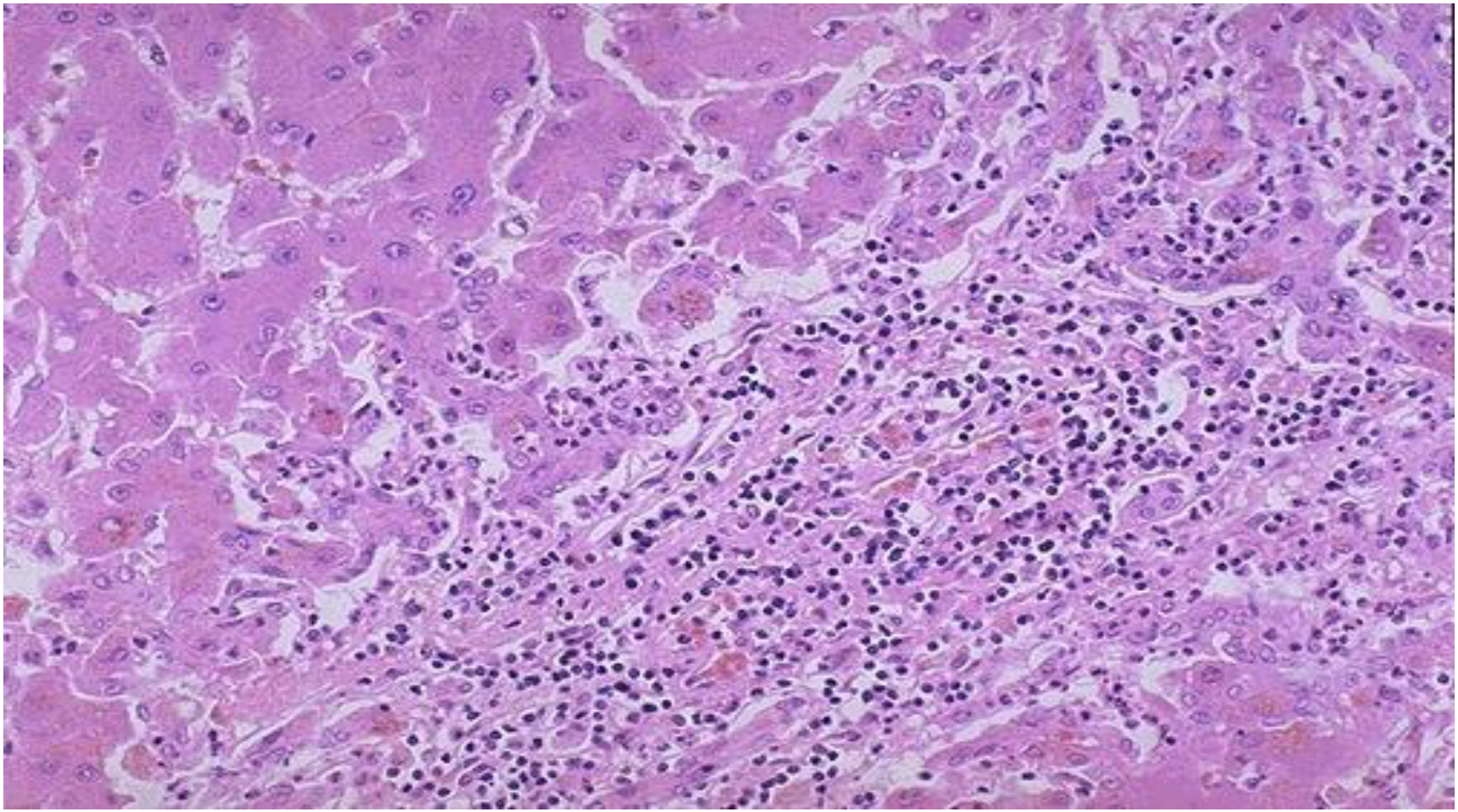
- **Mild to severe**

1.Protal inflammation
2.Lymphoid aggregate
3.Necrosis of hepatocytes-councilman bodies
4.Bile duct damage
5.Steatosis
6.Interface hepatitis
7.Bridging necrosis & fibrosis
8.Fibrosis
9.Ground-glass appearance
10.Sanded nuclei
11.Lobular disarray

Chronic hepatitis

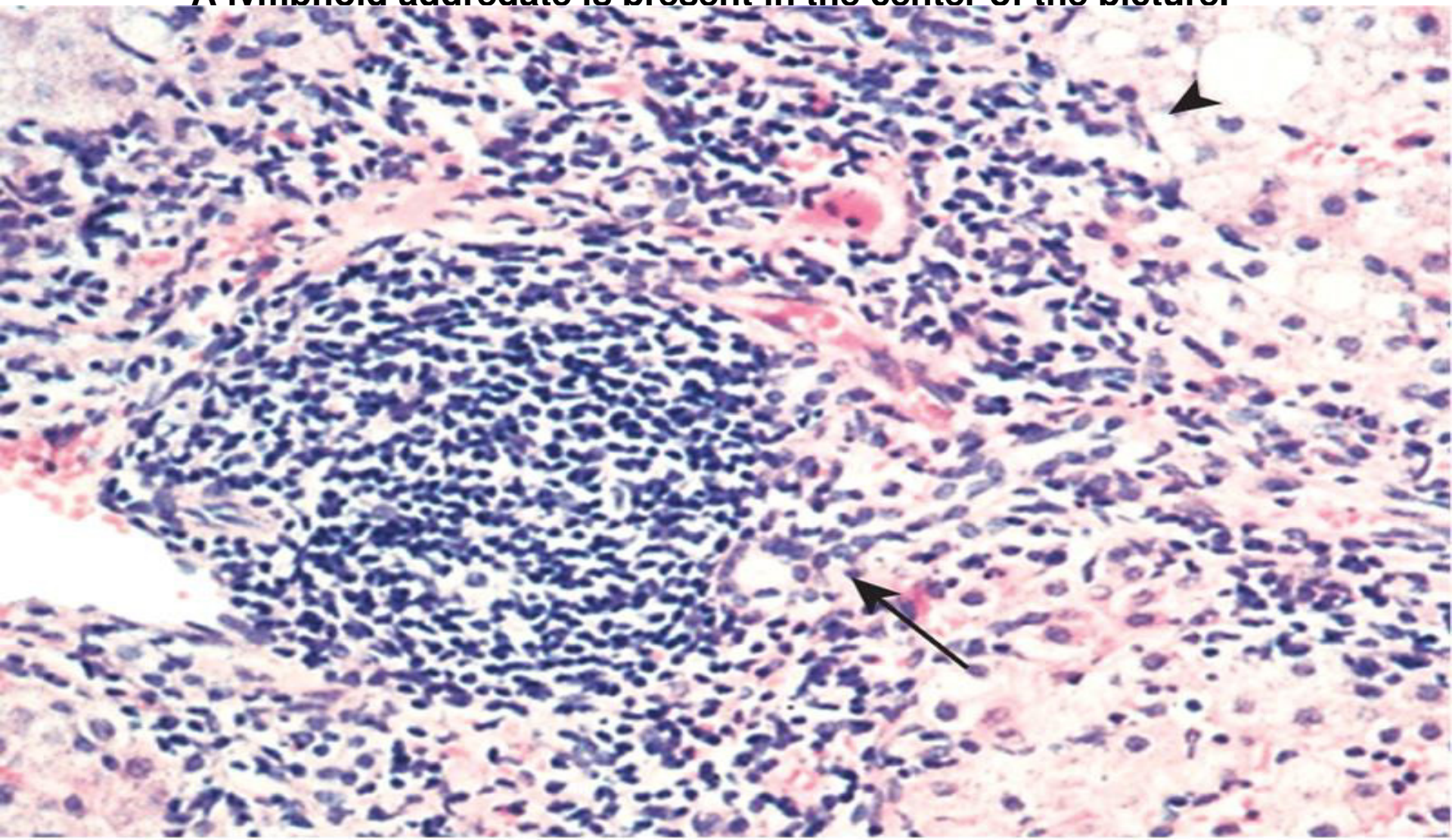


Chronic hepatitis

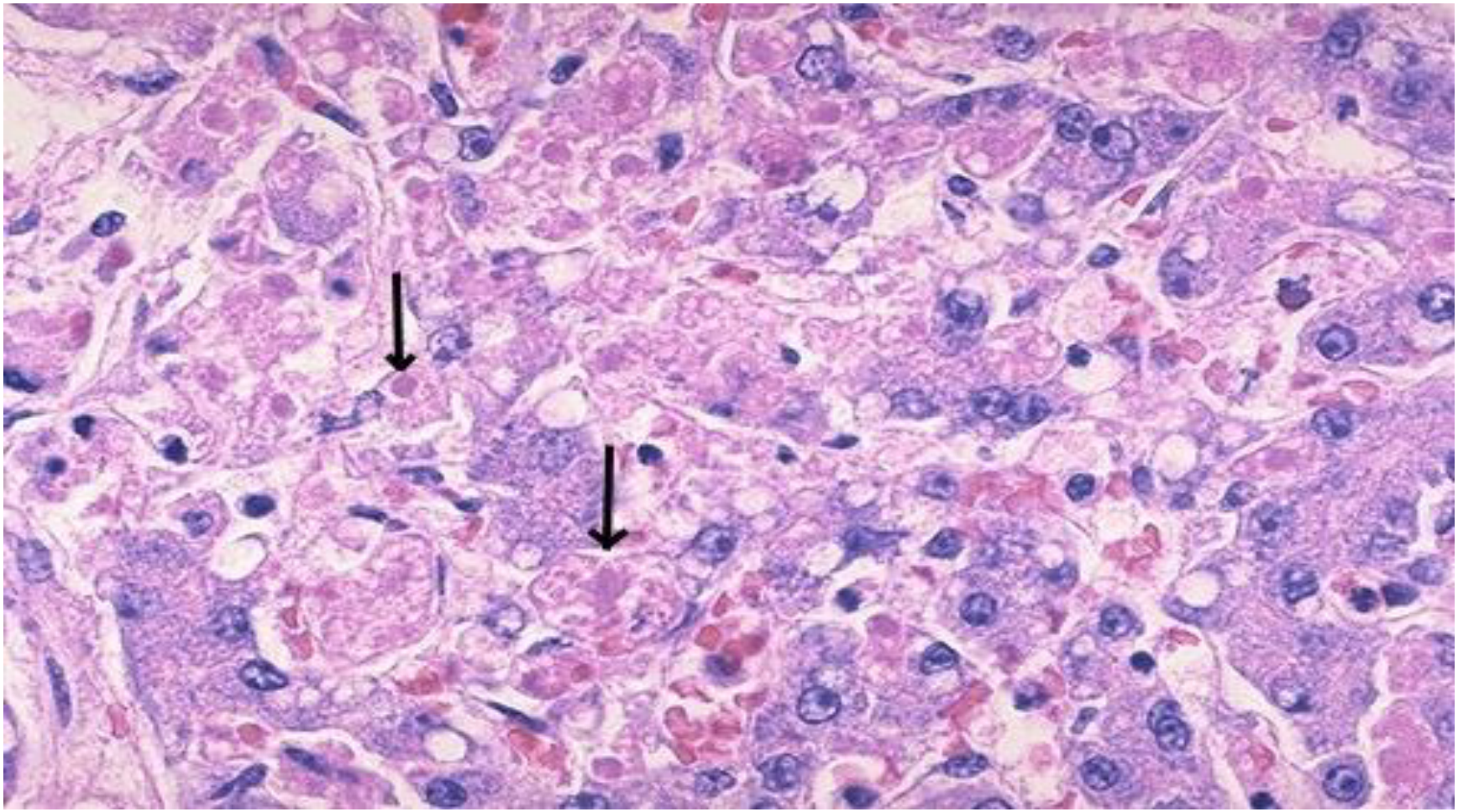


Chronic hepatitis C showing portal tract expansion with inflammatory cells and fibrous tissue (*arrow*), and interface hepatitis with spillover of inflammation into the parenchyma (*arrowhead*).

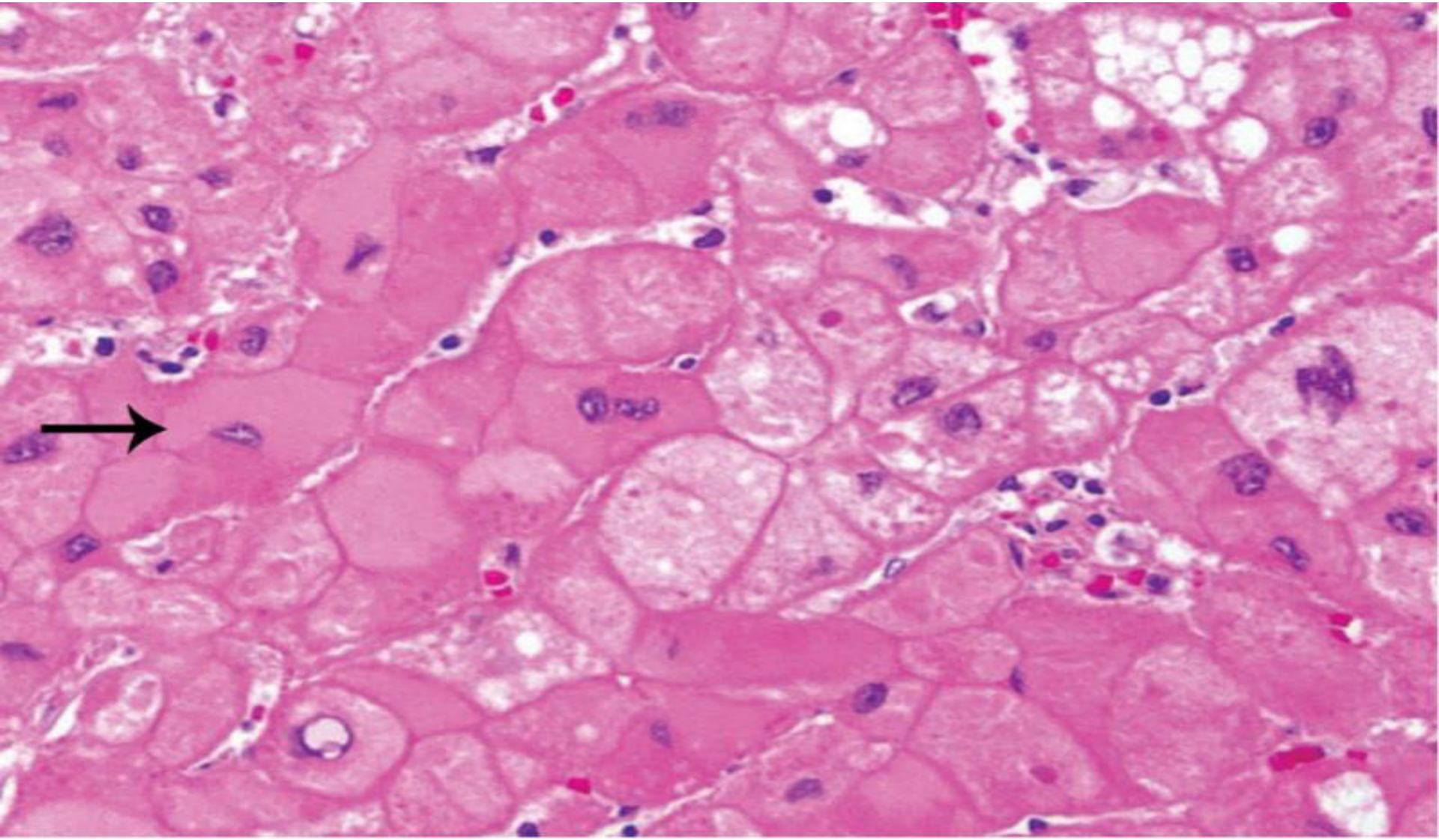
A lymphoid aggregate is present in the center of the picture.



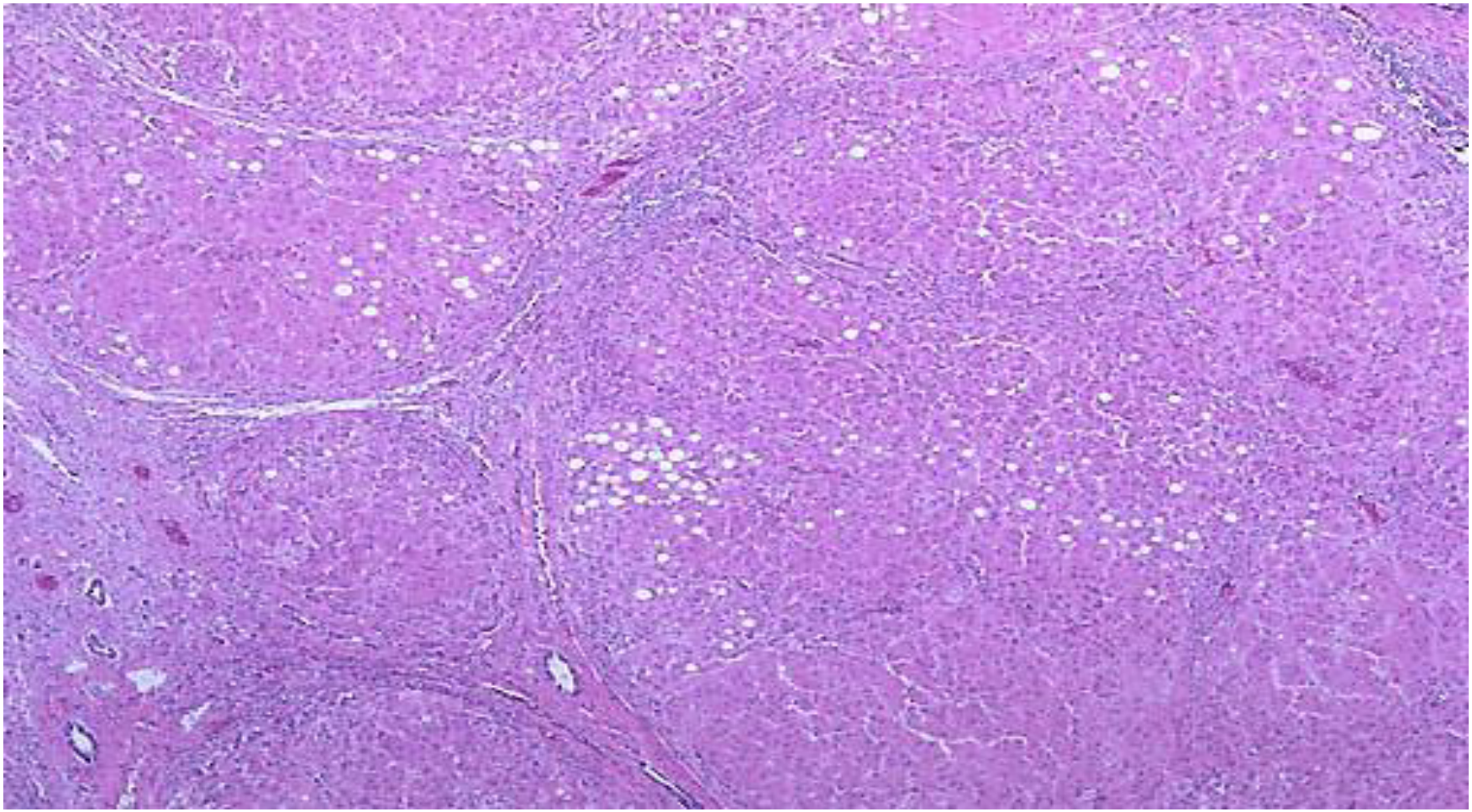
Necrosis of hepatocytes-councilman bodies (arrows)



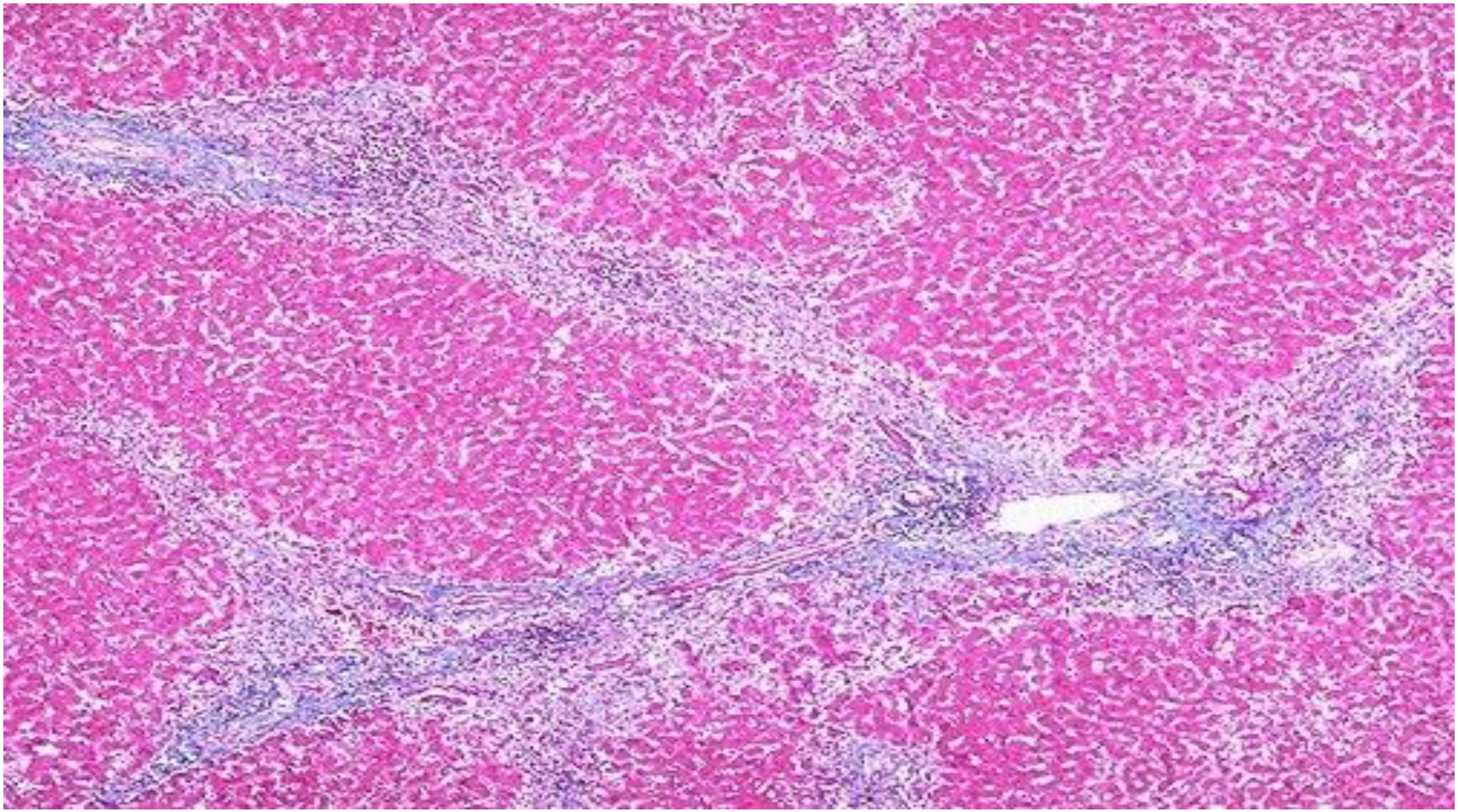
Ground-glass hepatocytes *(arrow)* in chronic hepatitis B, caused by accumulation of HBsAg in cytoplasm.



Fibrosis in chronic hepatitis



Fibrosis in chronic hepatitis



Carrier state

- Carriers are:
- (1) those who harbor one of the viruses but are suffering little or no adverse effects
- (2) those who have nonprogressive liver damage but are essentially free of symptoms or disability
- Both constitute reservoirs of infection.

Predisposing factors

- 1-HBV infection early in life, particularly through vertical transmission during childbirth, produces a carrier state 90-95% of the time.
- only 1-10% of HBV infections acquired in adulthood yield a carrier state.
- 2-impaired immunity
- 3-HBV, HCV, ?HDV