Liver

Notes:
1- Slides (1-13) are just an introduction and most of them are physiology and histology. Study them quickly and you won't be asked about them in the exam.

Functions of the Liver

In order to understand the effect of liver damage, we have to know its normal functions. Whenever we have liver failure, for example, all of the functions mentioned below will be impaired. See the following slides.

Functions of the Liver

- Metabolic Functions:

  ex: Metabolism of Glucose (Glycogen Synthesis, Gluconeogenesis, Glycogenolysis)
  → Liver damage causes distortion of the normal body metabolism

- Synthetic Functions
  ex: Synthesis of
  a- Albumin b- clotting factors

  → Liver damage causes hypoalbuminemia and increased bleeding tendency (lack of clotting factors)

- Detoxification: Drugs, hormones , NH_3 (ammonia)

Functions of the Liver

- Storage of
  a- Glycogen b- Triglycerides
  c- Heavy metals: Fe, Cu
  d- Some vitamins

- Excretory Functions
  ex: Bile
  → Liver damage causes jaundice (i.e when the liver doesn't excrete bile, it goes to the blood and causes jaundice.)

  Jaundice (اليرقان): Yellowish pigmentation of the skin and sclera of the eyes.

Liver

- Weight: 1400g – 1600g (2.5% of the body weight)

  It weighs more if the patient has hepatomegaly (تضخم الكبد)

Blood supply of the Liver

The liver receives blood from the portal vein (venous blood, deoxygenated, and nutrient-rich) and the hepatic artery (arterial blood, oxygenated and nutrient-poor)

60-70 % from the portal vein
30-40% from the hepatic artery

Why??
- Carbohydrates, amino acids, and fats absorbed through the gut go into the portal vein, and then to the liver where they are metabolized and utilized for protein, fat and glycogen synthesis. That's why the liver has to take most of its blood supply from the portal vein (60-70 %). However, all these metabolic processes need oxygen. Hence, the liver is also supplied arterial blood.

Histology of the Liver

- The liver is divided into hexagonal lobules. Within each lobule, there are 6 acini.

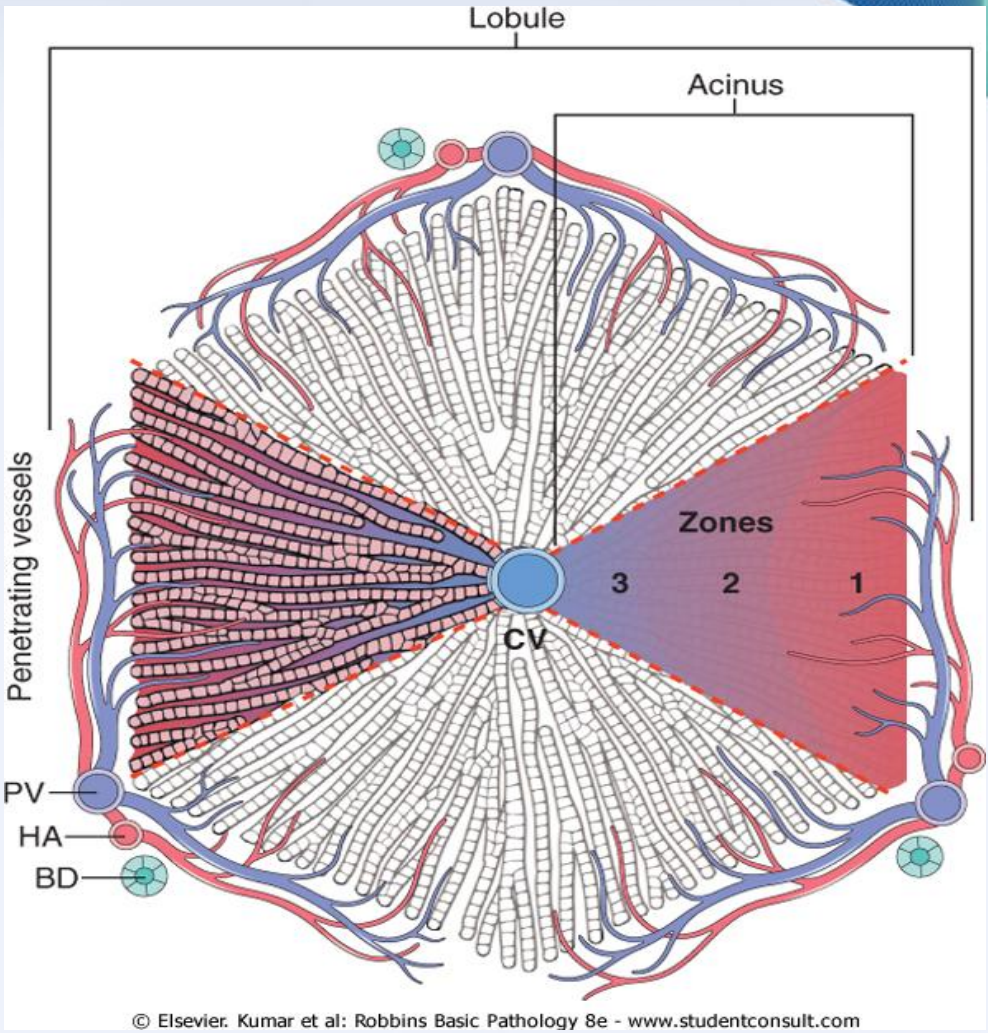
- Each acinus is divided into 3 zones:

Zone 1 → Periportal areas – closest to the vascular supply (the portal triad)

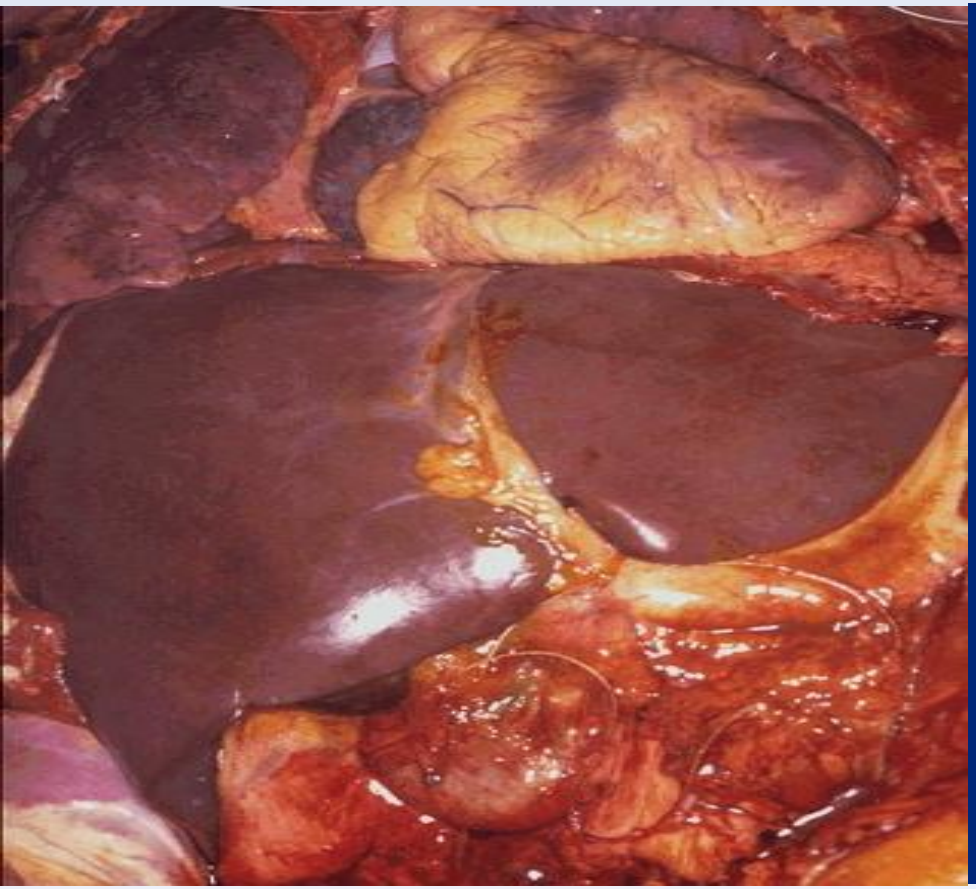
Zone 3 → Pericentral area (around the central vein).

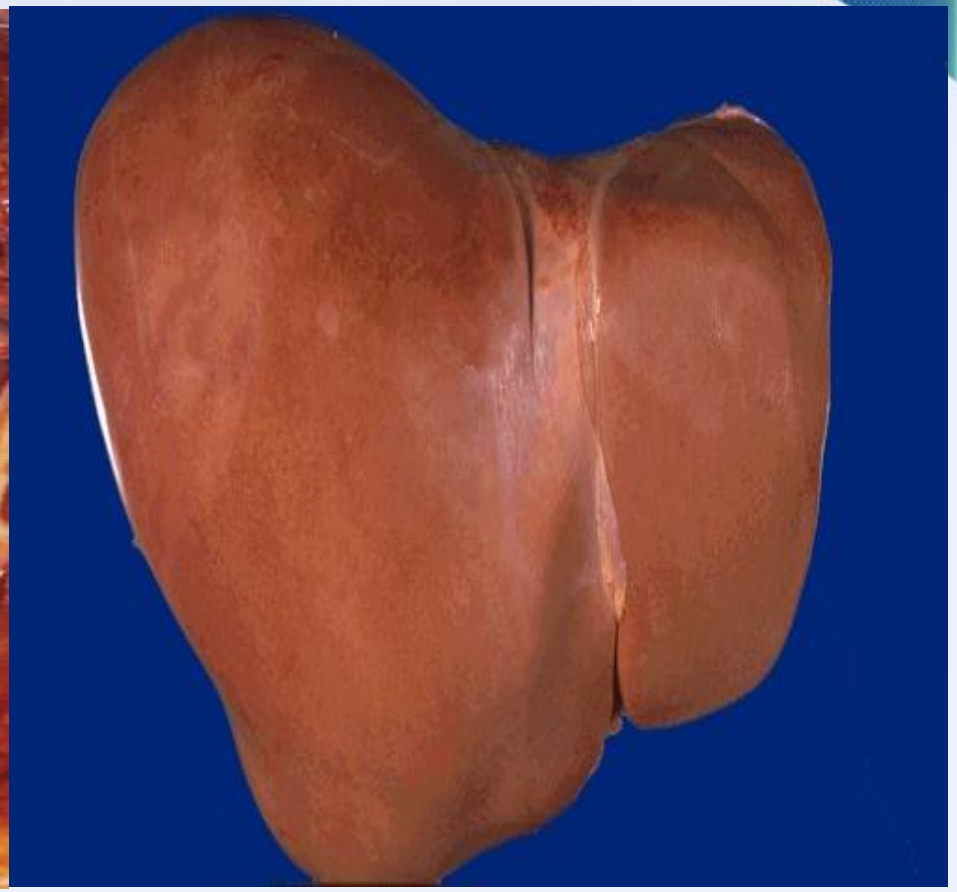
Zone 2 → Inrermediate between Zone 1 and 2 (midzonal area).

- These zones are important because certain types of liver injury are distributed according to these zones (This concept will be clear later. Leave it for now)



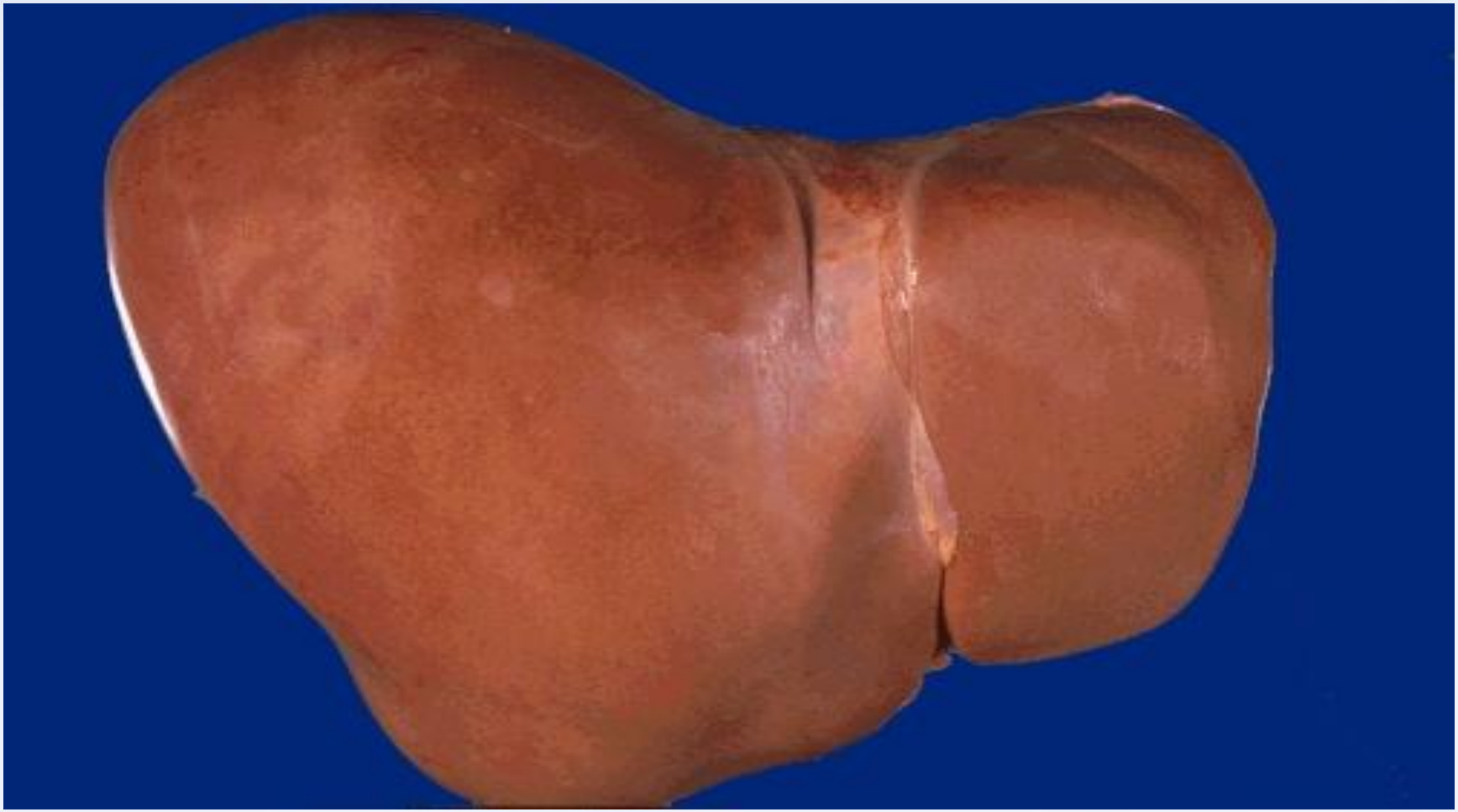
Normal liver



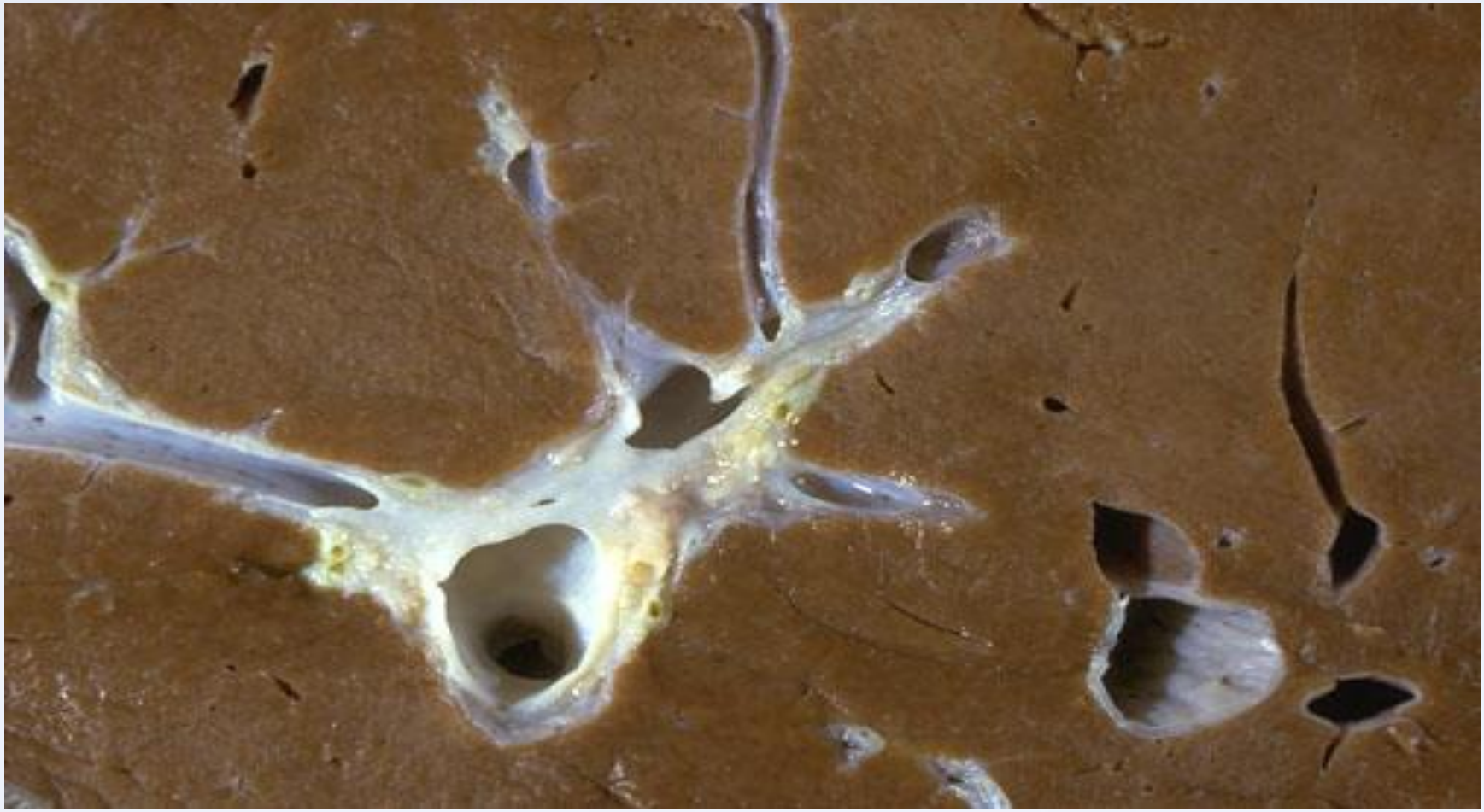


It’s important to know how the liver normally looks like in order to differentiate between normal liver and diseased liver (In cirrhosis, for example, the architecture of the liver will change significantly)

Normal liver

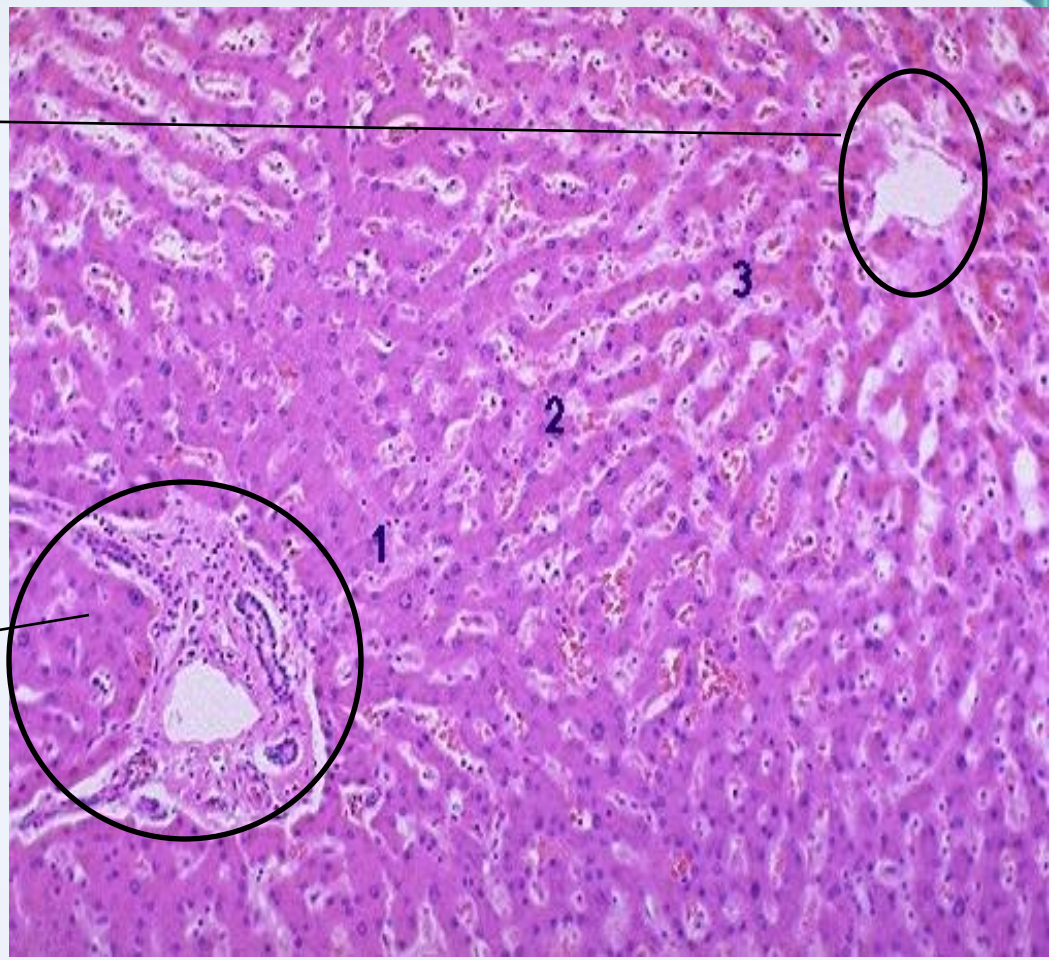


Cross section of normal liver



Liver zones

Central vein (Terminal hepatic vein)



Portal triad

Histology of the Liver

- The parenchyma of the liver is organized into sheets or “plates” of hepatocytes, extending radially from the portal tracts to the central veins.

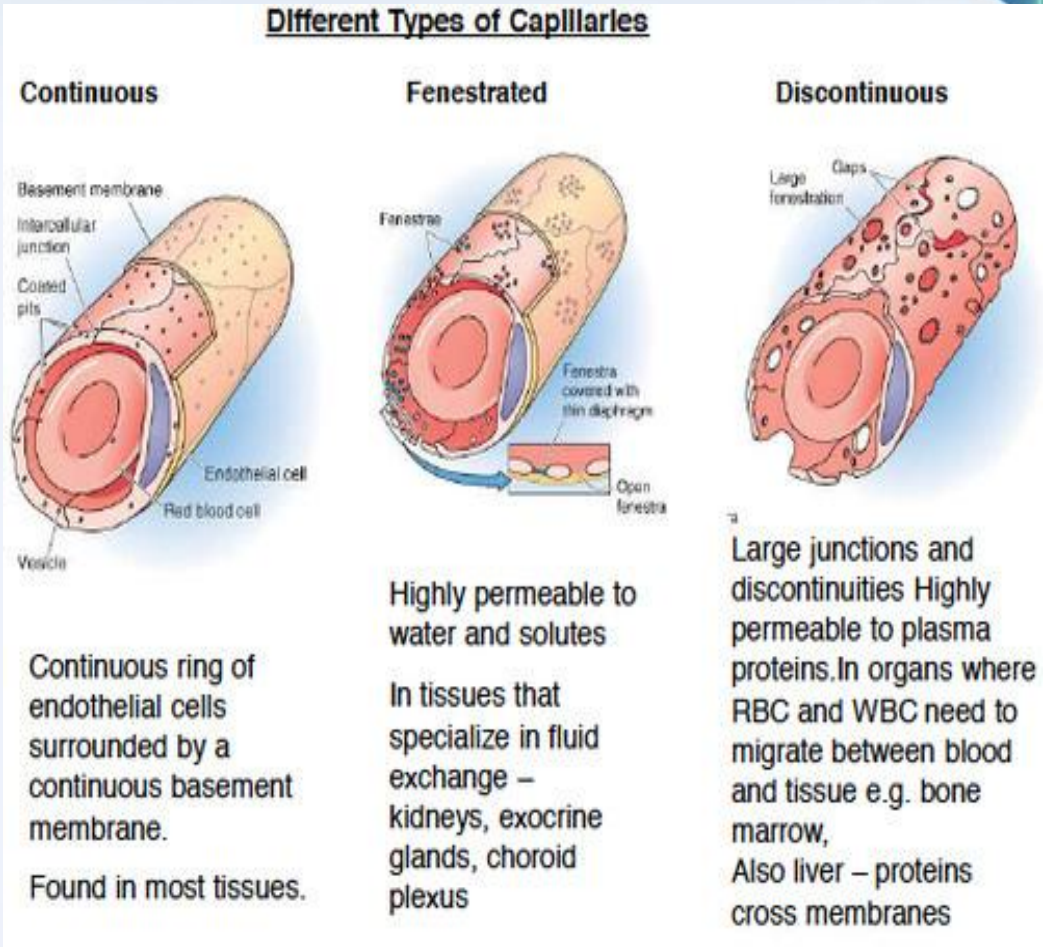
- Hepatocytes:
  1- Uniform size: show only minimal variation in the overall size.
  2- Nuclei may vary in size, number & ploidy especially with advancing age.

- Between these cords of hepatocytes are the vascular sinusoids.

Physiology Connection …

Liver sinusoids are of the discontinuous type and this is very important for the function of the liver. Why?

Ex: The liver receives amino acids to synthesize albumin, for example, which is a plasma protein. If liver capillaries where continuous or fenestrated (i.e impermeable to proteins), albumin will never leave the liver into the blood. Hence, for the structure to fit the function, liver capillaries must be discontinuous.



Patterns of Hepatic Injury

1-Inflammation (Hepatitis)
2-Degeneration
3- Steatosis (Fatty Change)
4- Necrosis
5- Regeneration
6- Fibrosis
7- Cirrhosis
8- Ductular proliferation

Inflammation

- Hepatitis:

Can be caused by:

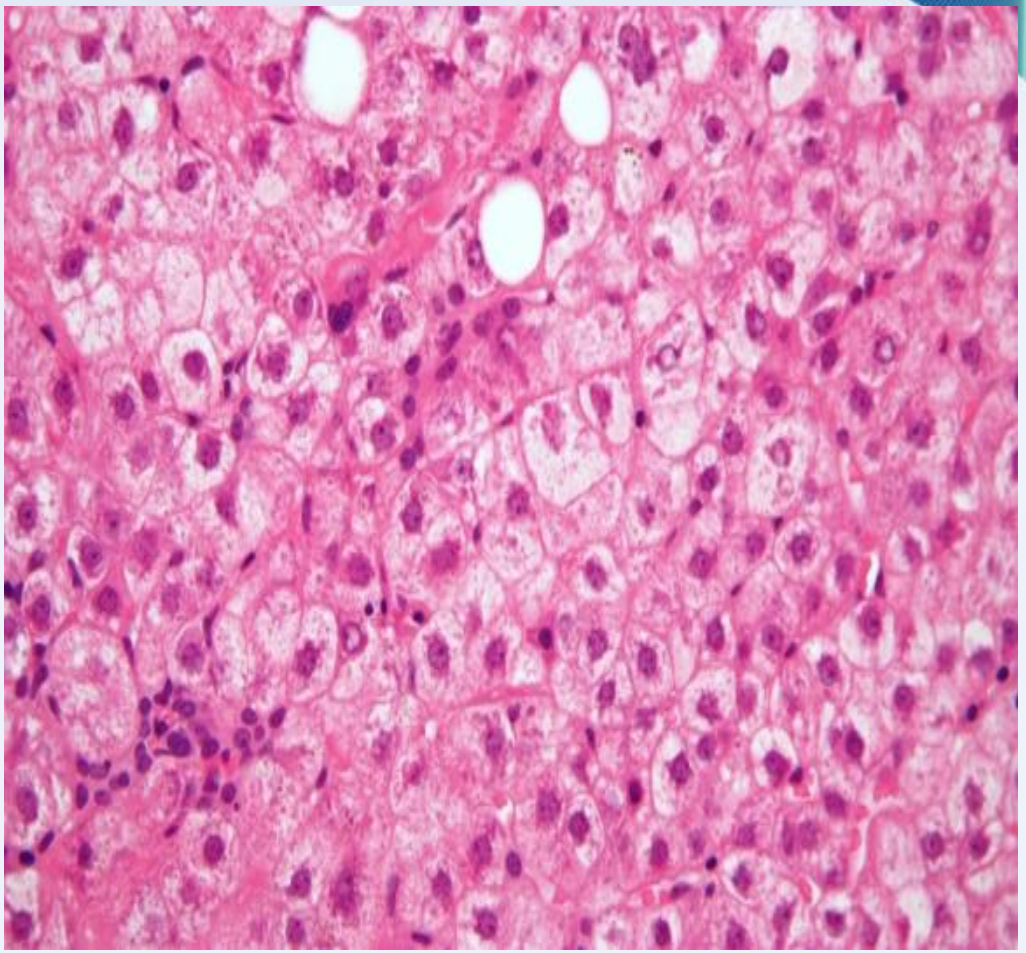
Viruses (Hepatitis A, B, C, D and E).

Autoimmune Hepatitis

Degeneration

- Ballooning degeneration “Ballooning” indicates the increase in the size of hepatocytes.

- Feathery degeneration: retained biliary material, and accumulation of iron ,copper



Ballooning Degeneration

Steatosis (fatty change)

Occurs due to accumulation of fat inside hepatocyte. This fat accumulates within vesicles in the cytoplasm. When the vesicles are large enough to distort the nucleus, the condition is known as macrovesicular steatosis; otherwise, the condition is known as microvesicular steatosis.

A- **Microvesicular Steatosis:**

Seen in:

ALD (Alcoholic Liver Disease).

Reye's syndrome.

Acute fatty change of pregnancy.

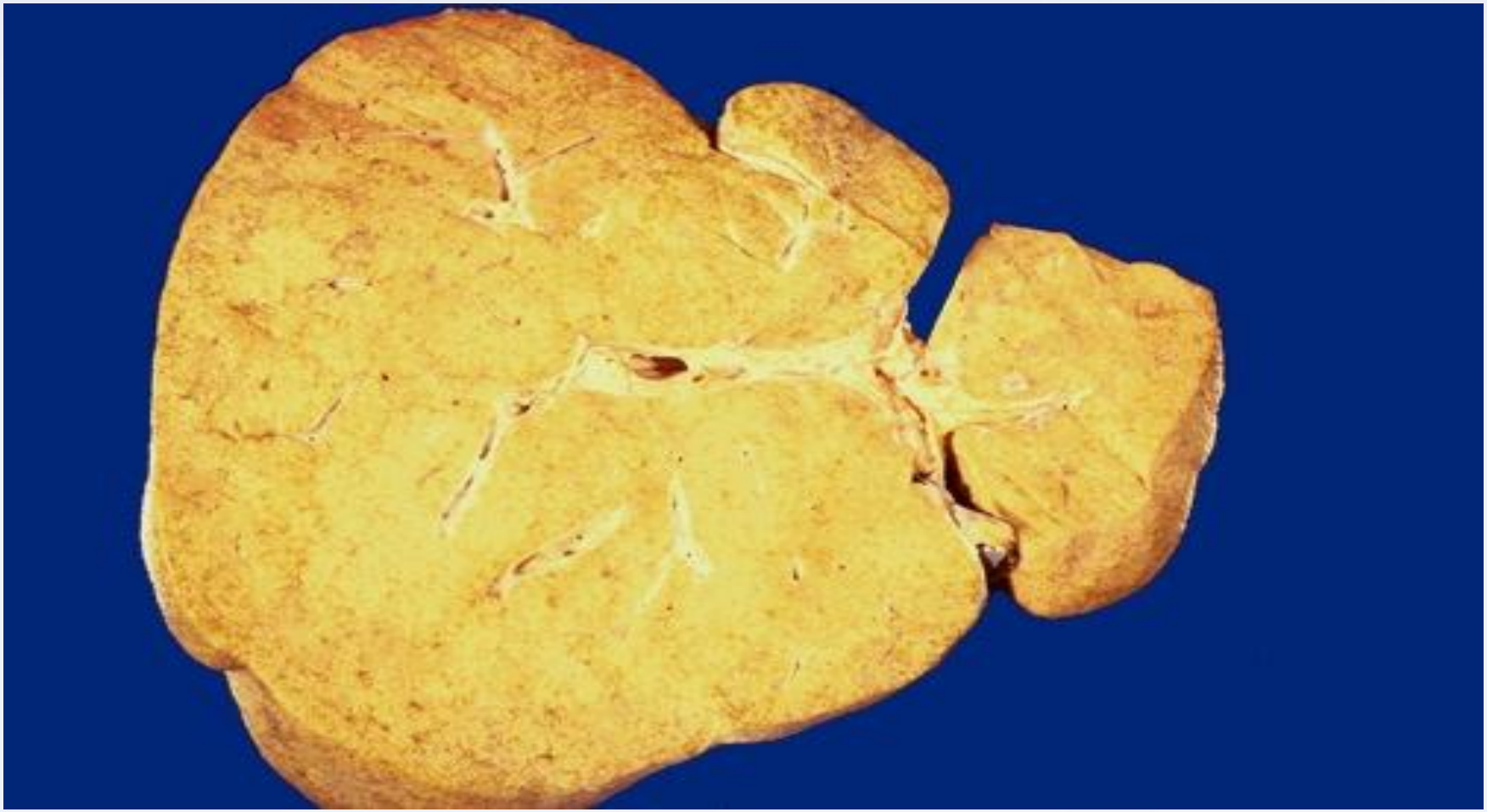
B- **Macrovesicular Steatosis:**

Seen in:

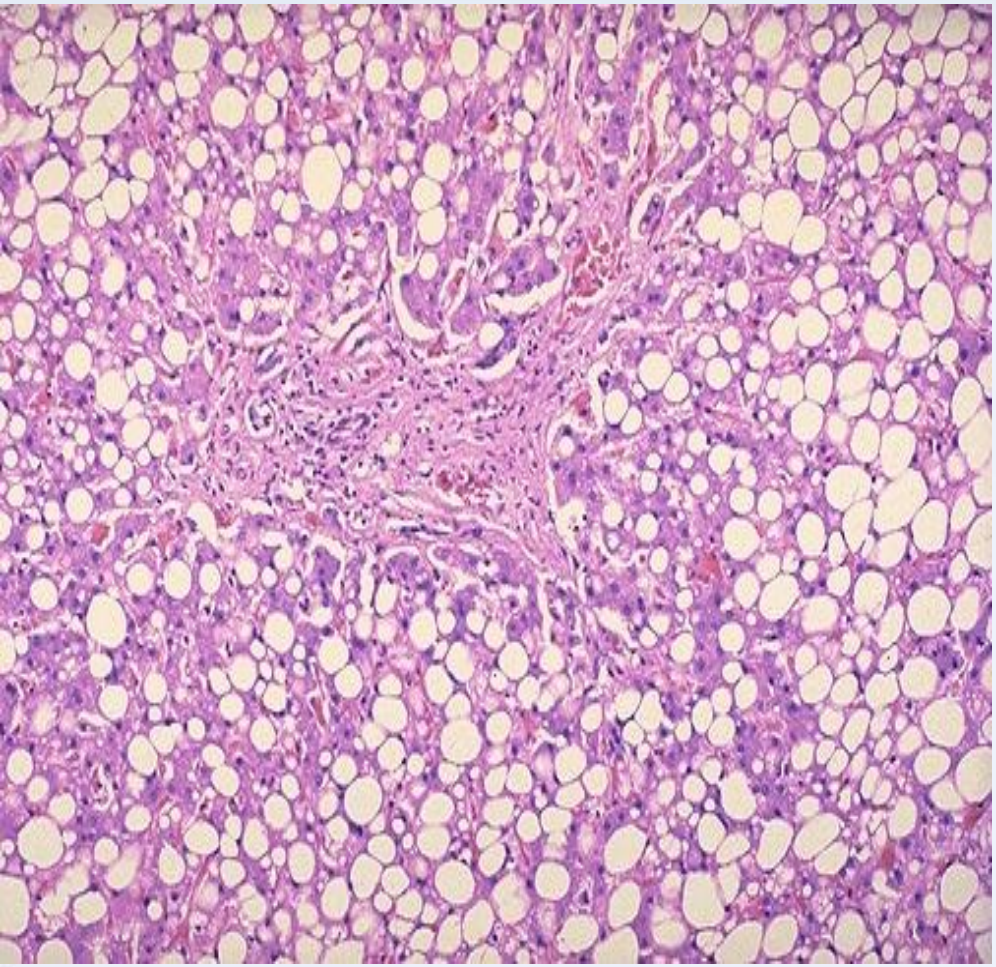
DM (Diabetes Mellitus)

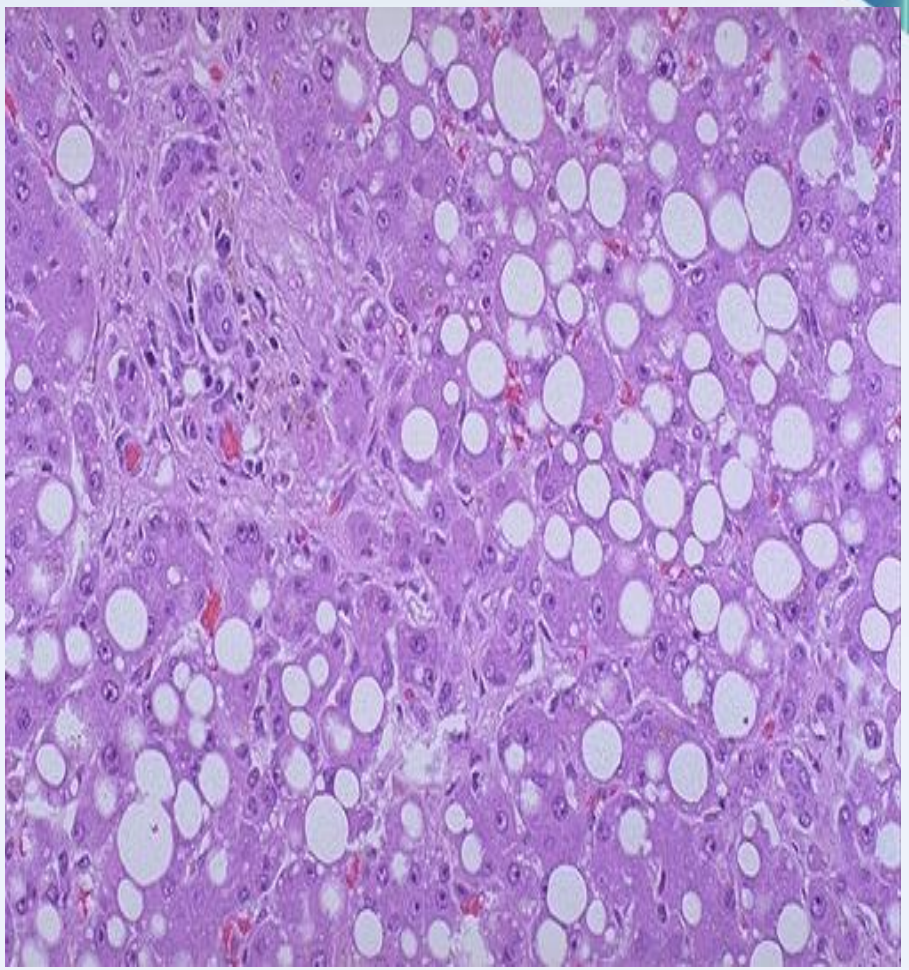
Obesity

Fatty change



fatty change





Necrosis

Necrosis of the liver can be classified according to:

1- Type:

Coagulative necrosis

Councilman bodies

Lytic necrosis

2- Cause

Ischemic: Hepatocytes die due to lack of blood supply.

Toxic : Toxic materials cause hepatocyte necrosis.

3- Location:

Centrilobular necrosis : Zone 3

Mid zonal: Zone 2

Periportal: Zone 1interface hepatitis

Focal:

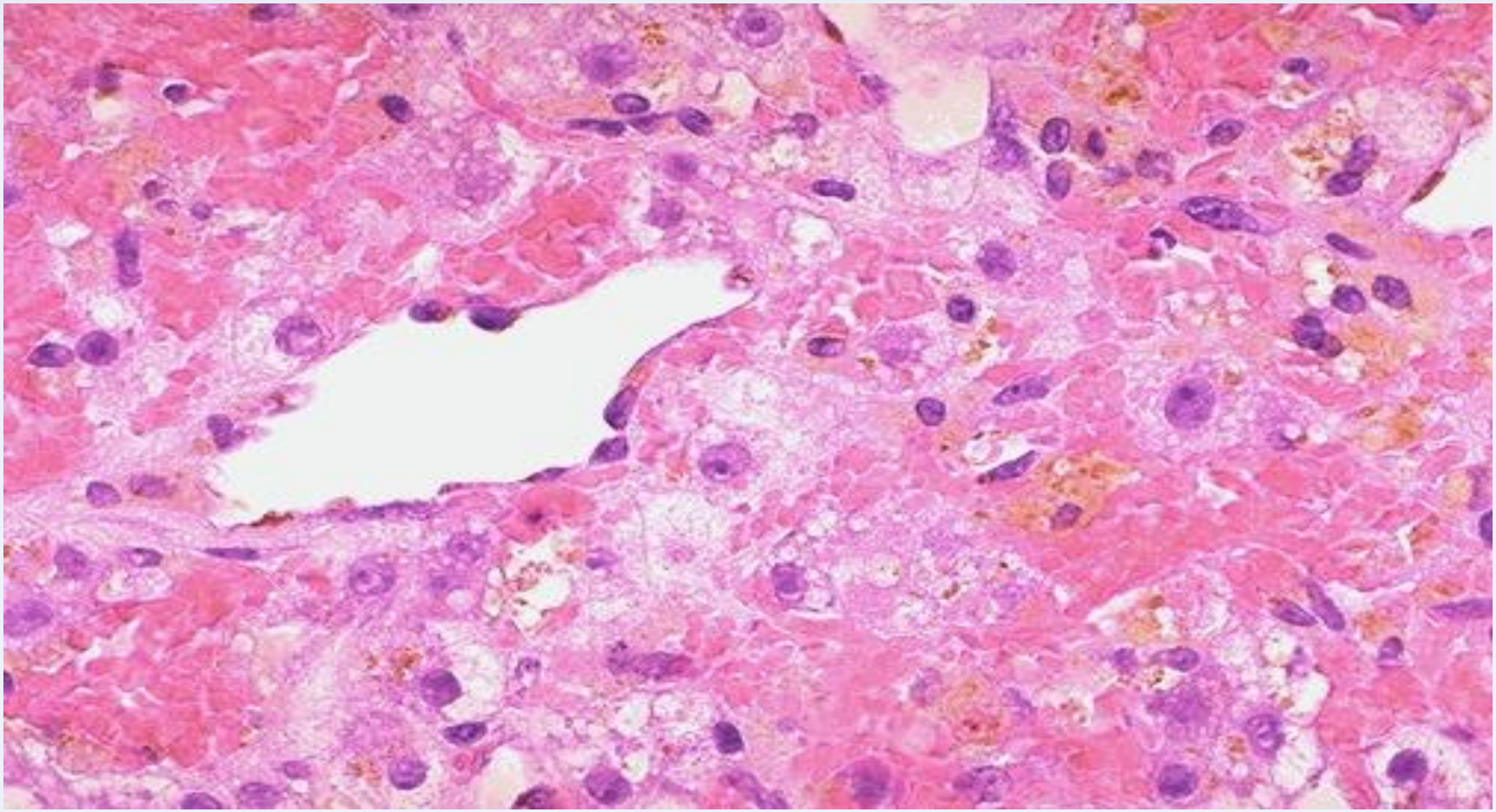
Piece meal necrosis

bridging necrosis

Diffuse:

massive & submassive necrosis

Necrosis of liver



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).

Fibrosis

bridging fibrosis

Cirrhosis

micronodular

Macronodular

8-Ductular proliferation

Clinical Syndromes of the Liver

CLINICAL SYNDROMES

- The major clinical syndromes of liver disease are:
- 1- Hepatic failure (Liver Failure)
- 2- Cirrhosis
- 3- Portal hypertension
- 4- Cholestasis

liver failure

- Liver Failure = الفشل الكبدي

It doesn’t occur at the beginning of liver damage. Why?
Because the liver can regenerate easily, and only 25% of it is enough to do its function. So, liver failure only occurs when 80-90% of the liver function is lost.

liver failure

- **Patterns of Liver Failure:**
- **1-** ***Acute liver failure with massive hepatic necrosis***
- ***2- Chronic liver disease***
- ***3- Hepatic dysfunction without overt necrosis.***

1-Acute liver failure الفشل الكبدي الحاد

- This is most often caused by *drugs* or *fulminant viral hepatitis*.
- Here, liver failure is acute. So, is it going to last for a few weeks or months?
  Definitely, for weeks.
- Knowing that it lasts for only 2-3 weeks, how can the disease cause liver failure (loss of 80-90% of liver function) in such a short period of time?
  Because it's associated with massive hepatic necrosis, the disease develops very rapidly.

Acute Liver Failure

- 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.

Remember:
Acute → lasting for less than a month
Subacute → 1-3 months
Chronic → more than 3 months

Acute Liver Failure

The histologic correlate of acute liver failure is massive hepatic necrosis. Actually, this is what makes it acute (i.e. able to cause liver damage within 2-3 weeks).

- It is an uncommon but life-threatening condition that often requires liver transplantation.
  Why is it uncommon? Because it's caused by fulminant viral hepatitis (which is rare) and drugs (which is also not that common).

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.**
- **Chronic liver disease usually ends in cirrhosis.**

Chronic Liver Disease

- Liver failure is more common in the case of chronic liver damage than the acute. DOES THAT MAKE SENSE?
  Yes. For liver failure to occur, 80-90% of the liver function has to be lost. In the chronic disease, there's a very long time for this huge loss to occur. On the other hand, it's more unlikely for a disease occurring for only 2-3 weeks to cause such a huge damage.

  Ex: Chronic Hepatitis C or B may cause cirrhosis, chronic liver damage and ultimately liver failure. Why? Because it lasts for a long time.
  Acute Hepatitis A or E never cause liver failure. Why? Because they only last for weeks, and this time isn't sufficient to cause liver failure.

3-Hepatic dysfunction without overt necrosis.

- This form is less common than acute and chronic liver failure. In this case, hepatocytes may be viable (no overt necrosis) but unable to perform normal metabolic function. This may be seen in:
- 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 of Chronic Liver Failure

Liver Failure= The liver fails to do its functions. (All of the clinical features depend on this)

- **Impaired bile excretion → Jaundice**
- **Impaired synthesis and excretion of bile →**
  Hypoalbuminemia → edema.
  Why hypoalbuminemia causes edema?
  Albumin is the most abundant protein in the plasma. When its level decreases, reabsorption of fluids from tissues decreases, causing edema.

Clinical features of Chronic Liver Failure

- **Impaired urea cycle → Hyperammonemia**

  Remember: Urea cycle is responsible for disposal of NH3.

- **Impaired estrogen metabolism**

  →hyperestrogenemia

  When estrogen levels increase in men, they would show some feminine characteristics (**Gynecomastia** and **Hypogonadism**)

Clinical features of Acute Liver Failure

- In **acute liver failure**, there's no time to develop gynecomastia, hypogonadism, or prominent edema. So, most of the features of chronic liver failure are absent.
- **Acute** liver failure manifestations:
  Jaundice
  Hepatic encephalopathy after 2-3 weeks

Complications of Liver Failure

- Multiple organ failure

  Respiratory failure, with pneumonia and sepsis can give rise to **renal failure**.

- **Coagulopathy**: Impaired synthesis of blood clotting factors II, VII, IX, X → impaired coagulation → **bleeding tendency** in the GI and elsewhere in the body.

- **Hepatic encephalopathy (discussed later).**

- **Hepatorenal Syndrome (discussed later).**

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

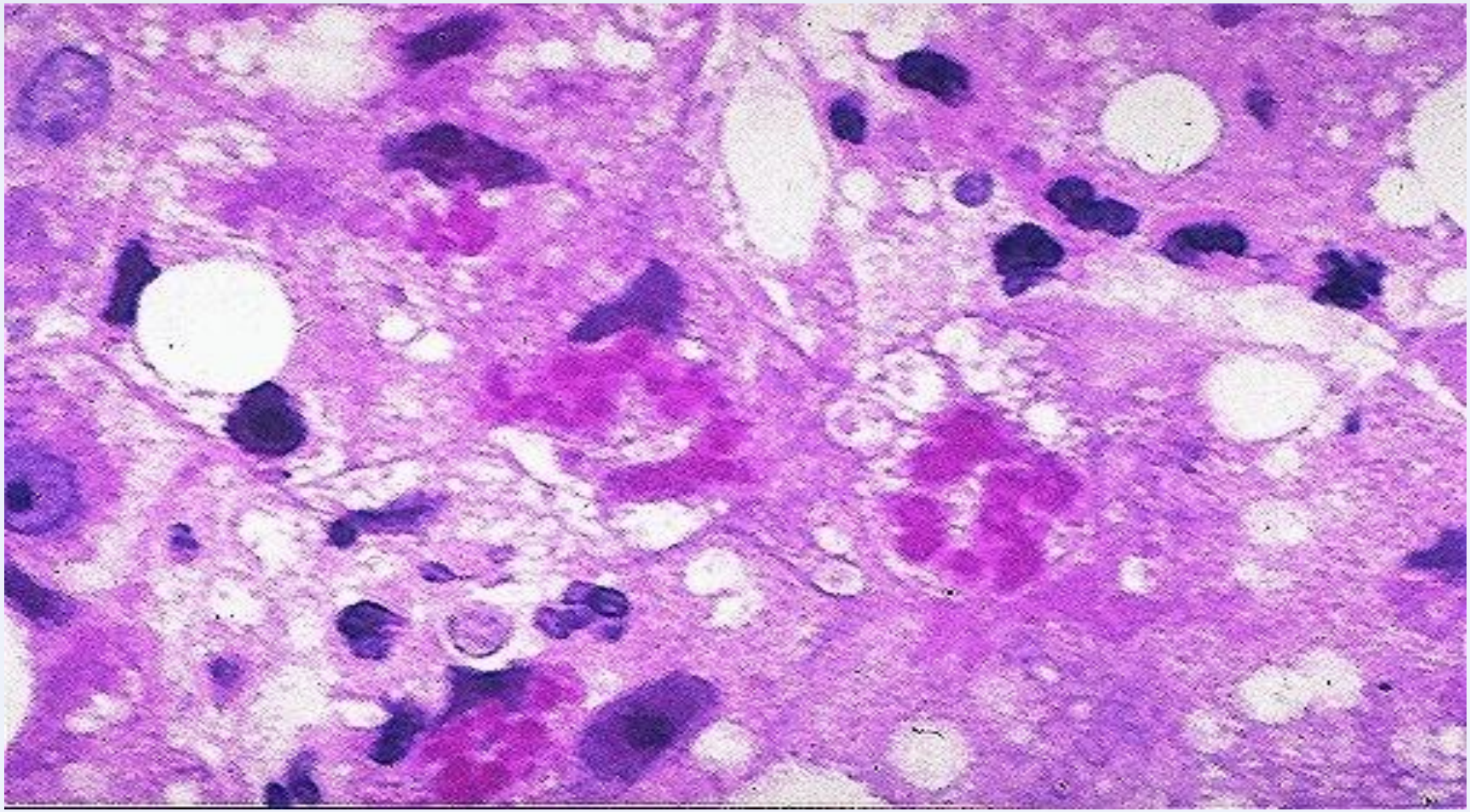
-Cholestasis

-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

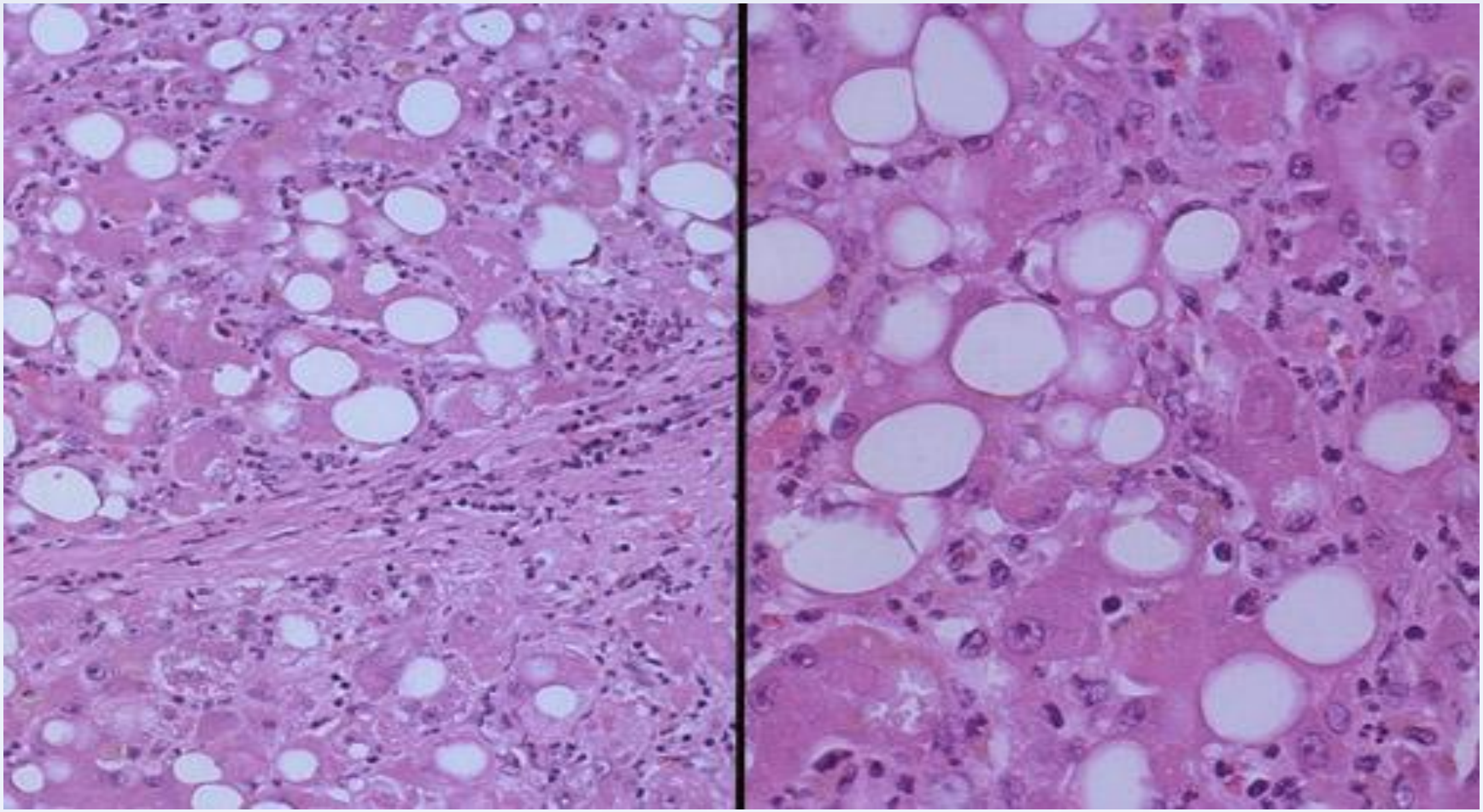
-Sinusoidal & perivenular fibrosis

-Periportal fibrosis

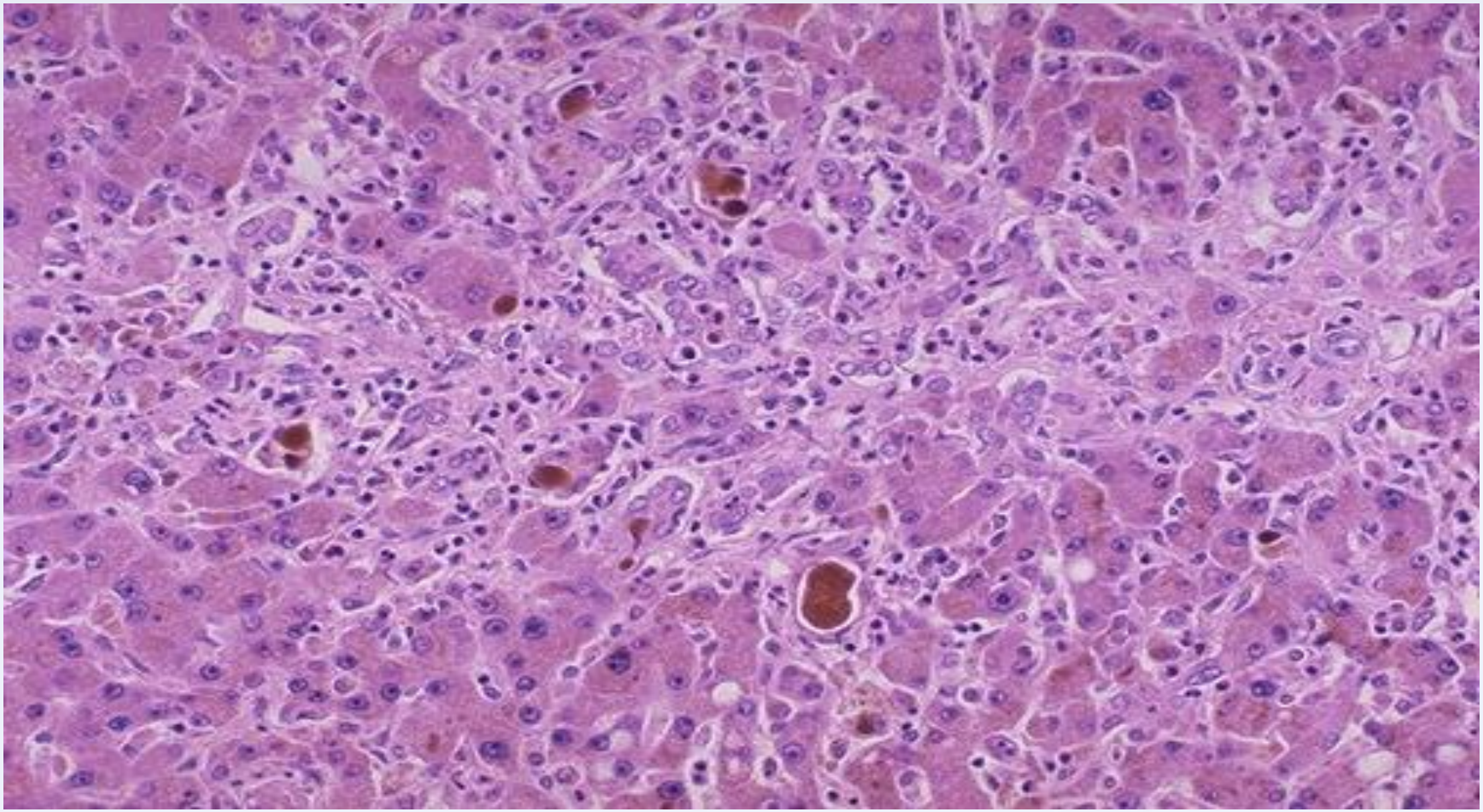
5-Cholestasis

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

CH_3CH_2OH → $CH_3C(=O)H$

↑

-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

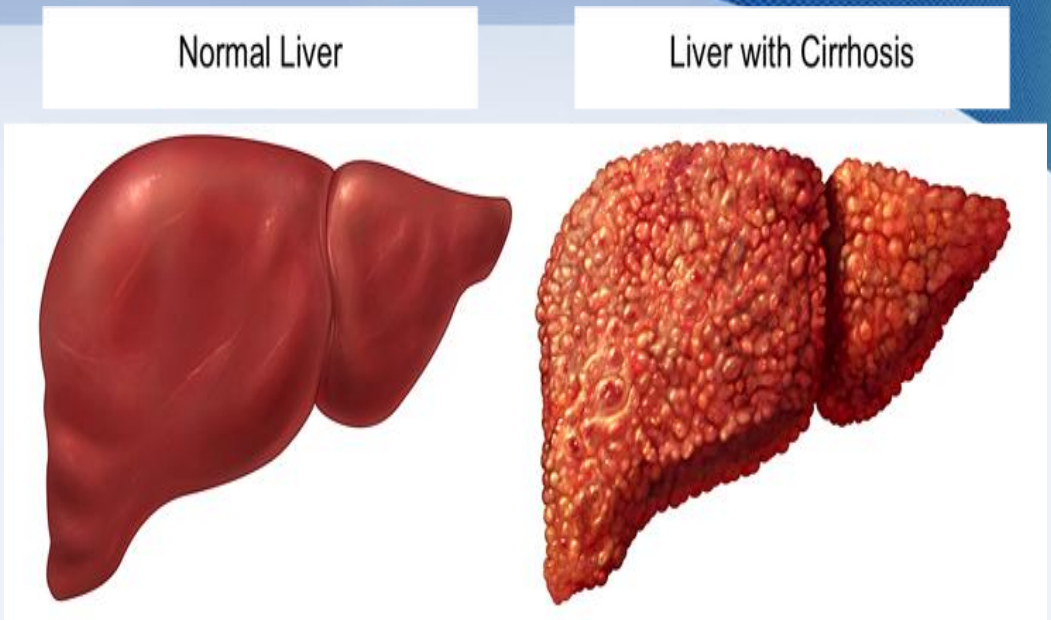
3-Infections

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**



- Diffuse = not localized to a certain region of the liver (not focal).
- Notice how the parenchyma of the liver is converted into nodules.
- Cirrhosis involves most (if not all) of the liver.

Cirrhosis

- **Main characteristics**

1. Bridging fibrous septae (Fibrous septae separating one nodule from the adjacent ones).
2. Parenchymal nodules encircled by fibrotic bands.
3. Diffuse architecture disruption (i.e. the architecture of the liver is converted into the characteristic nodule-appearance.

Types of Nodules

- **Types :**

Micronodules < 3mm in diameter

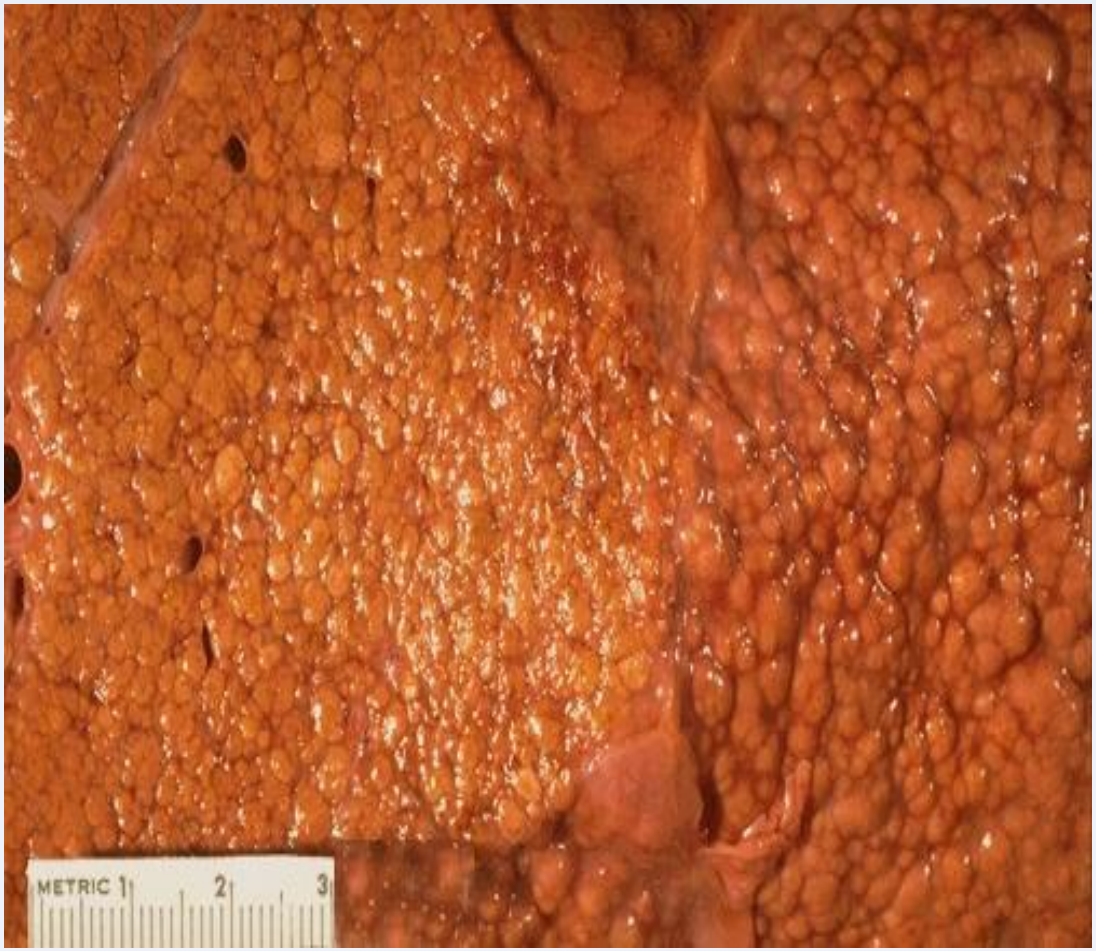
Macronodules > 3 mm in diameter

- They can also be mixed (micronodules with macronodules)

Micronodular cirrhosis

- Nodules are less than 3 mm in diameter.

  - Uniform size



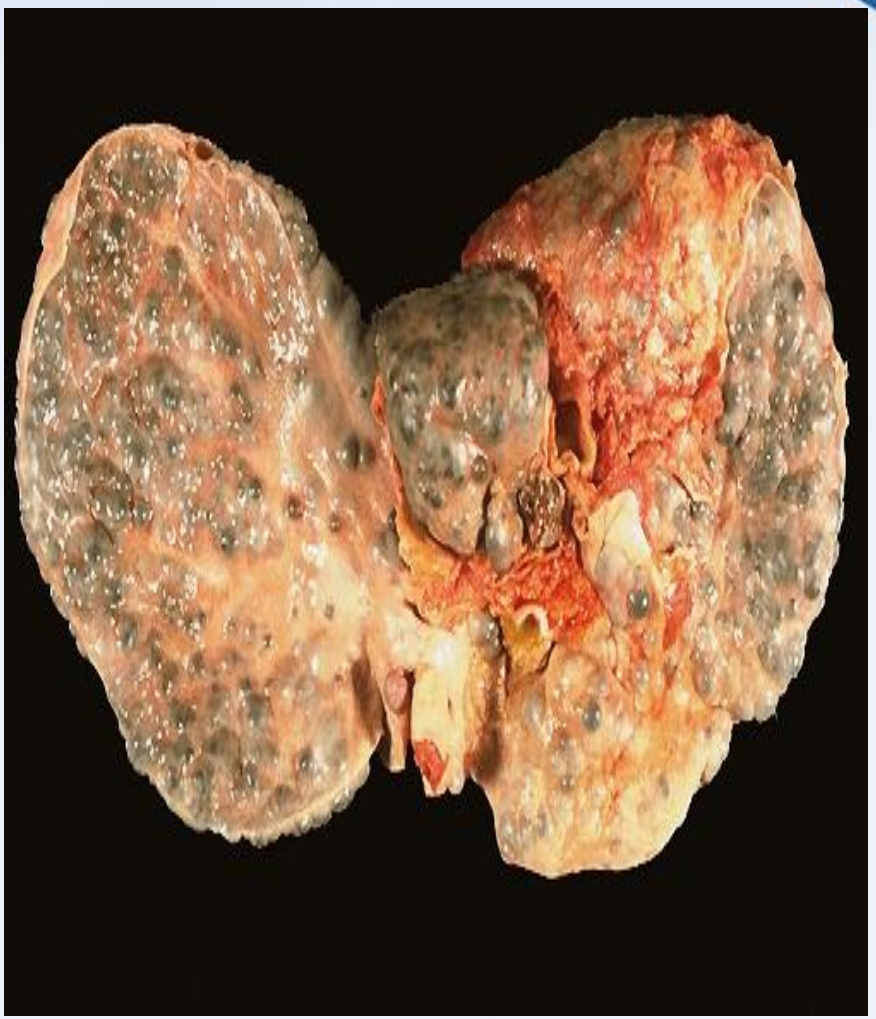
Macronodular cirrhosis

- Nodules > 3 mm in diameter

  - Increased risk of hepatocellular carcinoma.

  - Not uniform is size (some nodules are small and others are large.

  - The liver is shrunken due to the formation of fibrous tissue.

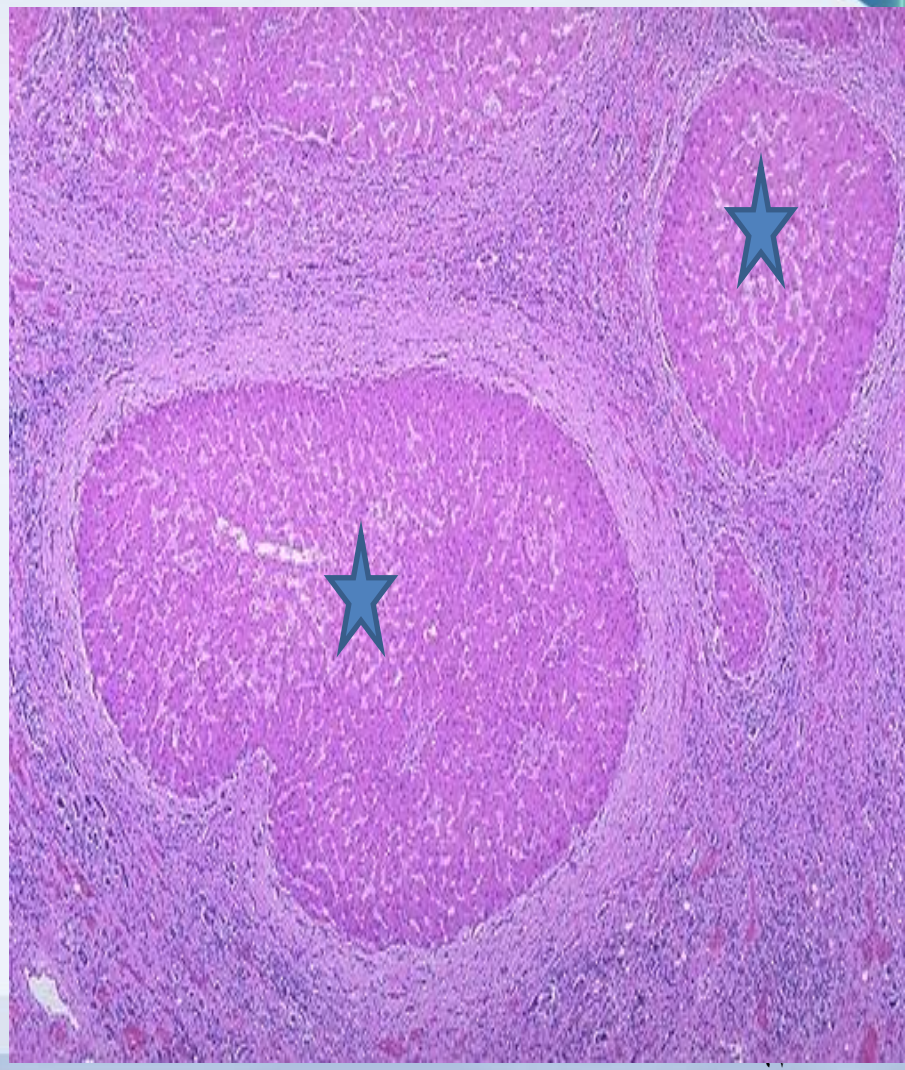


Histology of Cirrhotic Nodules

- ★ = nodules
  Notice that nodules may vary in size.

  - Each nodule is surrounded by fibrous bands.

- In terms of inflammation, cirrhosis can be either dormant of active.
  - Here, the fibrous bands show inflammatory infiltrate indicating activity, rather than dormancy.



Causes of cirrhosis

- Knowing the causes of cirrhosis is essential to understand how a patient will present, and what your history should include. Cirrhosis patients usually present as chronic alcoholics.
- Cirrhosis needs years of chronic liver damage to occur. Hence, cirrhosis is always caused by a chronic disease.
- The most common cause of cirrhosis is chronic alcoholism.

Think of chronic liver diseases that may be the cause …

Causes of cirrhosis

1- Fatty Liver Disease (Steatohepatitis)
   Alcoholic fatty liver disease (The most common cause of cirrhosis).
   & Non-alcoholic fatty liver disease

2- Chronic viral infection HBV & HCV
3- Biliary disease
4- Autoimmune hepatitis

   Metabolic Diseases:
5- Hemochromatosis (iron overload)
6- Wilson disease
7- α-1- antitrypsin deficiency

Causes of cirrhosis

Rare causes

Galactosemia / Tyrosinosis / Glycogen storage disease III &IV / Lipid storage disease / Hereditary fructose intolerance

Drug induced e.g methyldopa

Cryptogenic cirrhosis 10%

Most cases of cryptogenic cirrhosis are caused by non-alcoholic fatty liver disease.

Conclusion

- When a patient presents with cirrhosis, think first of alcoholism, viral hepatitis, autoimmune hepatitis.
  If all these were excluded, think of metabolic diseases, among which hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency are the most important.

- If a patient presents with cirrhosis of uknown cause (all of the above-mentioned causes were excluded), think of cryptogenic cirrhosis, which is mostly caused by non-alcoholic fatty liver disease.
- Presentation: impaired liver function (similar to the signs of liver failure).

Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

1-Hepatocellular death and regeneration

2- Progressive fibrosis (Deposition of ECM)

3- Vascular Reorganization

Pathogenesis

- **The development of cirrhosis requires that cell death occurs over long periods of time and be accompanied by fibrosis, that's why cirrhosis is always caused by chronic diseases.**
- **Fibrosis progresses to scar formation when the injury involves not only the parenchyma but also the supporting connective tissue.**

Pathogenesis (Changes in the ECM and Connective Tissue)

Normal Connective Tissue and ECM in the Liver:

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

- In the liver, there's no true basement membrane. Instead, there's a Delicate framework of type IV collagen & other proteins that lies in space of Disse.

Pathogenesis (Changes in the ECM and Connective Tissue)

- Changes in the ECM and connective tissue are essential to the development of cirrhosis.
-

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

The source of Collagen in Cirrhosis

- In the space of disse, there's a type of cells called "perisinusoidal stellate cells" or "Ito Cells". These cells function normally as storage cells for vitamin A.
- During fibrosis, there are many stimuli that convert this cell from a vitamin-A-storage cell into an active myofibroblast.

The source of Collagen in Cirrhosis

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 (these are produced by damaged hepatocytes or by stimulated kupffer cells and sinusoidal endothelial cells).

* Notice that stellate cells are transformed into myofibroblasts only when inflammatory mediators. This explains how stellate cells are converted into myofibroblasts in cirrhosis but in normal conditions.

The source of Collagen in Cirrhosis

- Activated stellate cells themselves produce growth factors, cytokines, and chemokines that cause their further proliferation and collagen synthesis.
- TGF-β is the main fibrogenic agent for stellate cells.
- As a conclusion, stellate cells are activated and transformed into myofibroblasts by inflammatory mediators (ROS, cytokines) and once activated they produce more growth factors, cytokines and chemokines, causing further proliferation and collagen synthesis. Being self-activated in this way explains the progressive feature of fibrosis.

Pathogenesis (Vascular Reorganization).

- The main vascular change that contribute to defects in liver function is the **loss of sinusoidal endothelial cell fenestrations**. When these fenestrations are lost, vascular shunts will develop (portal vein-hepatic vein and hepatic artery-portal vein vascular shunts).
- The normal function of these fenestration is to allow free exchange of solutes between the plasma and hepatocytes.

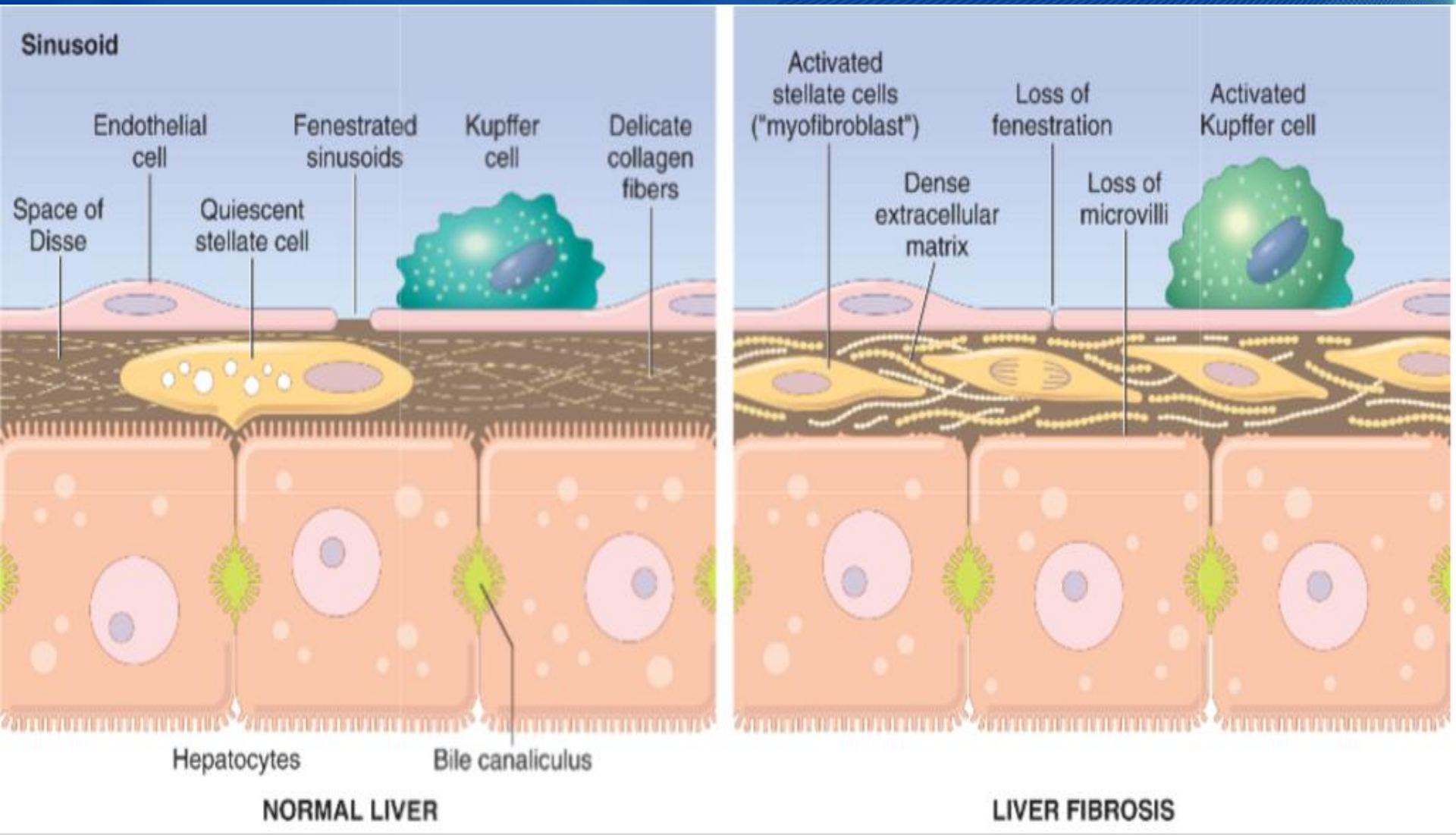
Pathogenesis (Vascular Reorganization).

- Vascular changes:
  1- Loss of fenestrations (No free exchange of solutes between the plasma and hepatocytes).
  2- Collagen deposition in the basement membranes of sinusoids.
- Due to these changes, sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes are converted into higher pressure fast-flowing vascular channels without such solute exchange.

Pathogenesis (Vascular Reorganization).

- Due to the inability to exchange solutes between the liver and the plasma, the movement of proteins (e.g., albumin, clotting factors, lipoproteins between hepatocytes and the plasma is markedly impaired. This explains hypoalbuminemia, bleeding tendency and many other symptoms.

- These functional changes are aggravated by the loss of microvilli from the hepatocyte surface which diminishes the transport capacity of the cell.



- See the next slide.

Comparison Between Normal and Fibrotic Liver

	Normal	Liver fibrois
Space of Disse	Delicate network of collagen	Dense ECM
Stellate Cells	Quiescent (not activated)	Activated stellate cells (myofibroblasts)
Sinusoids	Have Fenestrations Thin wall Allow free exchange of solutes between the plasma and hepatocytes	Loss of fenestrations Thick wall No exchange of solutes → hypoalbuminemia + no clotting factors (coagulopathy)
Kupffer Cells	Not activated	Activated (they produce cytokines that contribute to activation of stellate cells).
Hepatocytes	Have microvilli	Loss of microvilli

-Clinical features of cirrhosis :

-Silent

-Anorexia, wt loss, weakness

-Complications :

1-Progressive hepatic failure

2-Portal hypertension

3-Hepatocellular carcinoma

Portal Hypertension

Portal hypertension

- Increased 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
- This may be caused by prehepatic, intrahepatic or posthepatic causes.

Causes of portal hypertension

I.Prehepatic

1-Portal vein thrombosis
2-Massive splenomegaly

II. Post hepatic

1-Severe right-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 such as sarcoidosis, TB
5-Disease of portal microcirculation such 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. However, many liters may accumulate, causing massive abdominal distension.

-**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 are present

5- The presence of neutrophils is a sign of infection

6- The presence of RBCs is a sign of disseminated intrabdominal cancer

-Pathogenesis → the pathogenesis is complex and it involves one or more of the following mechanisms:

1- Sinusoidal hypertension and hypoalbuminemia → movement of intravascular fluid into the extravascular space of disse.

3-Leakage of fluid from the hepatic interstitium into the peritoneal cavity. Normal thoracic duct lymph flow is 800-1000 ml/d. With cirrhosis it may approach 20L /day, exceeding thoracic duct capacity.

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

Portosystemic shunt

- Because of increased portal venous pressure, shunts develop wherever the systemic & portal circulation share capillary beds (i.e. at sites of connection between the systemic and portal circulation)

- Sites where systemic and portal circulation share capillary beds:

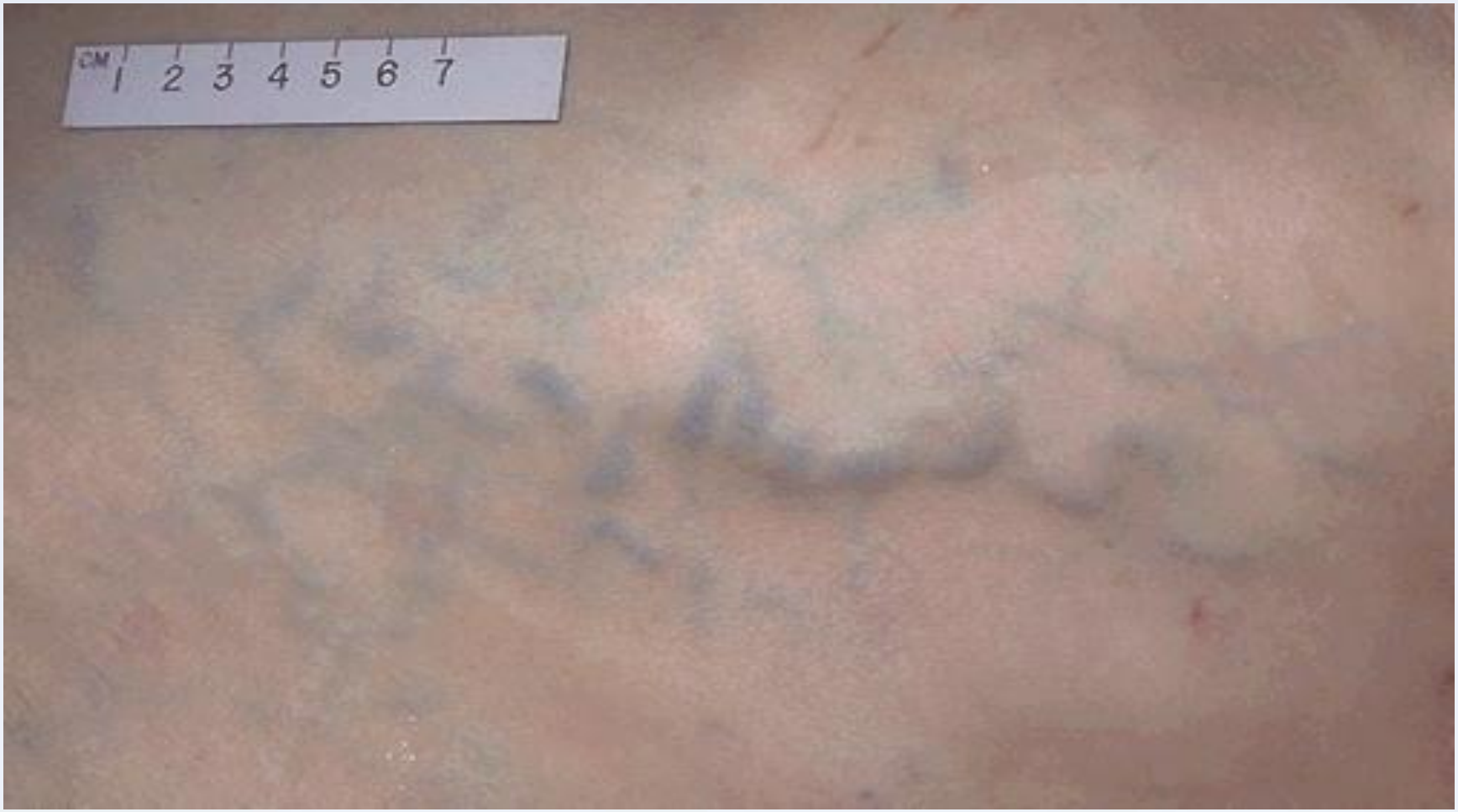
1-Around & within the rectum (Hemorrhoids)

2-Gastroesophageal junction (Esophageal Varicies)

3-Retroperitoneum

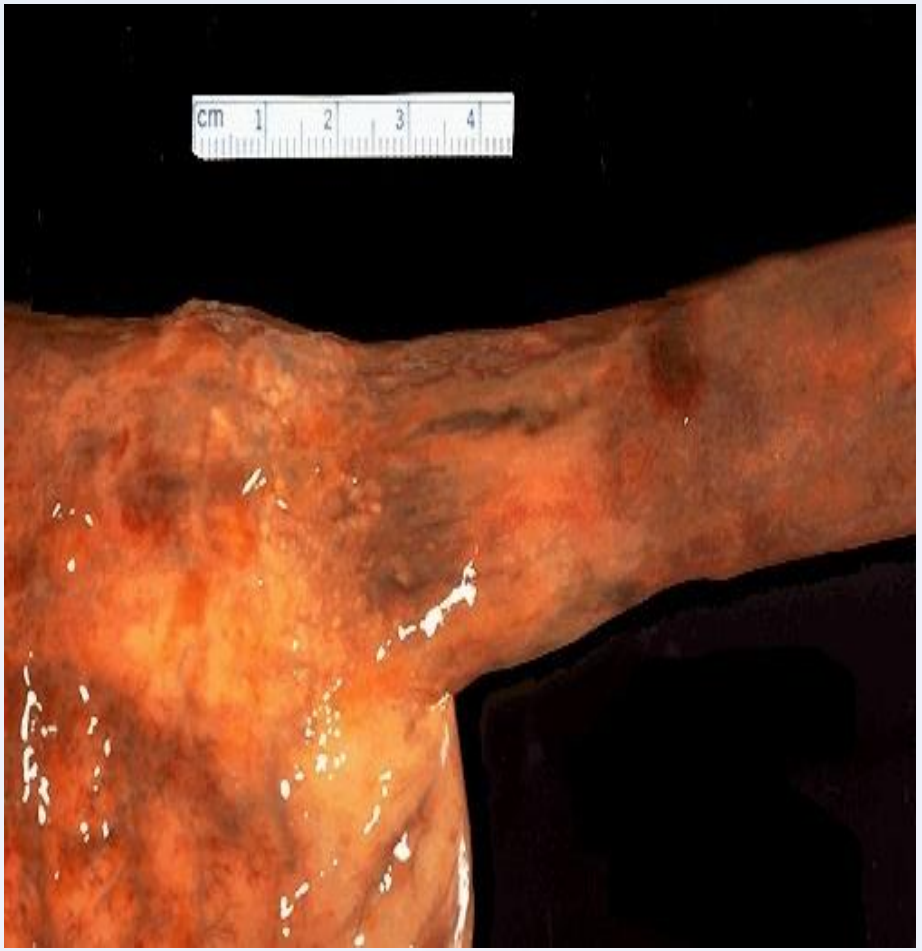
4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

Caput medusae-abdominal skin



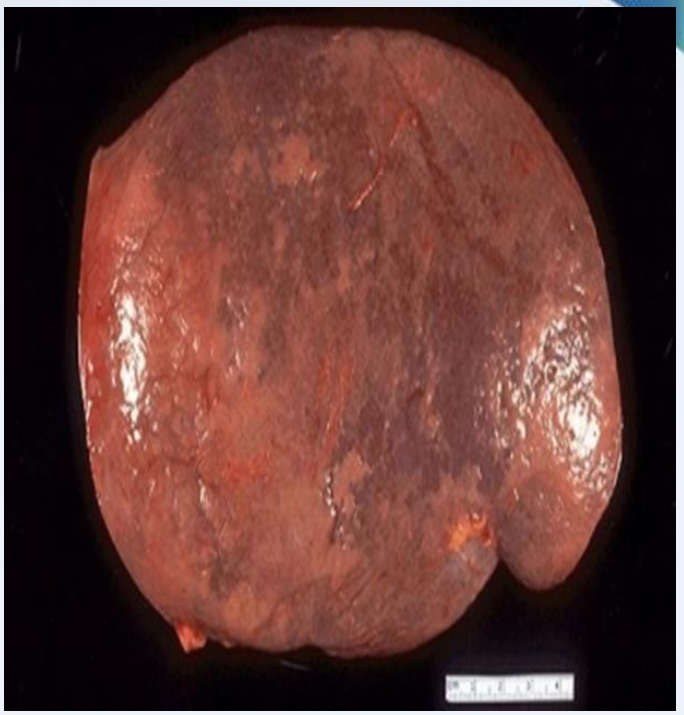
Esophageal varicies

- **Esophageal varicies appear in 65% of patients with advanced cirrhosis & cause death in 50% of them due to upper GI bleeding**
- **The main cause of death in cirrhosis**



Splenomegaly

- Enlargement of the spleen that results from long-standing congestion.
- Usually 500-1000 gms (Normal spleen < 300gms)
- Not necessarily correlated with other features of portal hypertension
- May result in hypersplenism (overactive spleen). This may secondarily cause hematological abnormalities.



Hepatic encephalopthy

-It is a complication of acute or chronic hepatic failure.

- It develops rapidly in the acute but insidiously in the chronic.

- Disturbance in brain function ranging from subtle behavioral changes to marked confusion & stupor to deep coma & death

- The changes may progress over hours or days in case of acute liver failure or gradually in case of chronic liver failure.

- **Neurological signs:**

Rigidity

Hyperreflexia

Nonspecific 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 :-

The liver is responsible for getting rid of toxic metabolites. However, in the case of liver failure, the liver fails to do so. Therefore, the brain gets exposed to toxic metabolites and that's why hepatic encephalopathy results in neurological abnormalities

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 amino acid metabolism (this affects the synthesis of neurotransmitters)

Hepatorenal Syndrome

- Appears only 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 toxic 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.**

- The exact cause is unknown
- Kidney function promptly improves if hepatic failure is reversed, which proves that hepatic failure is central to the development of the syndrome
- Pathogenesis: 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 blood urea nitrogen and creatinine values (indicators of renal failure)**.
- The renal failure may increase the risk of death in the patient with acute fulminant or advanced chronic hepatic disease.

Drug-Induced Liver Damage

Drug – Induced liver disease

- Drug reactions can be:

1-Predictable (intrinsic): drug reactions that may occur in anyone who accumulates a sufficient dose **(dose-dependent).**

2-Unpredictable (idiosyncratic): reactions that 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. So **how can we distinguish them?**

  By **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:
Ex: acetaminophen, CCl_4 , and 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

Table 18-5 Patterns of Drug- and Toxin-Induced Hepatic Injury

Pattern of Injury	Morphologic Findings	Examples of Associated Agents
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids, antibiotics, HAART
Cholestatic hepatitis	Cholestasis with lobular necroinflammatory activity; may show bile duct destruction	Antibiotics, phenothiazines, statins
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldopa, phenytoin
	Massive necrosis	Acetaminophen, halothane
	Chronic hepatitis	Isoniazid
Fatty liver disease	Large and small droplet fat	Ethanol, corticosteroids, methotrexate, total parenteral nutrition
	"Microvesicular steatosis" (diffuse small droplet fat)	Valproate, tetracycline, aspirin (Reye syndrome), HAART
	Steatohepatitis with Mallory-Denk bodies	Ethanol, amiodarone
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Alcohol, methotrexate, enalapril, vitamin A and other retinoids
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, amiodarone, isoniazid
	Fibrin ring granulomas	Allopurinol
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusive disease): obliteration of central veins	High-dose chemotherapy, bush teas
	Budd-Chiari syndrome	Oral contraceptives
	Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	Anabolic steroids, tamoxifen
Neoplasms	Hepatocellular adenoma	Oral contraceptives, anabolic steroids
	Hepatocellular carcinoma	Alcohol, thorotrast
	Cholangiocarcinoma	Thorotrast
	Angiosarcoma	Thorotrast, vinyl chloride

HAART, highly active anti-retroviral therapy. Adapted from Washington K: Metabolic and toxic conditions of the liver. In Iacobuzio-Donahue CA, Montgomery EA (eds): Gastrointestinal and Liver Pathology. Philadelphia, Churchill Livingstone; 2005.

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

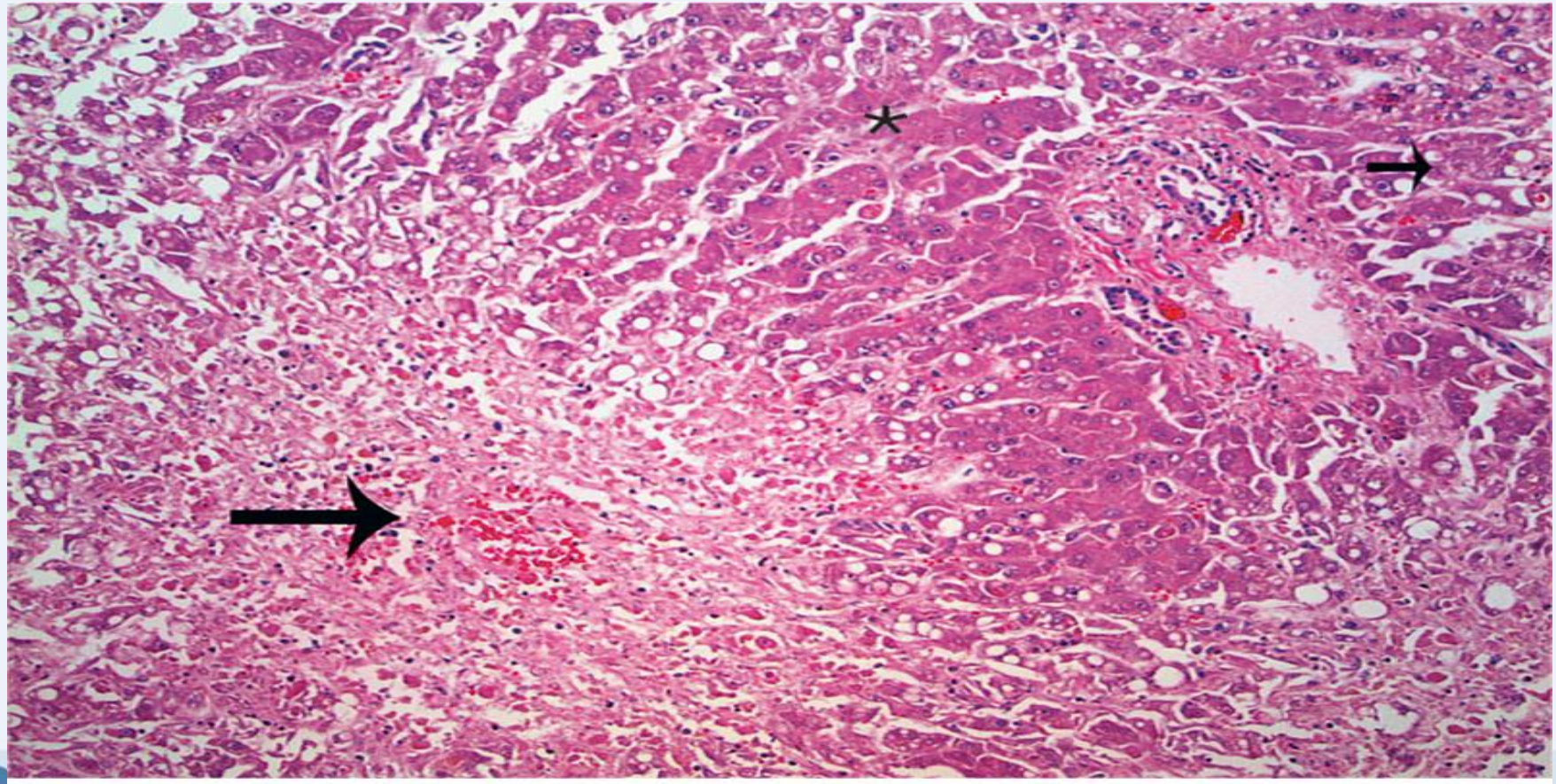
Submassive necrosis

Patchy necrosis

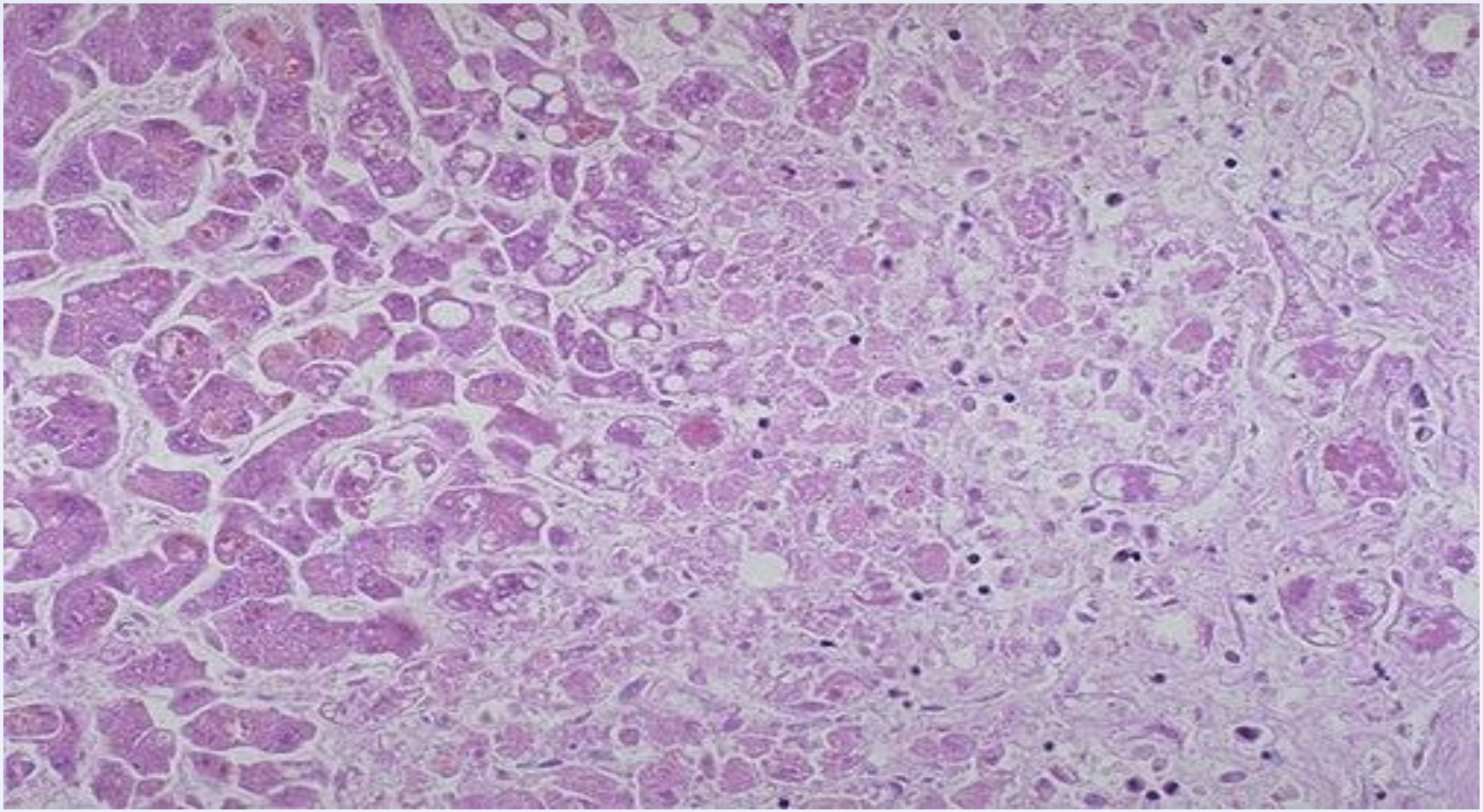
- Patient survival for more than a week permits regeneration of surviving hepatocytes.
- Regeneration is initially in the form of strings of ductular structures which mature into hepatocytes.
- If the parenchymal framework is preserved liver architecture is restored.
- With massive destruction of lobules 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



Autoimmune Hepatitis

- Chronic hepatitis with immunological abnormalities
- Histologic features are similar to chronic viral hepatitis
- It may run in an indolent or severe course
- Responds dramatically to immunosuppressive therapy

Features:

1- Female predominance (70%). It's autoimmune.

2- Negative serelogy for viral antigens (because it's autoimmune not a viral infection).

Remember: Histologic features of autoimmune and viral hepatitis are similar. So, serology is the key to distinguish.

3- Elevated serum IgG (> 2.5 g/dl)

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

5-The presence of other autoimmune diseases as rheumatoid arthritis, thyroiditis, Sjogern syndrome, ulcerative colitis in 60% of the cases

The type of autoantibodies

1- Anti-smooth muscle Antibodies

anti-actin

anti-troponin

anti-tropomyosin

2- liver/kidney microsomal Antibodies

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

Nonalcoholic Fatty Liver Disease

- Types:

1.Steatosis (Fatty liver)

2.Steatohepatitis

hepatocyte destruction

parenchymal inflammation

progressive pericellular fibrosis

- Alcohol is a well-known cause of fatty liver disease. However, some patients present with fatty liver without a history of excessive alcohol use. This is known as NAFLD.

Predisposing factors :

1-Type 2 DM

2-Obesity : body mass index

> 30 kg /m2 in caucasians

> 25 kg /m2 in Asians

3-Dyslipidemia (↑ TG, ↑LDL, ↓HDL)

→ NAFLD is associated with insulin resistance, obesity, diabetes mellitus, hypertension and dyslipidemia. This is known as the **Metabolic Syndrome.**

Mechanism of fatty accumulation

1. Impaired oxidation of fatty acids
2. Increased synthesis & uptake of FFA
3. Decreased hepatic secretion of VLDL

. ↑TNF , IL6 , chemokine →liver inflammation & damage

Clinically

- NAFLD is the most common cause of incidental increases in transaminases.
- Most patients are asymptomatic
- Non-specific symptoms

  Fatigue, malaise, right upper quadrant discomfort
- Severe symptoms
- Liver biopsy is required for diagnosis.
- NAFLD may be a significant contributor to cryptogenic cirrhosis

Inherited Metabolic Diseases

Hemochromatosis

- Excessive accumalation of body iron (liver, pancreas and heart)
- 1ry or 2ry (genetic or acquired)
- Genetic hemochromatosis (4 variants)
- The most common form is **autosomal recessive** disease of adult onset caused by mutations 3in the HFE gene on chromosome 6.

Causes of acquired hemosidrosis :

1- **Multiple transfusions**

2- Ineffective erythropoiesis (β-thalassemia)

3-increased iron intake (Bantu sidrosis)

4-chronic liver disease

Hemochromatosis

Clinical Features:

1-Micronodular cirrhosis (all patients)

2-D.M (75 – 80%)

3-skin pigmentation (75-80%)

4- cardiomegaly (arrhythmias, cardiomyopathy)

5- joints disease

6- testicular atrophy

- **Symptoms appear after 5^{th} – 6^{th} decades (not before age 40).**

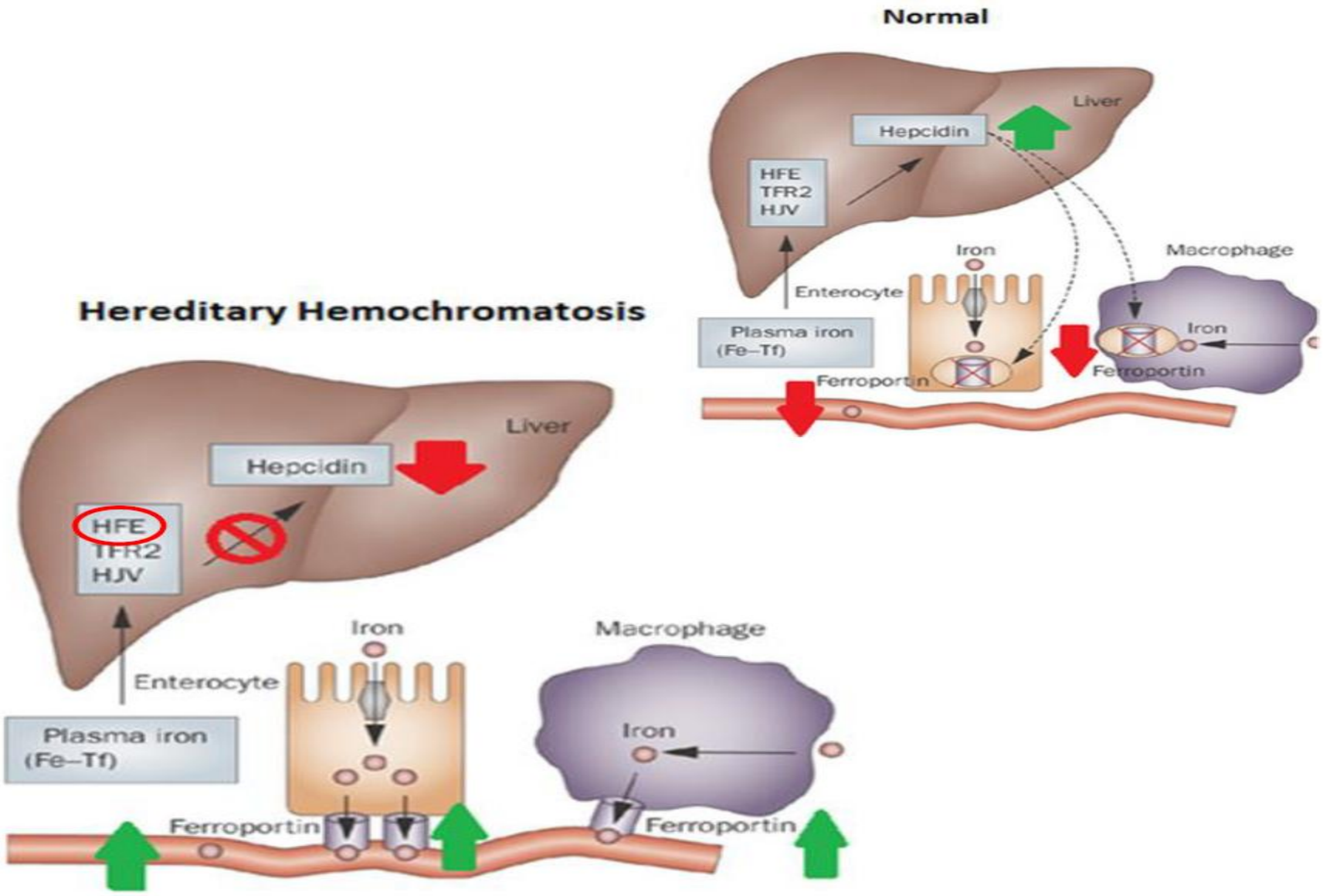
Very important

- **Symptoms appear after 5^{th} – 6^{th} decades (not before age 40).**
- M:F ratio 5 - 7: 1
- **earlier clinical presentation in males partly because physiologic iron loss (menstruation, pregnancy) retards iron accumulation in women.**

Pathogenesis

- Primary defect in intestinal absorption of dietary iron.
- Normally, total body iron 2-6 gm in adults (0.5gm in the liver, mostly in hepatocytes)

- In disease: > 50gm of iron accumulate in the body. One third of this is in the liver.
-There is a defect in regulation of intestinal absorption of dietary iron leading to **net iron accumulation of 0.5 – 1 gm/yr** (that's why it needs 40-60 years to develop the disease).


Normal
Liver
Hepcidin
HFE
TFR2
HJV
Iron
Macrophage
Enterocyte
Plasma iron
(Fe–Tf)
Iron
Ferroportin
Ferroportin
Hereditary Hemochromatosis
Liver
Hepcidin
HFE
TFR2
HJV
Iron
Macrophage
Enterocyte
Plasma iron
(Fe–Tf)
Iron
Ferroportin
Ferroportin

- **Pathogenesis of Genetic Hemochromatosis:**
- HFE gene (High Fe Gene) regulates the level of hepcidin hormone synthesized in liver.
- Hepicidin normally inhibits iron absorption.

→ When hepcidin levels are reduced there is increased iron absorption.

- HFE gene deletion causes→ ↓Hepcidin levels→ iron overload.

-Two mutations can occur in HFE gene:

1-Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282 (C282Y)

2-aspartate substitution for histidine at AA 63 (H63D)

10% of pts. have other gene mutations

- Carrier rate for C282Y is 1/70
- Homozygosity is 1/200
- 80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation
- 10% of patients are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation

- **Excessive Fe deposition → toxicity of the tissues :**
    1. **Lipid peroxidation**
    2. **Stimulation of collagen formation**
    3. **DNA damage**

Morphological changes

- **No inflammation**

1- Deposition of hemosiderin in diffferent organs

Liver, Pancreas , Myocardium, Pituitary ,Adrenal, Thyroid & parathyroid, Joints and Skin

2-Cirrhosis

3-Pancreatic fibrosis

4-Synovitis

5-Polyarthritis(pseudogout)

6-Pigmentation of liver

7-Fibrosis of pancreas & myocardium

8-Atrophy of testes

Causes of Death

- **Death may result from :**

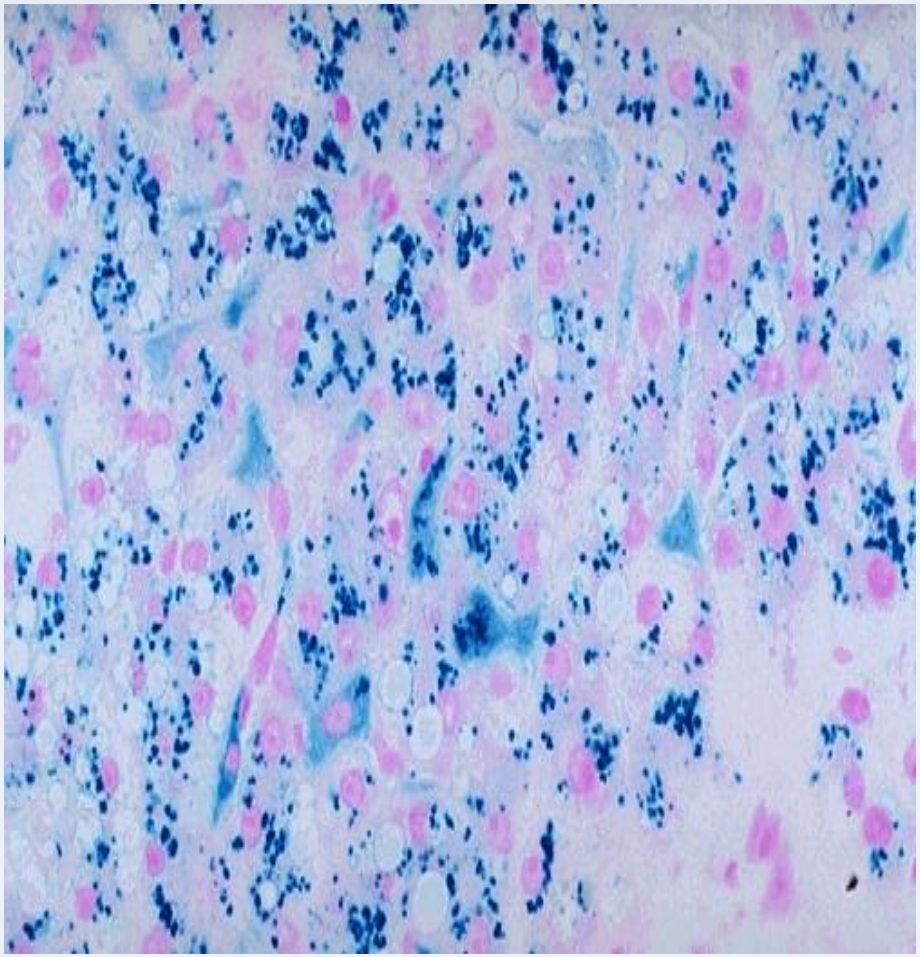
1- Cirrhosis

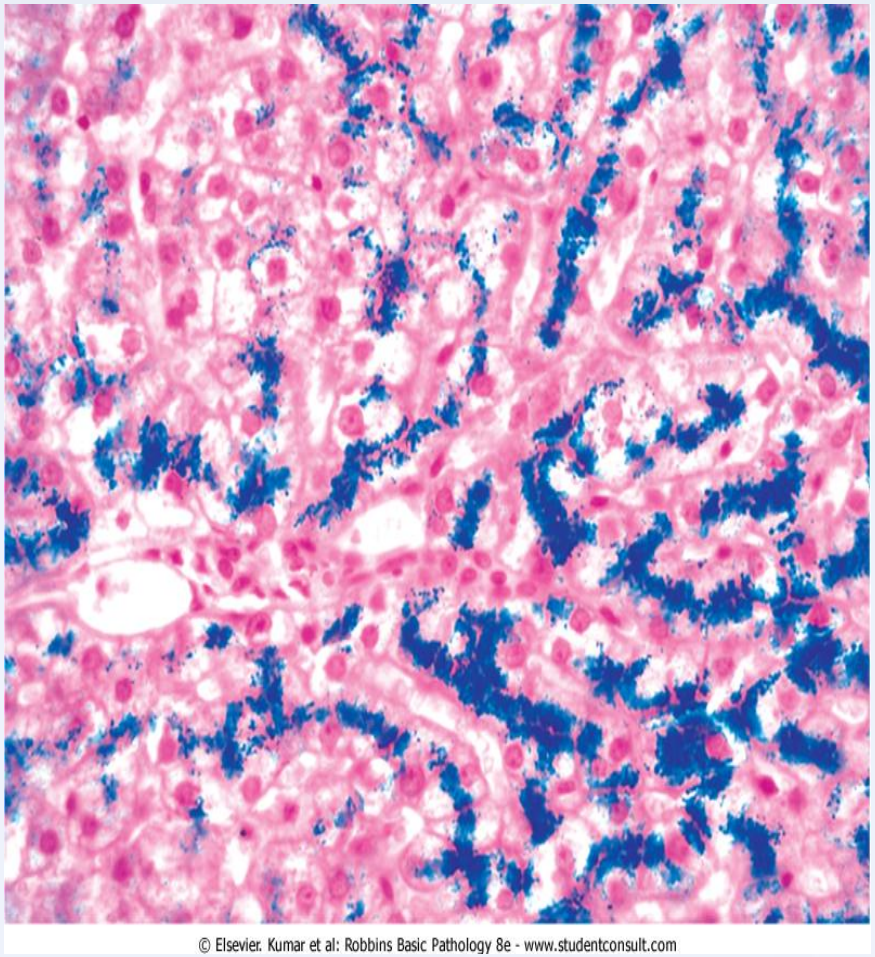
2- **Hepatocellular carcinoma**

- The risk of hepatocellular carcinoma development in patients with hemochromatosis is 200-fold higher than in normal populations

3- **Cardiac disease**

Hemosiderosis





Wilson Disease

- Autosomal Recessive disorder of Cu metabolism
- Mutations in ATP7B gene on chromosome 13 which encodes an ATPase metal ion transporter in Golgi region.
- > 80 mutations
- Gene freq. 1:200
- Incidence is 1:30000

Normal Copper Metabolism

Main source of Cu is from diet

↓

Absorption of ingested Cu (2-5 mg/d)

↓

Complex with albumin

↓

Hepatocellular uptake

↓

Incorporation with α-2-globulin to form

Ceruloplasmin

↓

Sec. into plasma

(90 – 95% of plasma Cu)

↓

Hepatic uptake of ceruloplasmin

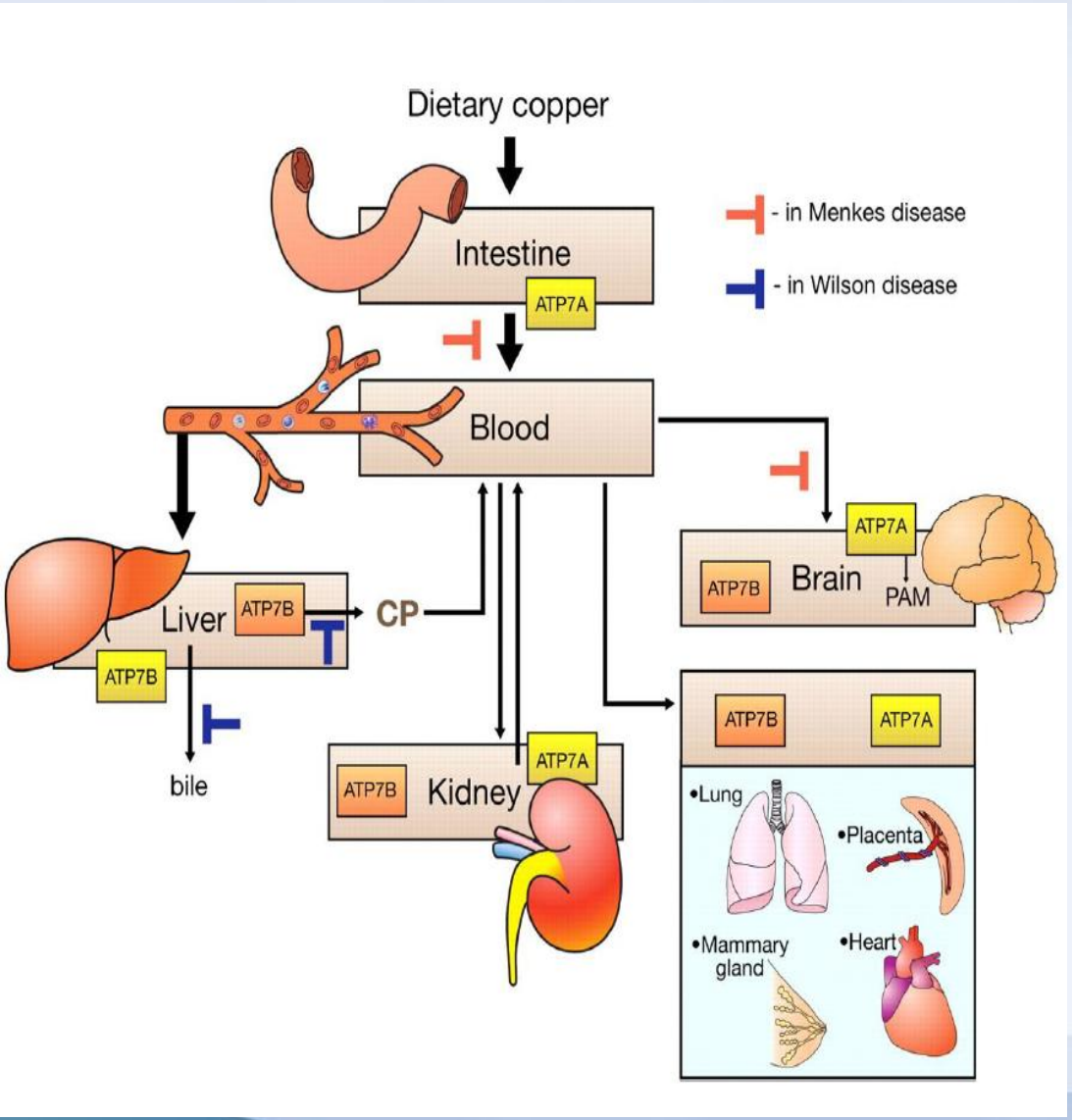
↓

Lysosomal degradation

↓

Secretion of free Cu into bile

Pathogenesis



- Wilson Disease results in excessive accumulation of copper in the liver.
- In Wilson disease, absorbed Cu fails to enter the circulation in the form of ceruloplasmin & the biliary excertion of Cu is reduced
- Defective function of ATP-7B → failure of Cu excretion into the bile & inhibits secretion of ceruloplasmin into the plasma → Cu. accumulation in liver

- ↑Cu. Accumulation in the liver reults in:-

1- Production of free radicals

2- Binding to sulfhydryl groups of cellular proteins

3- Displacement of other metals in hepatic metalloenzymes

- By the age of 5 years Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands

-Urinary excretion Of copper.

Morphology

Liver

1-Fatty change

2-Acute hepatitis

3-chronic hepatitis

4-cirrhosis

5-massive hepatic necrosis

(rhodanine stain or orcein stain)

Brain:

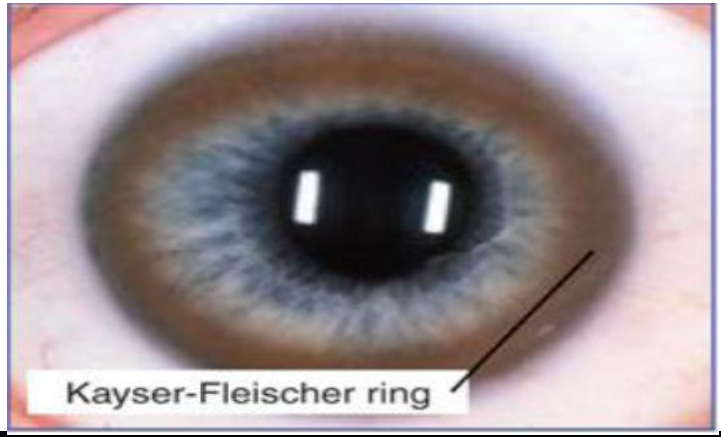
Toxic injury to basal ganglia especially the putamen causing atrophy & cavitation

Eye:

Kayser-Fleischer rings

green–brown deposits of Cu. in descement membrane in the limbus of the cornea

(hepatolenticular degeneration)



- **Clinical Features:**

- Presentation > 6 years of age.
- Most common presentation is acute on top of chronic hepatitis.
- Neuropsychiatric presentation can occur:
  - behavioral changes
  - Frank psychosis
  - Parkinson disease- like syndrome

- **Diagnosis**

1- ↓ in serum ceruloplasmin level

2- ↑ in urinary exc. Of Cu

3- ↑ hepatic content of copper
> 250 mg/gm dry weight

α-1-Antitrypsin Defeciency

- Autosomal **Recessive** disorder
- Frequency: 1:7000 in Northern American white population
- α-1-antiryrpsin is a **protease inhibtor.** It inhibits proteases such as elastase, cathepsinG , proteinase 3 which are released from neutrophils at the site of inflammation.
- When AAT is deficient

→ Proteases will not be inhibited → **Pulmonary Emphysema**
→ Mutant AAT will be retained within the liver → **liver disease**

α-1-Antitrypsin Defeciency

- AAT is a **glycoprotein** that's synthesized in hepatocytes. Its gene is located on chromosome 14.
- This gene is very polymorphic. More than 75 polymorphisms have been identified.
- In most polymorphisms, the individual has normal levels of AAT.
- However, homozygotes of the **Z allele** (PiZZ genotype) have reduced level of AAT (10% of normal). In this case, the individual is at a greater risk to develop clinical disease.

Pathogenesis

-The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes → This retention of the protein is the main cause of liver disease seen in AAT deficiency.

- Although all individuals with PiZZ genotype accumulate **α**-1-AT-Z protein, only 10% of them develop clinical liver disease .

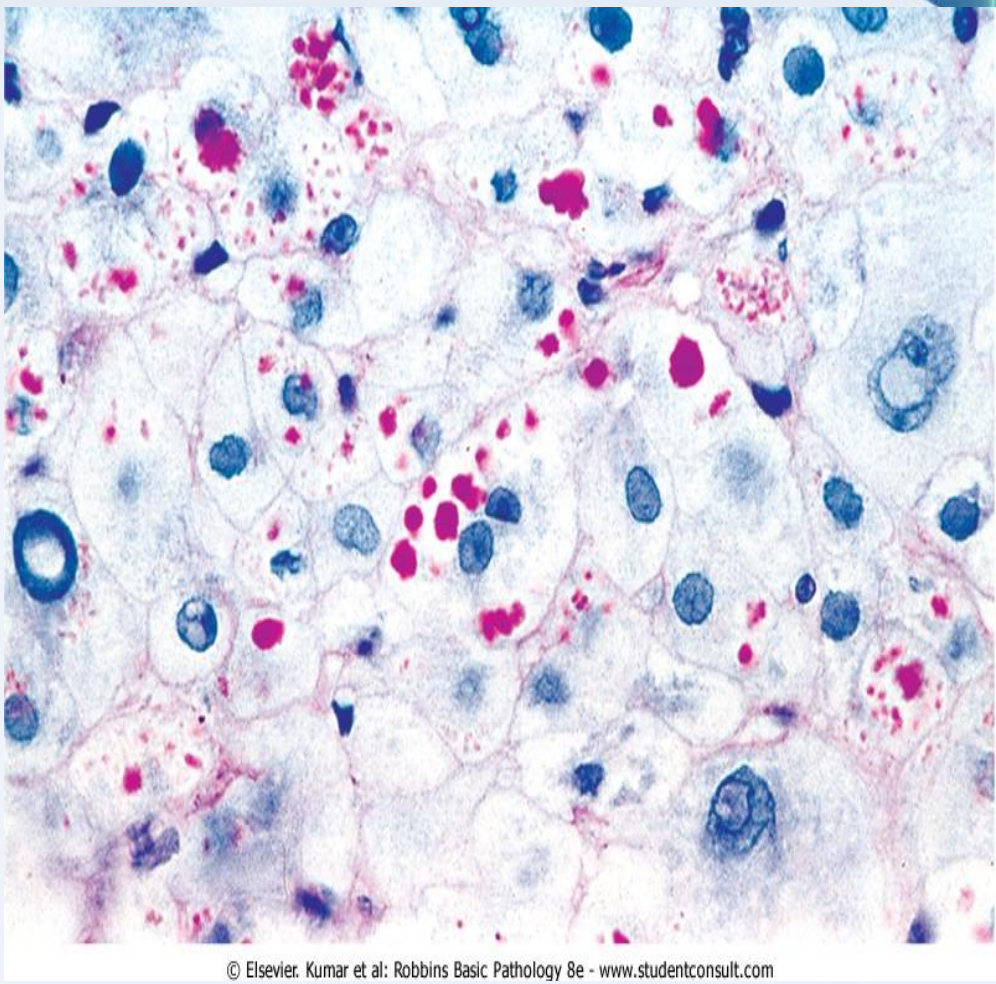
- This depends on the genetic tendency to degrade accumulated AAT within hepatocytes (i.e. individuals who are able to degrade AAT will not accumulate AAT a lot within hepatocytes and thus will not develop clinical liver disease, and vice versa).

- Accumulation of AAT within hepatocytes triggers the unfolded protein response, which activates apoptosis. Therefore, accumulated AAT seems not to be directly toxic to the liver.

- 8-10% of patients develop significant liver damage.

Morphology

- Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E sections.
- The inclusions are PAS +ve (remember: AAT is a glycoprotein) & diastase resistant.
- Morphology of liver disease associated with AAT deficiency:
  - Newborns → Cholestasis
  - Children → Cirrhosis
  - Later → chronic hepatitis



Clinical features

- Neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease .
- Attacks of hepatitis in adolescence
- Chronic hepatitis & cirrhosis
- Hepatocellular Carcinoma occurs in 2- 3 % of PiZZ adults

Reye's Syndrome

- Fatty change in liver & encephalopathy.
- Occurs before 4 years of age.
- 3– 5 days after viral illness.
- Abnormal liver function test.
- Vomiting lethargy.
- 25% may go into coma.
- Death occurs from progressive neurologic deterioration or liver failure.
- Survivors of more serious illness may be left with permanent neurologic impairments.

Pathogenesis

- The pathogenesis of Reye syndrome involves a **generalized loss of mitochondrial function**.
- Reye syndrome is now recognized as the prototype of a wide variety of conditions known as *"**mitochondrial hepatopathies**."*
- Reye syndrome has been associated with aspirin administration during viral illnesses, but there is no evidence that salicylates play a causal role in this disorder.

Morphology

- The key pathologic finding in the **liver** is **microvesicular steatosis**.
- Electron microscopy of hepatocellular mitochondria reveals pleomorphic enlargement and electron lucency of the matrices with disruption of cristae and loss of dense bodies.
- In the **brain,** cerebral edema is usually present.

Budd – Chiari Syndrome

Hepatic Vein Thrombosis

- Thrombotic occlusion results from the thrombosis of two or more major hepatic veins.

- Characteristics:

Hepatomegaly

Weight gain

Ascites

Abdominal Pain

Causes:

1- Polycythemia Vera

2- Pregnancy

3- Postpartum

4- Oral contraceptive

5- Paroxysmal Nocturnal Hemoglobinuria

7- Mechanical obstruction

8- Tumors as HCC

9- Idiopathic in 30% of the cases

-

- **Morphology**:

- Swollen liver with tense capsule

- Centrilobular congestion & necrosis

- Fibrosis

- Thrombi

Morphology

- Swollen liver with tense capsule
- Centrilobular congestion & necrosis
- Fibrosis
- Thrombi

Primary sclerosing cholangitis

- Inflammation, obliterative fibrosis & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts.
- In PSC, UC coexists in 70% of patients.
- In patients of UC, 4% develop PSC.
- 3-5th decades
- M: F 2:1

- Asymptomatic pts.
- Persistent increase in serum alkaline phosphatase
- Fatigue, pruritis, jaundice, weight loss, ascites, bleeding, encephalopathy.

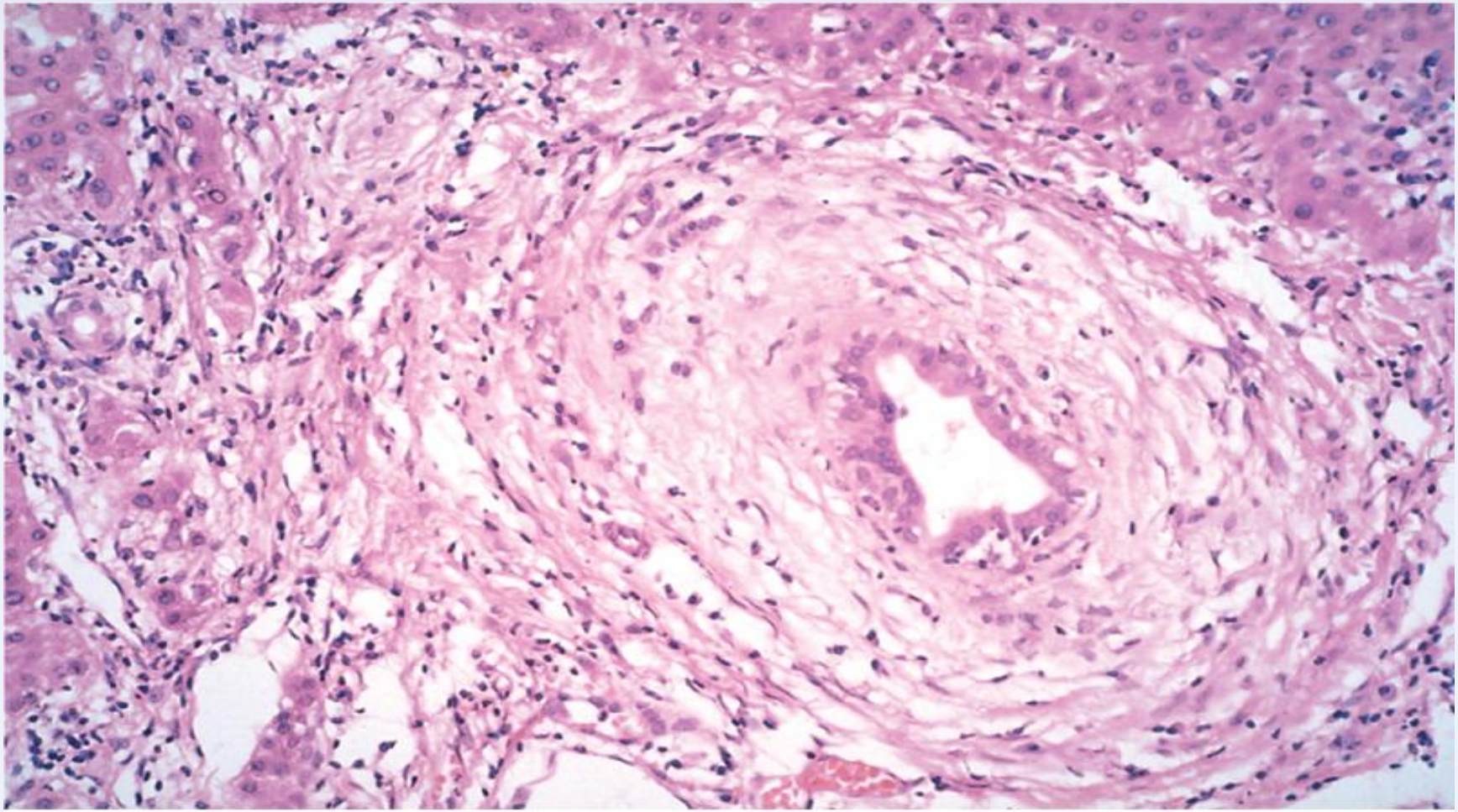
- antimitochondrial Abs < 10% of cases.
- **Antinuclear cytoplasmic Abs (ANCA)** in 80% of cases.

Morphology

-Concentric periductal onion-skin fibrosis & lymphocytic infilrate
-Atrophy & obliteration of bile ducts
-Dilation of bile ducts inbetween areas of stricture
-Cholestasis & fibrosis
-Cirrhosis, cholangiocarcinoma (10 – 15%)

Primary sclerosing cholangitis

A bile duct undergoing degeneration is entrapped in a dense, "onion-skin" concentric scar



Pathogenesis

-Exposure to gut derived toxins

-Immune attack

-Ischemia of biliary tree

biliary cirrhosis

- **1-primary**
- **2-Secondary**
- -Prolonged obst. To extrahepatic biliary tree
- **Causes:**
- 1-cholelithiasis
- 2-biliary atresia
- 3-malignancies
- 4-stricutres

Primary biliary Cirrhosis

- **Chronic** progressive & often fatal **cholestatic** liver disease, characterized by destruction of intrahepatic bile ducts, portal inflammation and scarring, and the development of cirrhosis and liver failure over years to decades.
- The main feature of the disease:
  Non-suppurative granulomatous destruction of small and medium-sized intrahepatic bile ducts.

Clinical Course of PB

Epidemiology:

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

F>M

- Insidious onset

- Pruritis, jaundice

- Cirrhosis over 2 or more decades

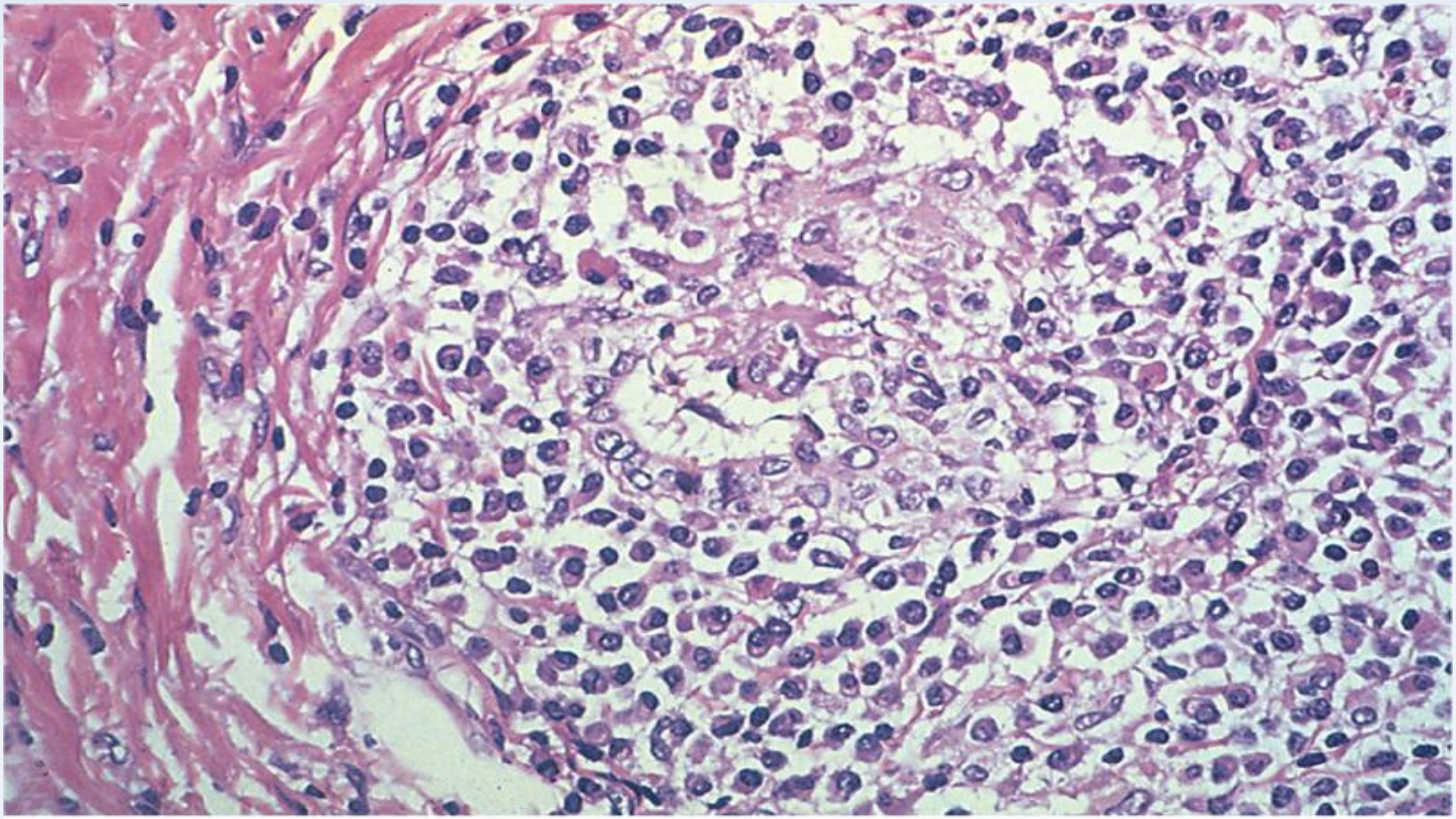
- ↑Alkaline phosphatase & cholesterol
- Hyperbilirubinemia = hepatic decompansation
- Antimitochondrial Abs > 90%

Antimitochondrial pyruvate dehydrogenase

- Associated conditions: Sjogren syndrome, Scleroderma thyroiditis, RA, Raynauds phenomenon, MGN, celiac disease.

- **Morphology**
- **interlobular bile ducts are absent or severely destructed (florid duct lesion)**
- **intra epithelial inflammation**
- **Granulomatous inflammation**
- **Bile ductular proliferation**
- **Cholestesis**
- **Necrosis of parenchyma**
- **Cirrhosis**

Primary biliary cirrhosis. A portal tract is markedly expanded by an infiltrate of lymphocytes and plasma cells. Note the granulomatous reaction to a bile duct undergoing destruction (florid duct lesion)



Sinusoidal Obstruction Syndrome
(Veno-occlusive disease)

- Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids.
- Obstruction syndrome is caused by toxic injury to sinusoidal endothelium.
- Damaged endothelial cells slough off and create emboli that block blood flow.

- **Endothelial damage is accompanied by passage of red blood cell into the space of Disse, proliferation of stellate cells, and fibrosis of terminal branches of the hepatic vein**
- **This occurs in the first 20-30 days after bone marrow transplantation**

. Which is caused by:

1-Drugs as cyclophosphamide

2-Total body radiation

.Incidence

-20% in recepients of allogeneic marrow transplant

-**Clinical presentation**

Mild – severe

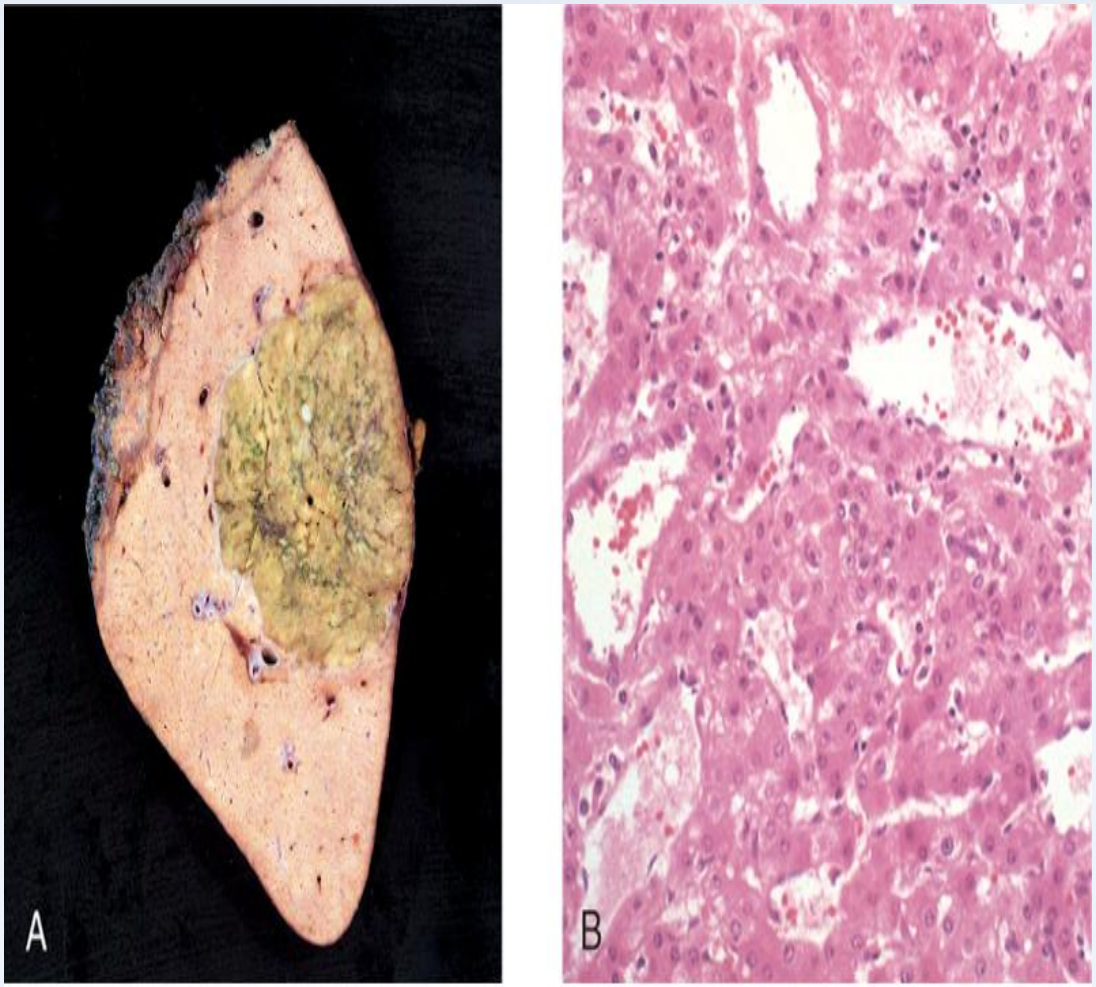
Death if does not resolve in 3 months

Liver tumors

- Most common benign tumor is cavernous hemagioma
- Usually < 2cm
- Subcapsular

Liver cell adenoma

- Young female
- Childbearing age who have used oral contraceptive steroids.
- It may regress on discontinuance of hormone use.



- Liver cell adenomas are significant for three reasons:
- (1) when they present as an intrahepatic mass, they may be mistaken for the more ominous hepatocellular carcinoma
- (2) subcapsular adenomas are at risk for rupture, particularly during pregnancy (under estrogenic stimulation), causing life-threatening intra-abdominal hemorrhage
- (3) although adenomas are not considered precursors of hepatocellular carcinoma, adenomas carrying β-catenin mutations carry a risk of developing into cancers.

Liver Nodules

Focal noudular hyperplasia

- Well demarcated hyperplastic hepatocytes with central scar.
- The liver is normal: not neoplastic + no cirrhosis
- Local vascular injury.
- Females of reproductive age.
- No risk of malignancy.
- 20% of cases have cavernous hemagnioma.

Macroregenerative Nodules

- Cirrhotic liver
- Larger than cirrhotic nodules
- No atypical features
- Reticulin is intact
- No malignant potential

Dysplastic nodules

- Larger than 1 mm
- Cirrhotic liver
- Atypical features, pleomorphism and crowding
- High proliferative activity
- High or low dysplasia
- Precancerous (monoclonal, +ve gene mutations
- Types:

1. Small – cell dysplastic nodules
2. Large – cell dysplastic nodules

Hepatocellular carcinoma

- 5.4% of all cancers
- Incidence:
  <5/100000 population in N&S America
  N& central Europe
  Australia
  15/100000 population in Mediterranean
  36/100000 population in Korea, Taiwan mozambique, china
- Blacks > white
- M:F ratio
  3:1 in low incidence areas. >60yr
  8:1 in high incidence areas. 20-40yr

Predisposing Factors

1. **Hepatitis carrier state**
   vertical transmission increases the risk 200X
   cirrhosis may be absent
   young age group (20-40yr)
2. **> 85% of cases of HCC occur in countries with high rates of chronic HBV infection**

3-Cirrhosis

In western countries cirrhosis is present in 85-90% of cases

>60yr

HCV & alcoholism

4. Aflatoxins

5. Hereditary tyrosinemia (in 40% of cases)

6. Hereditary hemochromatosis

Pathogenesis

1. Repeated cycles of cell death & regeneration
   HBC, HCV, gene mutations, genomic instability
2. Viral integration
   HBV DNA intergration which leads to clonal expansion of hepatocytes
3. HBV DNA intergration which leads to genomic instability not limited to integration site.
4. HBV
   X-protein which leads to transactivation of viral & cellular promoters,activation of oncogenes and Inhibition of apoptosis

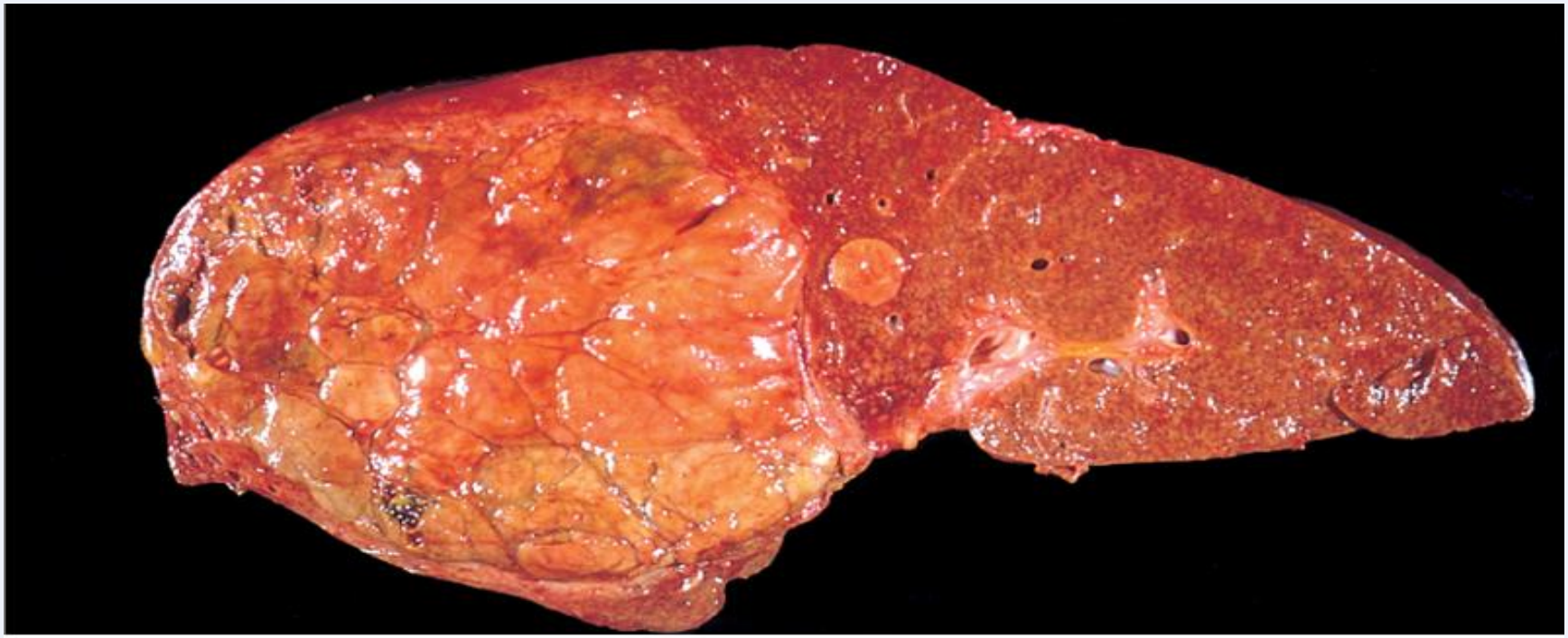
5. Aflatoxins (fungus Aspirgillus flavus)
   mutation of p53
6. Cirrhosis
   HCV
   Alcohol
   Hemochromatosis
   Tyrosinemia (40% of pts. Develop HCC despite adequate dietary control)

Morphology

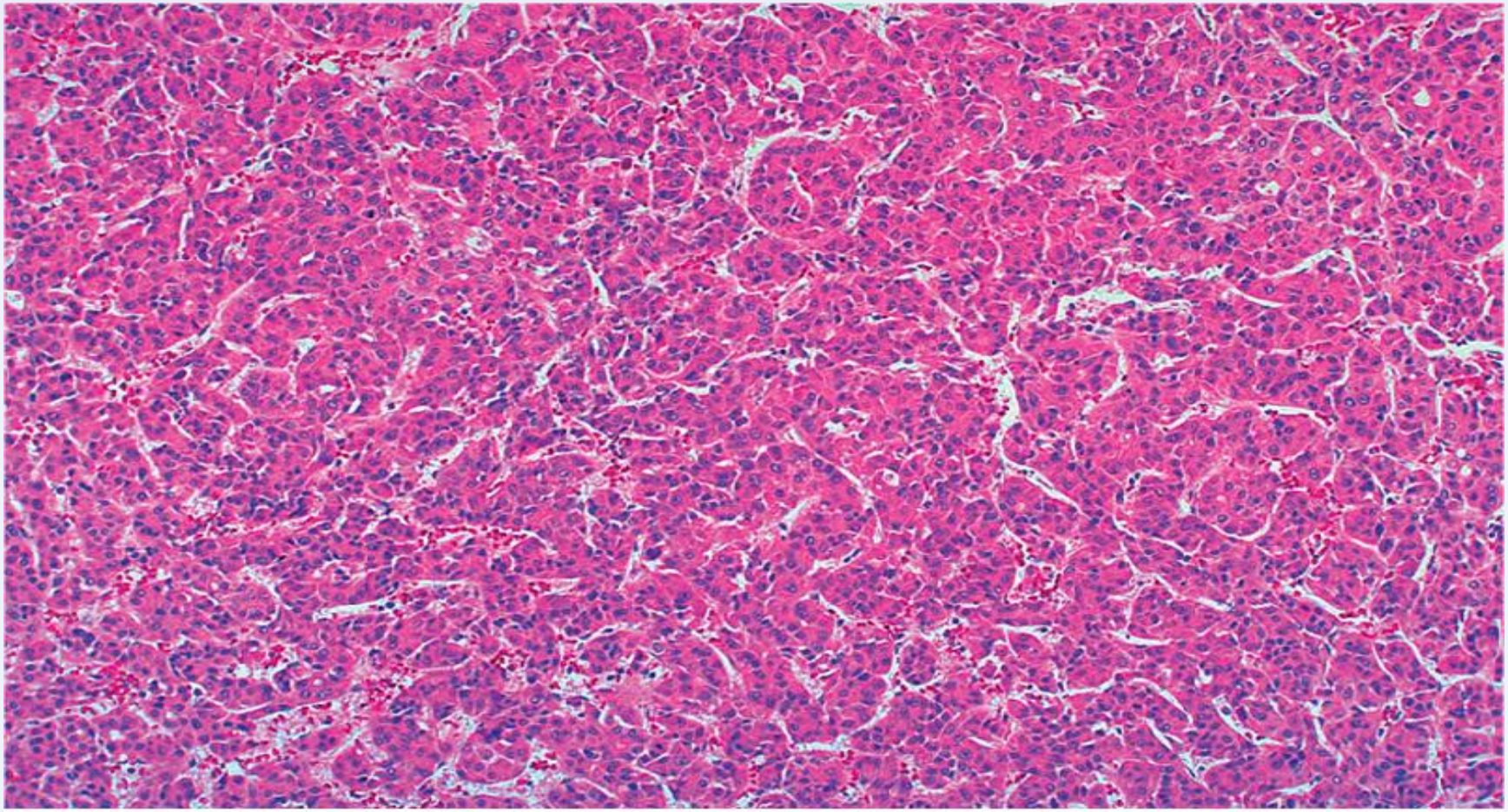
1. Hepatocellular carcinoma (HCC)
2. Cholangiocarcinoma (CC)
3. Mixed

- Unifocal
- Multfiocal
- Diffusely infiltrative

Hepatocellular carcinoma, unifocal, massive type. A large neoplasm with extensive areas of necrosis has replaced most of the right hepatic lobe in this noncirrhotic liver. A satellite tumor nodule is directly adjacent.



Hepatocellular carcinoma



- Vascular invasion is common in all types.
- Well ---- Anaplastic

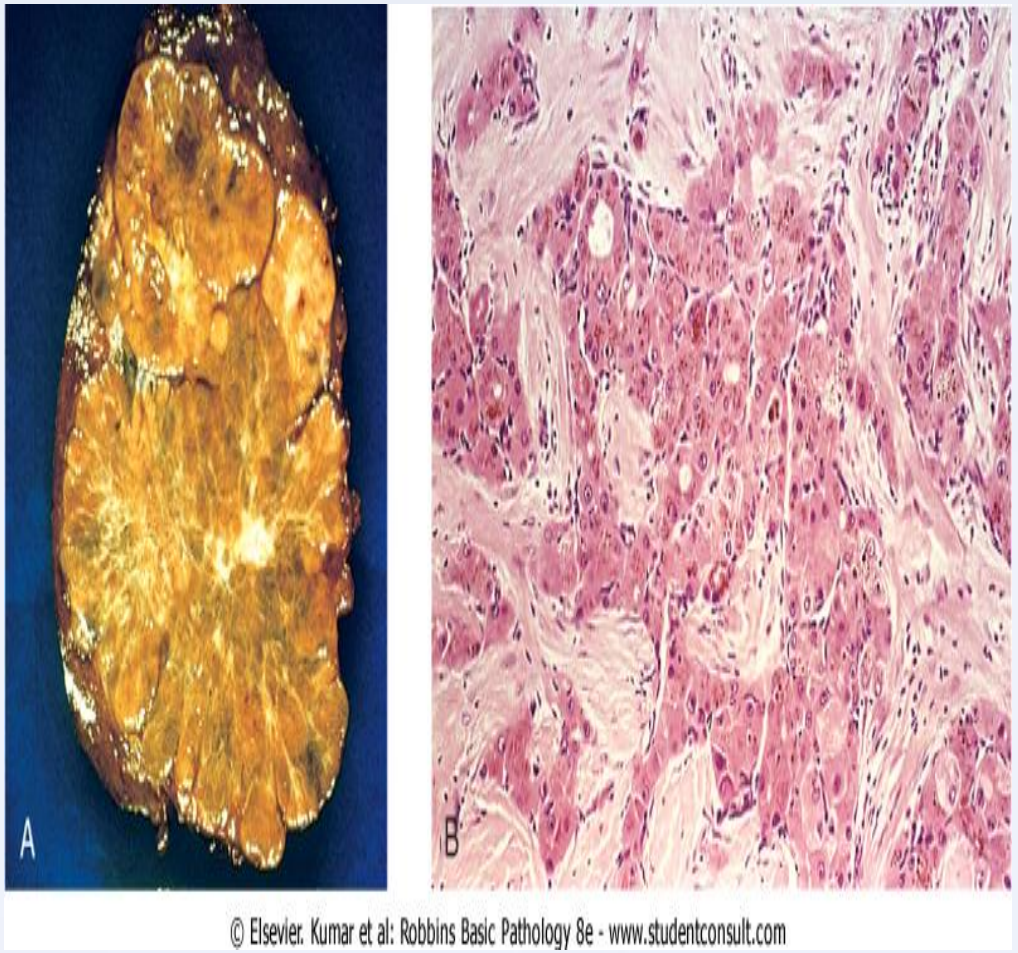
Fibrolamellar carcinoma .

* 20-40 yr. M=F

* No relation to HBV or cirrhosis

* better prognosis single hard scirrhous tumor

- Cholangiocarcinoma are desmoplastic



metastasis

Vascular – lungs, bones, adrenals, brain, in 50% of cholagiocarcinoma

Prognosis:

Death within 7 -10 months

Due to: Cachexia, GI bleeding, liver failure and tumor rupture and hemorrhage

- Clinical features:
  Abdominal Pain, malaise, weight loss
  increase α-feto protein in 60 – 75% of patients.
- α-feto protein increases also with:
  1-yolk sac tumor 2- cirrhosis, massive liver necrosis,

4-chronic hepatitis, 5-normal pregnancy,

6-fetal distress or death 7- fetal neural tube defect.

THE END