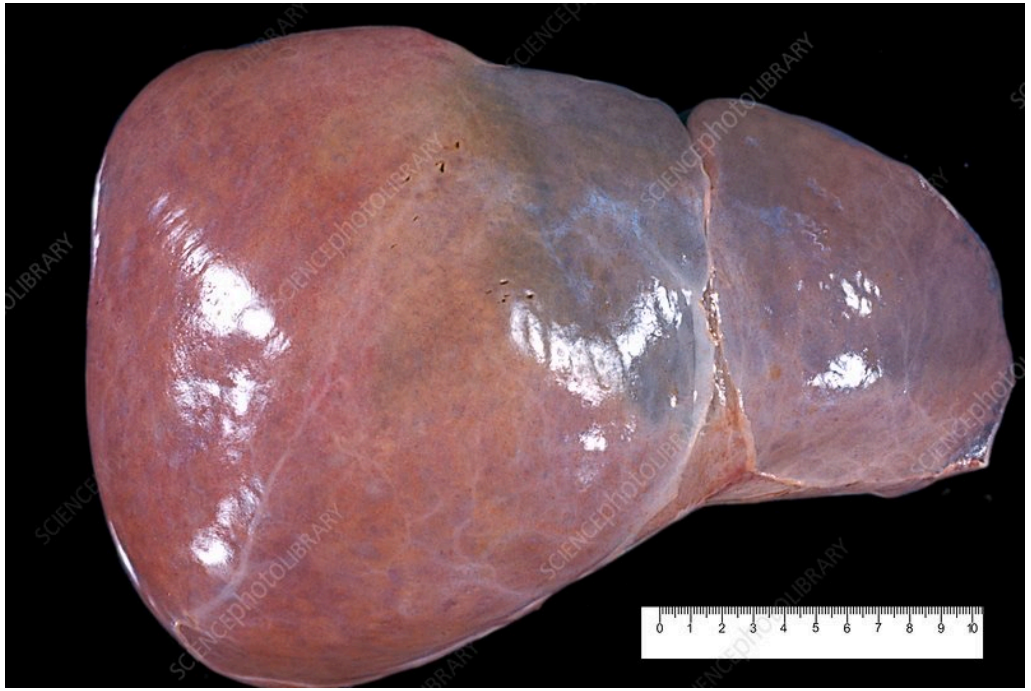
هاد موديفايد لدفعة 022 الله يعطيهم العافية ، عدلت عليه حذفت بعض المعلومات الزيادة والمكررة وعملت هايلايت لأهم المعلومات، ضفت بعض الصور للفهم و في كم رابط لفيديوهات osmosis ، وين ما بتلاقو further explanation بكون شرح بسيط من chat Gpt .

اللَّهُمَّ صَلِّ وَسَلِّمْ وَبَارِكْ على نَبِيِّنَا مُحمَّد

Liver



Done by : Joud Al-Zubaidi

Lec 1

Liver

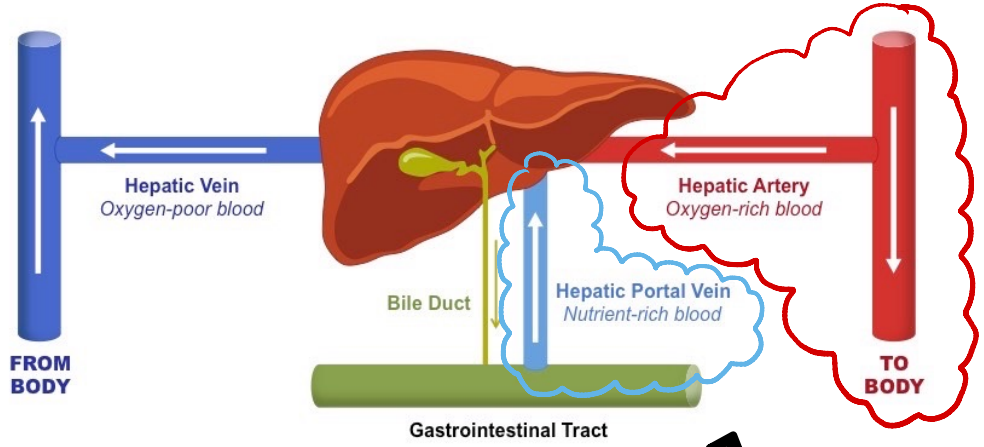
Liver is a gland with specific functions .

Any malfunction in the liver will present with clinical symptoms, and these symptoms may can be specific for the liver disease or they can be common with other diseases ; and with experience you will be able to tell from these symptoms what the problems are. But for now, we need to know about the normal structure and functions of the liver

- **Function:**

1. **Metabolic:** Glucose metabolism .
2. **Synthetic:** Albumin, clotting factors, enzymes and other substances.
3. **Detoxification:**(clearing of toxic materials): Drugs, hormones , NH3.
4. **Storage:** Glycogen, Triglyceride , Fe, Cu, vitamins ..
5. **Excretory**: Bile which is synthesized in the liver

So, any disease in the liver will affect one or more of these functions



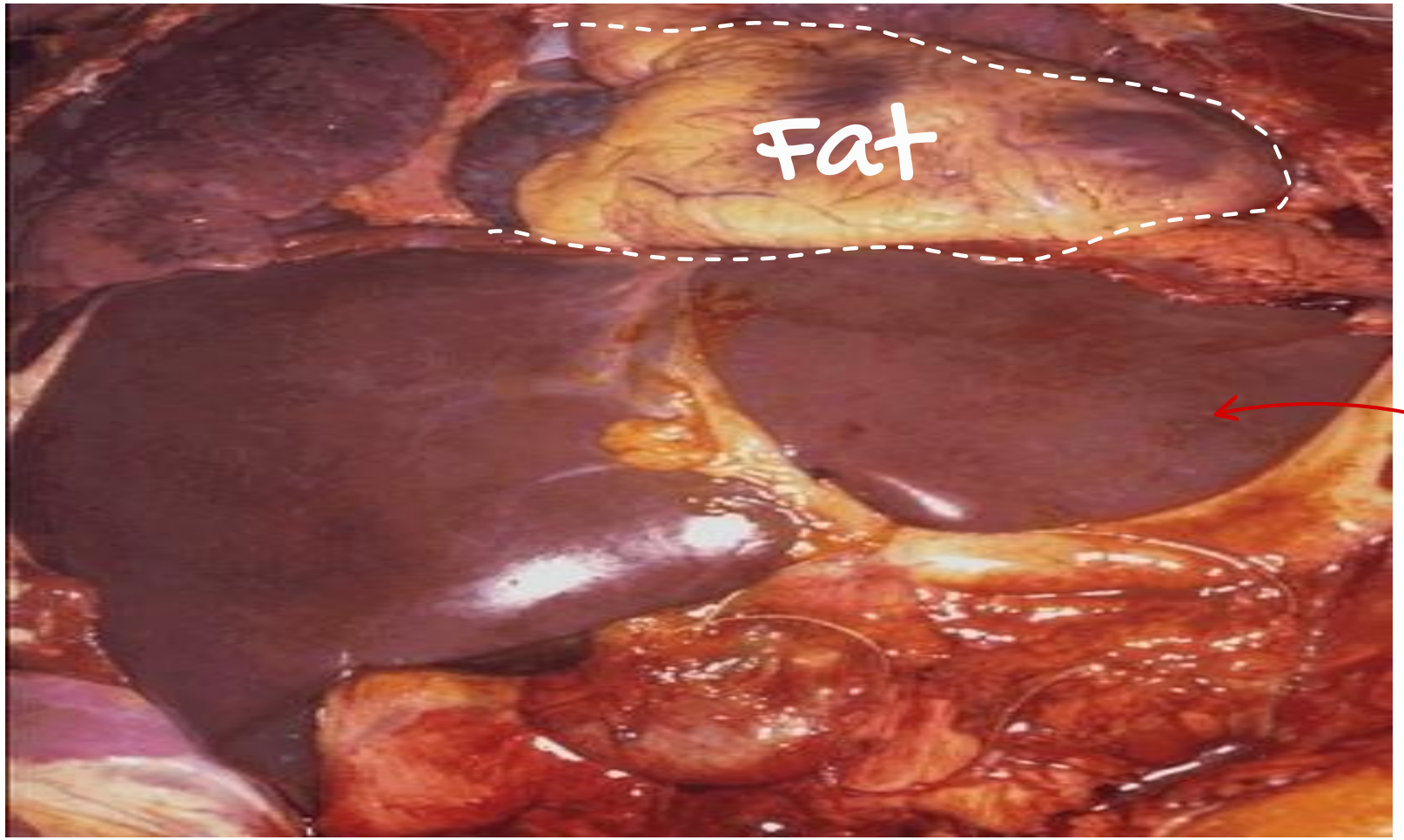
- Net wt.: 1400 – 1600gm (2.5% of body wt)
- Blood supply:
  - Portal vein: 60 – 70%
  - Hepatic artery: 30 – 40%

Some diseases affect vasculature.

- Microstructure
- Hexagonal lobules → 6 acini
- Acinus is divided into 3 zones:
  - Zone 1: Periportal areas – closest to the vascular supply
  - Zone 3: Pericentral area
  - Zone 2: Intermediate bet. Zone 1&3

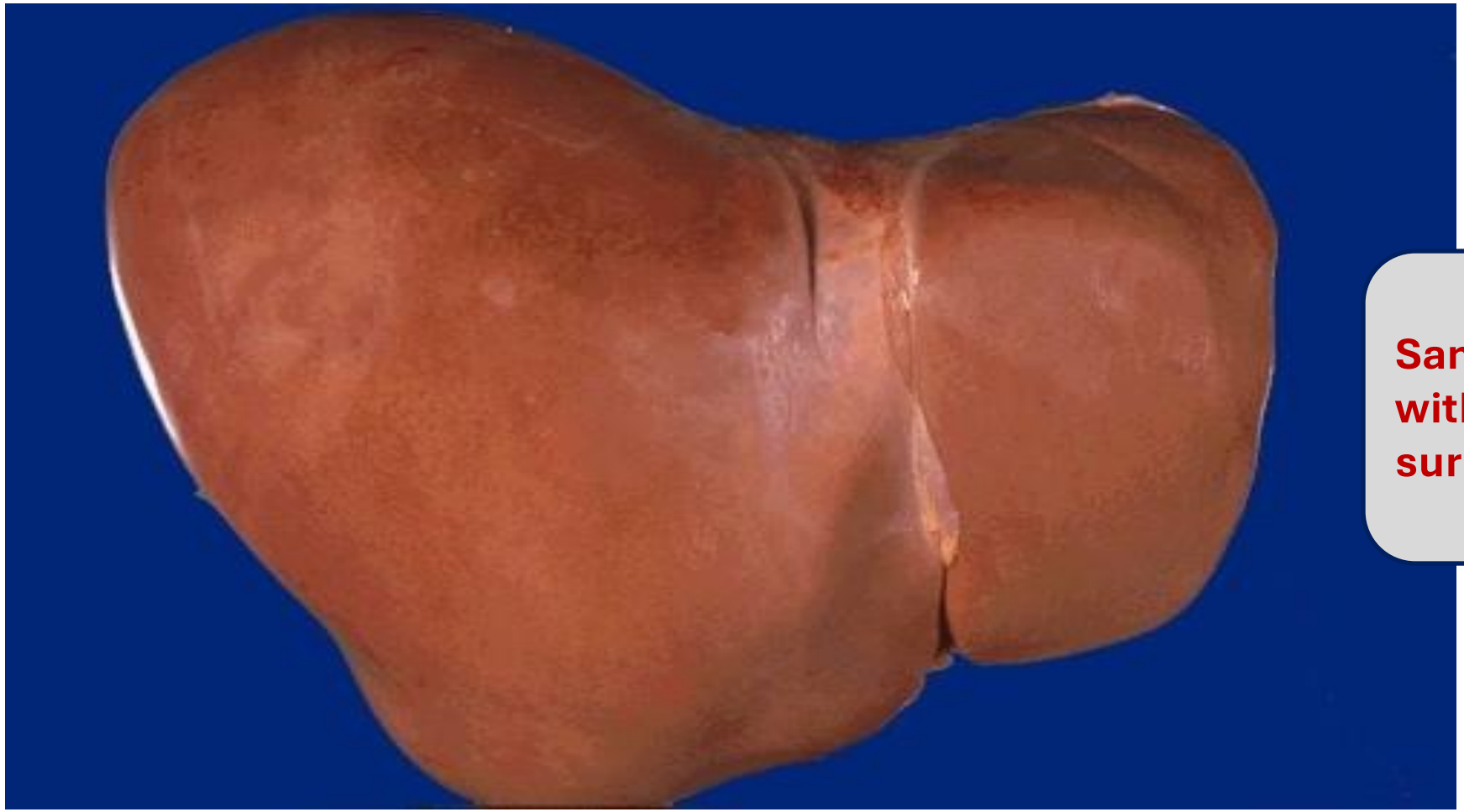
The structure of the liver is very important and unique. It is designed to carry out all the functions mentioned above. The functional unit of the liver is a hexagon. The localization of hepatocytes in the liver is important.

Normal liver



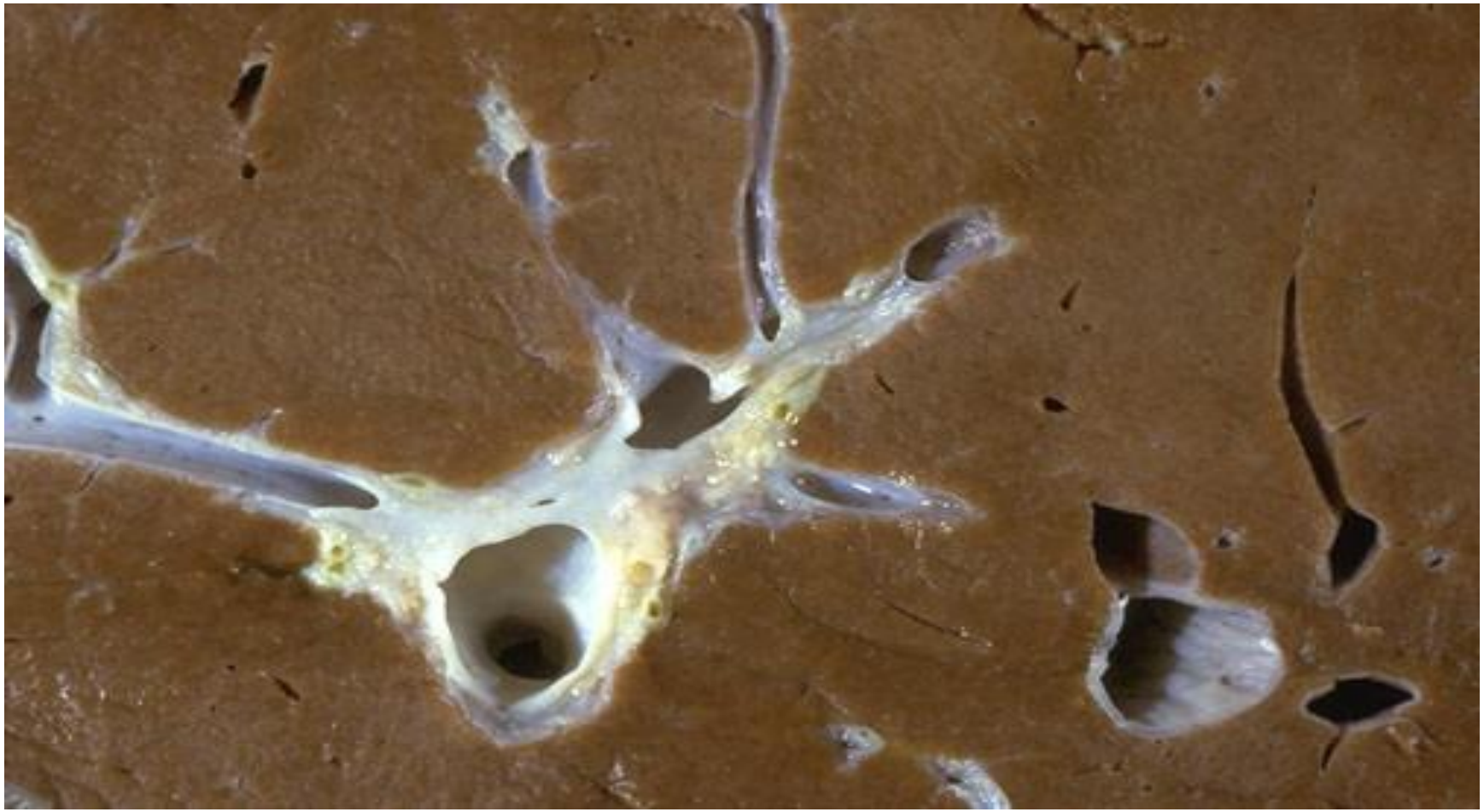
The normal liver has a smooth shiny surface and structures are well preserved. And it's brownish in color.

Normal liver



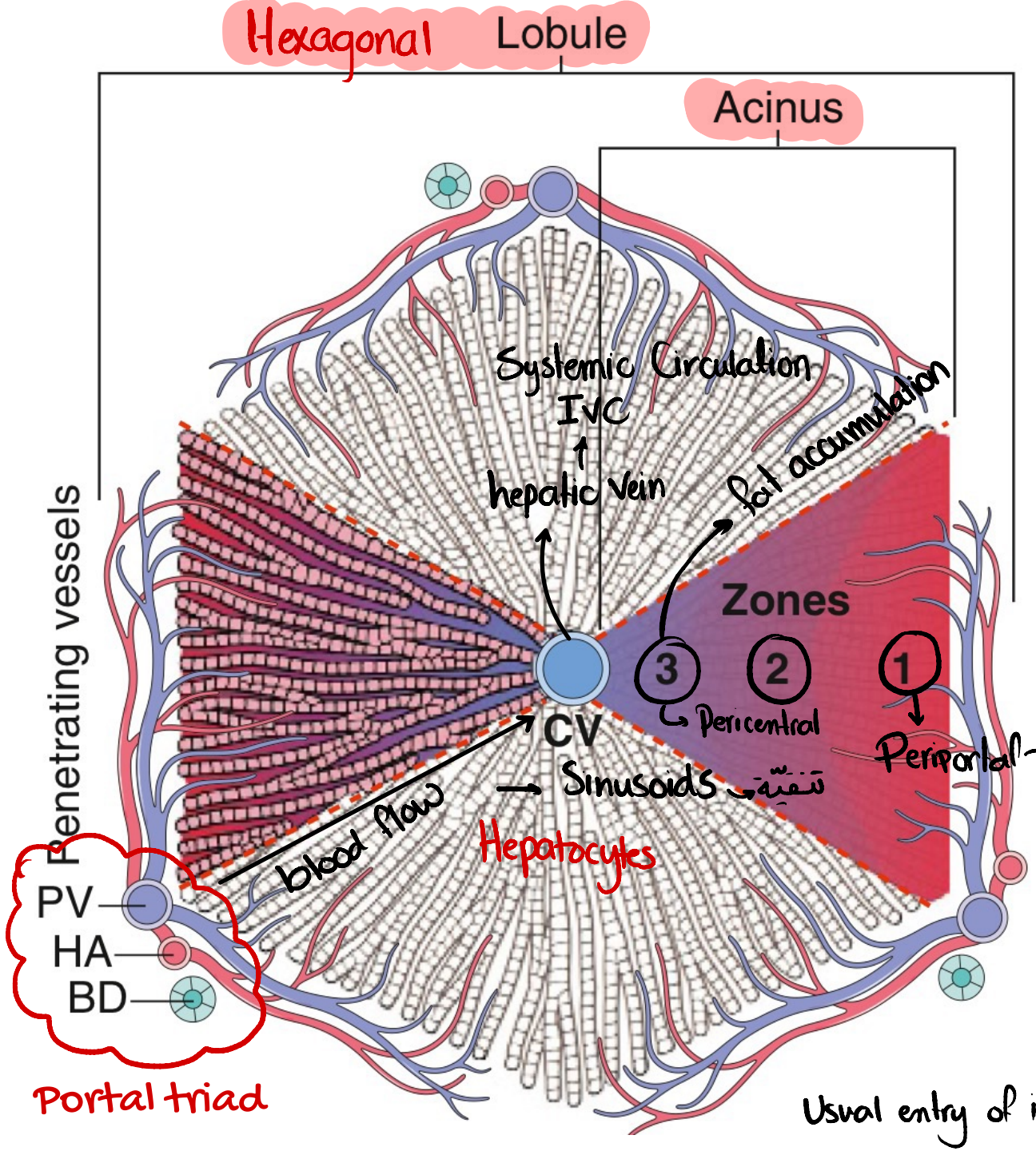
Same thing here but without the fat or surrounding structures.

Cross section of normal liver

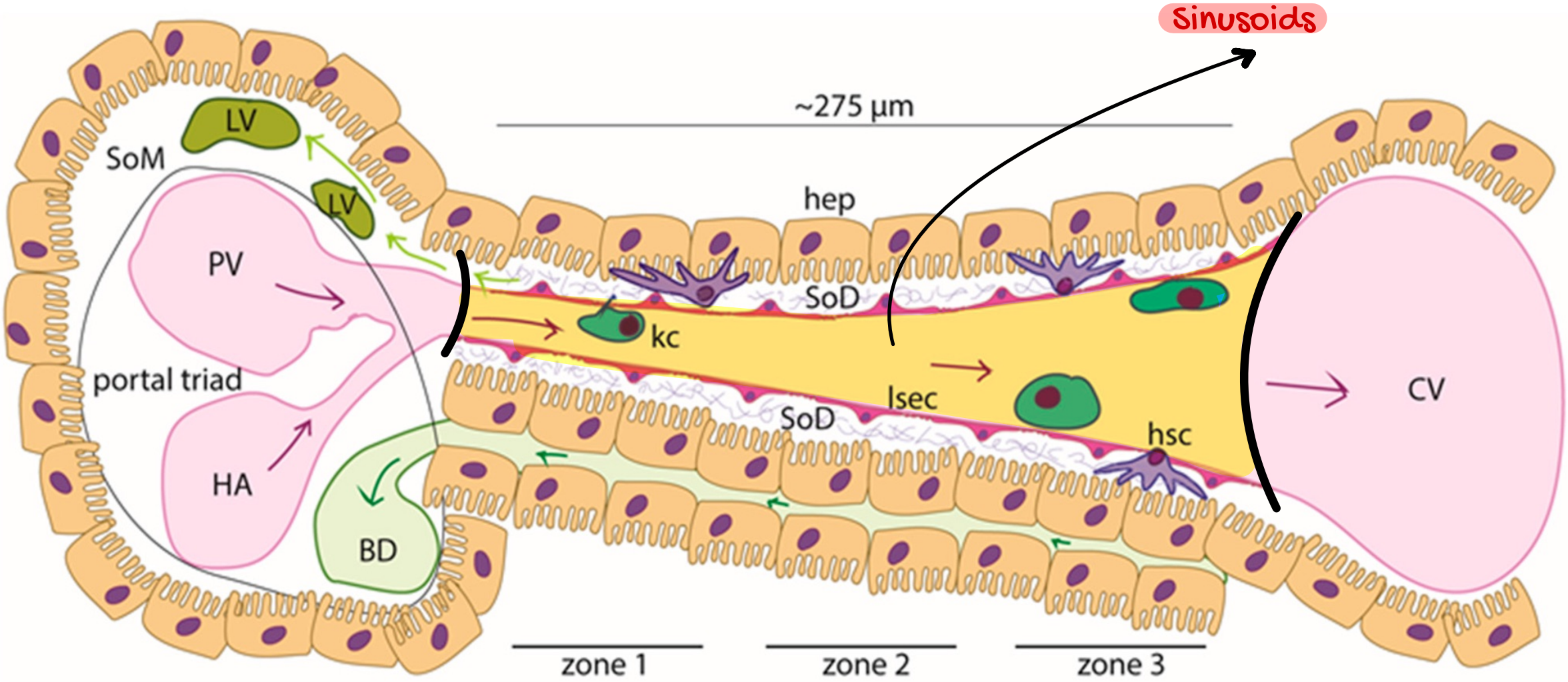


Normal liver parenchyma and vessels

The liver parenchyma refers to the functional tissue of the liver, primarily made up of hepatocytes (liver cells), which are responsible for the liver's essential functions like metabolism, detoxification, bile production, and protein synthesis.

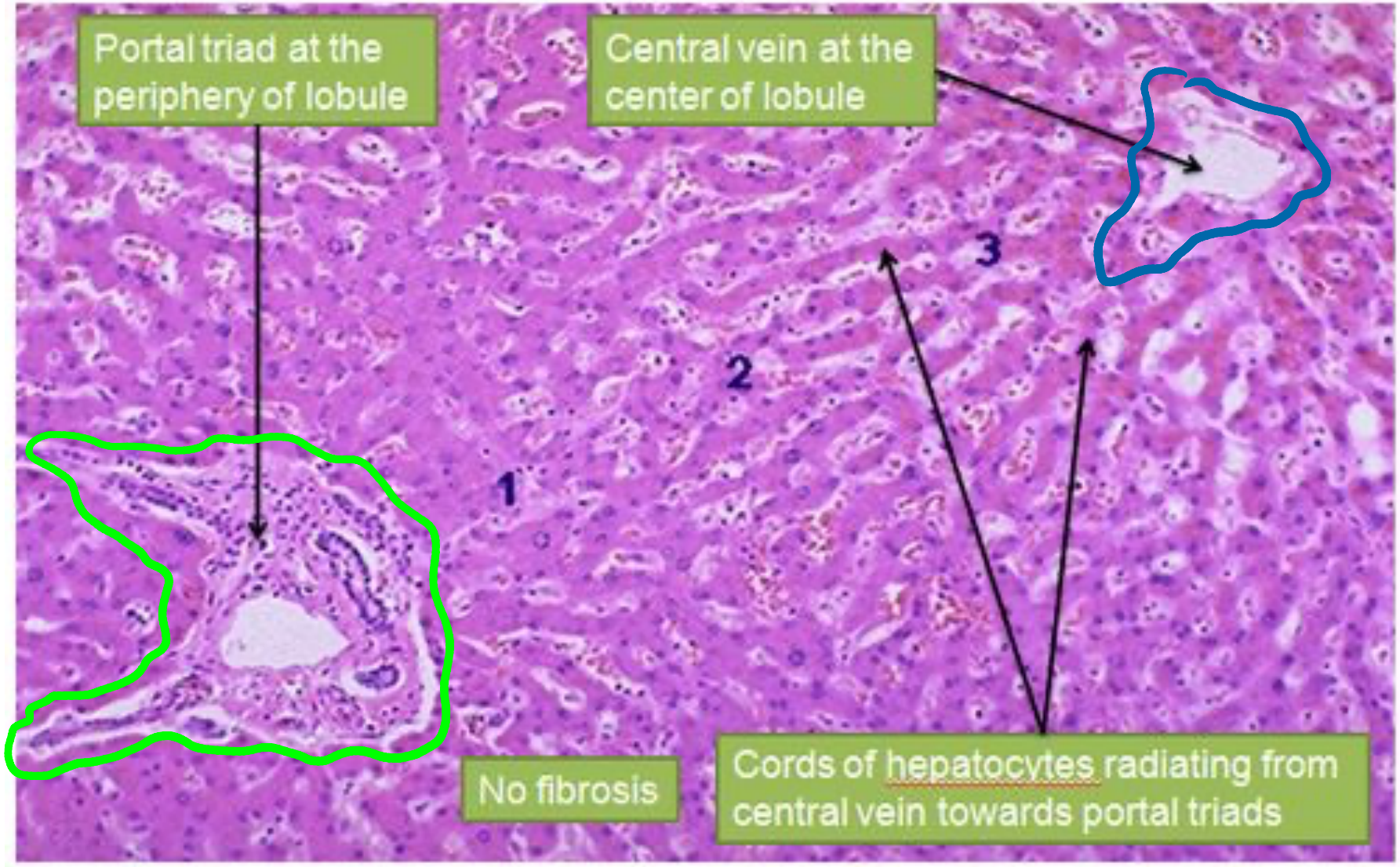


This is the hexagonal functional unit of the liver. It is composed of six triangles, each is called an acinus. There is a central vein in the middle of the hexagon. In each angle of the hexagon there is a portal vein, hepatic artery, and bile duct, and in between there is the hepatic parenchyma which is mainly composed of hepatocytes that are separated by sinusoids (vascular spaces lined by epithelial cells and contain Kupffer cells).


Sinusoids
~275 µm
LV
SoM
LV
PV
portal triad
HA
BD
hep
SoD
kc
lsec
SoD
hsc
CV
zone 1
zone 2
zone 3

Liver zones

Microscopic appearance of normal liver



Hepatocytes are arranged in lines that are one cell thick or sometimes two cell thick. More than that should be considered abnormal. You can see the central vein (in blue) ,and the portal (triad) area ;containing the portal v, hepatic a, and bile duct (in green). The three zones are not separated by clear lines.

- The parenchyma is organized into plates of hepatocytes.
- Hepatocytes are radially oriented around terminal hepatic vein (central v.)
- Hepatocytes show only minimal variation in the overall size, but nuclei may vary in size, number & ploidy esp. with advancing age
- Vascular sinusoids present bet. cords of hepatocytes

In most liver diseases we need a biopsy to recognize the exact disease. Many diseases can share similar characteristics. Liver biopsies help in shortening our differential diagnoses. The patient also needs to be followed up to evaluate if the patient is responding to treatment, or if the disease is transforming to a chronic state. The biopsy could be a needle biopsy or wedge biopsy. The routine stain is H&E, but we can use other specialized stains if needed. Lab tests are also helpful in reaching diagnosis.

Hepatic injury

Further explanation

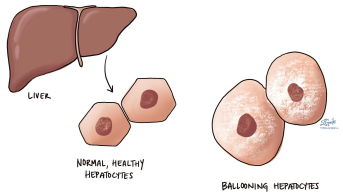
Summary Table: Hypoxia → Ballooning

Event	Effect
↓ Oxygen	↓ ATP production
↓ ATP	Failure of Na^+/K^+-ATPase pump
Na^+ accumulation	Water enters cell (osmosis)
Water accumulation	Cellular swelling and organelle damage
Result	Ballooning degeneration of hepatocytes

ballooning degeneration: swelling due to water entering the liver which is caused by hypoxia<<<<loss of oxygen<<<<reduced ATP production. Swelling can also be due to deposition of substances (fat, iron, copper, biliary material).

Manifestations of Hepatic injury

1. Inflammation (Hepatitis)
2. Ballooning degeneration:



-irregularly clumped cytoplasm showing large, clear spaces.

-Substances may accumulate in viable hepatocytes, including fat, iron, copper, and retained biliary material.

Inflammation is evident by seeing inflammatory infiltrate including acute (neutrophils) and chronic (lymphocytes). They indicate whether the injury is acute or chronic. So, the first indicator of injury is inflammation. It starts primarily within the portal areas, and depending on the severity, it can extend into the parenchyma. Spread of inflammation to parenchyma increases risk of the condition becoming chronic.

3-Steatosis (fatty change)

microvesicular:

ALD;(alcoholic liver disease) .

Reye syndrome, .

acute fatty change of pregnancy .

macrovesicular: Metabolic issues

DM, Diabetic mellitus .

obesity .

-Hepatic steatosis, or fatty infiltration of the liver, is indeed a significant manifestation of various diseases.

-The deposition of fat within hepatocytes can occur in different forms, including small droplets within the cytoplasm (microvesicular) or larger droplets occupying the entire cytoplasm (macrovesicular). Both forms indicate an abnormal condition within the liver.

-While the outcome of the process may not differ significantly between microvesicular and macrovesicular fatty deposition, but the underlying causes can vary.

A fatty change, is not a diagnosis, okay? I mean, because the diseases that are associated with fatty infiltration of liver too many, a fatty infiltration is a finding.

After we see liver is involved by fatty infiltration, we have to go and look for the underlying cause, okay? The underlying cause can be from different natures

fatty change

This is the cross section of liver involved by severe fatty infiltration.

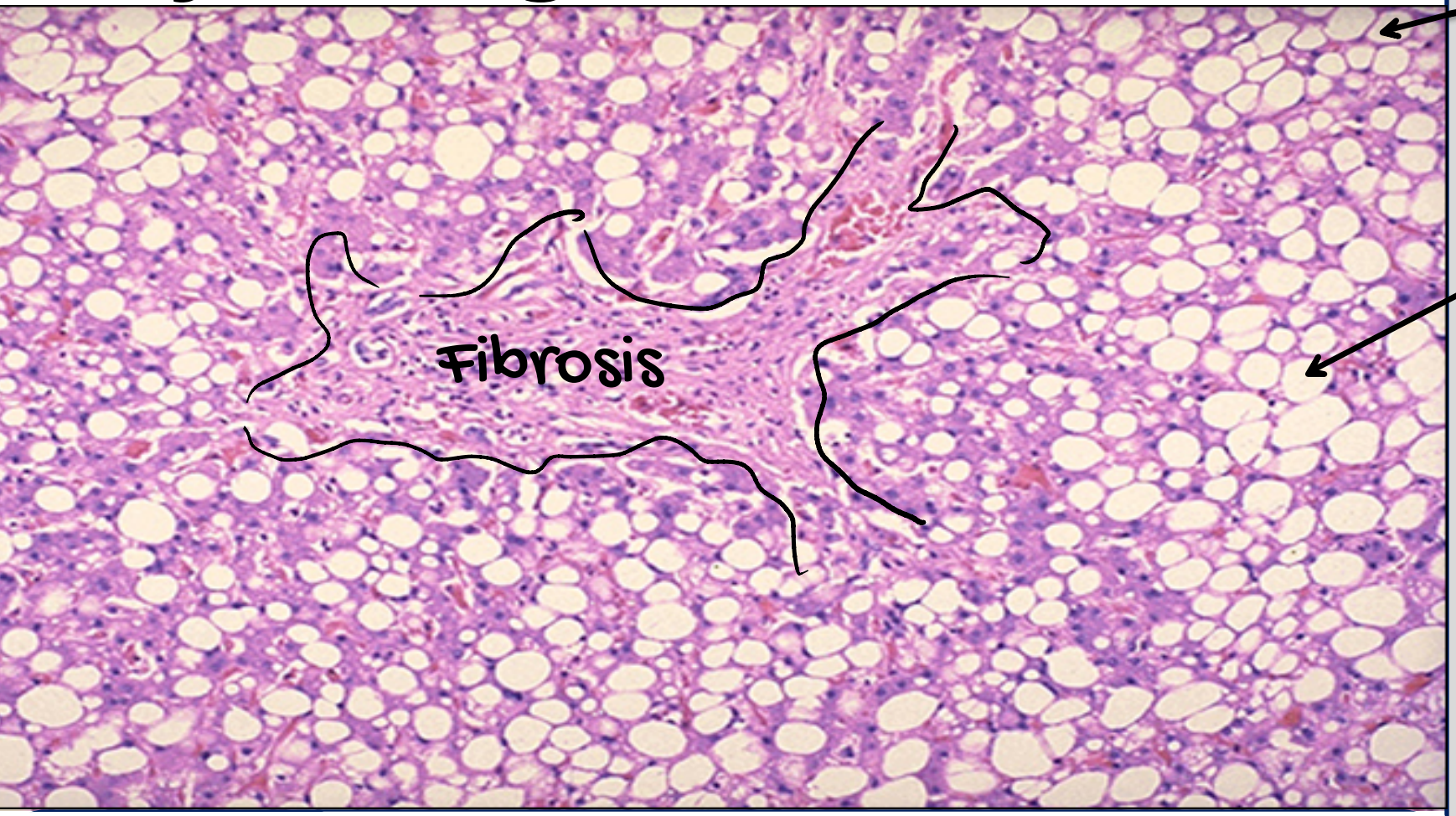
You can see the difference in color because the fat is normally yellow in color.

It is greasy in consistency.

Chronicity of the condition can lead to additional gross features becoming apparent. For example, with prolonged fatty infiltration and associated inflammation, there may be changes in liver texture, such as nodularity or firmness, indicating fibrosis or cirrhosis. These gross features provide valuable information to clinicians during physical examination and can guide further diagnostic and management decisions.

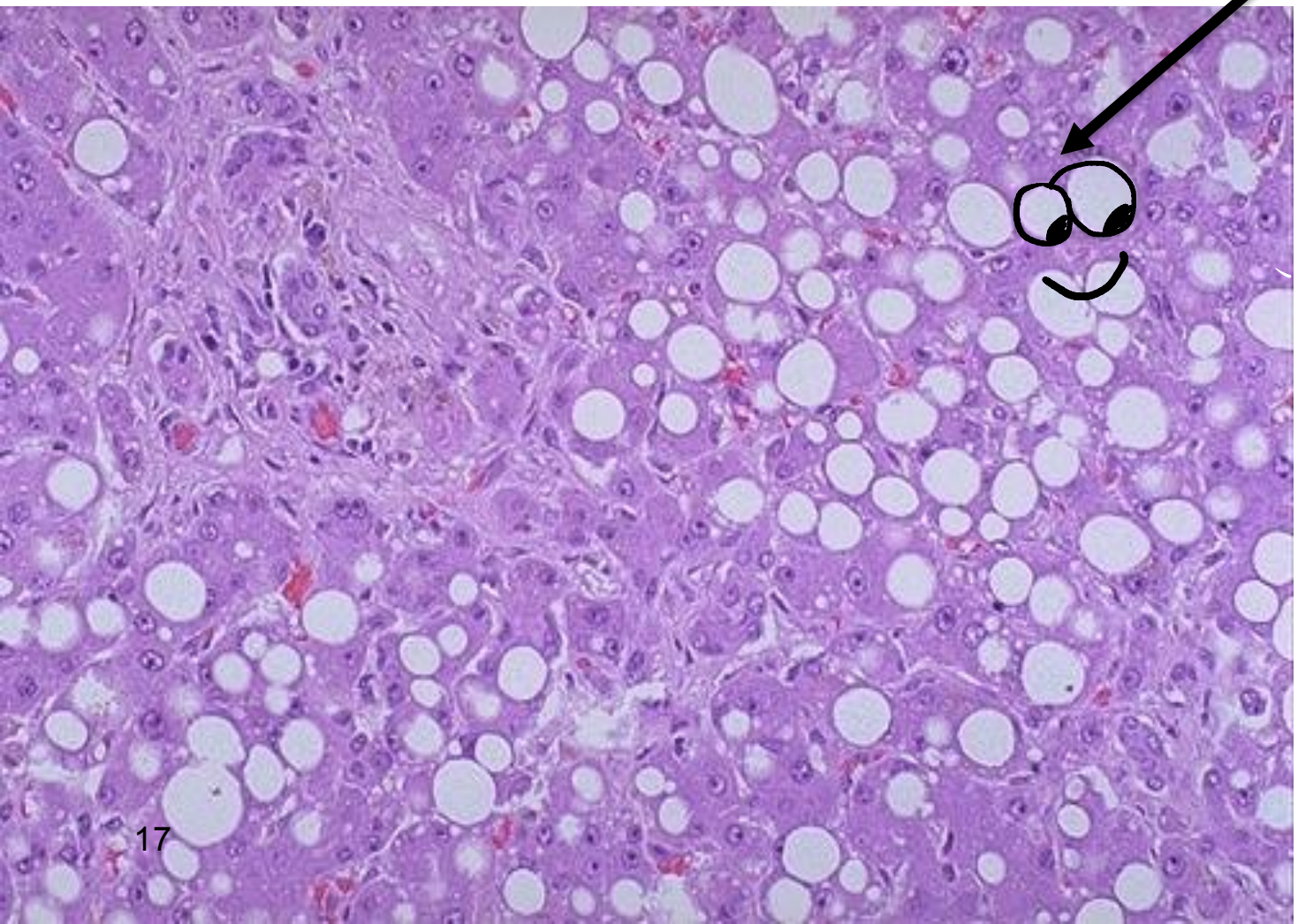
Fatty change of the liver is indeed a finding rather than a diagnosis in itself. It's a manifestation of various underlying conditions rather than a standalone disease.
Once fatty infiltration of the liver is observed, it serves as a red flag prompting further investigation into the underlying cause or causes.

fatty change



The ballooning observed in the hepatocytes is due to the deposition of fatty material within them. In the image, the round spaces that appear empty are actually filled with fat. However, during the preparation of the slide, solvents are often used to remove the fat, resulting in the appearance of empty spaces.

This is a higher magnification of the liver tissue. You can observe the presence of numerous empty spaces resembling Swiss cheese. These empty spaces indicate extensive fat infiltration within the liver parenchyma.



4-Necrosis

-Depending on the type:

1-coagulative necrosis:around central v.

2-Lytic(liquefactive) necrosis.

3-Councilman bodies.

-Depending on the cause

Ischemic.

Toxic.

Necrosis is correlated to severity, the presence of necrosis is a crucial indicator of severity, as it signifies cell death resulting from injury.

Necrosis in the liver can arise from various causes, with two "primary" types being 1 coagulative necrosis 2 liquefactive necrosis.

Liquefactive necrosis, also known as lytic necrosis, typically arises from infectious agents.

Coagulative necrosis is often associated with ischemia or reduced blood flow.

-Initially, necrosis tends to occur around the central vein in the liver.

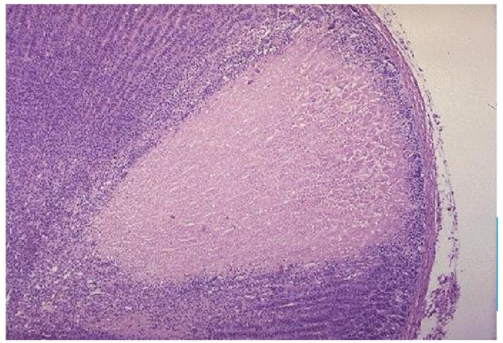
-Lytic necrosis, however, can manifest at any site and is frequently linked with the formation of abscesses. When observing lytic necrosis or abscess development, infectious etiologies should be considered. In the liver, these may include bacterial or parasitic infections.

يُتبع

Coagulative necrosis

- Conserved tissue architecture initially.
- Enzyme dysfunction.
- Anuclear eosinophilic on LM
- Wedge shaped (following blood supply)
- Leukocyte lysosomal enzymes and phagocytosis required for clearance.
- Ischemia to all solid organ (infarcts) except the brain

✓ It is called coagulative necrosis because the tissue architecture is conserved initially for a few days before the onset of inflammation which will damage it.



-Depending on type , necrosis also can manifest as individual cell death, a phenomenon known as Councilman bodies. These bodies indicate necrosis of hepatocytes, typically involving one or two cells. -- Under a microscope, these necrotic cells are characterized by several distinctive features:-

1- the cytoplasm appears more eosinophilic.

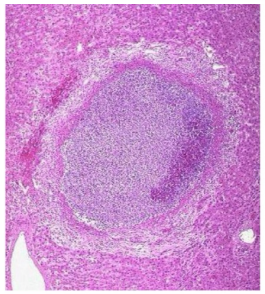
2-the nucleus of these cells becomes irregular, pyknotic, or fragmented.

-Councilman bodies can be seen in many different diseases, So it is important to look for and to see whether it presents or not like other findings.

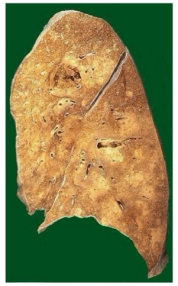
Liquefactive necrosis

- Focal infections by Bacterial and fungal organisms. Which are usually accompanied by production of Pus. Material
- CNS infarcts
- Center liquefies and digested tissue is removed by phagocytosis

✓ From its name, it is a liquid form of material that accumulates.
✓ It is associated with ischemia to the CNS→ which will result in a liquefactive pattern of necrosis instead of the coagulative necrosis which occurs in the other solid organs.

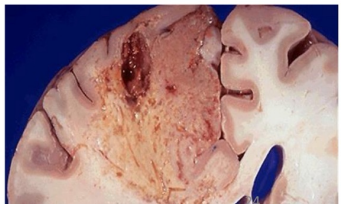


Under the microscope, liquefactive necrosis is characterized by a collection of inflammatory cells, mainly acute inflammatory cells (neutrophils).



Macroscopically, liquefactive necrosis appears as a cavity lesion in the lung.

This is an image of a brain with a cavitary lesion corresponding to an area of infarction.



شرح زيادة عن أنواع الـ necrosis من ذكريات الفصل الأول عادي اعملو skip

-depending on location

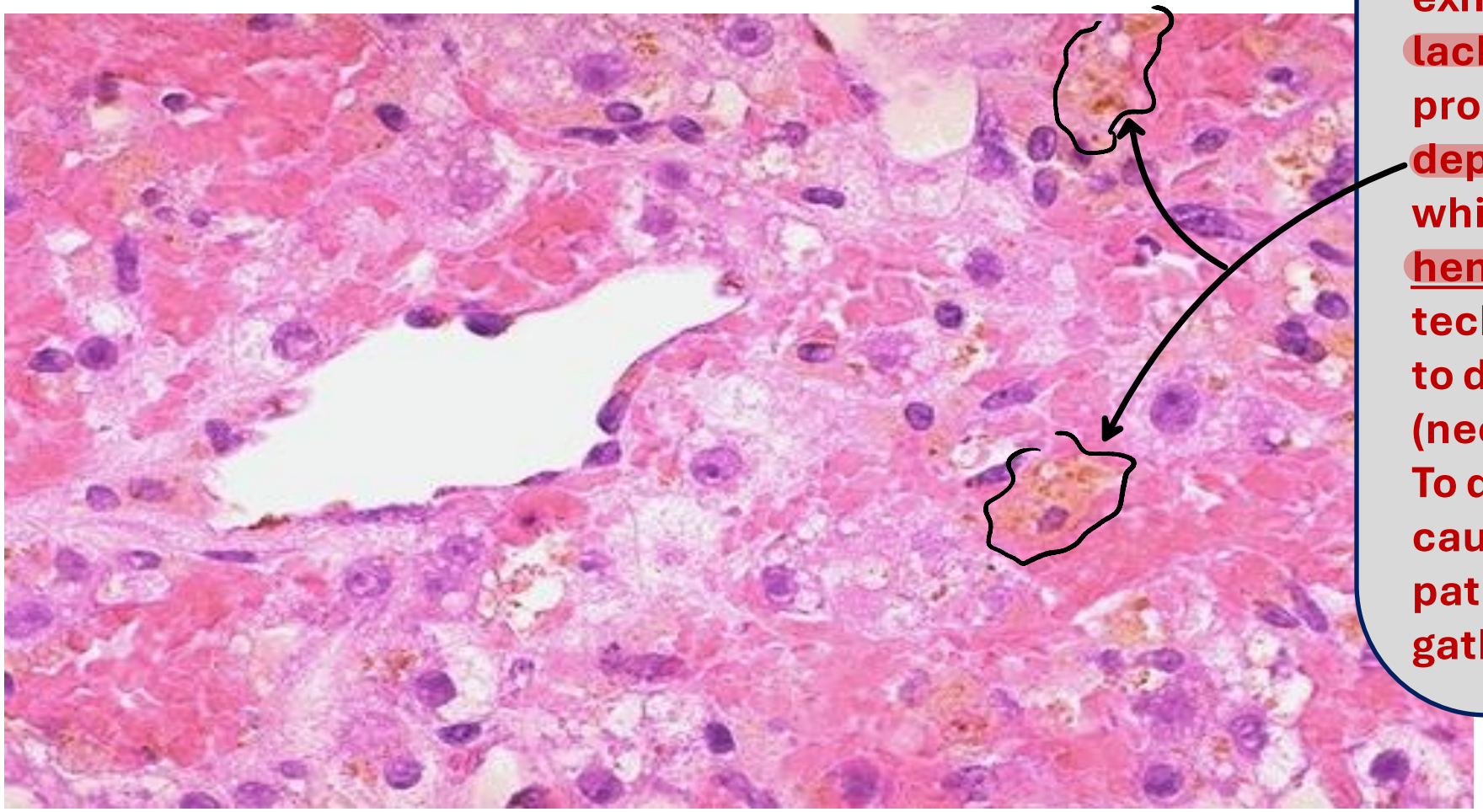
- Centrilobular necrosis:
- Mid zonal :
- Periportal : interface hepatitis
- Focal:
  - Piece meal necrosis
  - bridging necrosis
- Diffuse:

massive & submassive necrosis

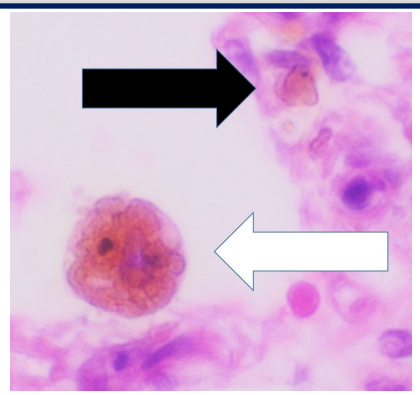
important to emphasize that these findings may not be present in all cases, particularly in severe instances. Early detection of these signs could aid in diagnosis and treatment.

Diffuse Necrosis: Necrosis that affects a large area or the entirely of the liver. It can be further classified into massive necrosis (involving a significant portion of the liver or whole liver) or submassive necrosis (a less extensive but still significant amount of necrosis).

Necrosis of liver



This figure for liver tissue exhibiting necrosis, where cells lacking nuclei are necrotic. The problem we got here is the deposition of bile material, which could potentially be hemosiderin. Special staining techniques are necessary to differentiate between the two (necrotic & bile material) .
To determine the underlying cause, we need to review the patient's medical history and gather additional information.



Hemosidrerin

5-Regeneration

-evidenced by increased mitosis or cell cycle markers.

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

Extra explanation about liver regeneration

🧠 **Main Idea: Liver Regeneration Mechanisms**

🔷 **1. Mild/Moderate Injury: Regeneration by Hepatocytes**

- When liver cells (**hepatocytes**) die, the **neighboring healthy hepatocytes** divide (mitosis) to replace them.
- This is the main way the liver repairs itself in most cases.

🔷 **2. Severe Acute Injury: Possible Role for Stem Cells**

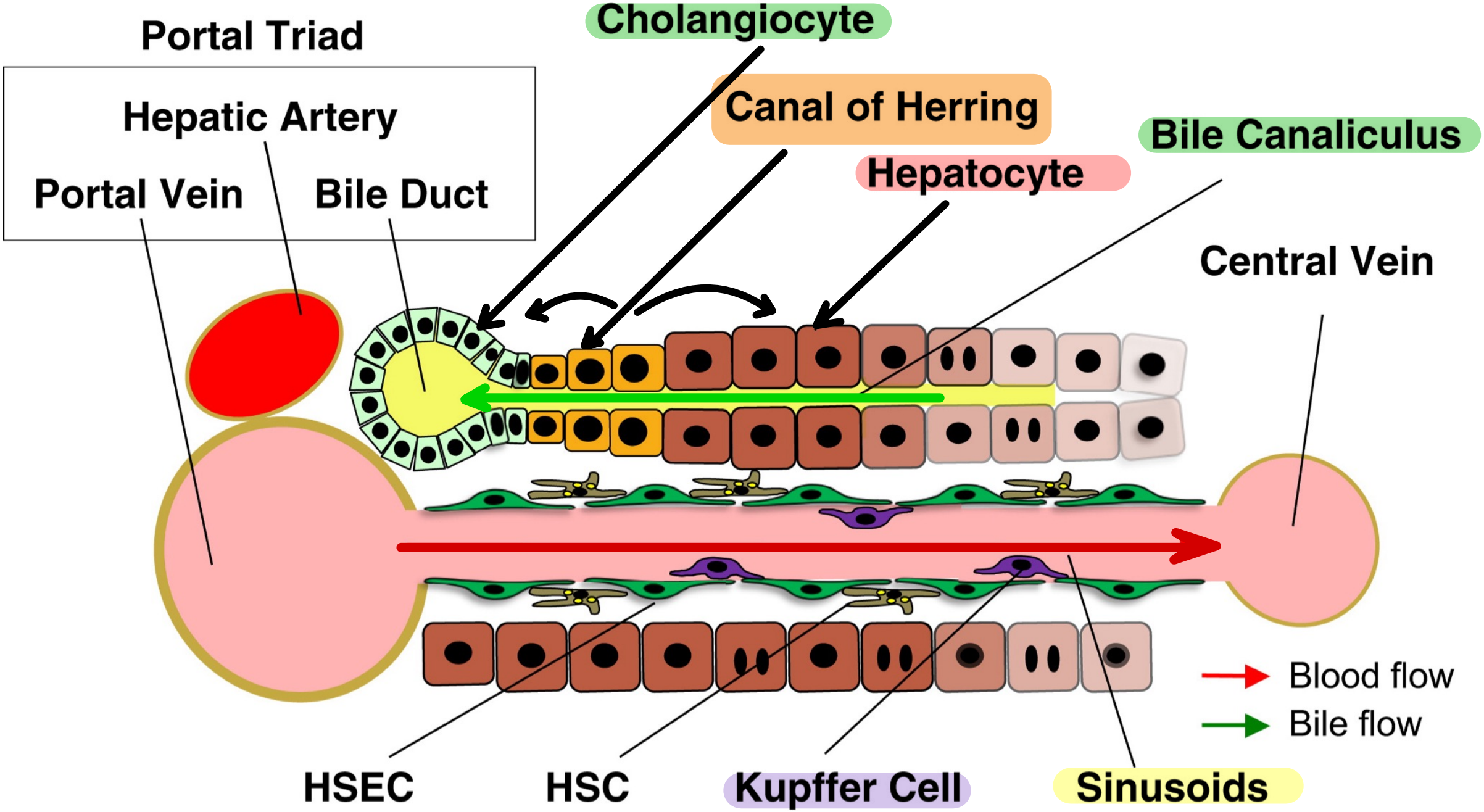
- In very severe liver damage, **hepatic stem cells** (located near the **canal of Hering**) may also start dividing.
- However, it's still **uncertain** how much these stem cells contribute to **regenerating hepatocytes** in **acute** damage.

🔷 **3. Chronic Liver Disease: Stem Cells Play a Bigger Role**

- In **long-term (chronic)** liver diseases, regular hepatocytes lose their ability to keep dividing (**senescence**).
- In this case, **stem cells** become more important:
  - They **divide and differentiate** into new liver cells.
  - They form **duct-like structures** (called **ductular reactions**), which are **markers of stem cell activity**.

A crucial feature of the liver is its remarkable ability to regenerate. Liver cells possess a significant capacity for regeneration, with regenerative cells being a part of the response to injury. This regenerative process is evidenced by the presence of mitosis in the liver.

In cases of liver failure, the organ can maintain its functionality, even when more than 90% of hepatocytes are damaged, due to its regenerative capacity.


Portal Triad
Hepatic Artery
Portal Vein
Bile Duct
Cholangiocyte
Canal of Herring
Hepatocyte
Bile Canaliculus
Central Vein
HSEC
HSC
Kupffer Cell
Sinusoids
Blood flow
Bile flow

6-Fibrosis:

1-portal or periportal fibrosis.

2-pericentral: around the central vein.

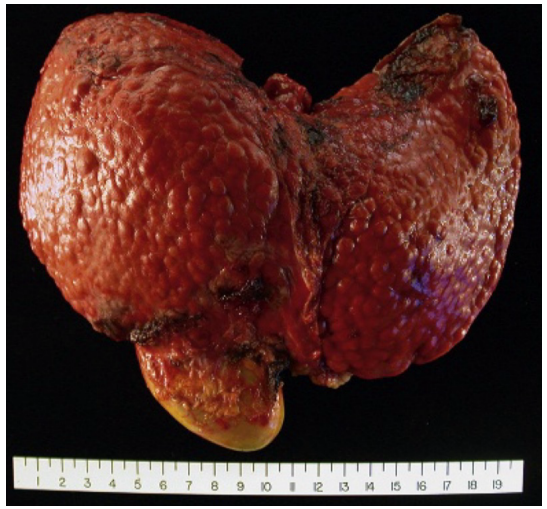
3-pericellular fibrosis or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes

4-bridging fibrosis

7-Cirrhosis:

Micronodular

Macronodular



8-Ductular proliferation:

Further explanation

Types of Liver Fibrosis:

Type	Location & Description
1. Portal or Periportal Fibrosis	Fibrous tissue forms **around the portal tracts** (portal triads). Common early change in hepatitis.
2. Pericentral Fibrosis	Fibrosis forms **around the central vein (zone 3)**, often seen in **alcoholic liver disease** or **chronic congestion**.
3. Pericellular Fibrosis	Fibrosis surrounds **individual hepatocytes** or groups of them, often within **sinusoids**. Seen in **NASH** and **alcoholic steatohepatitis**.
4. Bridging Fibrosis	Fibrous bands connect:
→ **Portal-to-portal**	
→ **Portal-to-central**	
→ **Central-to-central**	
A sign of **progressive disease**, often **pre-cirrhotic**.	

CLINICAL SYNDROMES

ما تشغلو حالكم فيهم هلا رح ينشرحو بالتفصيل واحد واحد

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

Hepatic Failure

-It results when the hepatic functional capacity is almost totally lost (80 – 90%)

-Causes

1.Massive hepatic necrosis

-Fulminant viral hepatitis

-Drugs & chemicals

- acetominophen
- halothane
- anti TB drugs
- CCL4 poisoning
- Mushroom poisoning

2-Chronic liver disease → cirrhosis

Massive hepatic necrosis

Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2 -3 wks).

Subfulminant → (within 3 months).

Causes:

1-Viral hepatitis 50 – 65% (B, B-D, A,C hepatitis)

2-Drugs & chemicals 20 – 30%

3-Heat stroke

4-Hepatic vein obstruction

5-Wilson disease

6-Acute fatty liver of pregnancy

7-Massive malignant infiltration

8-Reactivation of chronic HBV hepatitis on HDV superimposed infection

9-Autoimmune hepatitis

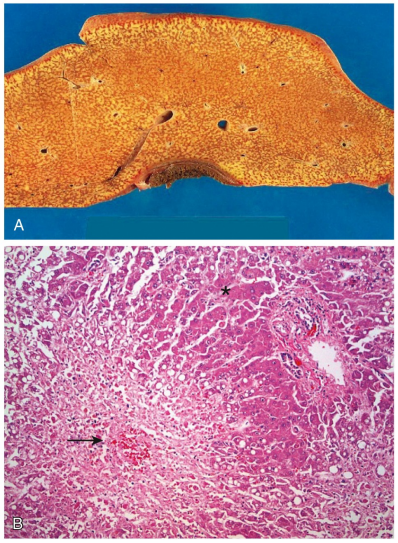


FIG. 14.4 Massive liver necrosis. (A) The liver is small (700 gm), bile-stained, soft, and congested. (B) Hepatocellular necrosis caused by acetaminophen overdose. Confluent necrosis is seen in the perivenular region (zone 3, *arrow*). There is little inflammation. Residual normal tissue is indicated by the *star*. (Courtesy of Dr. Matthew Yeh, University of Washington, Seattle, Washington.)

Subtype of acute hepatitis

3-Hepatic dysfunction without overt cirrhosis

- -Reye's syndrome
- -Tetracyline toxicity
- -Acute fatty liver of pregnancy

Often in children after viral infection with aspirin

Further explanation

Feature	Why It Happens
Jaundice	Liver can't remove **bilirubin** → yellow skin/ eyes.
Hypoalbuminemia	Liver stops making **albumin** → causes **edema (swelling)**.
Hyperammonemia	Liver can't detoxify **ammonia** → toxic to the brain.
Fetor hepaticus	Musty/sweet-smelling breath from toxins.
Palmar erythema & **Spider angiomas**	From **high estrogen** (liver can't break it down).
Hypogonadism & Gynecomastia	Due to **hormonal imbalance** (estrogen > testosterone).

What Do we see in a patient with hepatic failure ??

Clinical features

1-Jaundice
2-Hypoalbuminemia →edema
3-Hyperammonemia
4-Fetor hepaticus (musty or sweet & sour)
5-Palmar erythema
↳ hyperestrogenemia
6-Spider angiomas
7-Hypogonadism & gynecomastia

What is the consequences that happened to a patient with hepatic failure ??

Consequences:

1-Multiple organ failure → kidneys & lung

2-Coagulopathy → bleeding

↳ def. factors → II, VII, IX, X (clotting factors)

3-Hepatic encephalopathy

- ↓level of conseiousness
- Rigidity
- Hyperreflexia
- EEG changes
- Seizures
- Asterixis

Further explanation

What happens in hepatic encephalopathy?

The **liver fails** to:

- **Convert ammonia** (produced by gut bacteria from protein metabolism) into **urea**, which is normally excreted.
- As a result, **ammonia and other toxins** build up in the blood.
- These toxins **cross the blood-brain barrier** and **alter brain function**.

Symptoms Explained:

Symptom	Explanation
↓ Level of consciousness	Ranges from mild confusion to deep coma due to brain toxicity
Rigidity	Muscle stiffness, caused by nervous system dysfunction
Hyperreflexia	Overactive reflexes due to abnormal brain signaling
EEG changes	Brain wave patterns become abnormal; may show slow waves or triphasic waves
Seizures	Uncontrolled brain activity due to neurotoxicity
Asterixis (liver flap)	A tremor of the hand when the wrist is extended; caused by poor motor control (classic sign of HE)

4-Hepatorenal syndrome

Renal failure in patients with severe liver disease with no morpholagic or functional causes for renal failure

Click here to watch osmosis video about Alcoholic liver disease

https://youtu.be/RudR2_VVoaw?feature=shared

Alcoholic liver disease

Lec 2

Alcohol is a toxic substance that affect the liver and cause injury.

-Alcohol is most widely abused agent

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

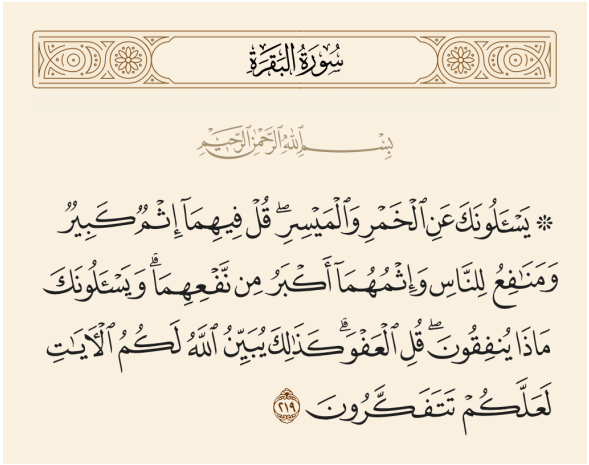
1.accidents

2.Cirrhosis

-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

-Short term ingestion of 80 gms/d of ethanol is associated with fatty change in liver



Excessive ethanol consumption causes more than revil cinorhc fo 60%disease.

- BAC (blood alcohol concentration) >> 80-100 mg/dl is high level of alcohol, below this level would be a minimal effect .

-27In 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

Further explanation

1. Blood Alcohol Concentration (BAC) Levels and Effects:

- In people who **drink occasionally (non-habitual drinkers)**:
  - **200 mg/dL** → can cause **coma**
  - **300–400 mg/dL** → can lead to **respiratory failure and death**
- In **habitual (chronic) drinkers**:
  - They can tolerate **very high BAC**, even up to **700 mg/dL**, **without serious effects**.

2. Why? → Metabolic Tolerance:

- Chronic drinkers **develop tolerance** because their liver adapts.
- The liver **increases the production of enzymes** that break down alcohol, especially:

👉 **Cytochrome P-450 System**

- This is a group of enzymes in the liver that help metabolize toxins and drugs.
- One key enzyme is **CYP2E1**.

3. Role of CYP2E1:

- In habitual drinkers, **CYP2E1 is increased 5–10 times**.
- This enzyme helps **break down ethanol (alcohol)** more efficiently.
- It also **increases the metabolism of other substances** like:
  - **Cocaine**
  - **Acetaminophen (Panadol)**

⚠️ **Important Point:**

- While this may protect against the **acute effects** of alcohol, it **increases the production of toxic byproducts** (like acetaldehyde and free radicals), which can damage the liver over time and lead to **liver disease**.

- The consumption of alcohol and ethanol in quantities leading to an elevation of Blood Alcohol Concentration (BAC) is associated with increased risk of injury. This elevation in BAC correlates with elevated levels of triglycerides, lactic acid, and liver enzymes.

Forms of alcoholic liver disease

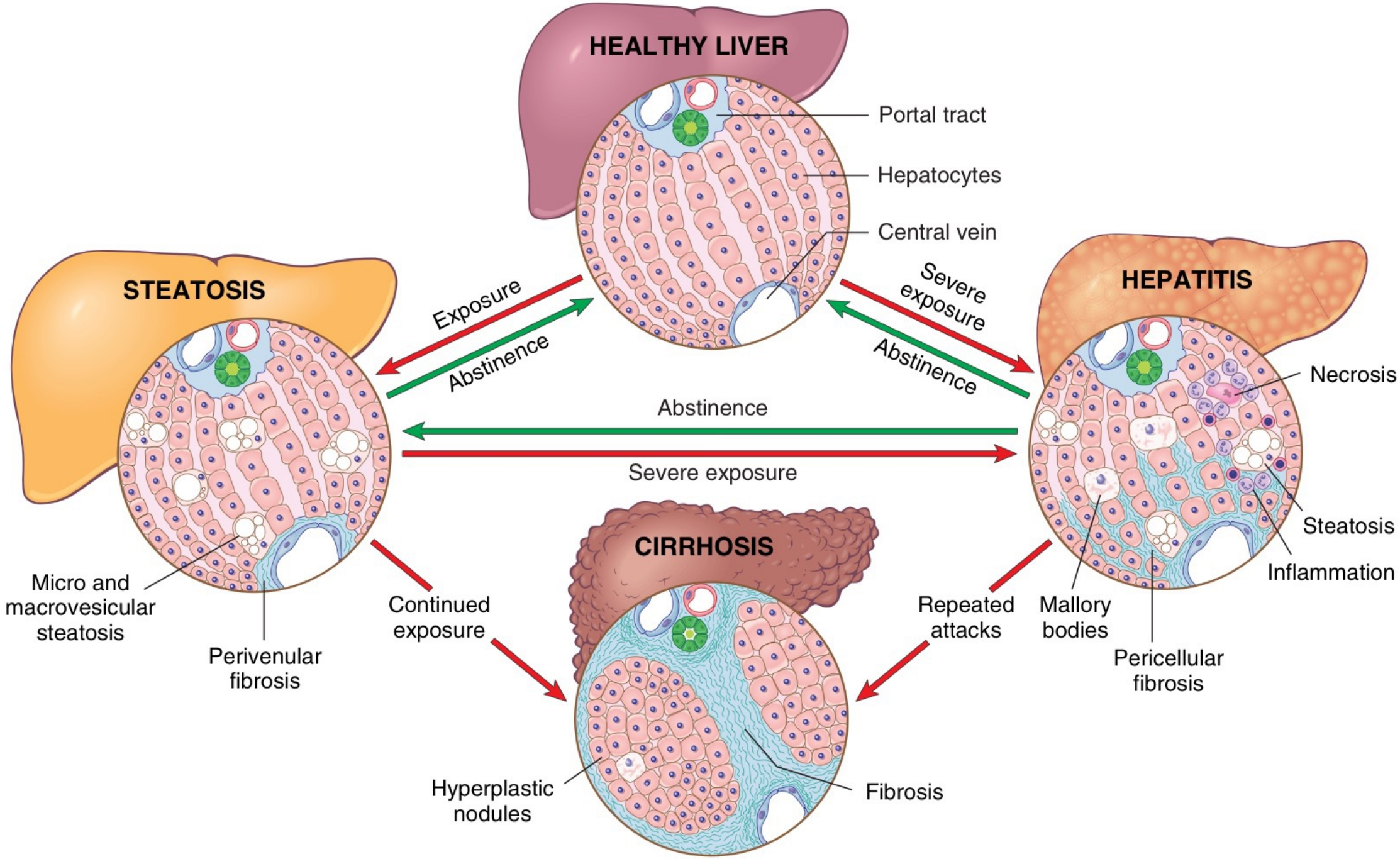
- Hepatic steatosis occurs almost in all alcoholic drinkers.
- -Cirrhosis is the outcome of chronic uptake of alcohol.
- Steatosis or fatty change occurs even in moderate uptake of alcohol
- However, the severity of fatty infiltration is related to the duration of the uptake.

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

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

3-Cirrhosis (14% of drinkers) Irreversible

-Steatosis & hepatitis may develop independently And should be considered as an early sign for cirrhosis in the future


HEALTHY LIVER
Portal tract
Hepatocytes
Central vein
STEATOSIS
HEPATITIS
Exposure
Abstinence
Severe exposure
Abstinence
Abstinence
Severe exposure
Necrosis
Steatosis
Inflammation
Micro and macrovesicular steatosis
Perivenular fibrosis
Continued exposure
CIRRHOSIS
Repeated attacks
Mallory bodies
Pericellular fibrosis
Hyperplastic nodules
Fibrosis

1. Hepatic steatosis

1. Can occur following even **moderate intake** of alcohol in form of **microvesicular steatosis** .

2. **Chronic intake** is associated with the development of **diffuse steatosis**, leading to enlargement of the liver (**hepatomegaly** 4-6 Kg), and it becomes **soft yellow** and **greasy**.

- **Fatty change** is **reversible** with complete abstention from further intake of alcohol, However upon continuation of intake this can progress to **Fibrosis** which is **irreversible**.

- Initially the uptake of alcohol will cause fatty change, this could be reversible when the patient completely stop the uptake of alcohol and the liver would back to normal state .

- If the patient continue the uptake of alcohol it would progress to irreversible and develop fibrosis .

→ Remember that each type of these injuries present or develop by its own so these aren't stages of the development in injury.

Alcoholic hepatitis

2.

- This is more sever than fatty change.
- There will be inflammatory components and necrosis due to the injury of hepatocytes

Characteristic findings :

1-Hepatocyte swelling & necrosis

-Accumulation of fat & water & proteins

-Cholestasis

-Hemosidrein deposition in hepatocytocytes & kupffer cells

2-Mallory-hayline bodies

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

- Ethanol is toxic and cause injury so in Mallory hyaline bodies there will be a collapsing of proteins and accumulation in cytoplasm.

Cholestasis is a condition in which the flow of bile from the liver is impaired. When bile flow is obstructed or diminished, it can lead to a buildup of bile acids in the liver and bloodstream.

Mallory-hayline bodies

-Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease.

- they are also seen in :

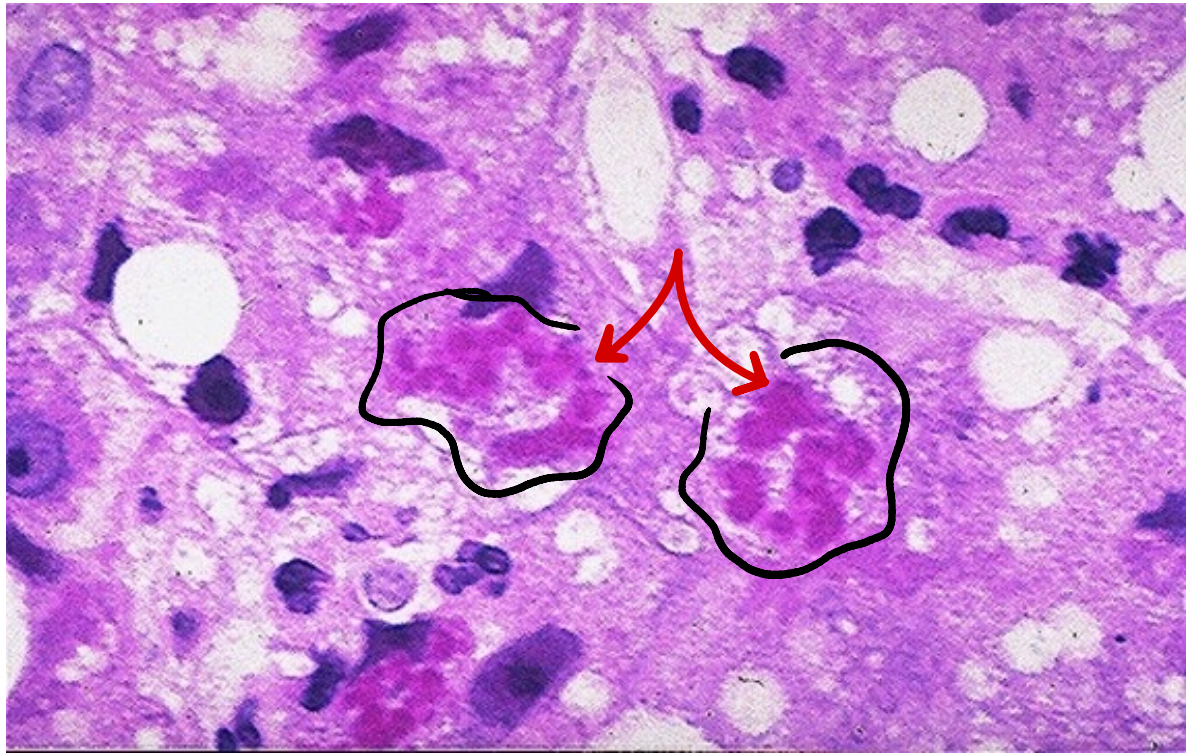
1-Primary biliary cirrhosis

2-Wilson disease

3-Chronic cholestatic syndromes

4-Hepatocellular carcinoma

It's not a special symptom that referred to a special order



- We have fatty change.
- Cytoplasm is large and eosinophilic.

Characteristic findings : (Alcoholic hepatitis)

3-Neutrophilic reaction

4-Fibrosis **(step forward to irreversiblity)**

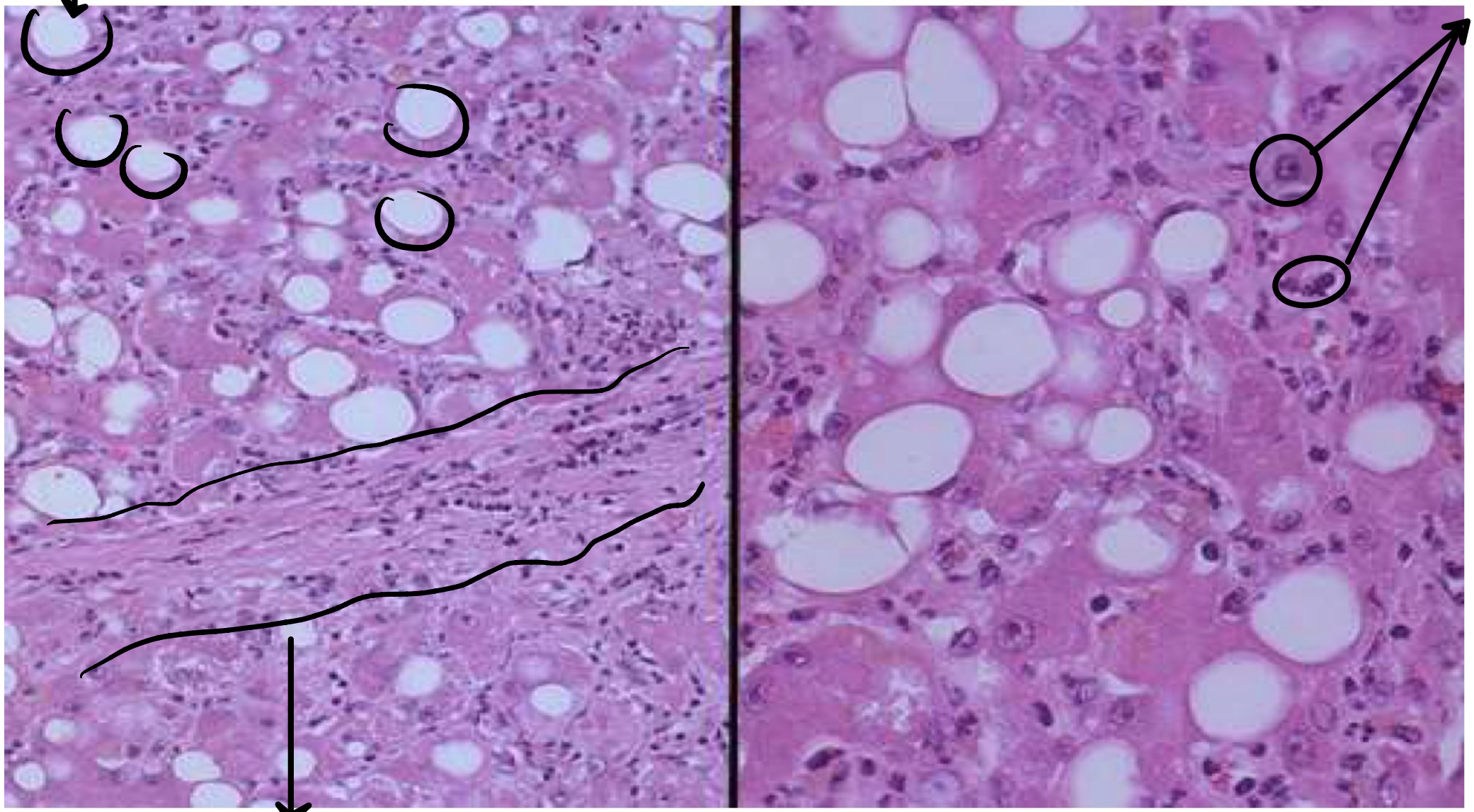
-Sinusoidal & perivenular fibrosis

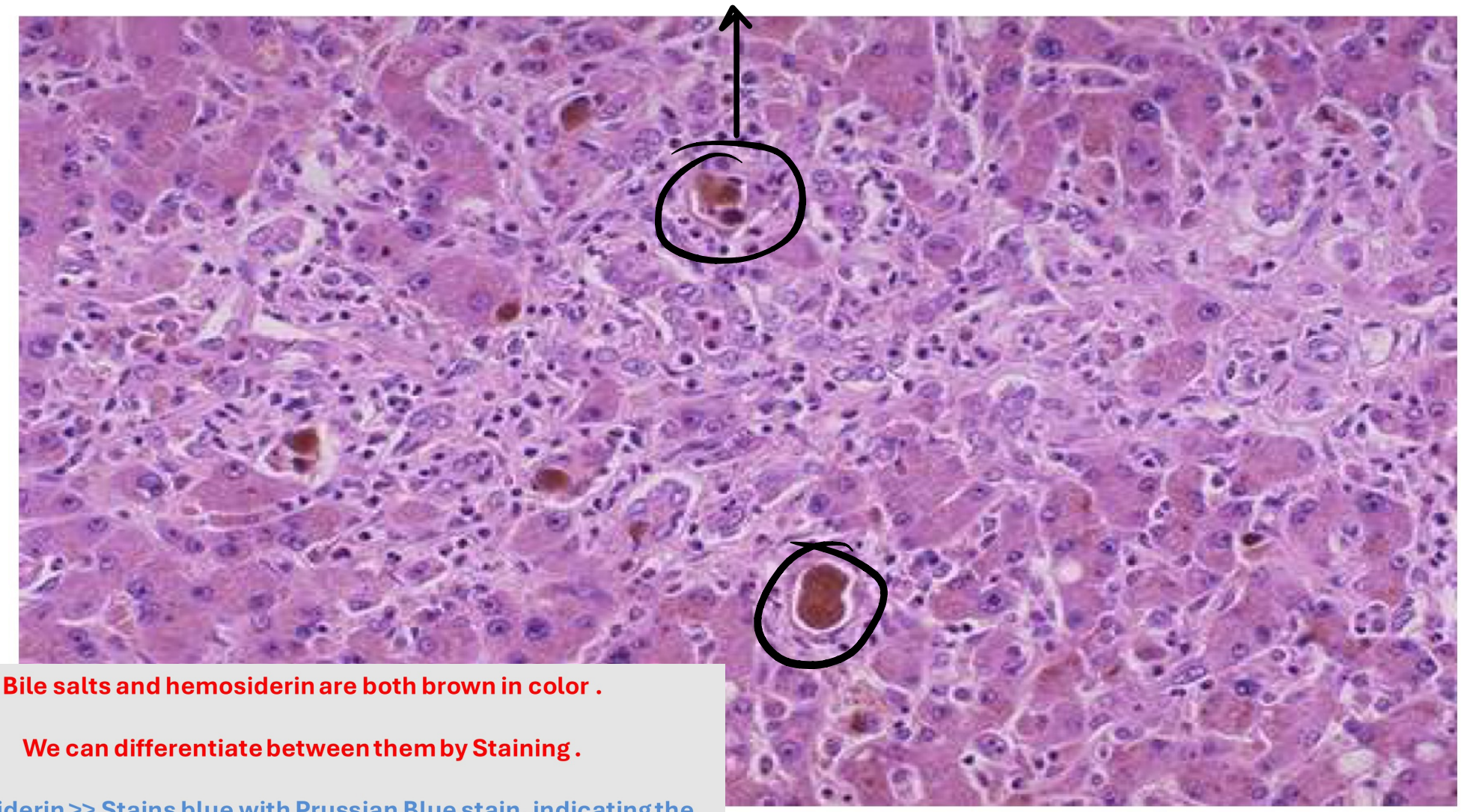
-Periportal fibrosis

5-Cholestasis **>> accumulation of bile salts in hepatocytes**

6-Mild deposition of hemosiderin in hepatocytes & kupffer cells

- **Mallory hyaline bodies + fatty infiltration + inflammation + fibrosis >>> we should think firstly of alcoholic hepatitis.**


Fat accumulation
Lymphocytes
Fibrosis



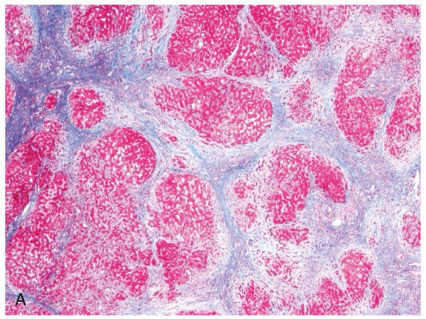
- **Bile salts and hemosiderin are both brown in color .**

- **We can differentiate between them by Staining .**

- **Hemosiderin >> Stains blue with Prussian Blue stain, indicating the presence of iron.**

- **Bile Salts >> Stains green with Hall's bile stain, indicating the presence of bile pigments.**

3. 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.

Due to the fibrosis

-Micronodular → mixed micro & macronodular

Nodules surrounded by scar tissue

-Laennec cirrhosis = scar tissue

-Bile stasis : The bile will Accumulate and cause jaundice

-Mallory bodies are only rarely evident at this stage

-Irreversible

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

regarding alcoholic cirrhosis, its development and progression are indeed closely tied to time. As individuals continue to consume alcohol excessively over an extended period(years of uptake), the damage to the liver accumulates, eventually leading to cirrhosis. The liver can become enlarged enough to be palpable below the costal margin during a physical examination.

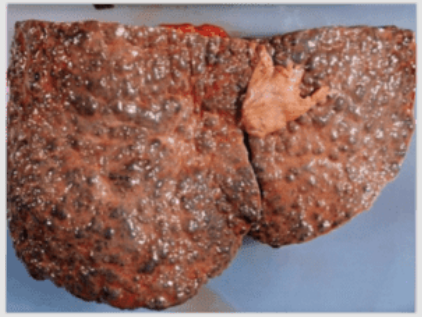
In alcoholic cirrhosis, the liver undergoes significant changes, including the development of nodules within the liver tissue. And these nodules will be small in size , they are referred to as micronodular cirrhosis and it can be mixed(micronodular and macronodular) later on.

Sometimes during over uptake of alcohol, fibrous tissue replaces the liver tissue . As the fibrous tissue continues to accumulate, it can lead to the loss of liver parenchyma and the transformation of the liver into a nodular, scarred organ which is known as Laennec cirrhosis .

-patient will have bile stasis and Malloy bodies .

-remember all these changes particularly fibrosis ,are irreversible .

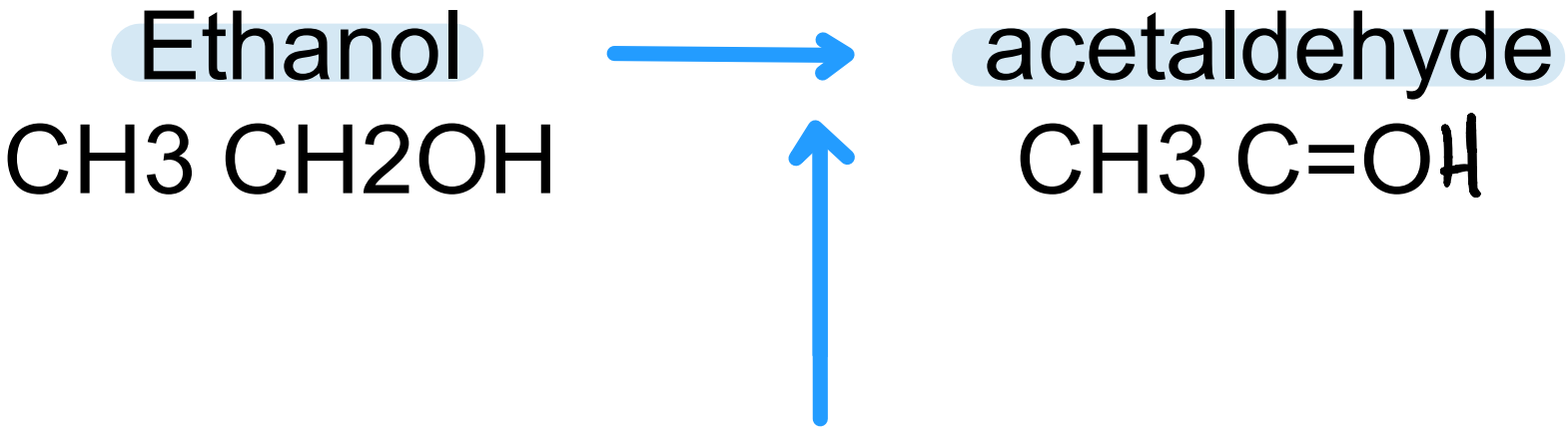
-Each type of hepatitis is associated with increased risk of cirrhosis .



Liver cirrhosis

This figure to show you the gross appearance of liver which is fibrotic. the surface is irregular , it is replaced by nodules (small in size so it is called micronodular cirrhosis)

Ethanol metabolism

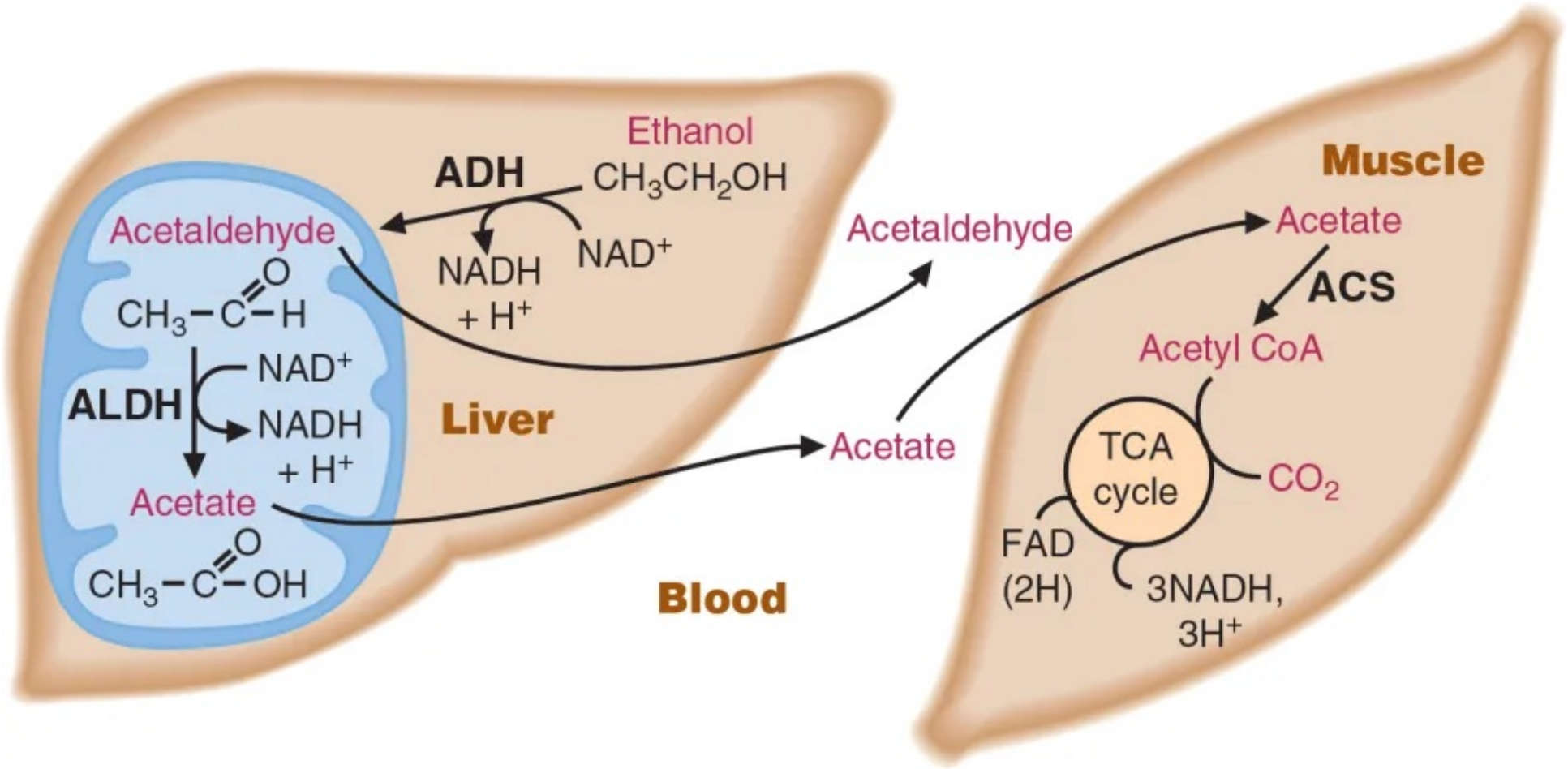


1. Alcohol dehydrogenase (stomach + liver)
2. Cytochrome P-450
3. Catalase (liver)

Acetaldehyde → Acetic acid

↑

Aldehyde dehydrogenase



After absorption ethanol is distributed as **Acetic acid** in all tissues & fluid in direct proportion to blood level acetic acid is present in all tissues and fluid in a concentration related to the concentration of the blood.

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. women will develop more severe manifestation due to toxicity

- Less than 10% of absorbed ethanol is excreted unchanged in urine , sweat & breathe (we can measure the concentration of ethanol through a person's breath)

-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 (الوجه احمرار) , tachycardia & hyperventilation.**

ALDH is an enzyme responsible for breaking down acetaldehyde, a toxic byproduct of alcohol metabolism, into acetate. However, genetic variations can affect the activity of this enzyme. When individuals have lower activity of the enzyme, particularly in the cytochrome P-450 system, they retain ethanol metabolites in the bloodstream for a longer duration before they are converted into acetic acid and excreted. This prolonged presence of metabolites can lead to symptoms such as facial flushing, increased heart rate (tachycardia), and high blood pressure (hypertension).

Pathogenesis of alcoholic liver disease

-Short term ingestion of 80gm of ethanol/day (8bears) → mild reversible hepatic changes (fatty liver)

-Long term ingestion (10-20yrs) of 160gm of ethanol per day → severe hepatic injury

-50 – 60gm/day → borderline effect

-Women are more susceptible to hepatic injury due to ↓gastric metabolism of ethanol .

-Only 8 – 20% of alcoholics develop cirrhosis

Mechanism of ethanol toxicity

هون رح نحكي عن ٩ أسباب كيف ال ethanol بيعمل liver damage

1-Fatty change

Further explanation in the next slide

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)

a. ✅ High NADH disrupts normal metabolism

🔄 **Normally:**

- **NAD⁺** is required for **fatty acid oxidation** (breaking down fats for energy)
- **NADH** is a signal that the cell is in a "high energy" state

But in alcohol metabolism:

- **NADH builds up too much → Inhibits fat breakdown** (beta-oxidation)
- The liver **stops catabolizing fat** and instead:
  - Promotes **lipid synthesis (lipogenesis)**
  - Converts acetyl-CoA into **fatty acids and triglycerides**

🧬 So: **Fat is synthesized instead of being broken down → Fat accumulates in liver cells**

✅ **Outcome: Fatty liver (hepatic steatosis)**

- **Triglycerides accumulate** in hepatocytes
- This is why **almost all heavy drinkers (90-100%) develop fatty liver** in early stages of alcoholic liver disease

🔷 c. ↑ Peripheral catabolism of fat → ↑ Free Fatty Acid (FFA) delivery to the liver

- **Alcohol consumption** increases **lipolysis (fat breakdown)** in peripheral tissues (like fat under your skin).
- This leads to **more free fatty acids (FFAs)** being released into the **bloodstream**.
- These FFAs travel to the **liver**.
- The **liver takes them in** and either:
  - Uses them for energy (oxidation) **OR**
  - Converts them to **triglycerides** (fat storage).

🔄 **Problem**: Because alcohol raises NADH levels (as explained before), the liver can't oxidize these FFAs effectively → so it stores them as fat instead.

b.

1. **Acetaldehyde binds to tubulin**
   - This forms **"adducts"** (chemical bonds that damage the protein).
   - So, **tubulin doesn't work properly**.
2. **Microtubule function is reduced**
   - Since tubulin is damaged, **microtubules can't form correctly**.
   - This **disrupts transport inside the liver cell**.
3. **Lipoproteins can't be transported out**
   - Normally, the liver packages fats into **lipoproteins** and exports them.
   - But now the **transport system is broken**, so fats **accumulate inside hepatocytes**.
4. ➤ Result: **Fatty liver (hepatic steatosis)**

🔷 d. ↓ Secretion of lipoproteins from hepatocytes

- **Normally**, the liver **packages fat** into **lipoproteins (like VLDL)** to export them out of liver cells into the blood.
- But **alcohol disrupts this process**, especially by damaging the **microtubules** needed for transporting lipoproteins.
- **Result**: Fat (triglycerides) gets **trapped inside liver cells**.

📌 This makes the liver **look pale and swollen with fat** under the microscope = **fatty liver**.

🔷 e. ↓ Oxidation of FFAs by mitochondria

- Alcohol metabolism creates **excess NADH**, which **inhibits mitochondrial β-oxidation** of fatty acids.
- So, **FFAs cannot be burned for energy**.
- They get **converted into triglycerides** instead and accumulate in liver cells.

-short term ingestion of 80 grams of ethanol per day is associated with fatty change, fatty change occurs in older patients .

-over long ingestion of higher amount of ethanol for long duration is associated in development of a significant hepatic injury, women are more susceptible to have injury more than men even with taking same amount due to lower level of metabolism .

-cirrhosis will develop in about 10% to 50% of patients . Why ethanol induced liver toxicity? Because it interferes with fat metabolism (ethanol interferes with all pathways of fat metabolism due to accumulation of free fatty acids) these free fatty acids will get deposited in different organs primarily the liver

3. ↑free radicals production due to (+) 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

Clinical presentations are related to the extent of damage, patients with a fatty infiltration can be asymptomatic or they can have a specific symptoms .
-patient can perform lab tests to measure liver enzymes particularly ***transaminases***, transaminases synthesized by hepatocytes , an increase in serum transaminase levels indicates that there is damage in hepatocytes, In this stage (hepatic steatosis) liver is not severely damaged only there is fat infiltration.

-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

↑ liver & spleen

↑ 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

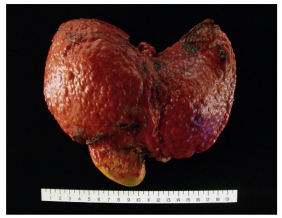
4-Hepatorenal syndrome

5-HCC in 3-6% of cases

Click here to watch osmosis video about cirrhosis

https://youtu.be/f46VFQG2S84?feature=shared

Cirrhosis



Involves the whole liver

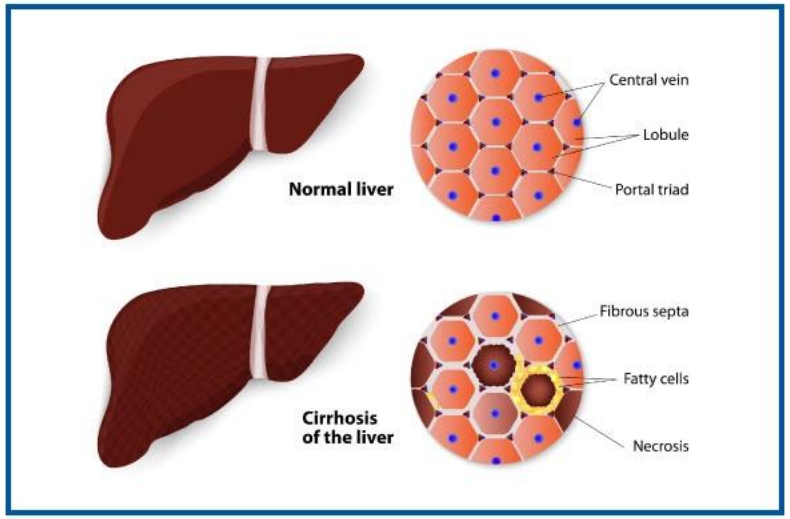
- It is a **diffuse** process characterized by **fibrosis** & the **conversion of liver parenchyma into nodules .**

-One of many diseases that is characterized by the damage of the liver
- It is a chronic process & irreversible , it develops over time (needs years to develop) but once it is developed it becomes irreversible , so the patient should live with cirrhosis or with the complications of cirrhosis for the rest of his life

- Cirrhosis is important because of the change in the liver's consistency or arrangement of cells and loss of the function of hepatocytes
- Actually the presentation and clinical manifestation of liver disease or cirrhosis is due to hepatocytes misfunction(they are injured) so the liver's normal arrangement is lost

There is some other conditions that show similarity to cirrhosis but it is FOCAL not diffused

Additional picture



- **Main characteristics**

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

In order to diagnose cirrhosis we need to see fibrosis , fibrous tissue forming nodules of regenerative liver parenchyma that is surrounded by fibrous tissue and separated by fibrous septa

If we took small biopsy , we need to be informed whether the disruption is a diffuesd or localized , because it is small , we will not know if the whole liver is disrupted , it can't tell us how diffused the disruption is

Depending on the size of the nodules , we can divide the nodules into :

- **Types :**

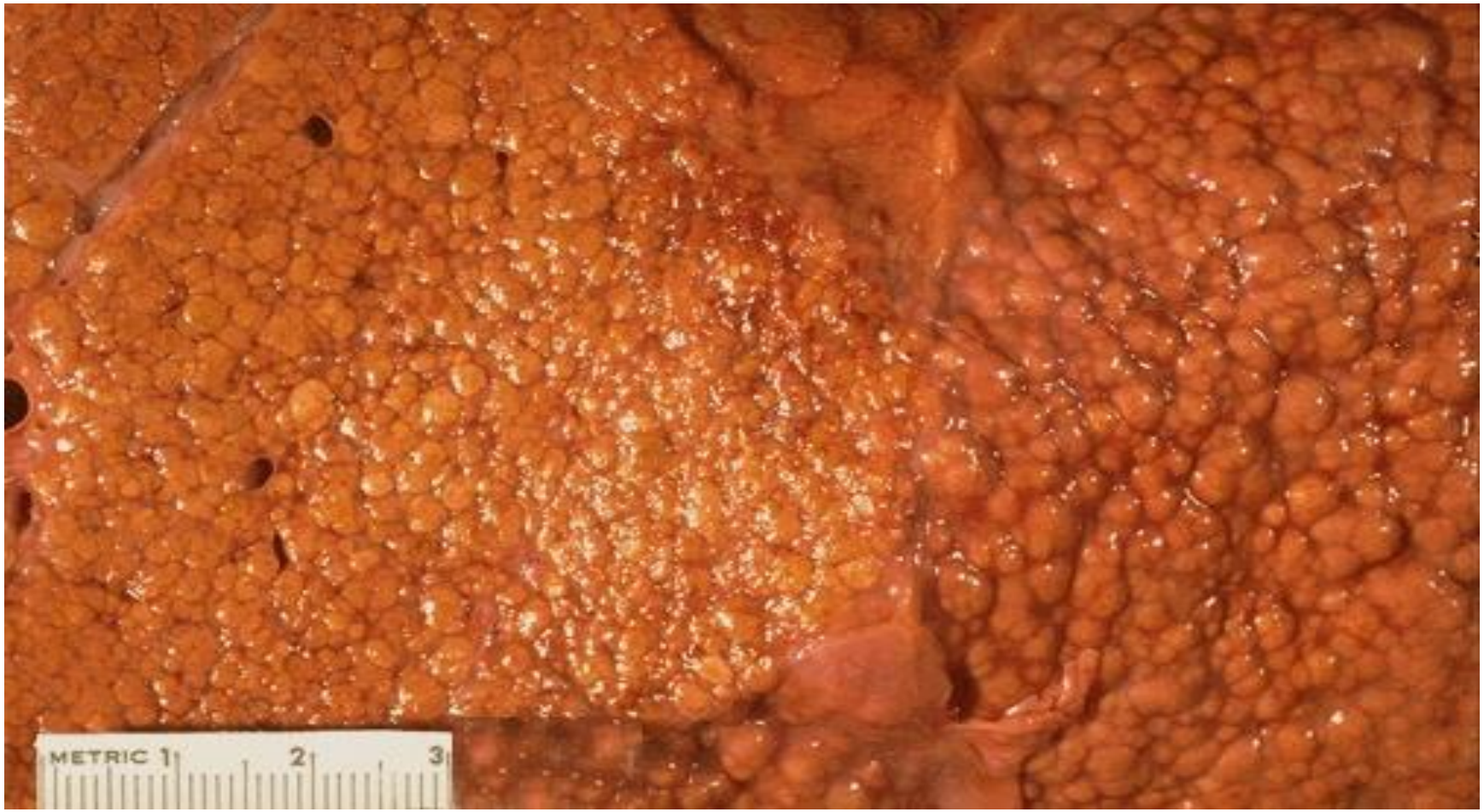
↳ Micronodules < 3mm in diameter

↳ Macronodules > 3 mm in diameter

Sometimes micronodules become macronodules when there is more formation of fibrous tissue

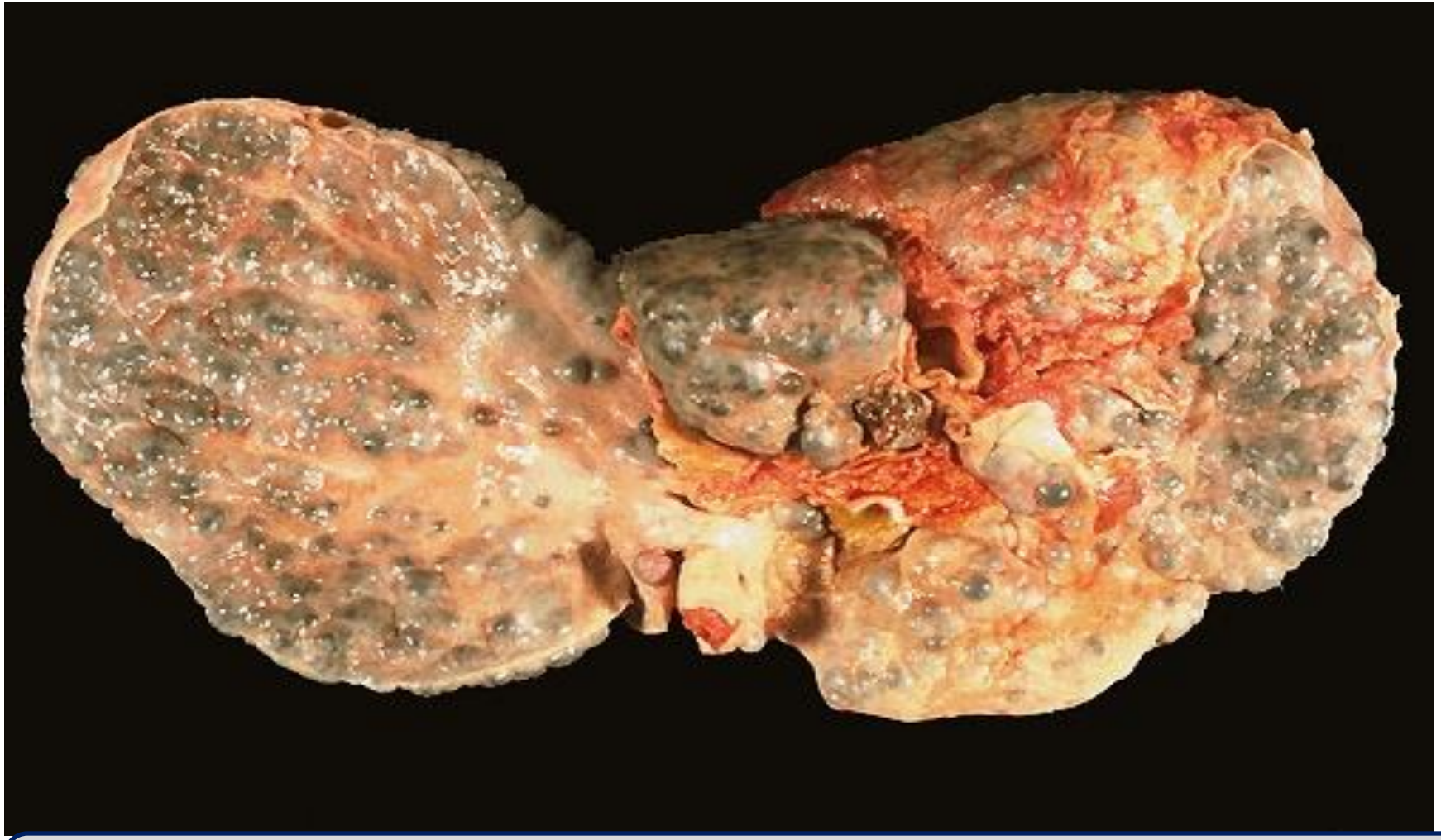
اللهمّ صلّ على سيدنا محمد وعلى آله وصحبه أجمعين

Micronodular cirrhosis



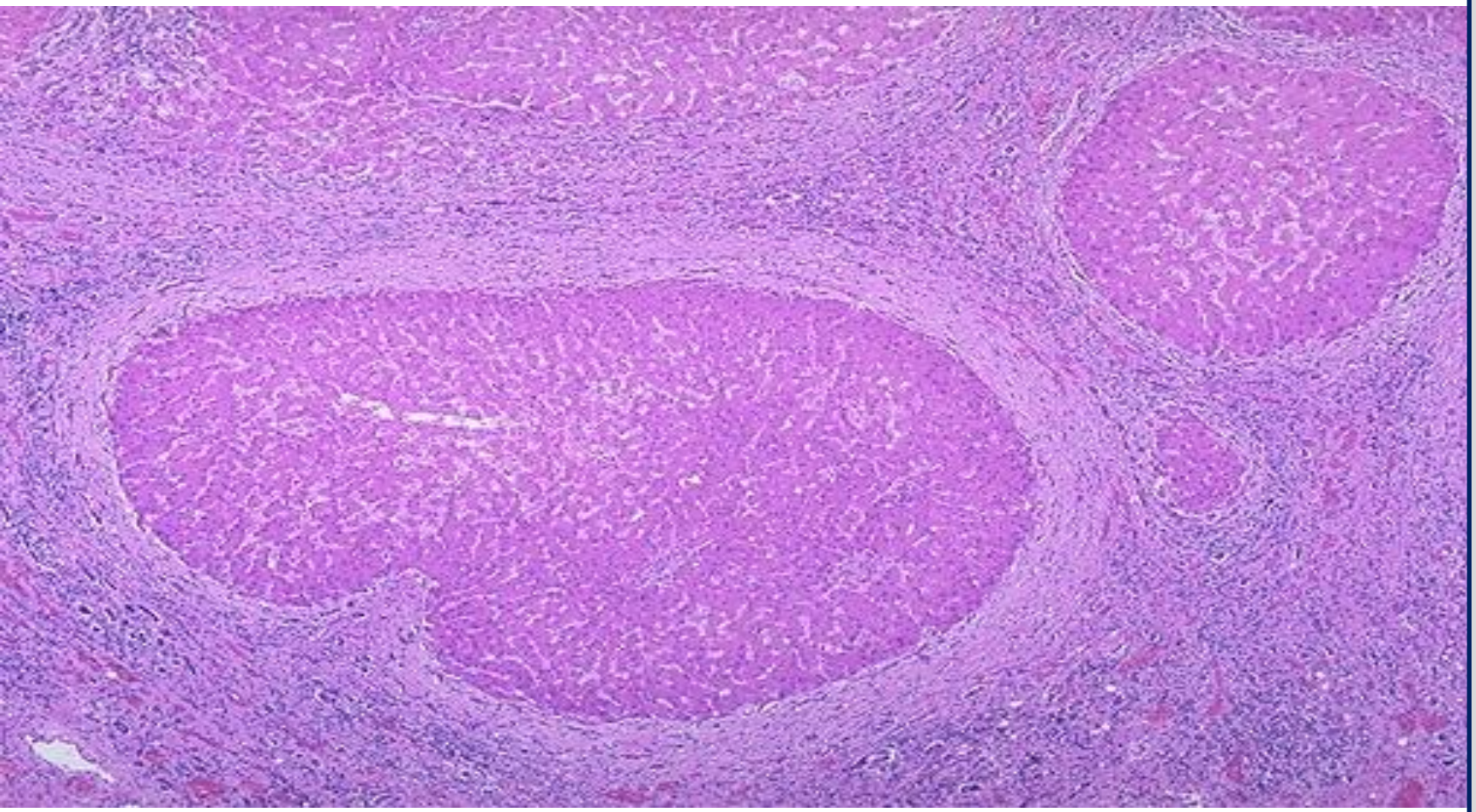
This is a gross appearance to the surface of the liver which shows small diffuesd nodules(INVOLVE ALL THE LIVER)

Macronodular cirrhosis



Macronodular cirrhosis create scarred distorted tissue because of the retraction of fibrous tissue which makes disformity of the liver

Cirrhosis



This is a microscopic appearance of cirrhosis , we have nodules of variable size , composed of regenerative hepatocytes (parenchyma) that is surrounded by fibrous tissue

-Within the fibrous tissue we find blood vessels and inflammatory cells

-If we look at the parenchyma itself , it is regenerative hepatocytes which can carry out some functional hepatocytes , that is why patients with cirrhosis can survive years with normal like function of the liver and they might be asymptomatic because of the function of these nodules

Causes of cirrhosis

If we have seen one of these conditions in the patient we should follow him up

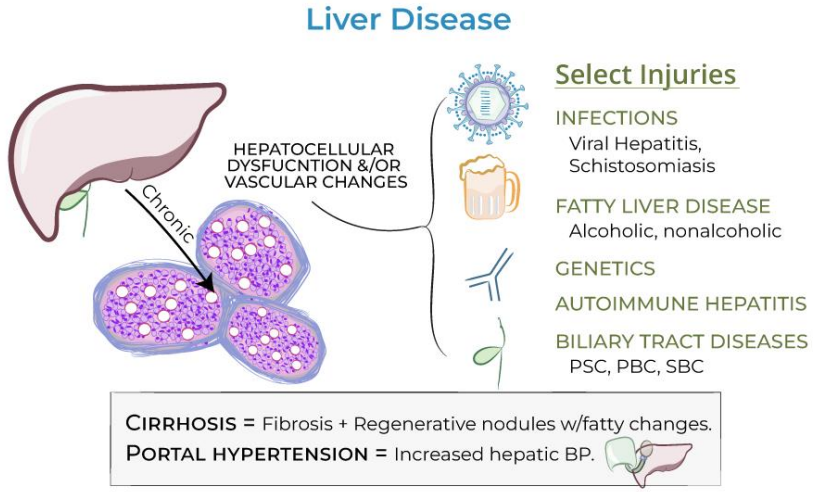
1. **Chronic alcoholism** — The most common cause

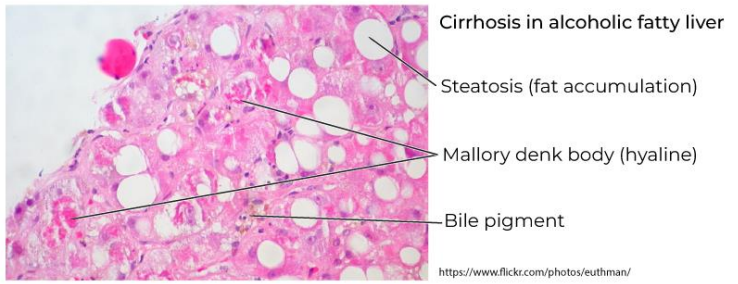
2. **Chronic viral infection HBV & HCV**

3. **Biliary disease** — -When we exclude the first two causes we should think of biliary diseases , certain diseases of the liver primary target biliary system , loss and construction can happen
- Chronic base can produce liver fibrosis because obstruction of biliary system can lead to the damage of surrounding hepatocytes in parenchyma

4. **Hemochromatosis** — Then If we excluded biliary disease , we think of metabolic diseases , and the most common cause here is Hemochromatosis which is characterized by deposition of iron in hepatocytes

Additional picture





5.Autoimmune hepatitis

Autoimmune hepatitis causes changes similar to that in hepatitis (damaging the liver parenchyma) , it is a chronic illness that can progress and give fibrosis

6.Wilson disease

It is also a metabolic disease which is characterized by deposition of copper in hepatocytes

7.α-1- antitrypsin deficiency

Due to enzyme deficiency, even though it is a rare cause but we should consider it if we have cirrhosis

Patients with cirrhosis (fully developed cirrhosis) might show features of cirrhosis not necessarily showing the features of original disease , that is why if the patient was diagnosed by cirrhosis we may not always be able to detect what was the underlaying cause , so for that we should think of these diseases (in previous and coming slides) depending on the patient's profile ,because some diseases present in early stages while others in older patients

8. Rare causes

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

-We consider them when all the other causes are excluded

- They are metabolic diseases , inherited ,due to enzyme deficiencies and characterized by deposition of substances within hepatocytes
- Remember any substance(even it is normally stored in the liver) increases in amount of deposition will stimulate cells regeneration and fibrosis

9. Cryptogenic cirrhosis 10%

It is important when the patient is presented with manifestations related to certain organs to check the liver , take biopsy and see if the liver is involved

More details in the next slides —>

8. Rare causes

Galactosemia & Hereditary fructose intolerance

Galactose and fructose are disaccharides and there is an enzyme deficiencies (which is responsible for breaking them down) so these disaccharides can't be metabolized , this result in deposition of these materials in hepatocytes

Tyrosinosis

Tyrosine is an amino acid , when it is accumulated due to metabolic problems it will cause damage. Patients with tyrosinosis have increased risk of malignancy even if the disease was controlled

Glycogen storage disease III &IV / Lipid storage disease

These are disease that present early in life , so they are pediatric diseases , they are inherited , characterized by enzyme deficiencies leading to accumulation of glycogen and lipids in different organs

8.Rare causes

Drug induced e.g :methyldopa (drug used in the treatment of hypertension)

Don't forget drugs !! Always consider drugs as underlaying cause of liver cirrhosis ,for example --> the chronic use of methyldopa

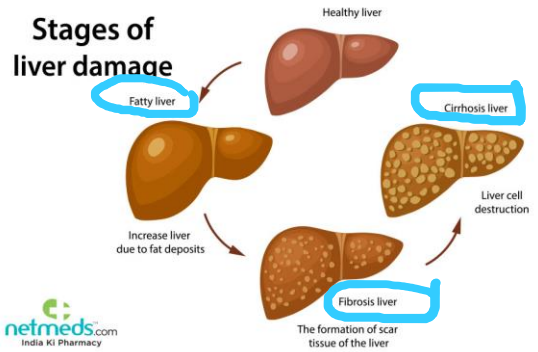
un - known origin for the disease

9. Cryptogenic cirrhosis 10%

When it is difficult to differentiate and know the underlying cause of cirrhosis, then it is cryptogrnic cirrhosis

One of the conditions that later on is recognized as a cause of cirrhosis is non-alcoholic fatty liver disease , related to metabolic problem , in the past we didn't consider it a cause of cirrhosis because we thought fatty changes and fatty infiltration are harmless and reversible , but now we recognizes that NAFD and fatty changes/infiltration in the liver can induce fibrosis

Additional picture



Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

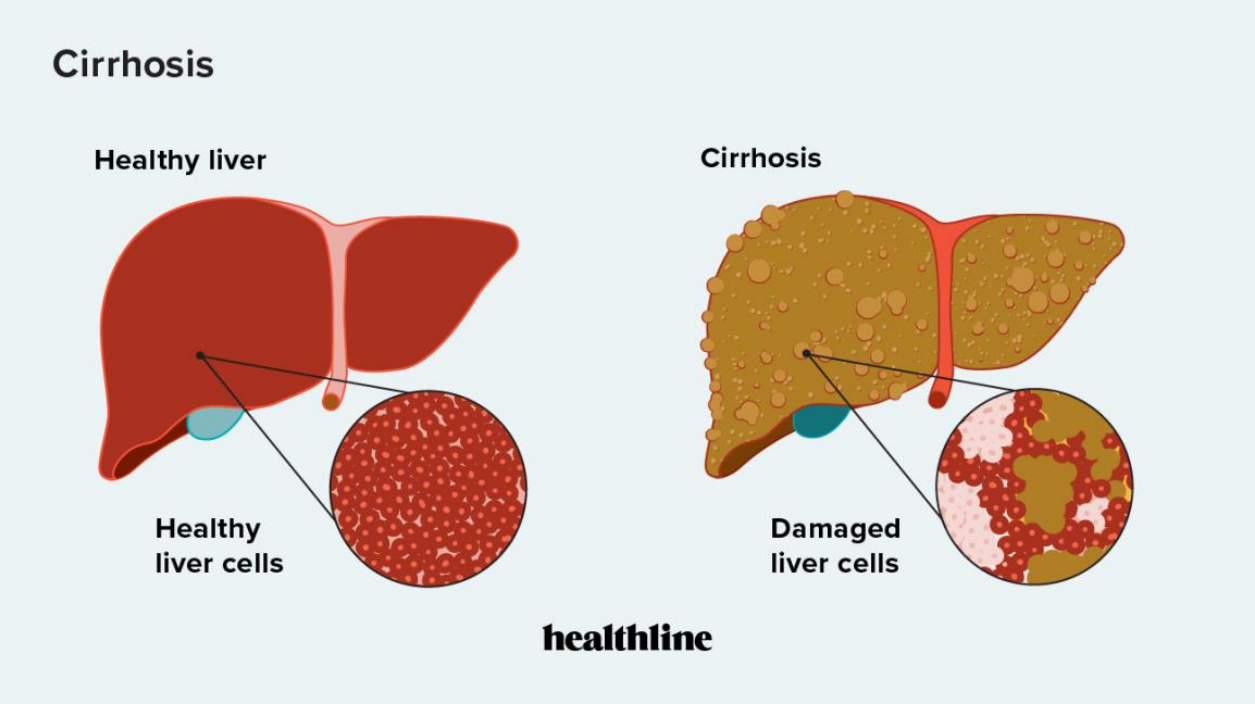
1-Hepatocellular death

2-Regeneration

3-Progressive fibrosis

4-Vascular changes

Additional picture



For details please go to the next slide

In order to have cirrhosis ,we have four requirements :

- Firstly hepatocellular death(or cell damage) , as you would imagine that different diseases which affect the liver can cause hepatocellular damage and cell damage associated with malfunction of hepatocytes and possibility in long term induction of fibrosis
- Secondly Regeneration of hepatocytes " cell damage is followed by cells regeneration " because hepatocytes are regenerative cells and their regeneration capacity is high
- Thirdly ,the regeneration is associated with progressive synthesis of collagen which is part of fibrous tissue , as we said fibrosis in the liver is minimal and can be induced by cells damage .Fibrosis must be in cirrhosis because the nodules are formed by fibrous tissue
- Fourthly , this process of fibrosis is associated with vascular changes and actually the complications of cirrhosis are very related to the development of vascular changes

Cell death should occur over a long period of time & accompanied by fibrosis

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

1. Liver capsule
2. Portal tracts
3. Around central vein

The Capsule itself is fibrous , it is not related to the function of the liver

Normally in parenchyma there is no fibrous tissue, that is why presentation of collagen in any degree in the parenchyma means always there is problem /cell death

- Actually in the parenchyma there is very thin layer in the basement membrane of collagen type 4 (IV) which is important to hold the cells in the basement membrane . If there is cirrhosis all types of collagen will be everywhere

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

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

Space of Disse is the space that connect hepatocytes and sinusoids (which have blood) , hepatocytes should be close to the sinusoids in order to carry it's function so the exchange can occur (the substances that are absorbed from intestines in portal blood should be absorbed by hepatocytes in order to deal with it) or the toxin substance that is resulted from metabolism in hepatocytes should be excreted to the blood .But in cirrhosis when the space of Disse and basement membrane are filled with fibrous tissue these processes will be affected and hepatocytes will be far away from sinsusoids(blood)

The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of Disse

-Perisinusoidal stellate cells act normally as storage cells for vit A & fat

upon stimulation myofibroblast- like cells

↓

transforming growth factor β (TGF-β)

Which stimulate the cells to produce fibrous tissue

↳ Upon disease process they change their function to become cells that produce collagen and start to fill spaces of Disse

Any damage effect or inflammatory process in the liver can induce the stimulation of ito cells to become cells that produce collagen

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

1-reactive oxygen species

Which can affect the cells in DNA and protein synthesis , causing damage to hepatocytes

2-Growth factors

Include fibrinogen growth factor

3-cytokines TNF, IL-I, lymphotoxins

So when we have disease process we have injury followed by the releasing of these factors to increase synthesis of fibrous tissue leading to the change in agriculture

Fibrosis(bridging fibrosis) ->increase amount of laying down collagen in the parenchyma -> forming nodules

Explanation for the previous 2 slides :

🧠 1. Who produces collagen in cirrhosis?

The **main source of collagen** in liver cirrhosis is:

> **Perisinusoidal stellate cells (Ito cells)**

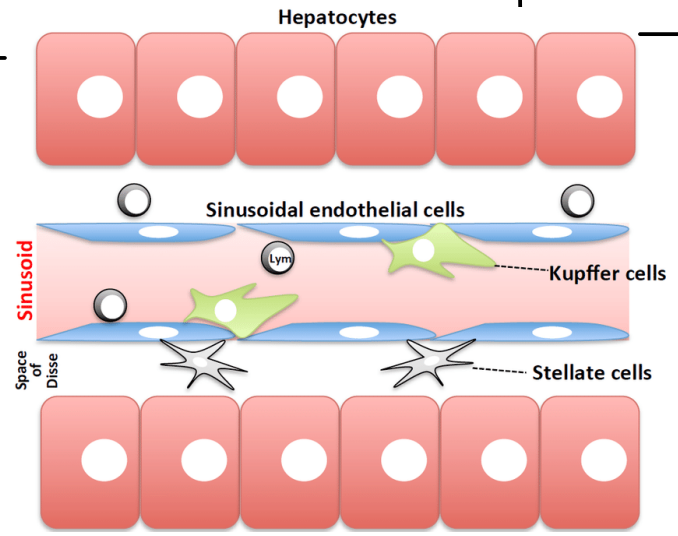
- These cells are located in the **space of Disse** (the small space between hepatocytes and sinusoidal endothelial cells).
- Under **normal conditions**, they **store vitamin A and fat**.

⚠️ 2. What happens during liver injury or inflammation?

When there is **liver damage** (from alcohol, hepatitis, toxins, etc.):

- These **Ito cells become activated** and **change their function**.
- They **transform into myofibroblast-like cells** that **produce collagen**.
- This transformation is stimulated by **Transforming Growth Factor-beta (TGF-β)**.

💥 **TGF-β** is a major signal that tells these cells:
"Start making scar (fibrous) tissue!"



🔥 3. What activates stellate cells to start fibrosis?

There are 3 main **stimuli**:

Stimulus	Effect
1. Reactive oxygen species (ROS)	Damages DNA and proteins in liver cells → triggers inflammation and repair
2. Growth factors	(e.g., fibrinogen growth factor) → Promote cell growth and fibrogenesis
3. Cytokines	TNF (Tumor Necrosis Factor), IL-1, IL-6, IL-18, Lymphotoxins → stimulate inflammation and cell activation

🧱 4. What is the result of all this?

- Stellate cells **lay down collagen** in the liver.
- This forms **fibrous bridges** between portal tracts and central veins
- The **architecture is distorted**, and **nodules form**.
- This is called **"bridging fibrosis"**, a **hallmark of cirrhosis**.

-The vascular changes include :

1-Loss of sinusoidal endothelial cell fenestration

2-development of vascular shunts as :

- Portal v- hepatic v
- Hepatic a – portal v

3- defect in liver function

4- Loss of microvilli from hepatocytes →↓ transport capacity of the cells

It will reduce the surface area and lower the efficiency of exchange

Important consequence of laying down the fibrous tissue is vascular problems, when the fibrous tissue start to surround the vessels and it is hard tissue not elastic and produce some pressure and rigidity on the vessel's wall , that will create some difficulty in blood flow so the vessels will try to compensate for these difficulties (slowing blood flow)by creating shunts that connect the arterial and venous circulation so :

1. Portal vein –hepatic vein shunt and hepatic artery –portal vein shunt

This means that the circulation and flow of blood in the liver is altered and the function is affected (the normal =blood come through sinuses ,exchange and interact with hepatocytes and then leave the liver through central vein and hepatic vein)

- Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
- the movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and the plasma is markedly impaired.
- These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell.

-Clinical features of cirrhosis :

-Silent

-Anorexia, wt loss, weakness

-Complications :

1-Progressive hepatic failure

2-Portal hypertension

3-Hepatocellular carcinoma

The End

The nodules (regenerative hepatocytes) for some time it will carry the function so patients can have a period without serious manifestations until the hepatocytes overloaded and can't stand the conditions and can't increase the functional capacity , in this stage the patient will start to have non specific clinical manifestations ,later on the patient will develop significant clinical manifestation related to progressive hepatic failure (liver failure) & portal hypertension and increase in the blood pressure of the veins (leading to shunts) ,the heigh BP of arterial circulation will be reflected in low pressure in portal circulation &increase the risk of developing malignancy in parenchyma , the patient who don't suffer from anything , once he develop tumors he will start to have manifestations of malignancy and the health will be lower than normal