THE LIVER

Functions

1-processing of dietary amino acids, carbohydrates, lipids, and vitamins.

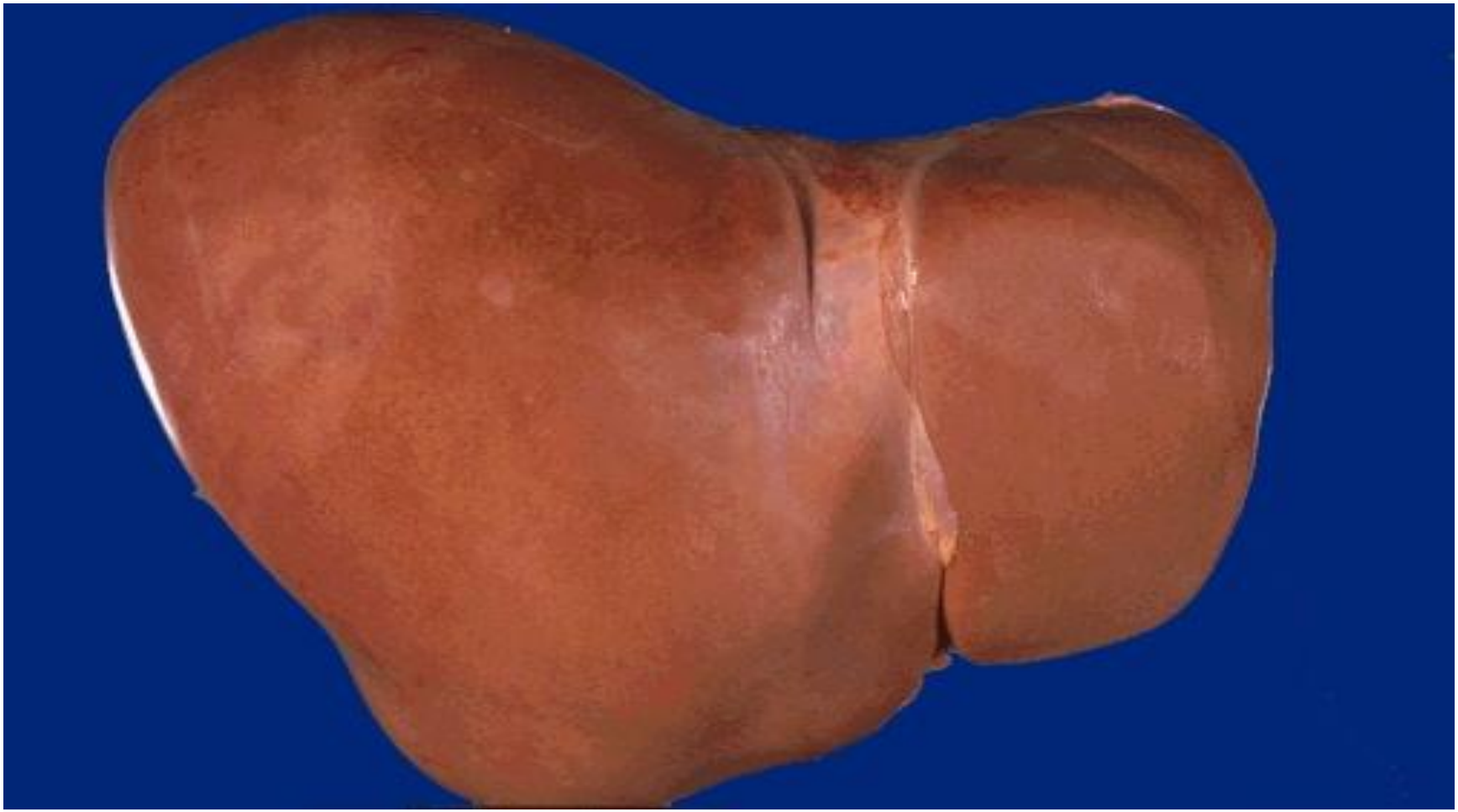
2-synthesis of serum proteins.

3-detoxification and excretion into bile of endogenous waste products and xenobiotics.

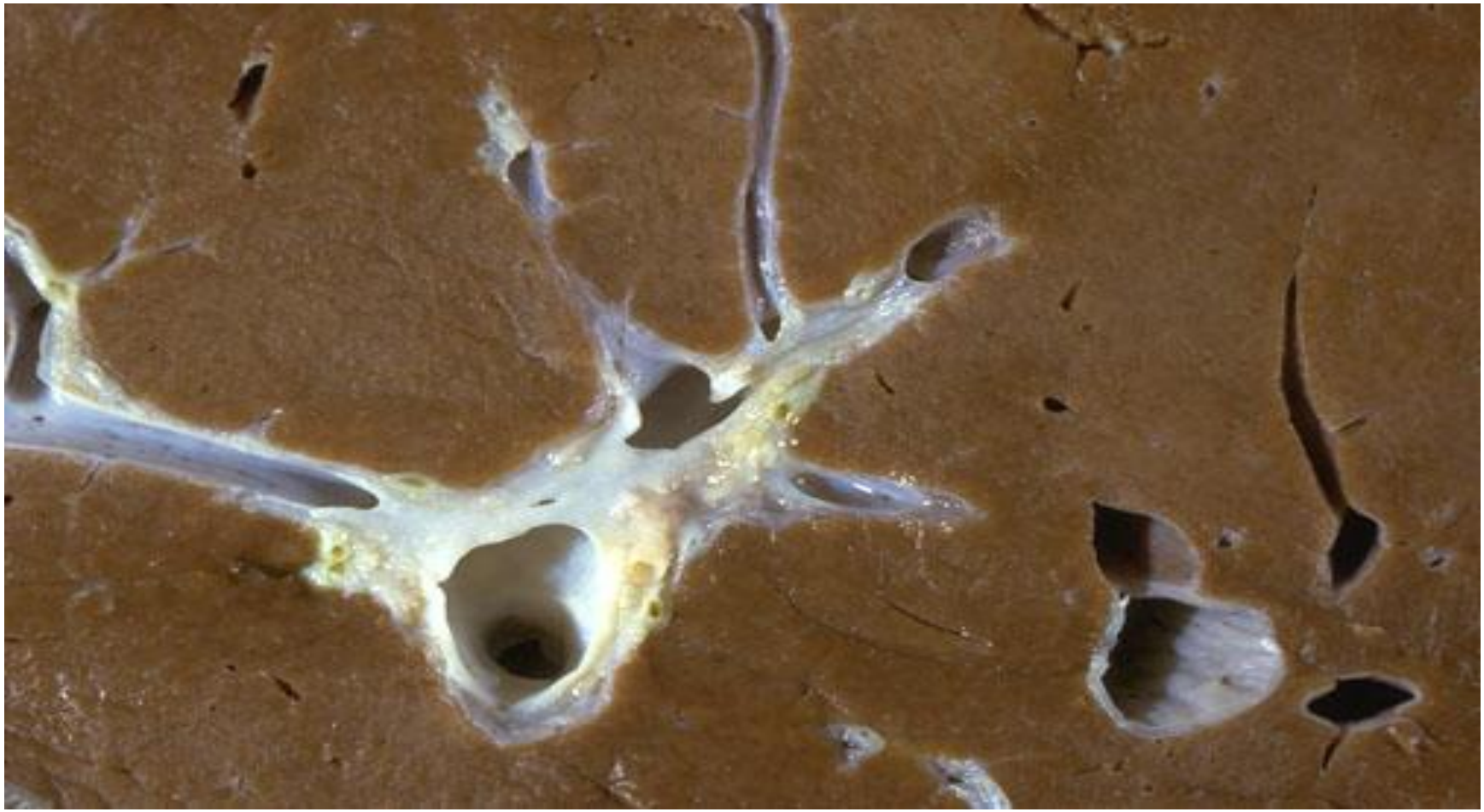
4- bile excresion

5- storage

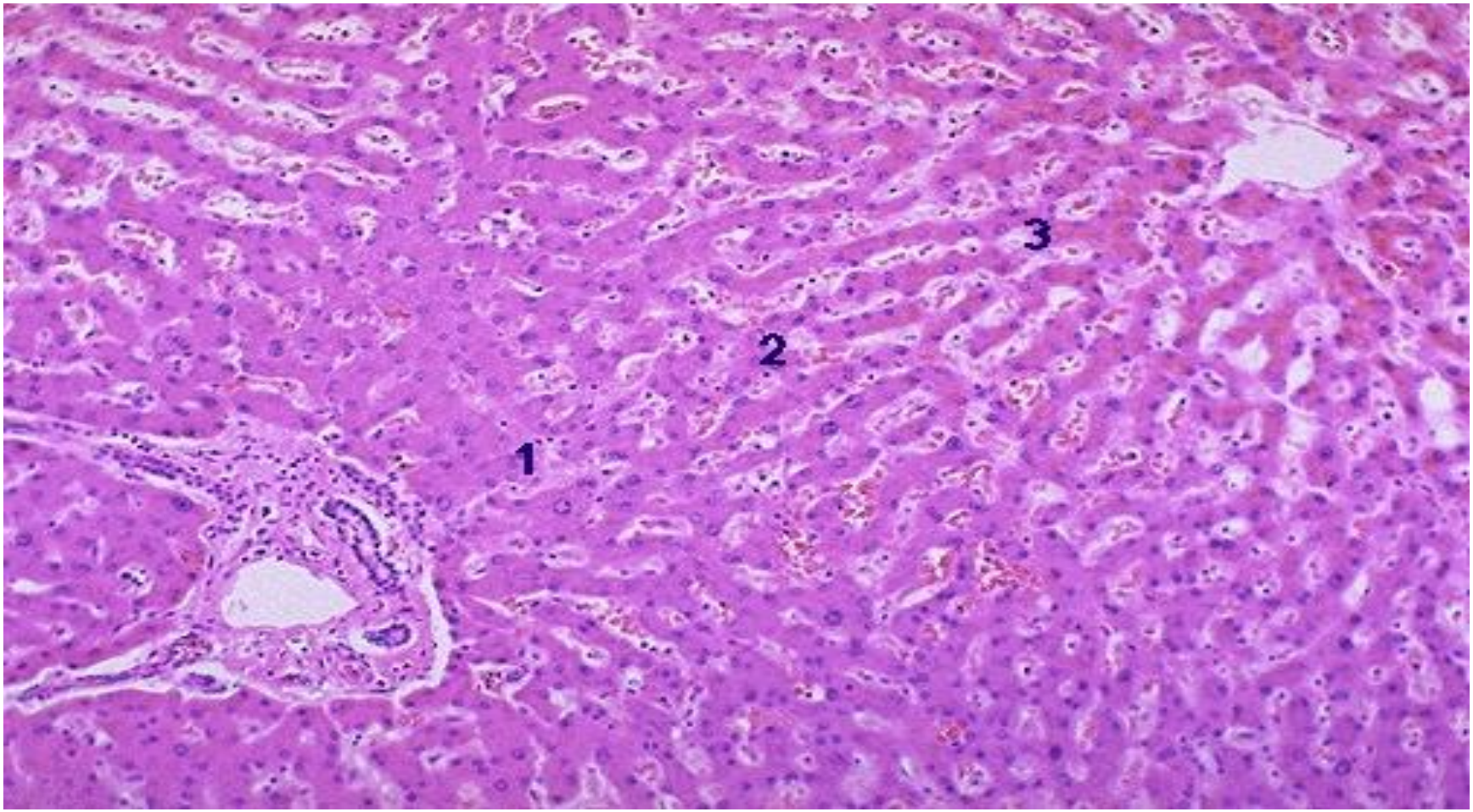
Normal liver



Cross section of normal liver



Liver zones



-Surgical removal of 60% of the liver in a normal person is followed by minimal and transient hepatic impairment with restoration of most of its mass by regeneration within 4-6 weeks.

-Perfect restoration may occur in persons who have sustained massive hepatic necrosis if the patient can survive the metabolic insult of liver failure.

- **80-90% of hepatic function must be lost before hepatic failure ensues.**
- **The balance may be moved toward decompensation by:**

A. systemic infections

B. electrolyte disturbances

C. major surgery

D. heart failure

E. GIT bleeding

CLINICAL SYNDROMES

The major clinical syndromes of liver disease are:

1- hepatic failure

2- cirrhosis

3- portal hypertension

4- cholestasis.

Hepatic Failure

-The most severe clinical consequence of liver disease.

-It can occur due to:

1-insidious piecemeal destruction of hepatocytes.

2-repetitive symptomatic parenchymal damage.

3-sudden massive destruction.

Patterns of injury

1-Acute liver failure with massive hepatic necrosis.

- Most often caused by drugs or viral hepatitis.
- Clinical hepatic insufficiency progresses from onset of symptoms to hepatic encephalopathy within 2-3 weeks.
- A course extending as long as 3 months is called subacute failure.
- Massive hepatic necrosis.

2-Chronic liver disease.

-The most common route to hepatic failure.

- **Mechanism:**
- **A.hepatocytic (or parenchymal) damage**
- **B.biliary disease**
- **C.vascular disease**
- **The end result is cirrhosis.**

3-Hepatic dysfunction without overt necrosis.

-Hepatocytes may be viable but unable to perform their normal metabolic function.

-Causes:

a. Mitochondrial injury in Reye syndrome
b. Acute fatty liver of pregnancy
c. Drug- or toxin-mediated injuries

Cirrhosis

-Cirrhosis is among the top 10 causes of death in the Western world.

-Its major causes include:

1- chronic viral infections

2- alcoholic or nonalcoholic steatohepatitis (NASH)

3- autoimmune diseases affecting hepatocytes and/or bile ducts

4- iron overload

5-Wilson disease

6-α-1- antitrypsin deficiency

7-Rare causes

Galactosemia
Tyrosinosis
Glycogen storage disease III &IV
Lipid storage disease
Hereditary fructose intolerance
Drug induced e.g methyldopa

-Cirrhosis is defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

-It is a diffuse process that includes:

1• Fibrous septa in the form of delicate bands or broad scars around multiple adjacent lobules.

2• Parenchymal nodules

-Nodules less than 3 mm in diameter=micronodules

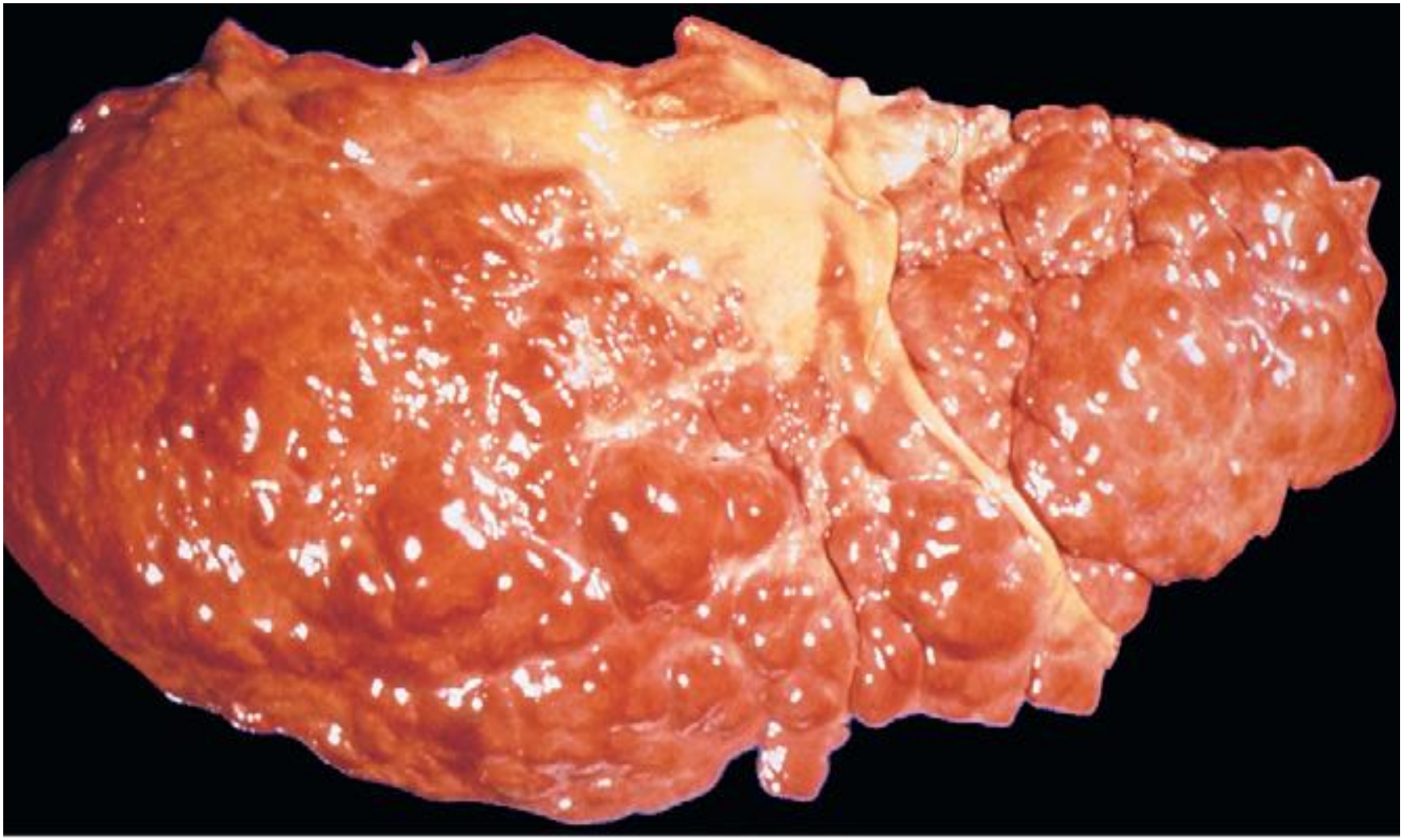
- Nodules larger than 3mm=macronodules

- Hepatocytes in these nodules derive from two sources:

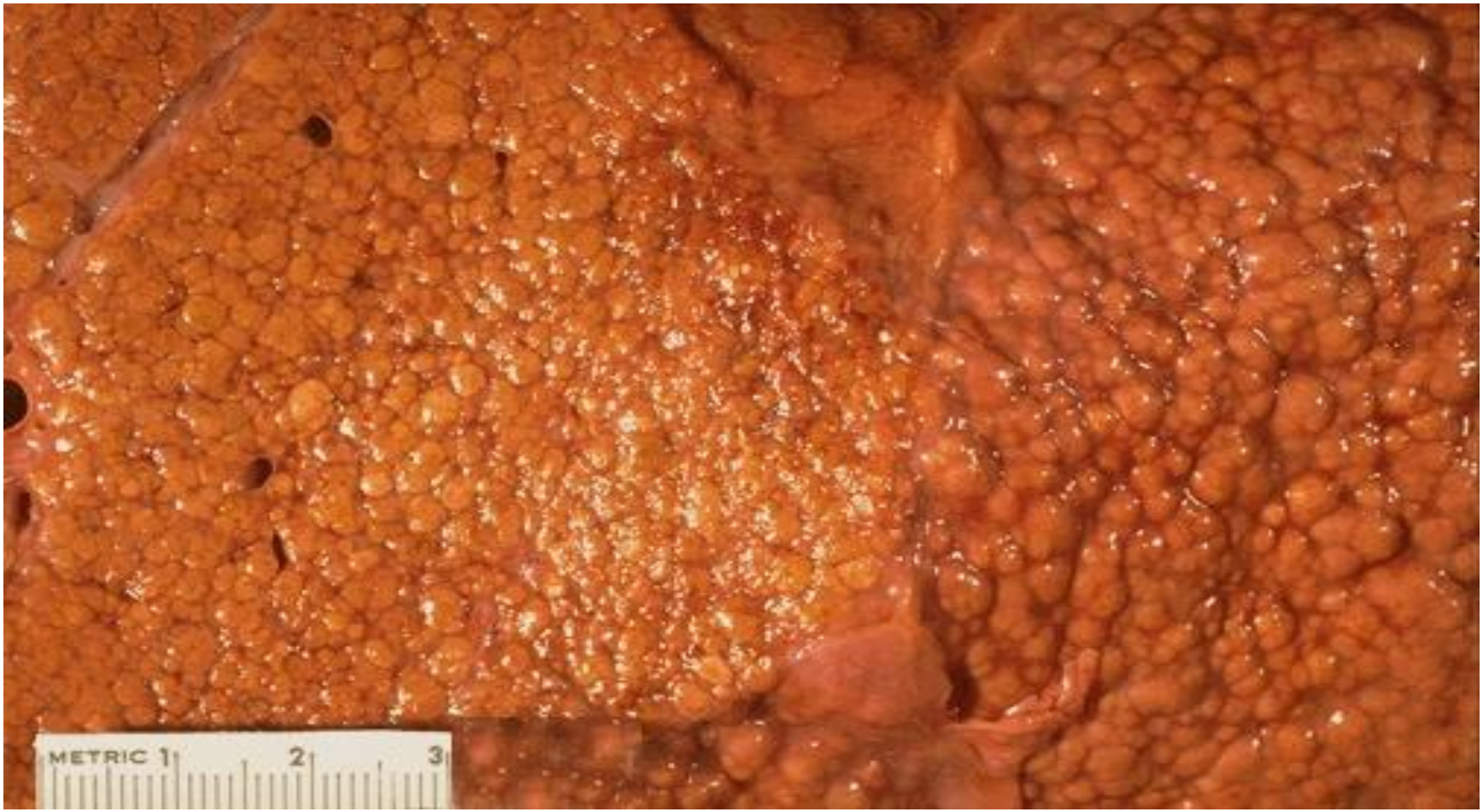
(1) preexistent, long-lived hepatocytes that by the time cirrhosis is established display features of replicative senescence

(2) newly formed hepatocytes capable of replication that are derived from stem/progenitor cells found adjacent to the canals of Hering and small bile ductules

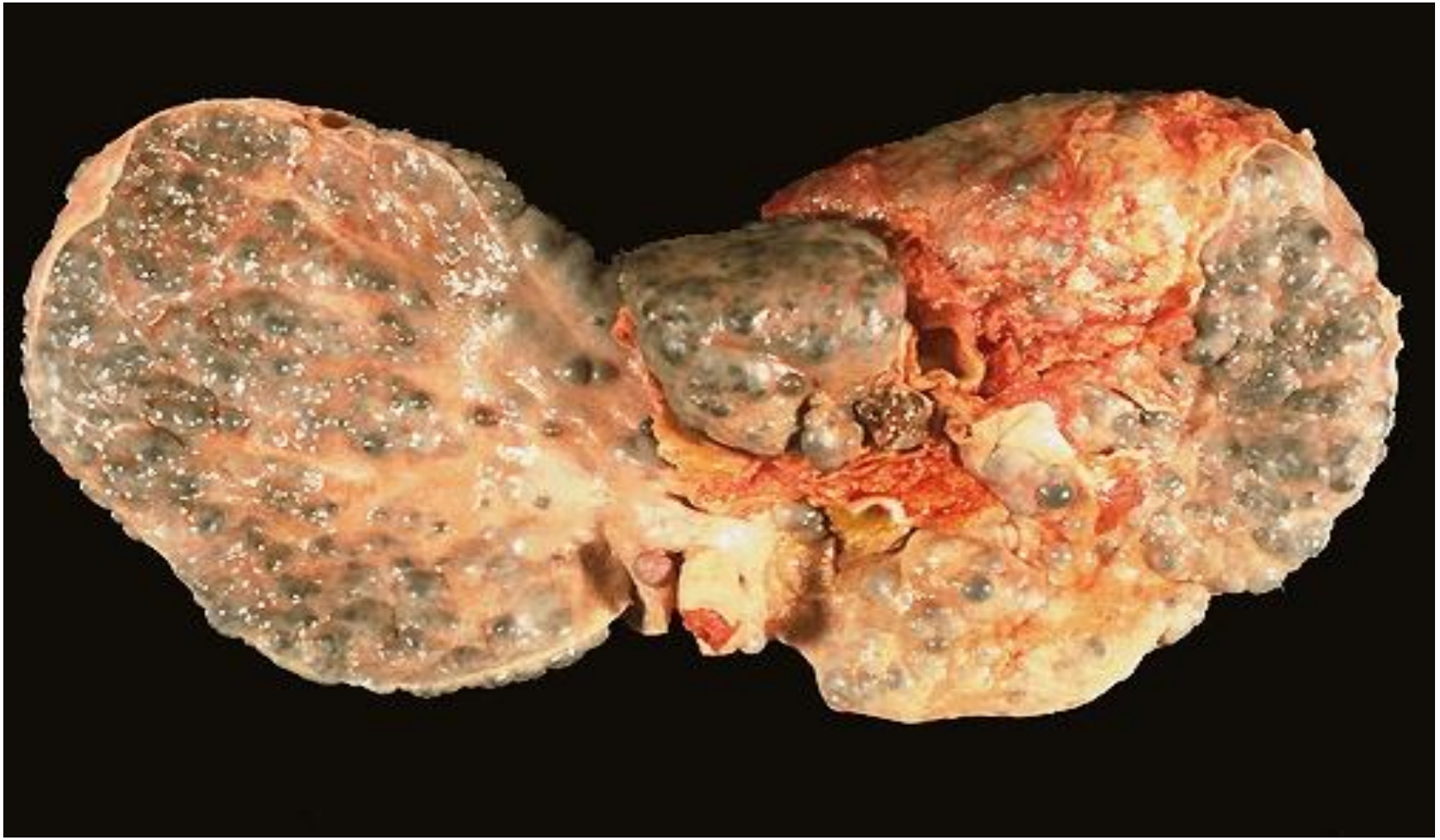
Cirrhotic liver

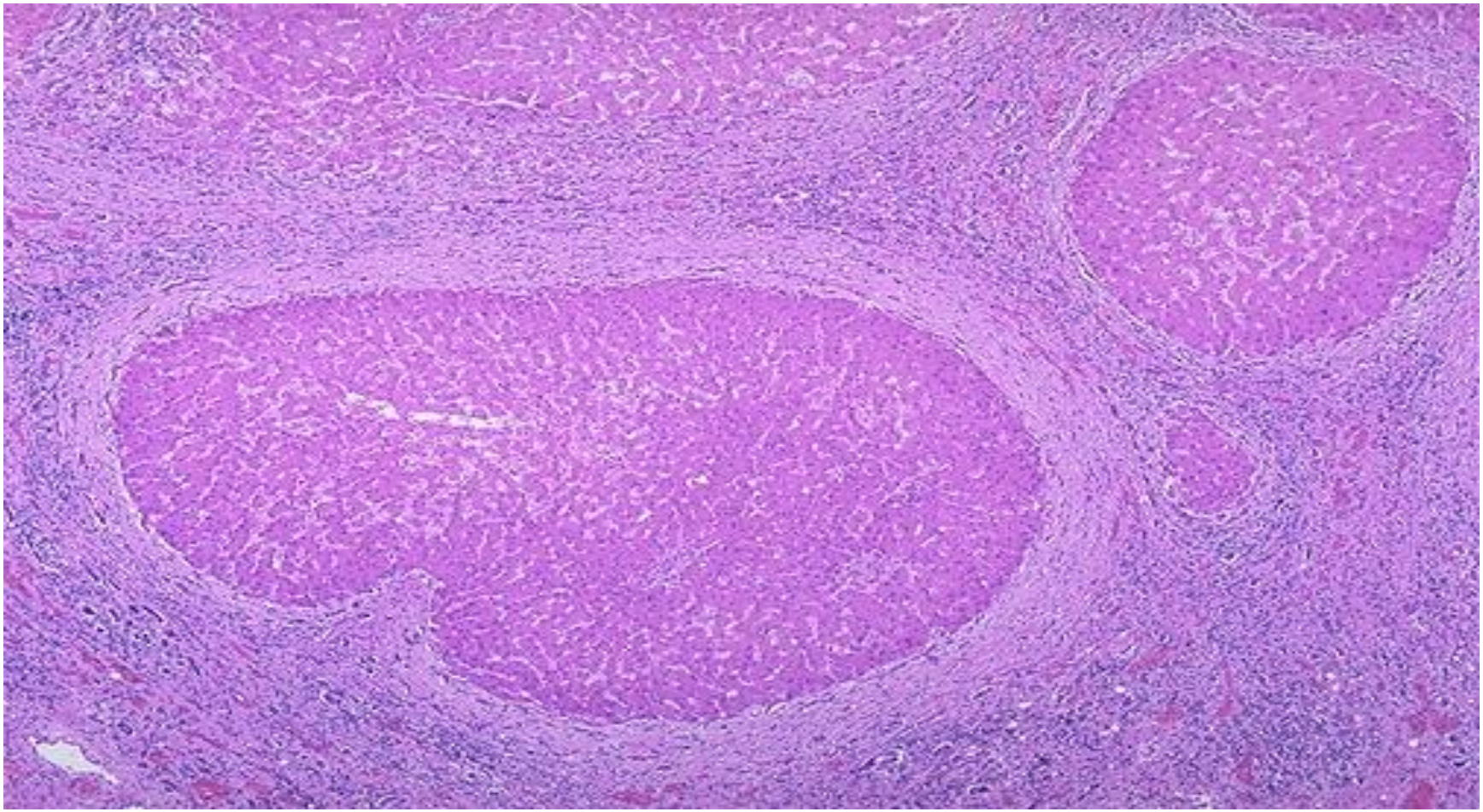


Micronodular cirrhosis



Macronodular cirrhosis





Pathogenesis

1. Death of hepatocytes
2. Extracellular matrix deposition
3. Vascular reorganization

-In the normal liver ECM consists of collagen types I, III, V, and XI which is present only in the capsule, portal tracts, and around central veins.

-Type IV collagen and other proteins present

in the space between sinusoidal endothelial cells and hepatocytes (the space of Disse).

-In cirrhosis, types I and III collagen and other ECM components are deposited in the space of Disse

- **The major source of excess collagen in cirrhosis are the perisinusoidal stellate cells (Ito cells) which lie in the space of Disse.**
- **Stellate cells normally function as storage cells for vitamin A.**
- **Upon activation,stellate cells transform into myofibroblasts.**

The stimuli for the activation of stellate cells and production of collagen are:

1. **Reactive oxygen species**
2. **Growth factors**
3. **Cytokines such as TNF, IL-1, and lymphotoxins.**

- **Activated stellate cells themselves produce growth factors, cytokines, and chemokines that cause their further proliferation and collagen synthesis—in particular, transforming growth factor-β (TGF-β).**

- **Vascular injuries and changes also play significant roles in remodeling of the liver into a cirrhotic state.**
- **Inflammation and thrombosis of portal veins, hepatic arteries, and/or central veins may lead to alternating zones of parenchymal hypoperfusion, with resulting parenchymal atrophy, and hyperperfusion, with overcompensating regeneration.**

-**<u>The major vascular lesions that contribute to defects in liver function are:</u>**

1- Loss of sinusoidal endothelial cell fenestrations.

2- The development of portal vein–hepatic vein and hepatic artery–portal vein vascular shunts.

3- Loss of fenestrations and increased basement membrane thickness lead to increase in sinusoidal pressure and loss of solute exchange.

(albumin, clotting factors, lipoproteins)

Clinical Features

- Clinically silent.
- Anorexia, weight loss, weakness, and, in advanced disease, frank debilitation.
- Hepatic failure.

Complications

1• Progressive liver failure

2• Portal hypertension

3• The development of hepatocellular carcinoma

Portal Hypertension

The intrahepatic causes are:

1- cirrhosis (most cases of portal hypertension).

2- schistosomiasis

3- massive fatty change

4- diffuse granulomatous diseases

(e.g., sarcoidosis, miliary tuberculosis)

5-diseases affecting the portal microcirculation

e.g nodular regenerative hyperplasia.

Mechanism of Portal hypertension in cirrhosis

- **1-Increased resistance to portal flow at the level of the sinusoids and compression of central veins by perivenular fibrosis and expanded parenchymal nodules.**
- **2-Arterial and portal systems in the fibrous bands impose arterial pressure on the normally low-pressure portal venous system.**

- **3-Increase in portal venous blood flow due to arterial vasodilation in the splanchnic circulation resulting from increased production of nitric oxide (NO) in the vascular bed.**

  Reduced clearance of bacterial DNA absorbed from the gut that bypasses the Kupffer cells due to intrahepatic shunting of blood from portal to systemic circulation increases the production of NO.

Clinical consequences of portal hypertension

- 1. Ascites
- 2- Portosystemic Shunt
- 3- Hepatic encephalopathy
- 4- Splenomegaly

Ascites

- collection of excess fluid in the peritoneal cavity.
- clinically detectable when at least 500 mL have accumulated.

- Ascites is a serous fluid containing as much as 3 g/dL of protein (largely albumin).
- The serum to ascites albumin gradient is ≥1.1 g/dL.
- The fluid may contain a scant number of mesothelial cells and mononuclear leukocytes.
- Influx of neutrophils suggests secondary Infection.
- The presence of red cells points to possible disseminated intraabdominal cancer.
- long-standing ascites may produce hydrothorax, more often on the right side.

Portosystemic Shunt

- **Shunts develop wherever the systemic and portal circulations share capillary beds.**
- **Principal sites are:**

1- veins around and within the rectum (hemorrhoids)

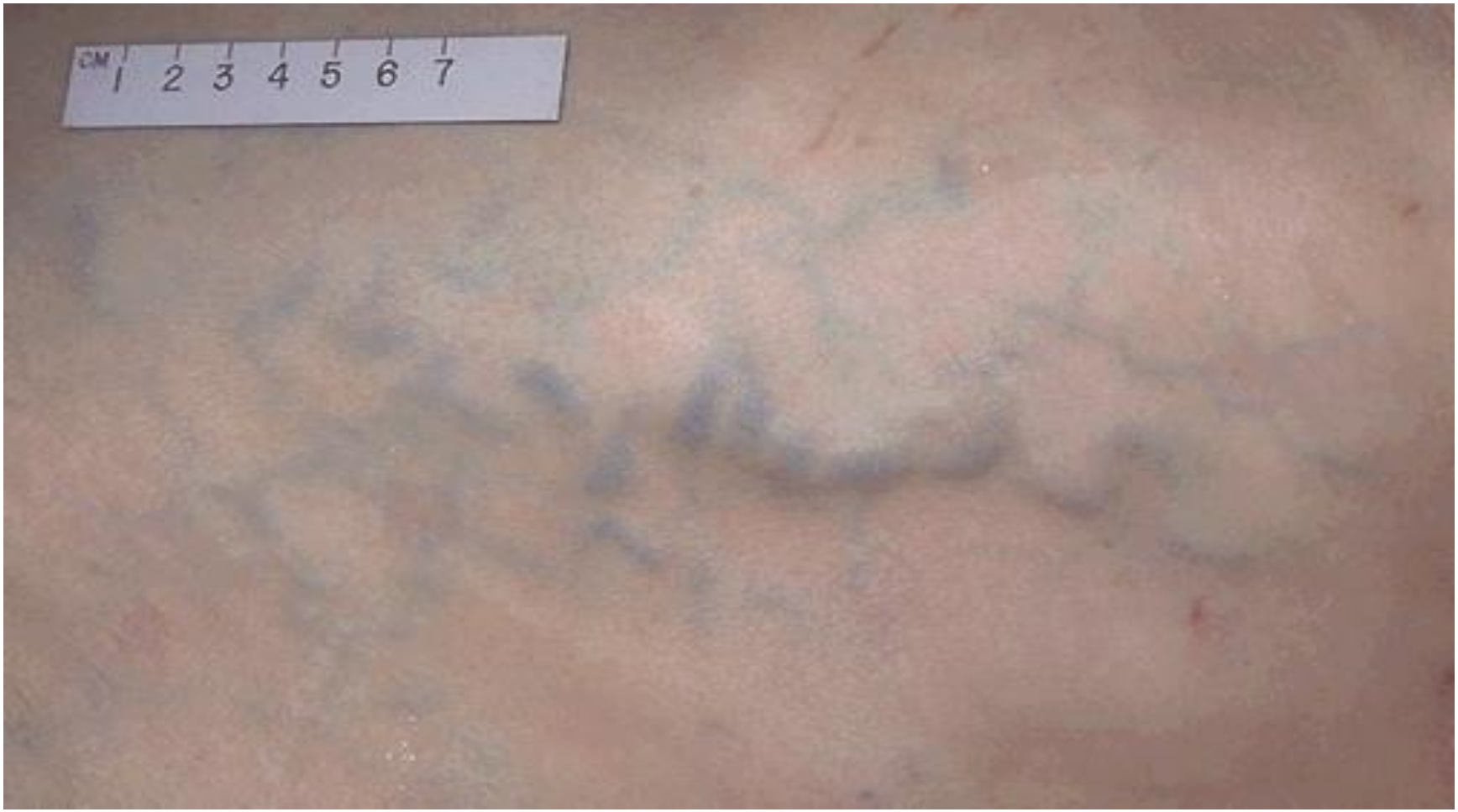
2- the cardioesophageal junction (esophagogastric varices).

3- the retroperitoneum.

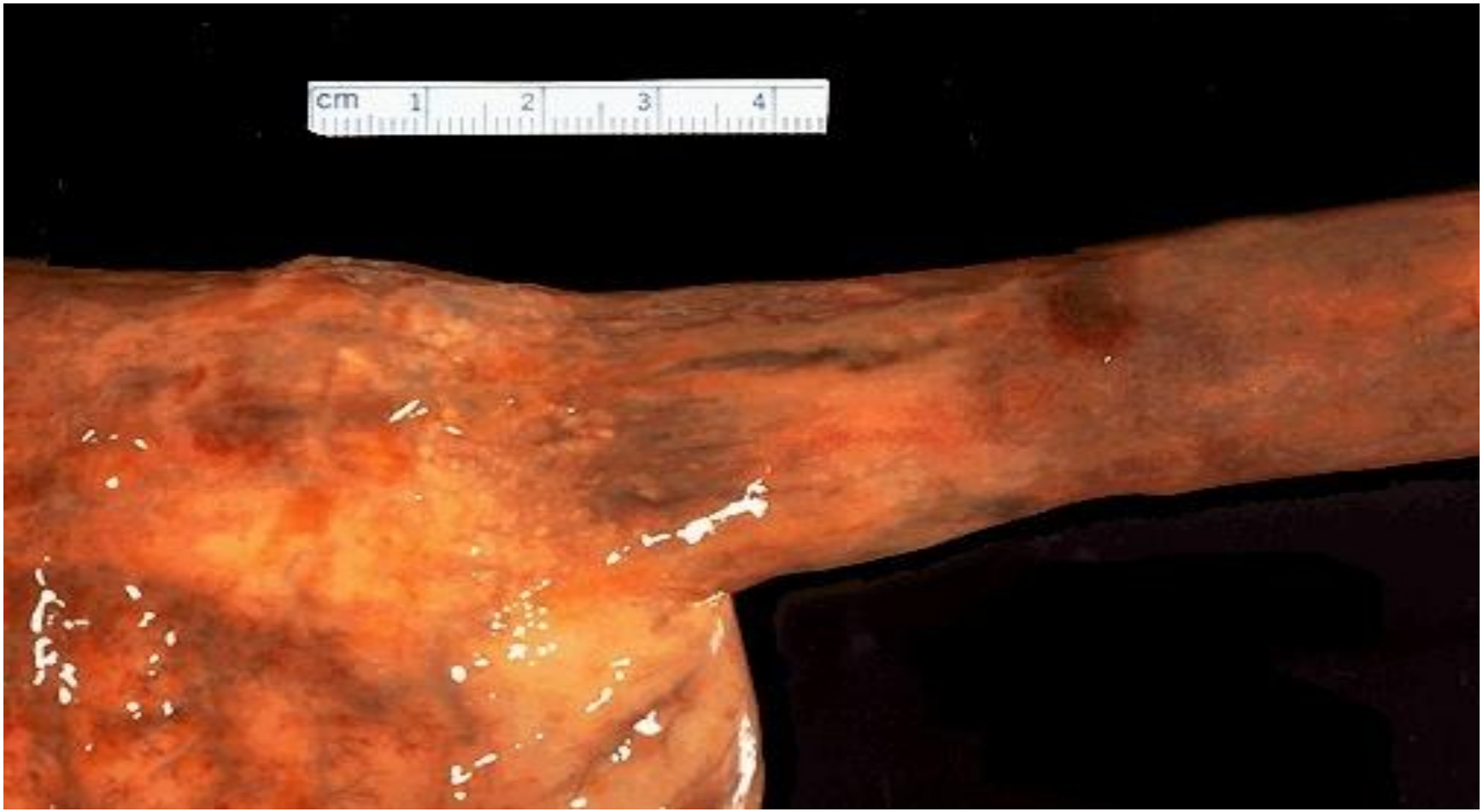
4- the falciform ligament of the liver (involving periumbilical and abdominal wall collaterals).

- **Esophagogastric varices *that appear in about 65% of persons with* advanced cirrhosis of the liver causing massive hematemesis.**
- **Abdominal wall collaterals appear as dilated subcutaneous veins extending outward from the umbilicus (*caput medusae).***

Caput medusae-abdominal skin



Esophageal varicies



Hepatic Encephalopathy

- **Hepatic encephalopathy may develop rapidly in acute liver failure or insidiously with gradually evolving chronic liver failure from cirrhosis.**
- **Hepatic encephalopathy show a spectrum of brain dysfunction ranging from subtle behavioral abnormalities to marked confusion and stupor to deep coma and death.**

- **Associated neurologic signs include rigidity, hyperreflexia, nonspecific EEG changes, and, rarely, seizures.**
- **Characteristic is asterixis (also called flapping tremor) which is a pattern of nonrhythmic, rapid extension flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists.**

- In the brain there are only minor morphologic changes such as edema and an astrocytic reaction.

- Two factors seem to be important in the genesis of this disorder:

1• Severe loss of hepatocellular function.

2• Shunting of blood from portal to systemic circulation around the chronically diseased liver.

- **In the acute setting an elevation in blood ammonia which impairs neuronal function and promotes generalized brain edema.**
- **In the chronic setting deranged neurotransmitter production.**

Splenomegaly

- **Long-standing congestion may cause congestive splenomegaly.**
- **Usually 1000 g or less (N<300gms).**
- **It is not necessarily correlated with other features of portal hypertension.**
- **Massive splenomegaly may secondarily induce a variety of hematologic abnormalities due to hypersplenism.**

Hepatorenal Syndrome

- Appears only with severe liver disease and is marked by the development of renal failure without primary abnormalities of the kidneys themselves.

-Excluded by this definition are:

1 concomitant toxic damage to both the liver and the kidney as may occur in CCL4 & mushroom poisoning and the copper toxicity of Wilson disease.

2-circulatory collapse leads to acute tubular necrosis and renal failure.

-Kidney function promptly improves if hepatic failure is reversed.

-The exact mechanism is unknown although splanchnic vasodilatation and systemic vasoconstriction leading to a severe reduction in renal blood flow particularly to the cortex.

DRUG- OR TOXIN-INDUCED LIVER DISEASE

- **The liver is subject to injury from therapeutic and environmental chemicals.**
- **Injury may result from:**

1- direct toxicity through hepatic conversion of a xenobiotic to an active toxin.

2- by immune mechanisms.

- **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.***

- Drug reactions are classified as:

1- predictable

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 drug related antigen.**
- **2-the rate at which the host metabolizes the agent.**

Predictable drugs:

Acetaminophen
Tetracycline
Antineoplastic agents
CCL4
Alcohol

Unpredictable drugs

Chlorpromazine
Halothane
Sulfonamides
Methyldopa
Allopurinol

-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:

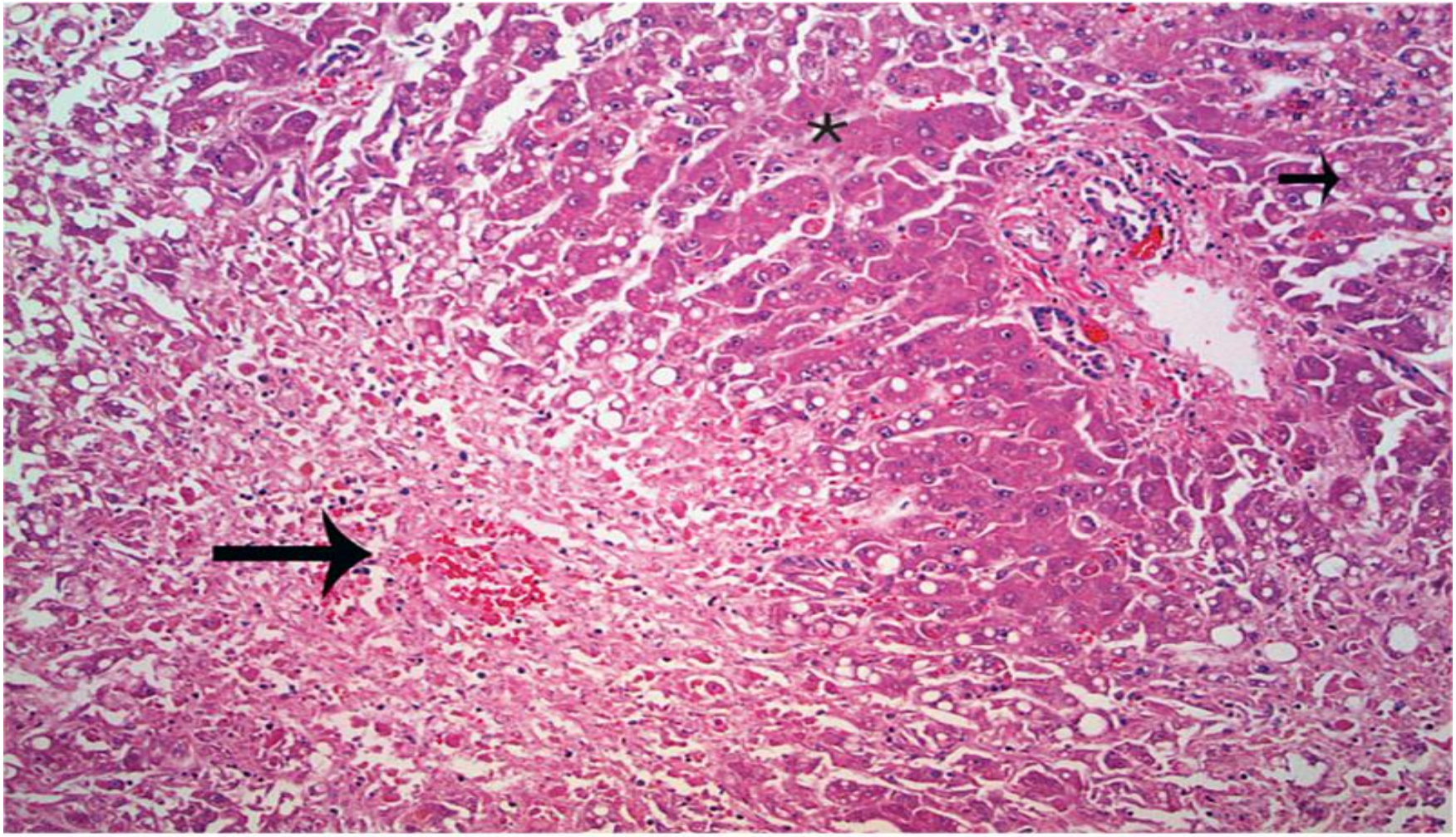
-Massive necrosis → 500–700 gm liver

Submassive necrosis

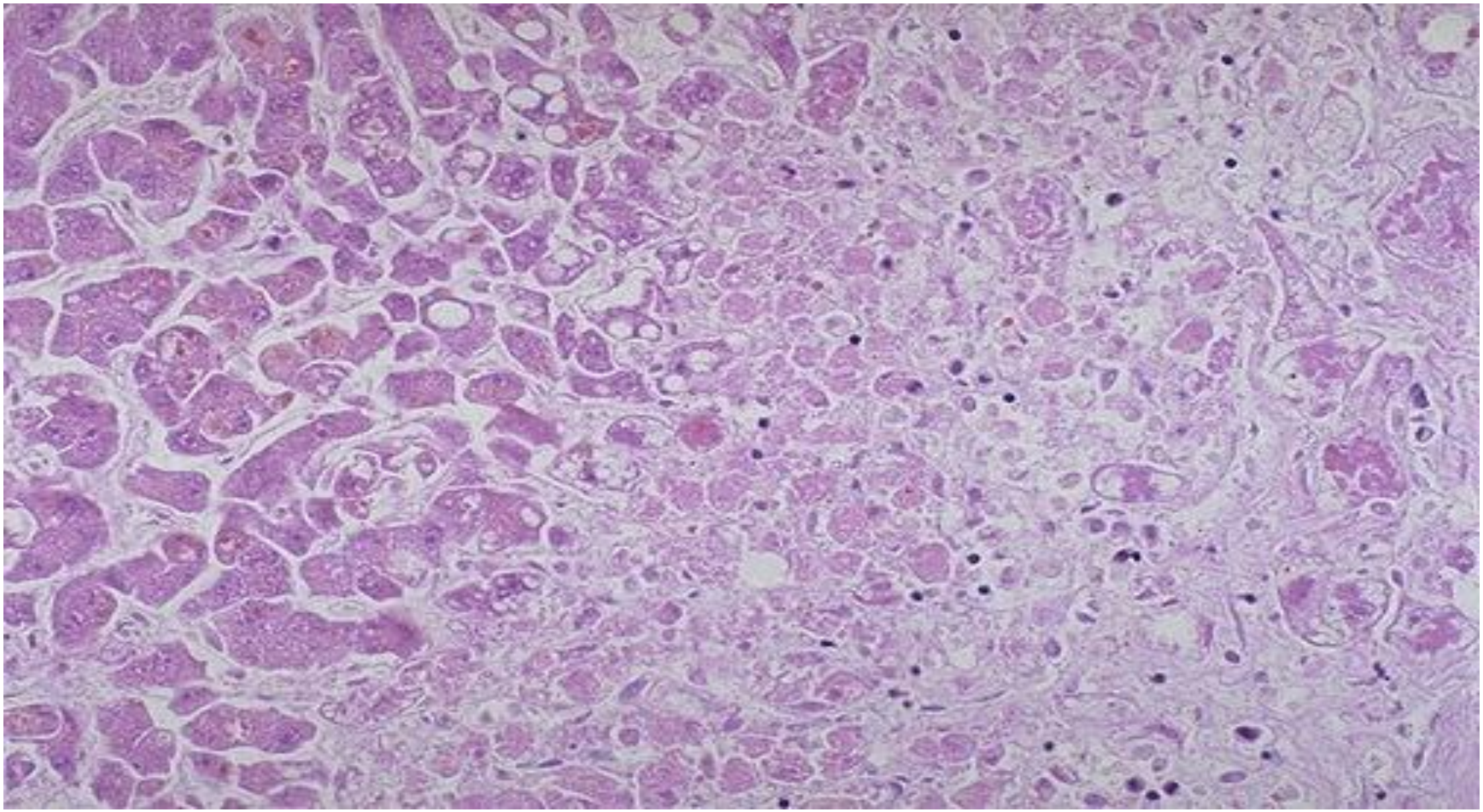
-Patchy necrosis

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



ACUTE AND CHRONIC HEPATITIS

- Acute and chronic forms of hepatitis are distinguished in part by **duration** and in part by the **pattern of cell injury**.
- Causative hepatotropic virus are hepatitis types A, B, C, D, and E.

- The mononuclear inflammatory cell infiltrate predominates in all phases of hepatitic diseases because the inflammation is T cell–mediated.

- The distinction between acute and chronic hepatitis is based on:
- 1- the pattern of cell injury.
- 2- the severity of inflammation.

Morphologic features of acute hepatitis

- **Enlarged, reddened liver; greenish if cholestatic Parenchymal Changes**
- **Swelling (ballooning degeneration)**
- **Cholestasis: canalicular bile plugs**
- **Mild fatty change of hepatocytes (HCV)**
- **Hepatocyte necrosis: isolated cells or clusters**
- **Cytolysis (rupture)**
- **Apoptosis (shrinkage)**
- **Bridging necrosis (portal-portal, central-central, portal-central)**

- **Lobular disarray: loss of normal architecture**
- **lobular hepatitis**
- **Regenerative changes: hepatocyte proliferation**
- **Sinusoidal cell reactive changes**

Accumulation of phagocytosed cellular debris in Kupffer cells.

Influx of mononuclear cells into sinusoids.

- **Portal tracts**

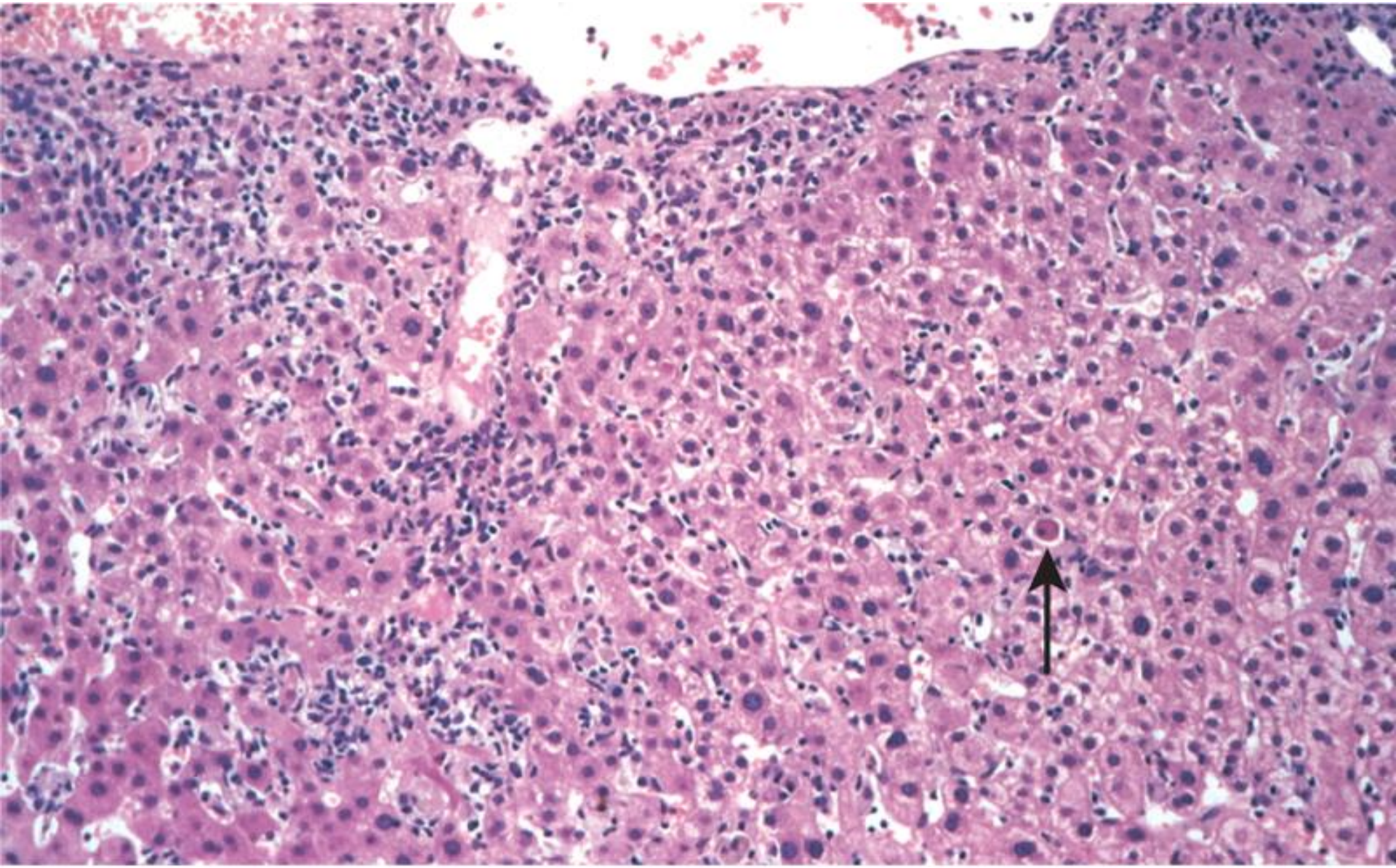
Inflammation: predominantly mononuclear.
Inflammatory spillover into adjacent parenchyma

with hepatocyte necrosis.

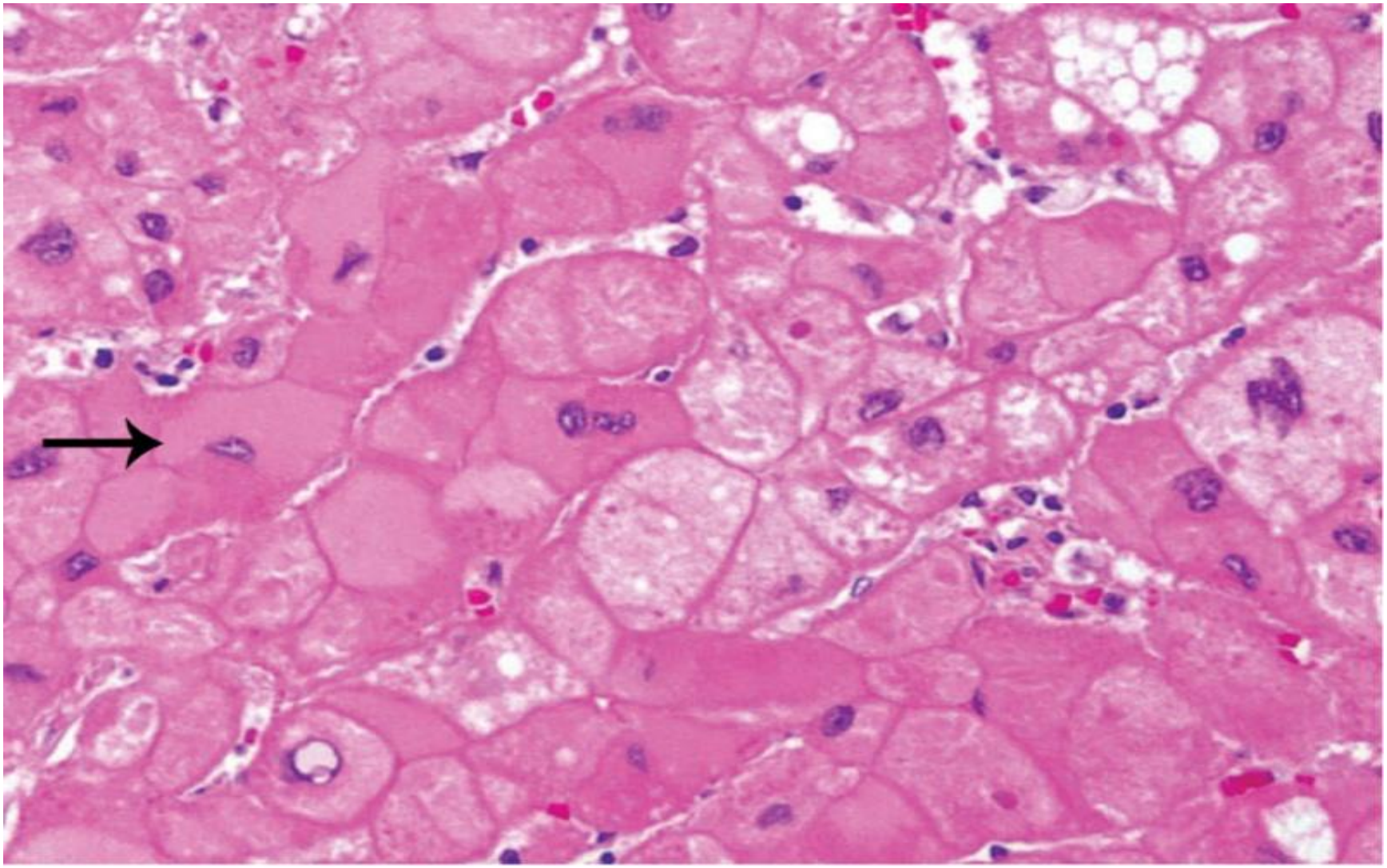
Morphologic features of chronic hepatitis

- **Changes shared with acute hepatitis**
- **Hepatocyte injury, necrosis and apoptosis, and regeneration**
- **Sinusoidal cell reactive changes**
- **Portal tracts Inflammation**
- **Inerface hepatititis: spillover into adjacent parenchyma, with necrosis of hepatocytes.**
- **Bridging inflammation and necrosis**
- **Fibrosis: portal deposition, or portal and periportal deposition, or Formation of bridging fibrous septa.**
- **HBV: ground-glass hepatocytes (accumulation of HBsAg).**
- **HCV: bile duct epithelial cell proliferation, lymphoid aggregate formation.**

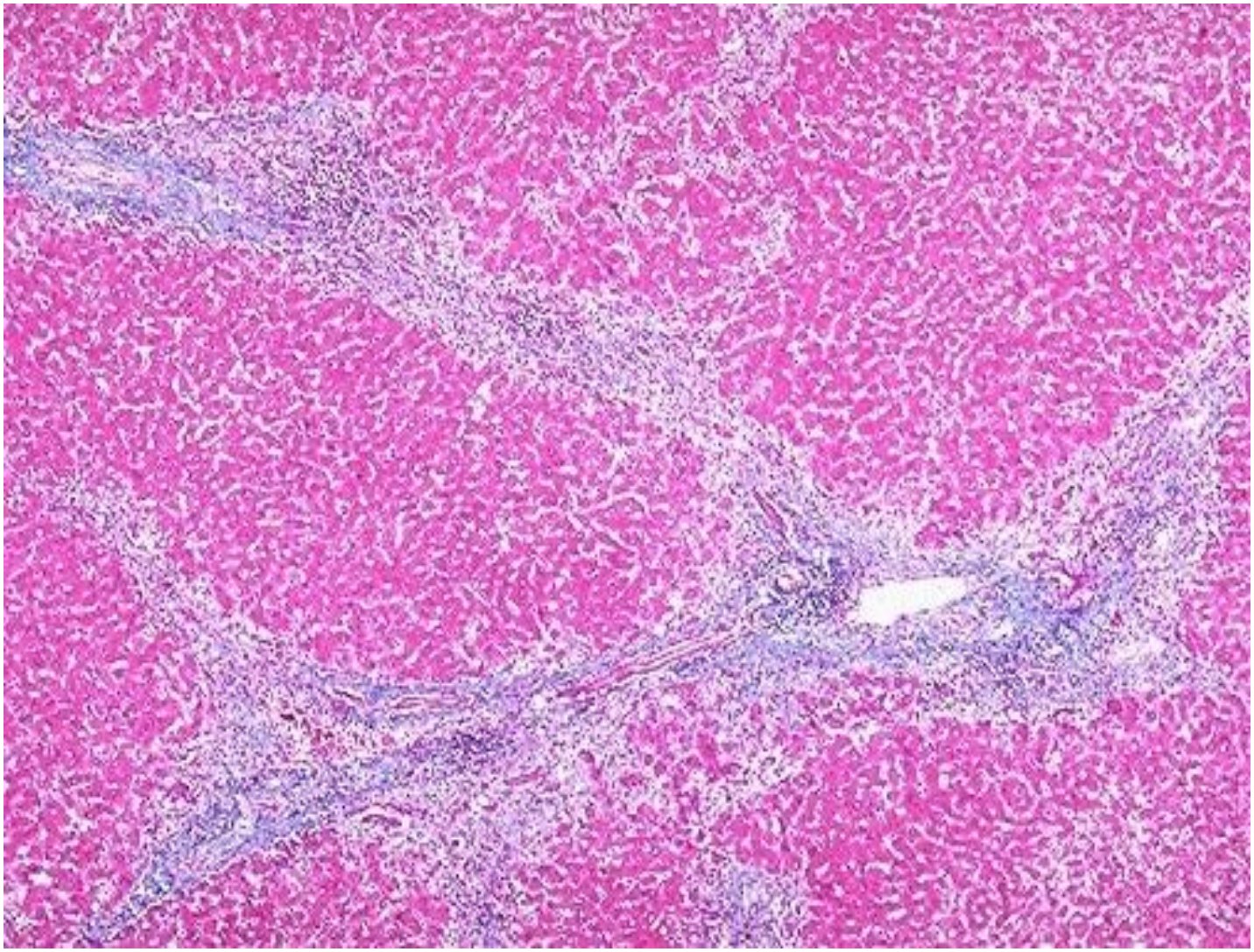
Acute viral hepatitis showing disruption of lobular architecture, inflammatory cells in sinusoids, and apoptotic cells *(arrow).*



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



Fibrosis in chronic hepatitis



Autoimmune Hepatitis

Chronic hepatitis with immunologic abnormalities

-Histologic features are similar to chronic viral hepatitis

-Indolent or severe course

-Dramatic response to immunosuppressive therapy

Features:

1-Female predominance (70%)

2-Negative serelogy for viral Ags.

3-↑serum Ig (>2.5 g/dl)

4-High titers of autoantibodies (80% of cases)

5-The presence of other autoimmune diseases as RA, thyroiditis, sjogern syndrome, UC in 60% of the cases

The type of autoantibodies

1- Antinuclear antibodies

2- Antismooth muscle Abs

- anti actin
- anti troponin
- anti tropomyosin

3- liver/kidney microsomal Abs

- anti cytochrome P-450 components
- anti UDP-glucuronosyl transferases

3- Anti-soluble liver / pancreas antigen

Outcome

Mild to severe chronic hepatitis

Full remission is unusual

Risk of cirrhosis is 5% which is the main cause of death

Alcoholic Liver Disease

- It accounts for 40-50% of deaths due to cirrhosis.
- More than 10 million Americans are alcoholics.
- Alcohol abuse is the fifth leading cause of death.

- **Alcohol-related fatty liver disease:**
- (1) hepatic steatosis (90-100%)
- (2) alcoholic hepatitis (10-35%)
- (3) fibrosis and cirrhosis (8-20%)

Pathogenesis

- Short-term ingestion of as much as 80 g of ethanol per day generally produces mild, reversible hepatic changes (fatty liver).
- Chronic intake of 40-80 g/day is considered a borderline risk factor for severe injury.

- **Women are more susceptible than men to hepatic injury due to decreased gastric metabolism of ethanol and differences in body composition.**

- **<u>Hepatocellular steatosis results from:</u>**

(1) shunting of substrates away from catabolism and toward lipid biosynthesis.

(2) impaired assembly and secretion of lipoproteins.

(3) increased peripheral catabolism of fat.

- **<u>Alcoholic hepatitis results from:</u>**

Toxic by products of ethanol and its metabolites:

1- **Acetaldehyde** induces lipid peroxidation and acetaldehyde-protein adduct formation which may disrupt cytoskeleton and membrane function.

- **2- Direct Alcohol toxicity** to cytoskeleton, mitochondrial function, and membrane fluidity.
- **3- Reactive oxygen species** generated during oxidation of ethanol react with and damage membranes and proteins.
- **4-Reactive oxygen species** also are produced by neutrophils, which infiltrate areas of hepatocyte necrosis.

- **5-Cytokine-mediated inflammation** and cell injury.
- TNF is considered to be the main effector of injury; IL-1, IL-6, and IL-8 may also contribute.

- The centrilobular region is most susceptible to toxic injury because the generation of acetaldehyde and free radicals is maximal in this region.
- Pericellular fibrosis and sinusoidal fibrosis develop in this area of the lobule.
- The prevalence of hepatitis C among persons with alcoholic disease is about 30% (and vice versa).

- Cirrhosis develops in only a small fraction of chronic alcoholics.
- With complete abstinence some regression of scar can be seen in all cases.
- The micronodular liver transforms with regeneration into a macronodular cirrhotic organ.

Morphology

- **Hepatocellular Steatosis**
- Fatty liver with widespread steatosis is large (weighing 4-6 kg or more), soft, yellow, and greasy.
- It begins in centrilobular hepatocytes.
- The lipid droplets range from small (microvesicular) to large (macrovesicular).

- **<u>Steatohepatitis.</u>**
- These changes typically are more pronounced with alcohol use than in NAFLD, but can be seen with variable degrees of prominence in fatty liver disease of any cause:

1 • Hepatocyte ballooning.

2 • Mallory-Denk bodies.

These consist of tangled skeins of intermediate filaments (including ubiquitinated keratins 8 and 18) and are visible as eosinophilic cytoplasmic inclusions in degenerating hepatocytes.

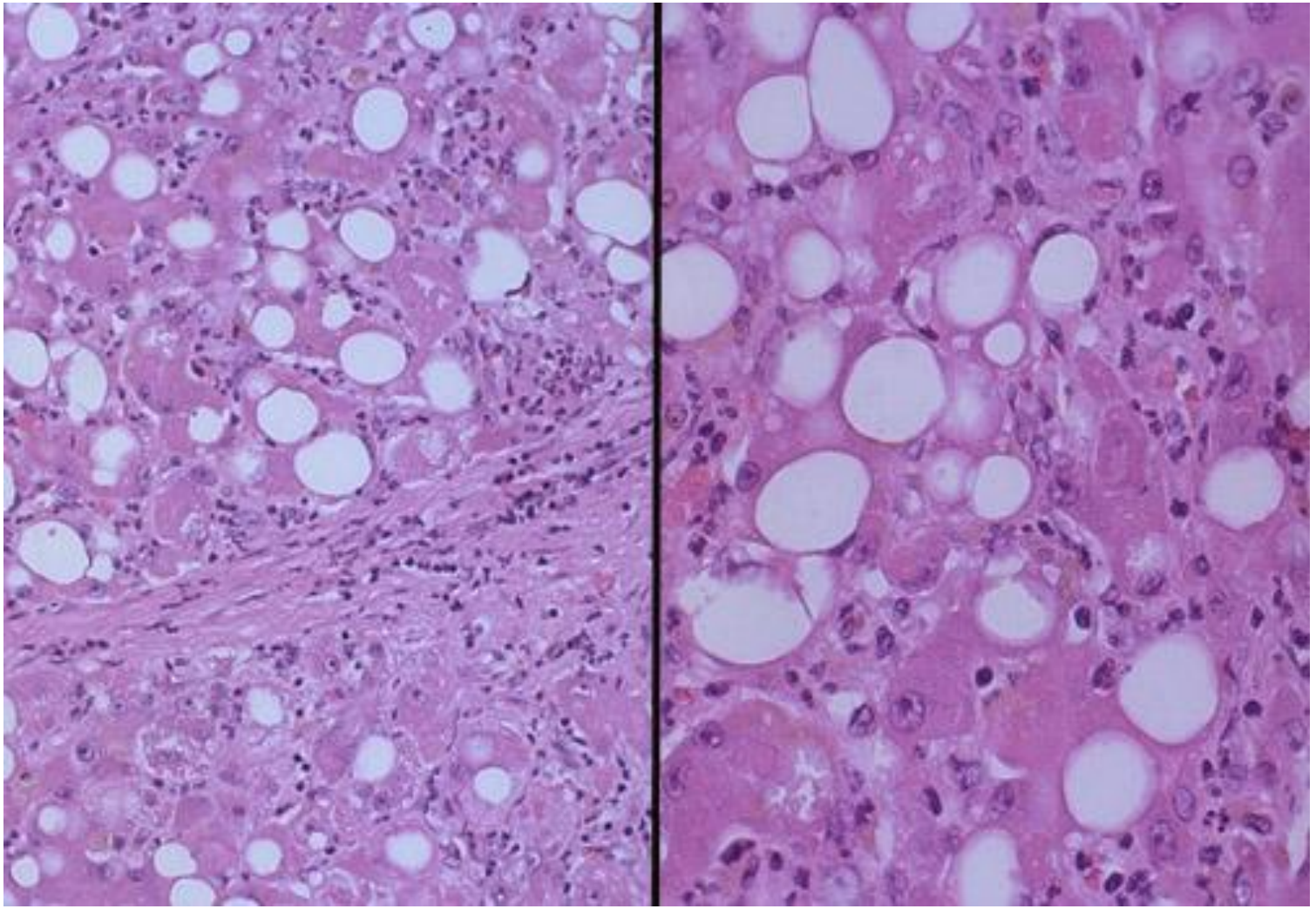
3 • Neutrophil infiltration.

Predominantly neutrophilic infiltration may permeate the lobule and accumulate around degenerating hepatocytes, particularly those containing Mallory-Denk bodies. Lymphocytes and macrophages also may be seen in portal tracts or parenchyma

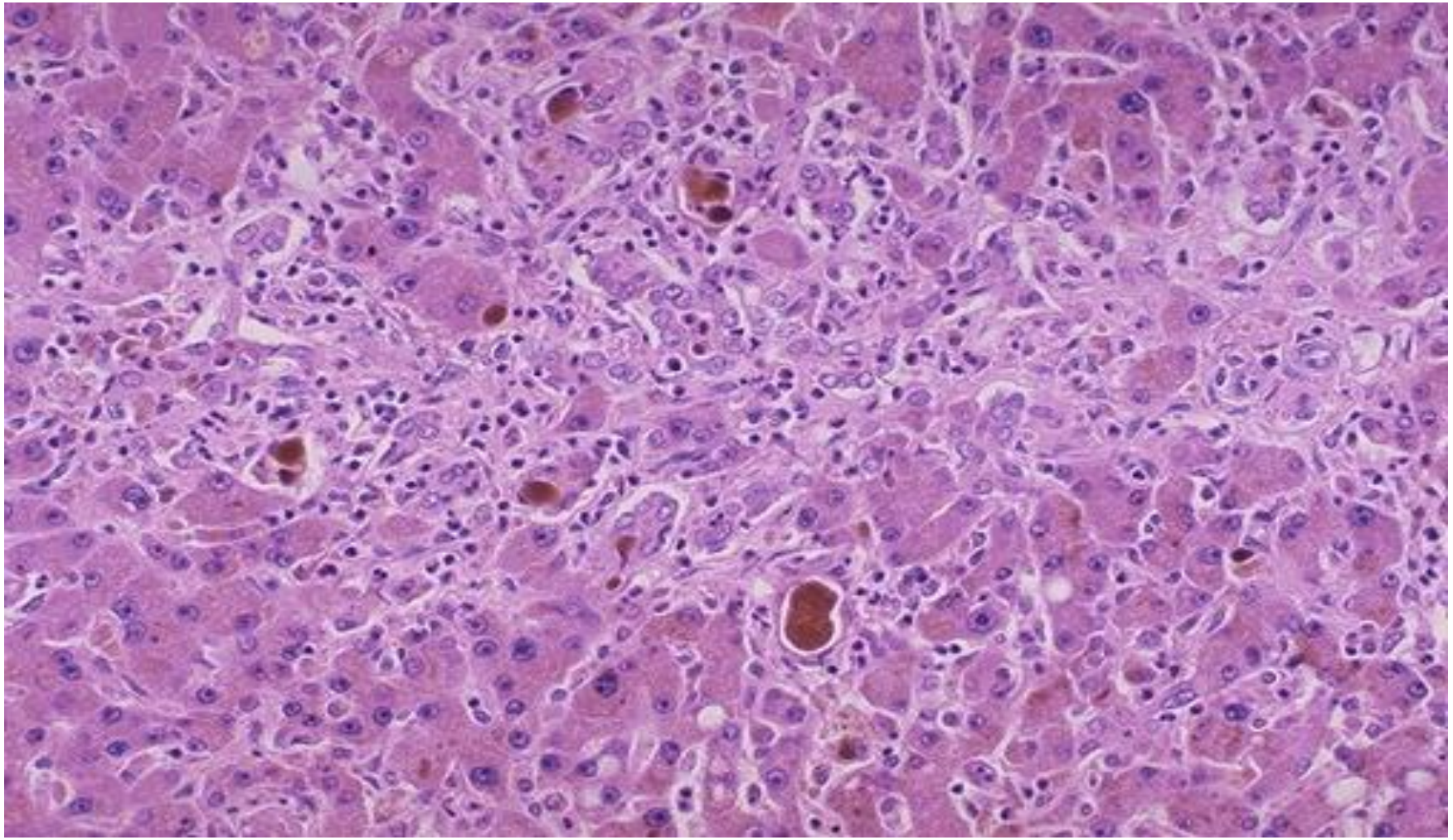
4 •Steatohepatitis with fibrosis.

5 •Micronodular or Laennec cirrhosis.

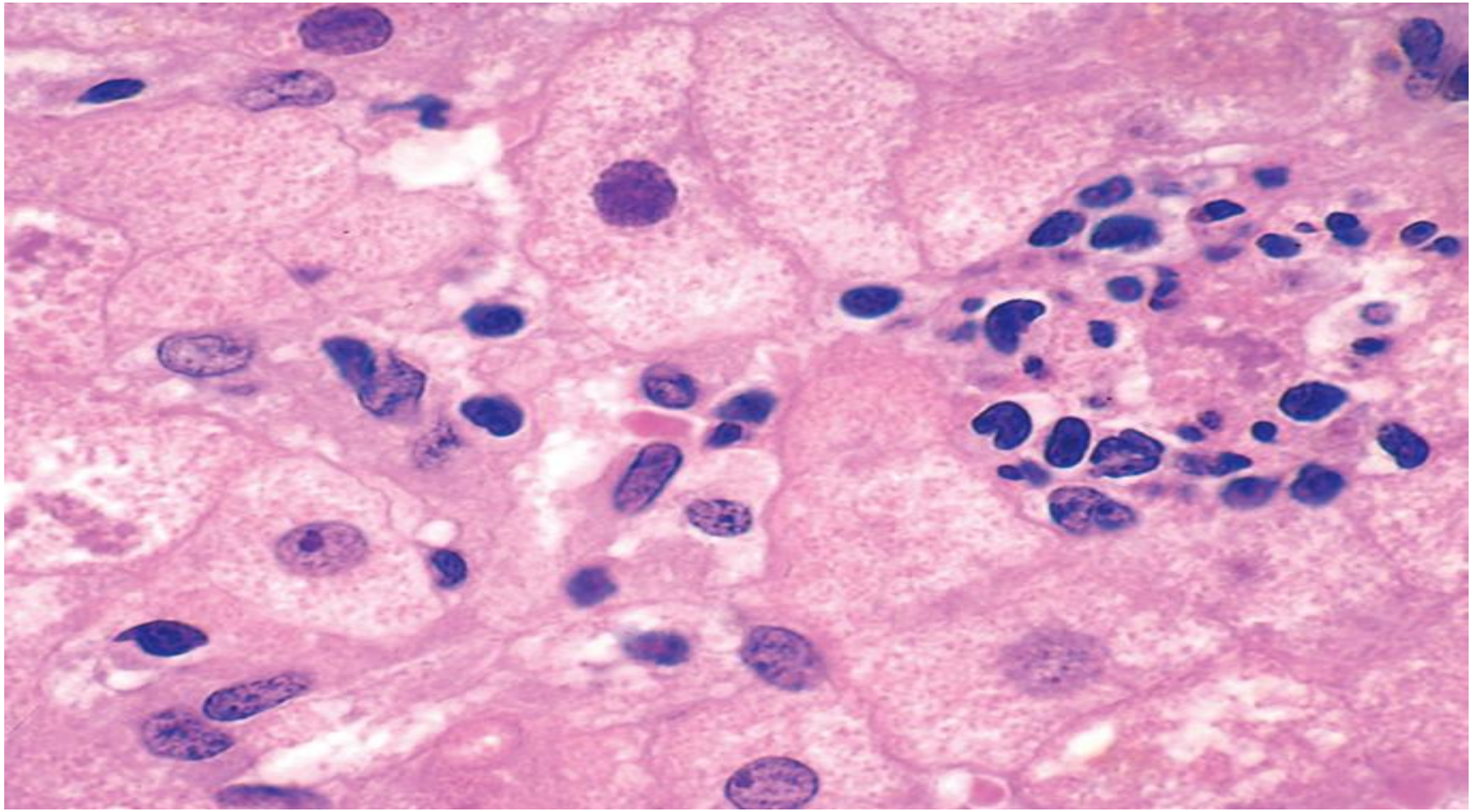
Alcoholic steatohepatitis



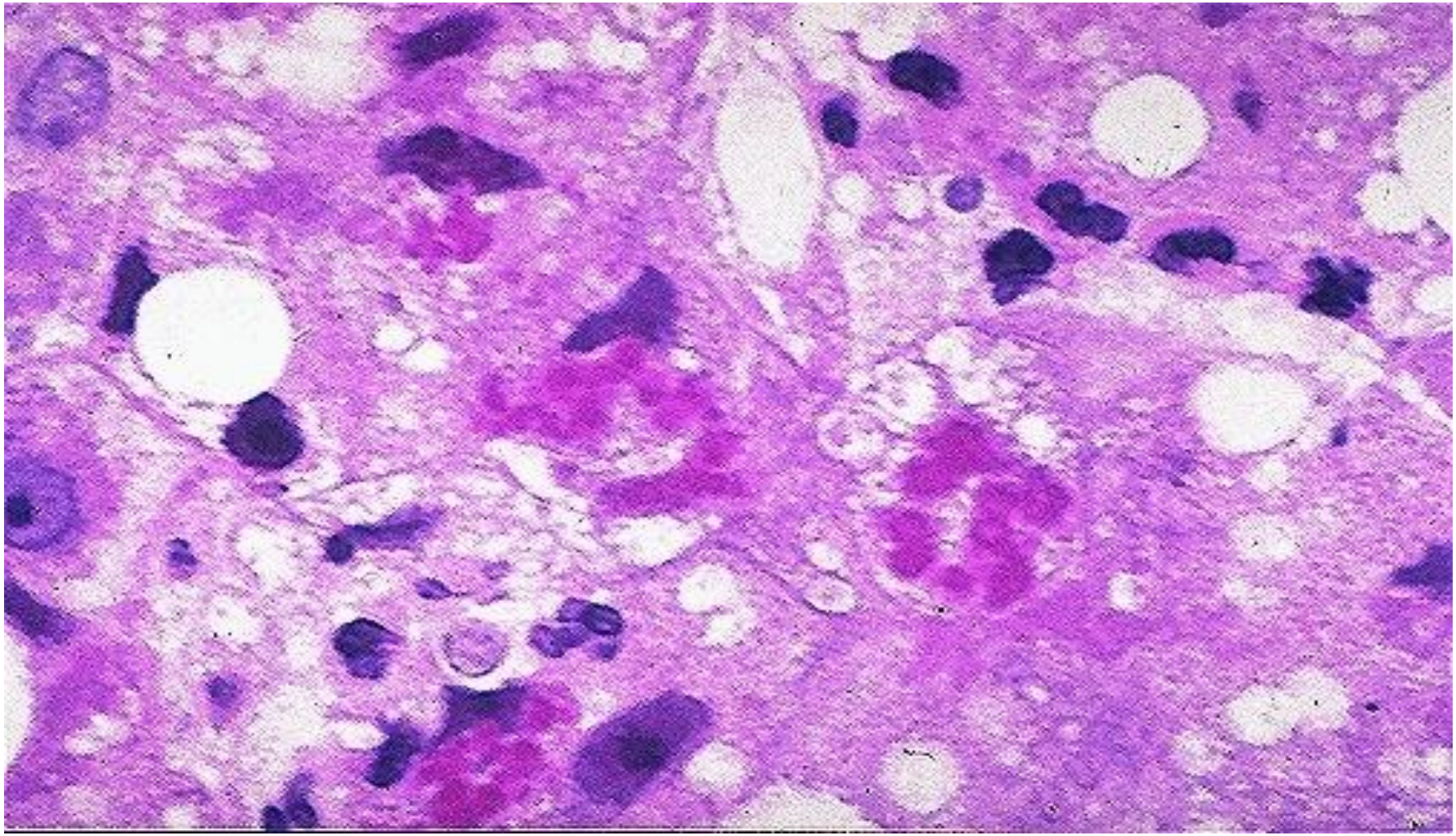
Cholestasis



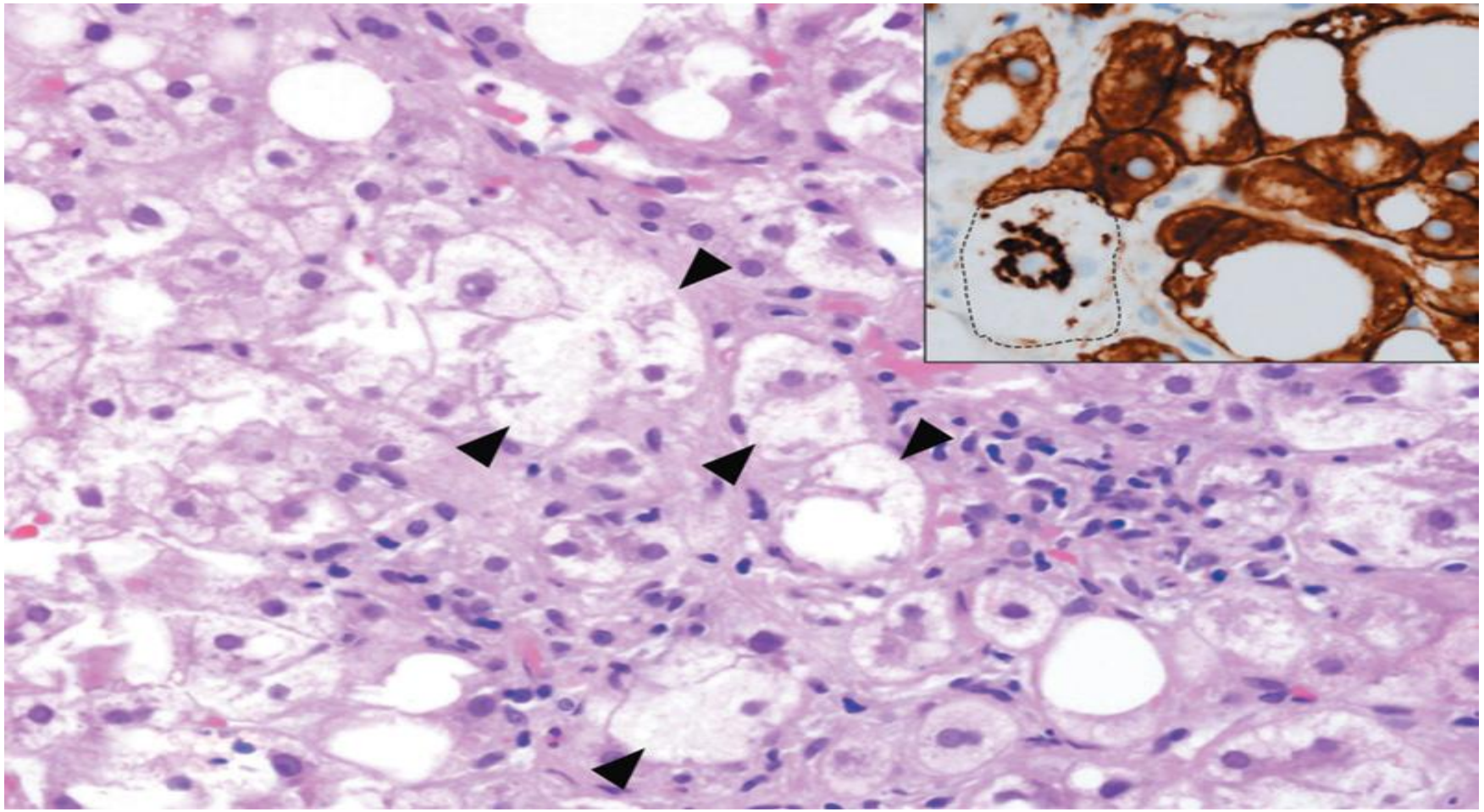
Alcoholic steatohepatitis



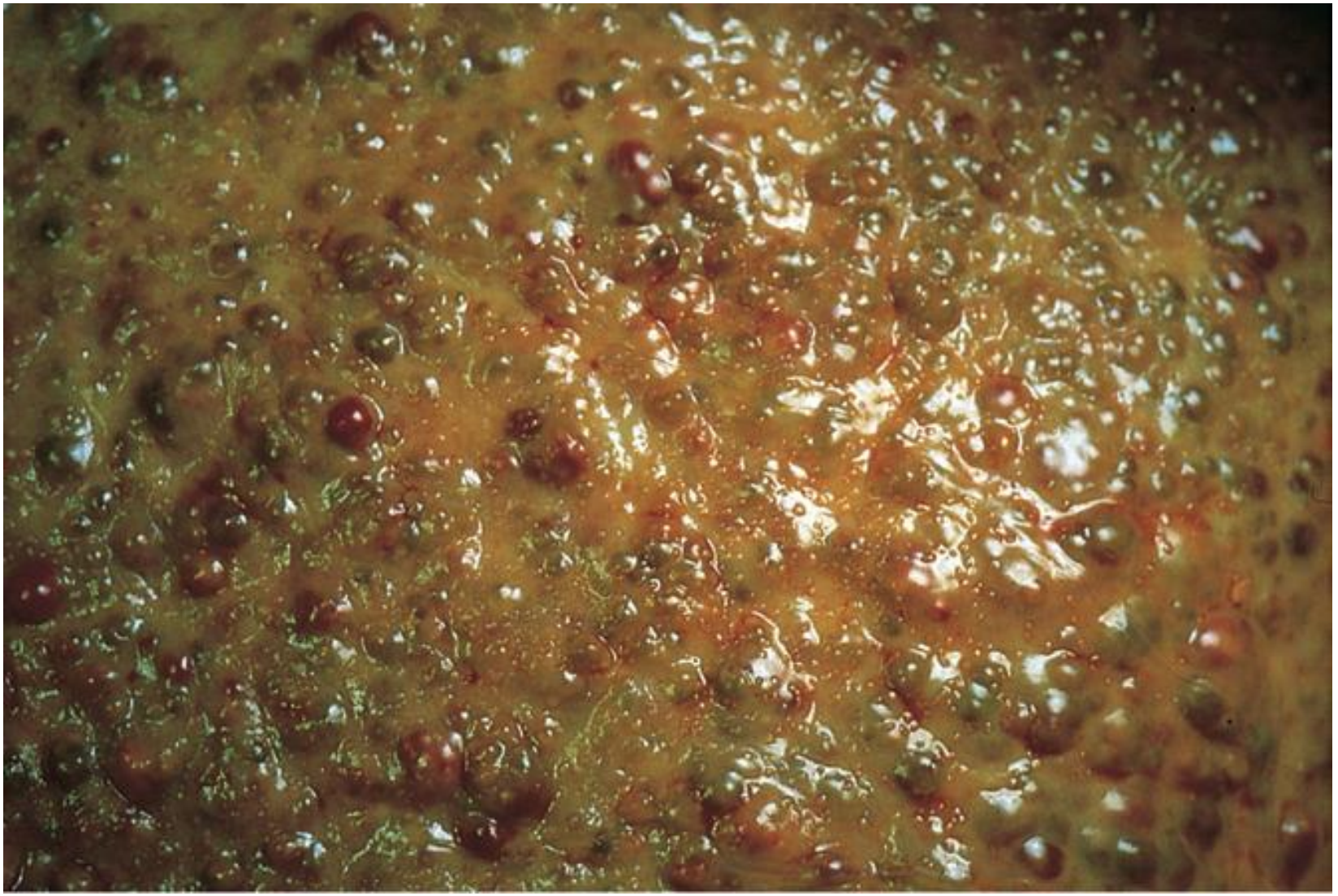
Mallory-Denk bodies



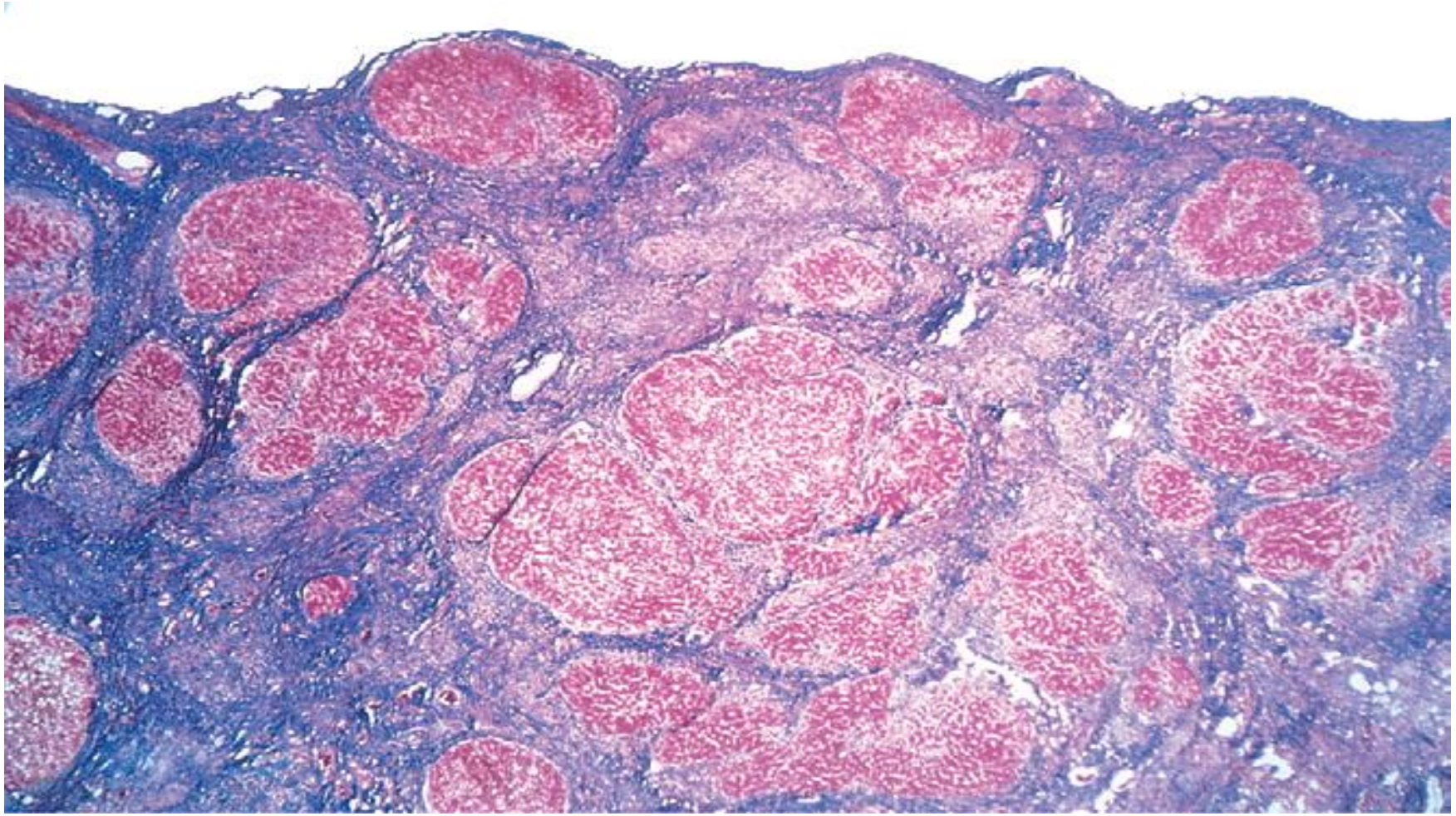
Mallory-Denk bodies; clusters of inflammatory cells are also seen
inset shows immunostaining for keratins 8 and 18 (brown)



Alcoholic Cirrhosis



Alcoholic Cirrhosis



Clinical Features

- **Steatosis:**
- Asymptomatic
- Hepatomegaly with mild elevations of serum bilirubin and alkaline phosphatase.

- **<u>Alcoholic hepatitis:</u>**
- Can occur after just weeks or months of consistent use.
- The onset is typically acute and often follows a bout of particularly heavy drinking.
- Symptoms and laboratory abnormalities may range from minimal to severe.

- malaise, anorexia, weight loss, upper abdominal discomfort, tender hepatomegaly, and fever.
- Hyperbilirubinemia, elevated alkaline phosphatase, and neutrophilic leukocytosis.
- Serum alanine aminotransferase and aspartate aminotransferase are elevated but usually remain below 500 U/ mL.

- Each bout of hepatitis carries about a 10-20% risk of death.
- Cirrhosis appears in about one third of patients within a few years with repated bouts.

- **Cirrhosis:**
- It is estimated that 15-20 years of excessive drinking are necessary to develop alcoholic cirrhosis.
- The first signs of cirrhosis relate to complications of portal hypertension.
- Variceal hemorrhage or hepatic encephalopathy.
- Malaise, weakness, weight loss, and loss of appetite.

- Cirrhosis may be clinically silent, discovered only at autopsy or when stress such as infection or trauma tips the balance toward hepatic insufficiency.
- Malnutrition and vitamin deficiencies (e.g., thiamine, vitamin B12).

- **<u>The immediate causes of death are:</u>**

1 • Hepatic failure

2 • Massive gastrointestinal hemorrhage

3 • Intercurrent infection

4 • Hepatorenal syndrome

5 • Hepatocellular carcinoma in 3-6% of cases

Nonalcoholic Fatty Liver Disease (NAFLD)

- It develops in persons who do not drink alcohol.
- The liver can show steatosis, steatohepatitis, and cirrhosis.

- The term **nonalcoholic steatohepatitis (NASH)** is used to describe overt clinical features of liver injury similar to those induced by alcohol.

- **NAFLD is consistently associated with:**

1• Type 2 diabetes (or family history of the condition)

2• Obesity, primarily central obesity (body mass index greater than 30 kg/m2 in whites and greater than 25 kg/m2 in Asians)

3• Dyslipidemia (hypertriglyceridemia, low HDL, highLDL

4• Hypertension

- Insulin resistance results in the accumulation of triglycerides in hepatocytes by:

1• Impaired oxidation of fatty acids

2• Increased synthesis and uptake of fatty acids

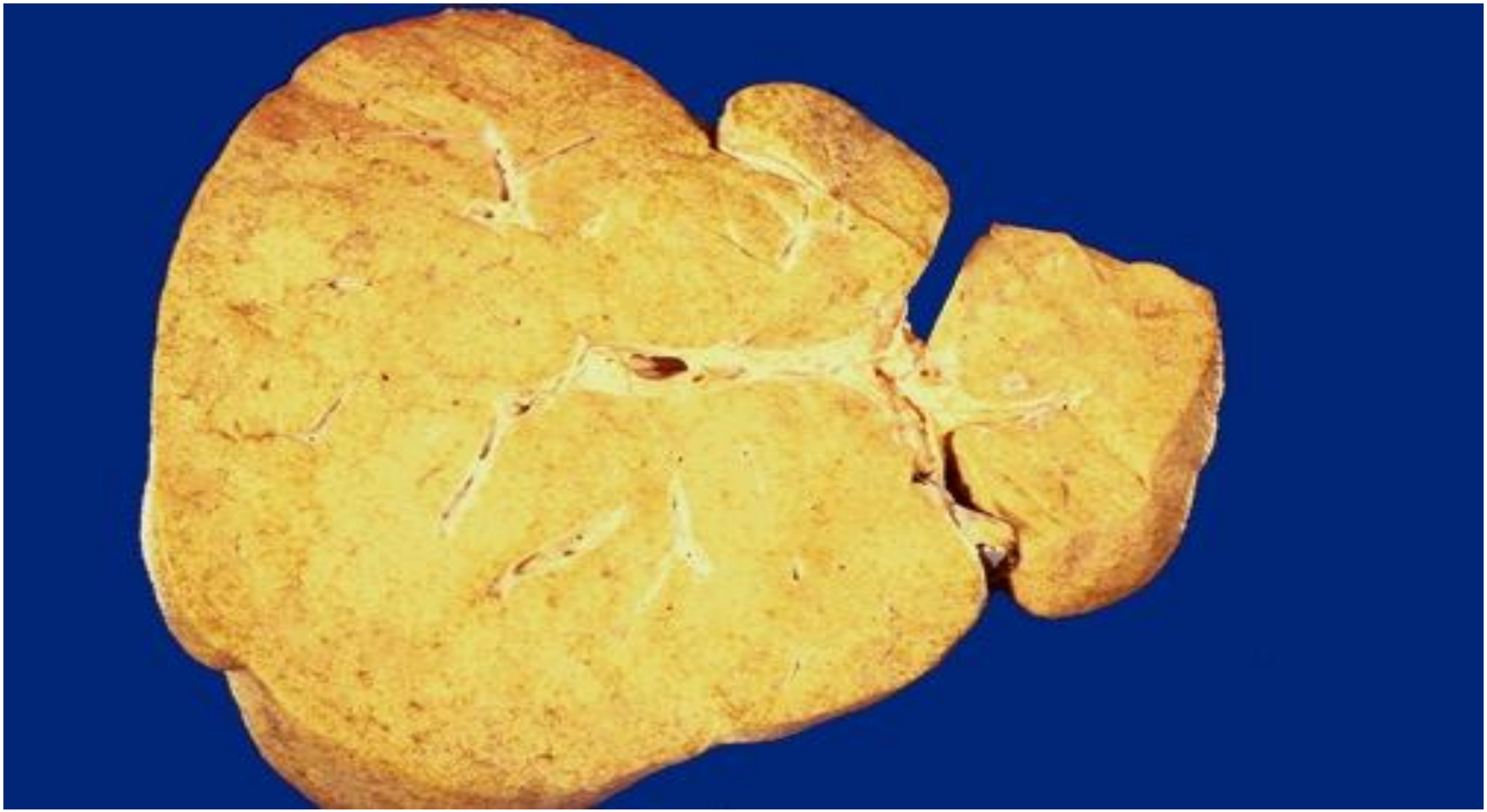
3• Decreased hepatic secretion of VLDL

- Fat-laden hepatocytes are highly sensitive to lipid peroxidation products generated by oxidative stress, which can damage mitochondrial and plasma membranes, causing apoptosis.
- levels of TNF, IL-6, and of the MCP-1 chemokine increase, contributing to liver damage and inflammation.

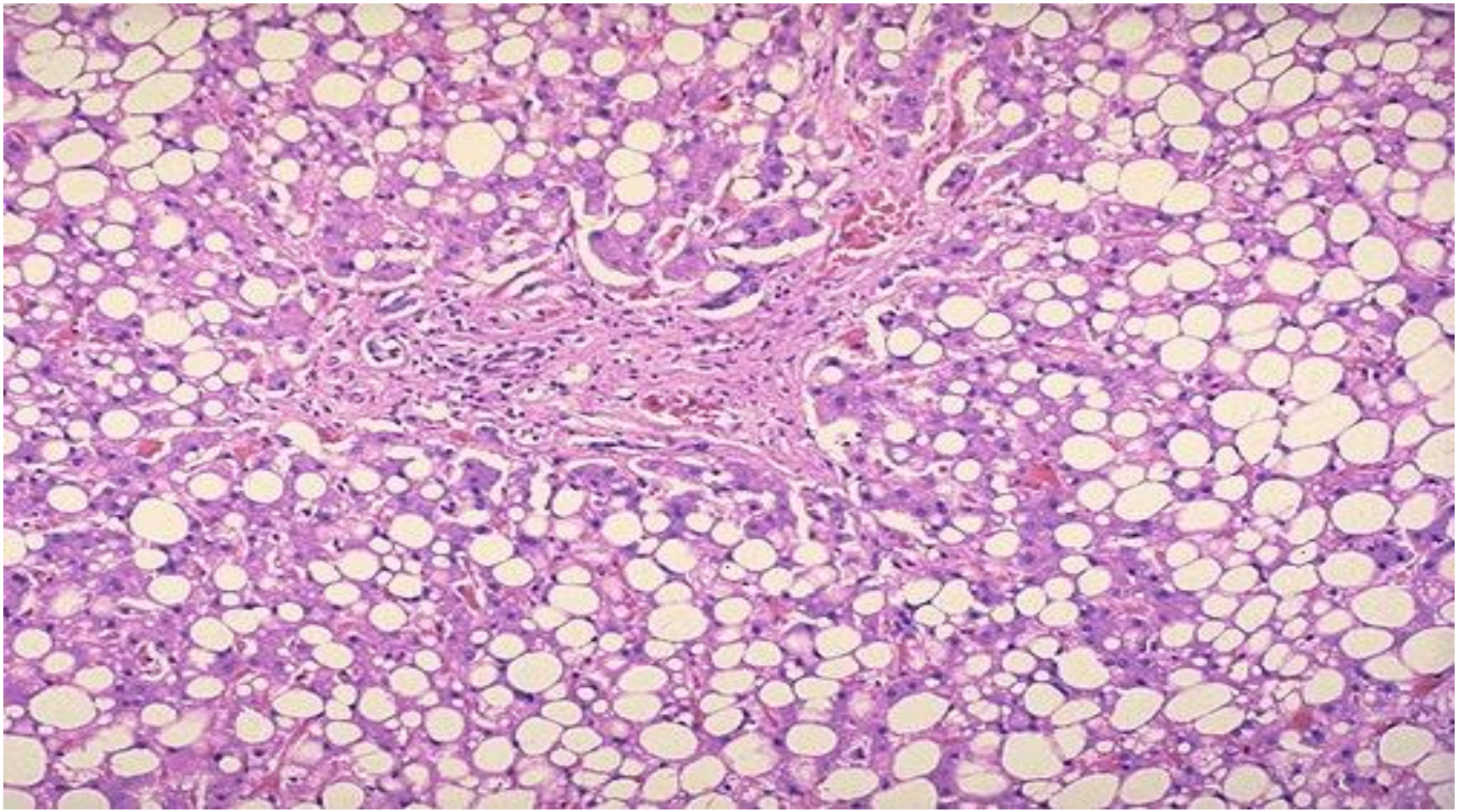
- NAFLD is the most common cause of incidental elevation of serum transaminases.
- Most persons with steatosis are asymptomatic.
- Patients with active steatohepatitis or fibrosis may also be asymptomatic, but some may have fatigue, malaise, right upper quadrant discomfort, or more severe symptoms of chronic liver disease.
- Liver biopsy is required for diagnosis.

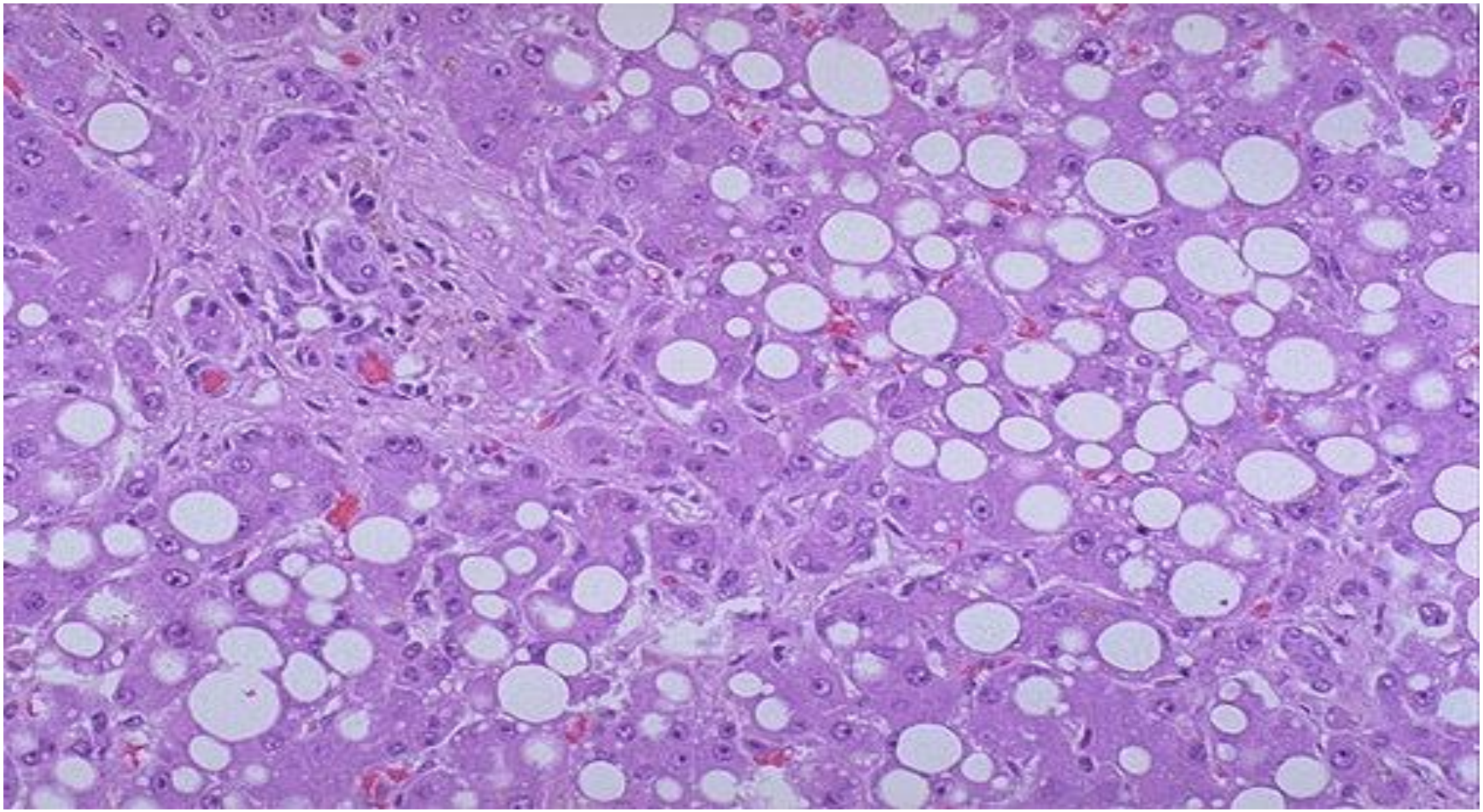
- The frequency of progression from steatosis to active steatohepatitis and then from active steatohepatitis to cirrhosis seems to be low.
- NAFLD is considered to be a significant contributor to the pathogenesis of “cryptogenic” cirrhosis.

Fatty change



fatty change





Primary Biliary Cirrhosis

- Chronic progressive & often fatal cholestatic liver disease.

-Non-suppurative granulomatous destruction of medium-sized intrahepatic bile ducts, portal inflammation & scarring.

Age 20-80yrs (peak 40-50yrs)

-F>M

-Insidious onset

-Pruritis, jaundice

-Cirrhosis over 2 or more decades

PATHOGENESIS

- **High titers of autoantibodies directed against several mitochondrial enzymes (>90%).**
- **Antimitochondrial pyruvate dehydrogenase autoantibodies .**

Clinical Course

- **The onset of PBC is insidious.**
- **Asymptomatic with elevated serum alkaline phosphatase .**
- **The diagnosis is usually made by demonstration of antimitochondrial antibodies and typical biopsy findings.**

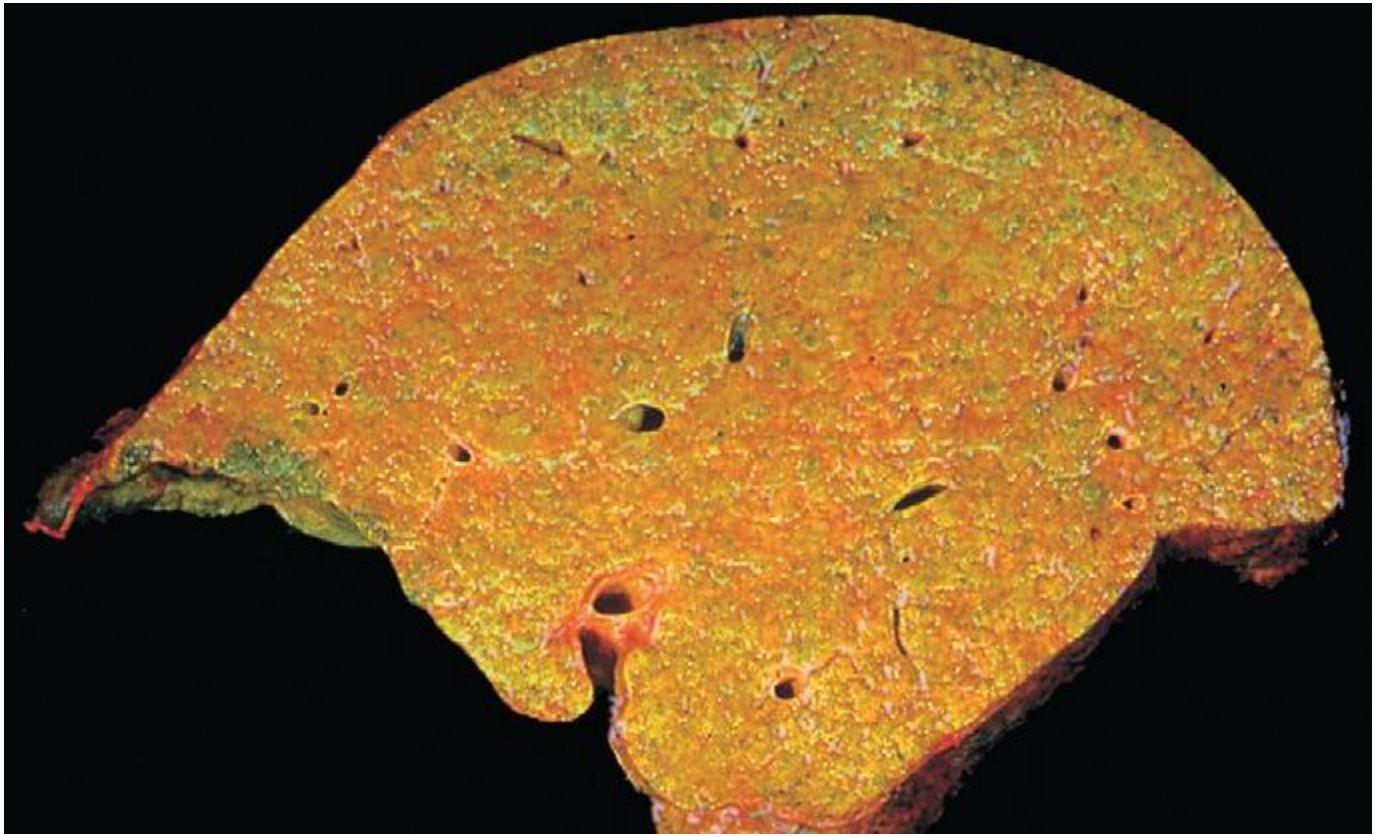
- **Patients often present with pruritus and usually prove to have advanced disease.**
- **Complications of cirrhosis over a period of 2 or more decades**

MORPHOLOGY

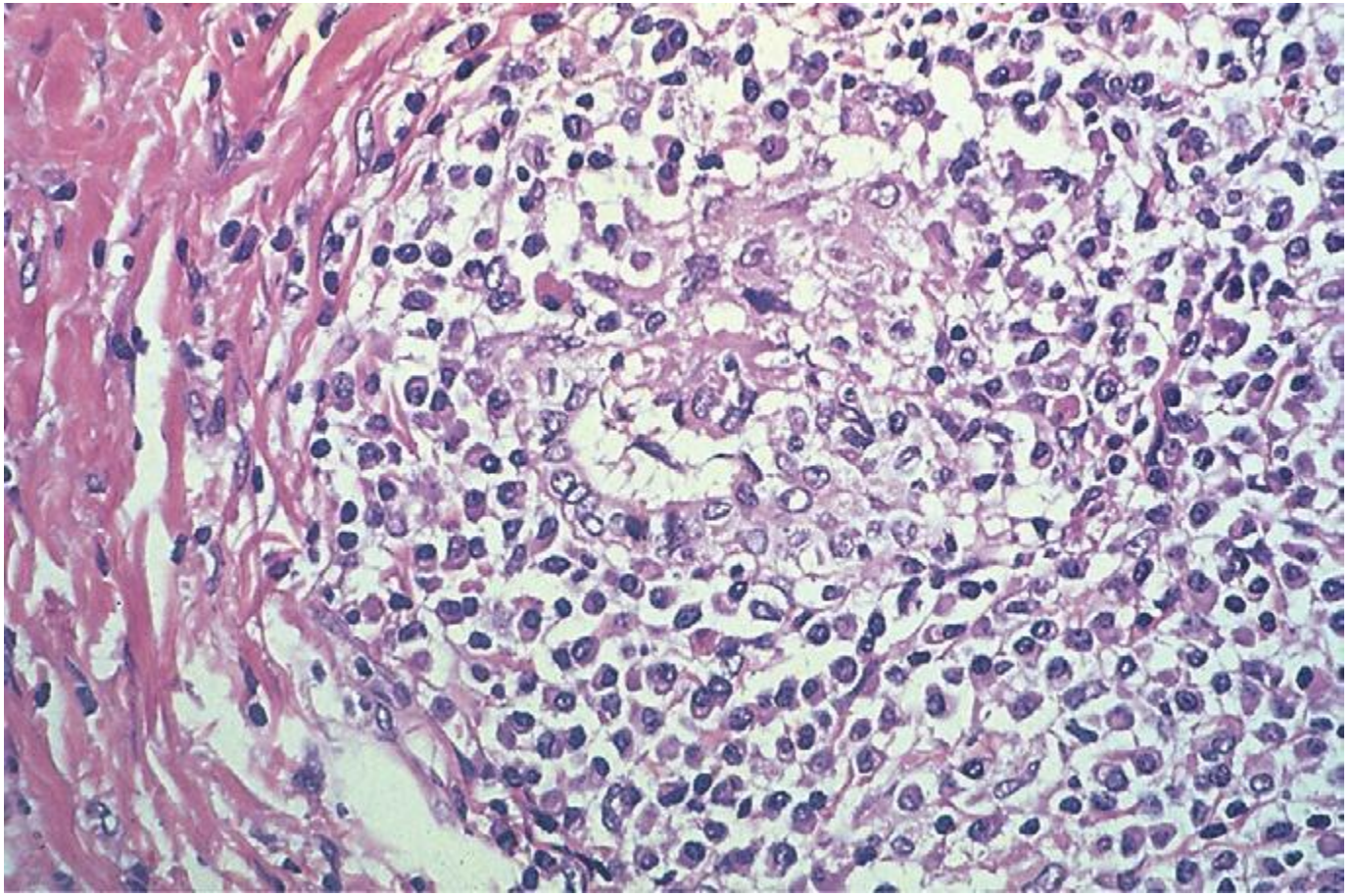
- **Interlobular bile ducts are actively destroyed by lymphocytic or plasmacytic inflammation with or without granulomas (the florid duct lesion).**
- **Portal tracts upstream from the damaged bile ducts show bile ductular proliferation and inflammation and necrosis of the adjacent periportal parenchyma.**

- **Profound cholestasis in periportal/periseptal areas associated with feathery degeneration.**
- **Mallory-Denk bodies.**

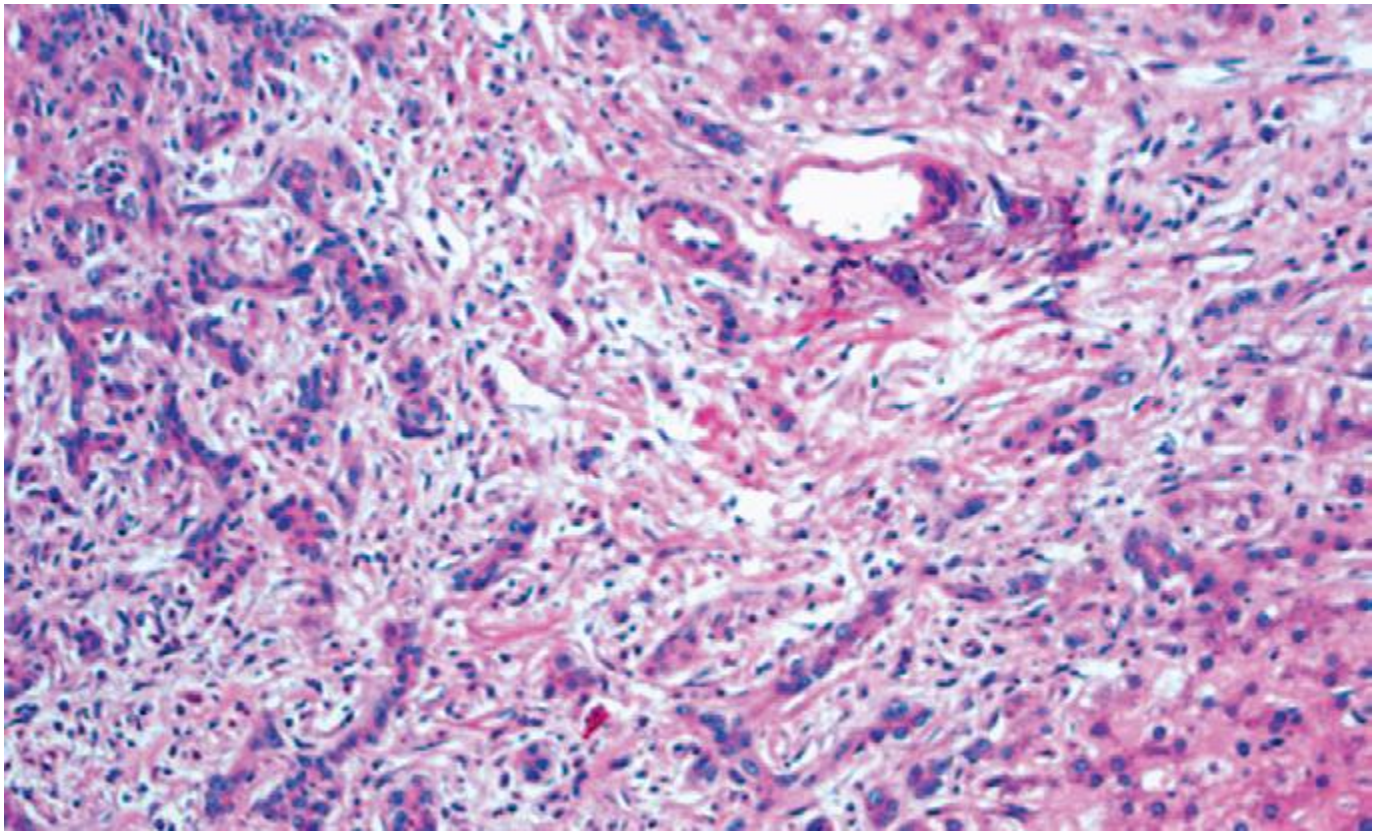
Primary biliary cirrhosis, end stage



Primary biliary cirrhosis



Ductular reaction in a fibrotic septum



Primary Sclerosing Cholangitis

- **Chronic cholestatic disorder, characterized by progressive fibrosis and destruction of extrahepatic and intrahepatic bile ducts of all sizes.**
- **The changes in the ducts are patchy, cholangiography shows a characteristic *beading in the affected segments of the biliary* tree due to narrow strictures alternating with normal sized or dilated ducts.**

-PSC and ulcerative colitis coexists in approximately 70% of

affected patients.

-The prevalence of PSC among persons with ulcerative colitis is about 4%.

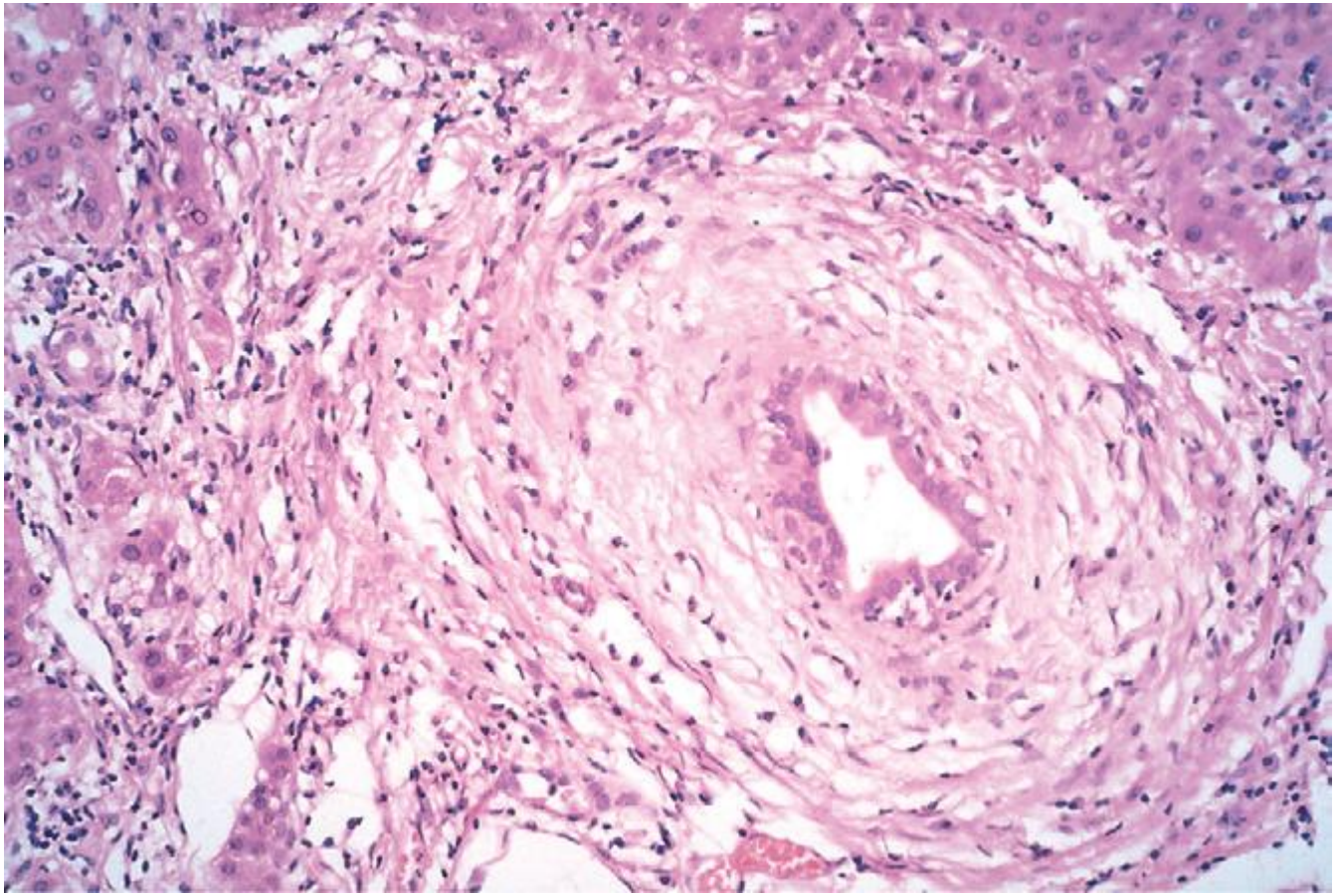
- **The cause of PSC is unknown.**
- **There is association with ulcerative colitis linkage with certain *HLA-DR alleles.***
- **Antinuclear cytoplasmic antibodies (ANCA) with a perinuclear localization present in 80% of cases.**

Morphology

- **The largest ducts have chronic inflammation with superimposed acute inflammation very similar to the mucosal lesions of ulcerative colitis.**
- **The smaller ducts often show mild inflammation but show a striking circumferential fibrosis often referred to as onion skinning around an increasingly atrophic duct lumen.**

- **Duct loss leads to bile ductular proliferation, portal-portal septal fibrosis, and cirrhosis.**
- **The end-stage liver is therefore usually cirrhotic and green.**

Primary sclerosing cholangitis.
A bile duct undergoing
degeneration is entrapped in a dense, onion-skin concentric scar.



Clinical Course

- **M:F 2:1**
- **3rd -5th decades of life**
- **Asymptomatic**
- **Persistently elevation of serum alkaline phosphatase.**
- **Acute cholangitis—fever, right upper quadrant tenderness, and sometimes acute jaundice.**
- **At later stages may have progressive fatigue, pruritus, and chronic jaundice.**
- **Cholangiocarcinoma develops in 10-15% of patients with PSC, with a median time from diagnosis to malignant transformation of 5 years.**