TOXIC RESPONSES OF LIVER

Hepatotoxicity

- **Hepatotoxicity** implies chemical-driven liver damage. They cause acute and chronic liver disease. The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents.
- The potential toxicants are:

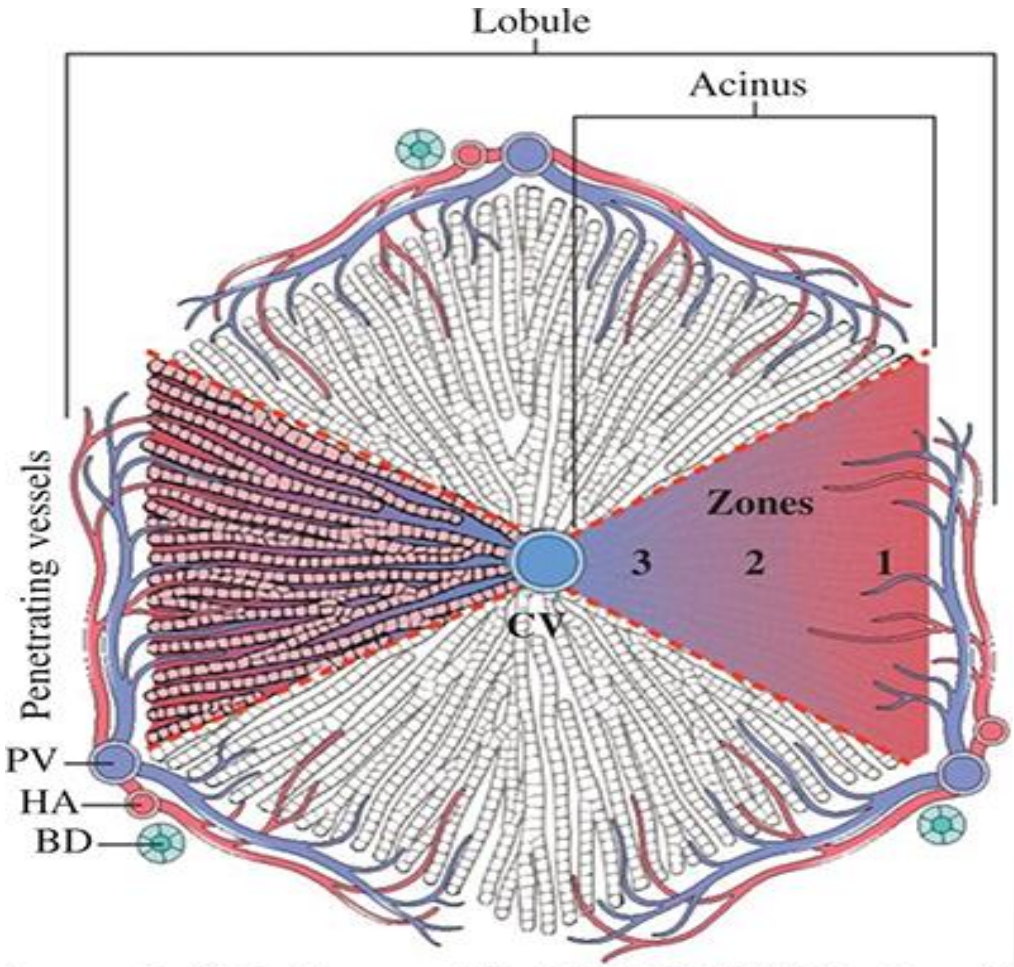
I. **Carbon tetrachloride**
II. **Vinyl chloride**
III. **Drugs**
IV. **Alcohol**
V. **Herbal medicines etc…**

Structural Organization of Liver:

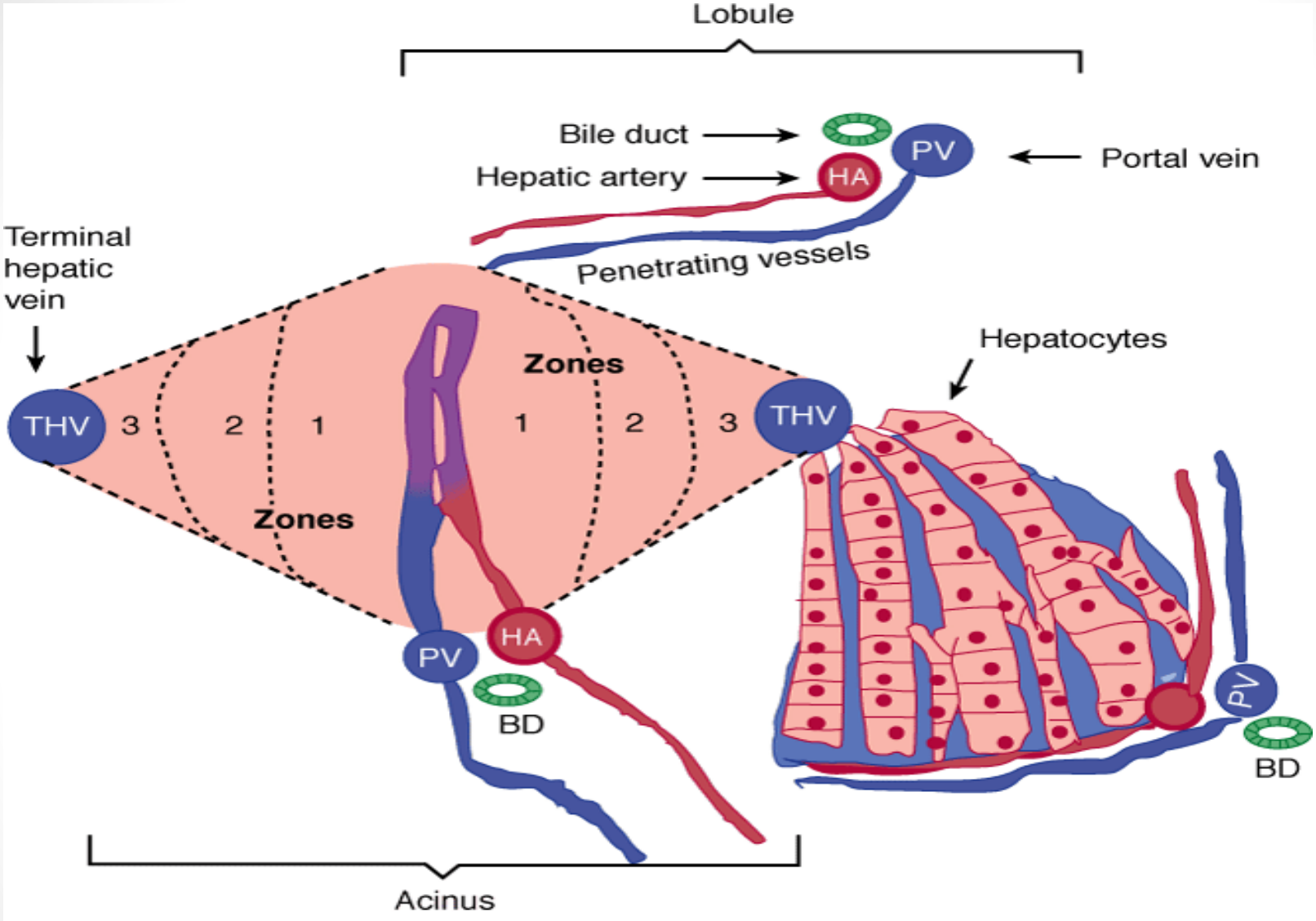
- There are 2 concepts of organization of liver into operational units:

I. Lobule

II. Acinus



Source: Curtis D. Klaassen, PhD, DABT, ATS, FAASLD: *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 9e



Source: Klaassen CD, Watkins JB: *Casarett & Doull's Essentials of Toxicology, 2nd Edition:* http://www.accesspharmacy.com

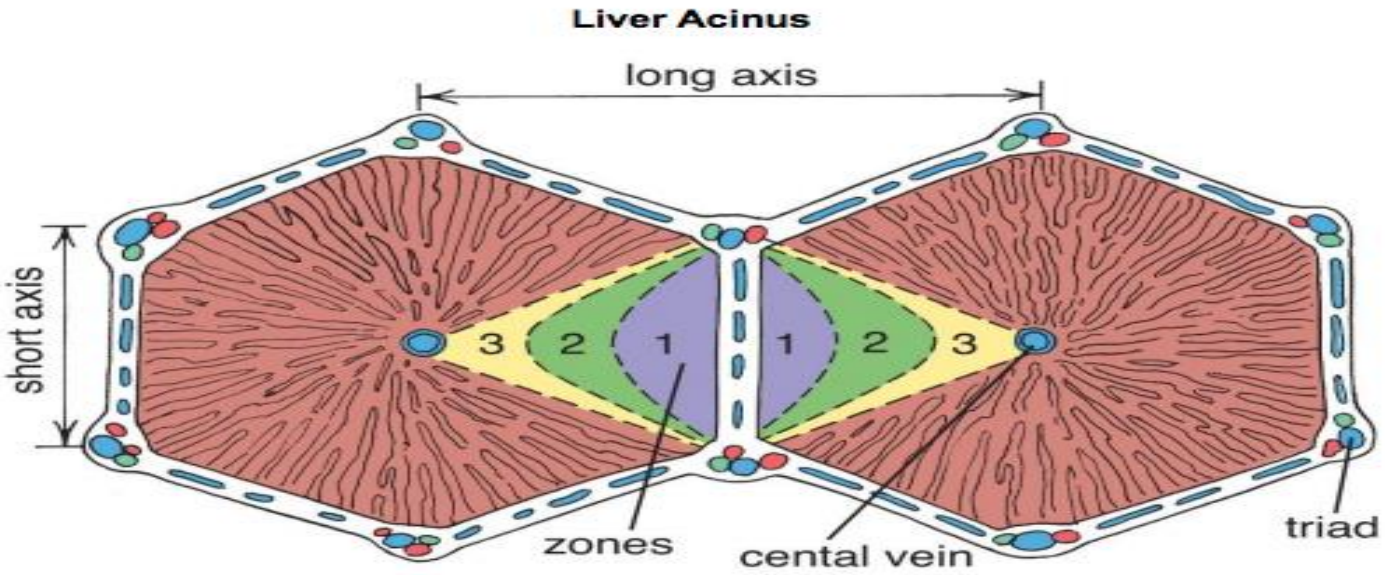
Zones of Acinus:

- **The acinus is roughly divided into 3 zones** :

I. **Zone 1**: closest to the entry of blood . They are the best oxygenated.

II. **Zone 2**: Intermediate.

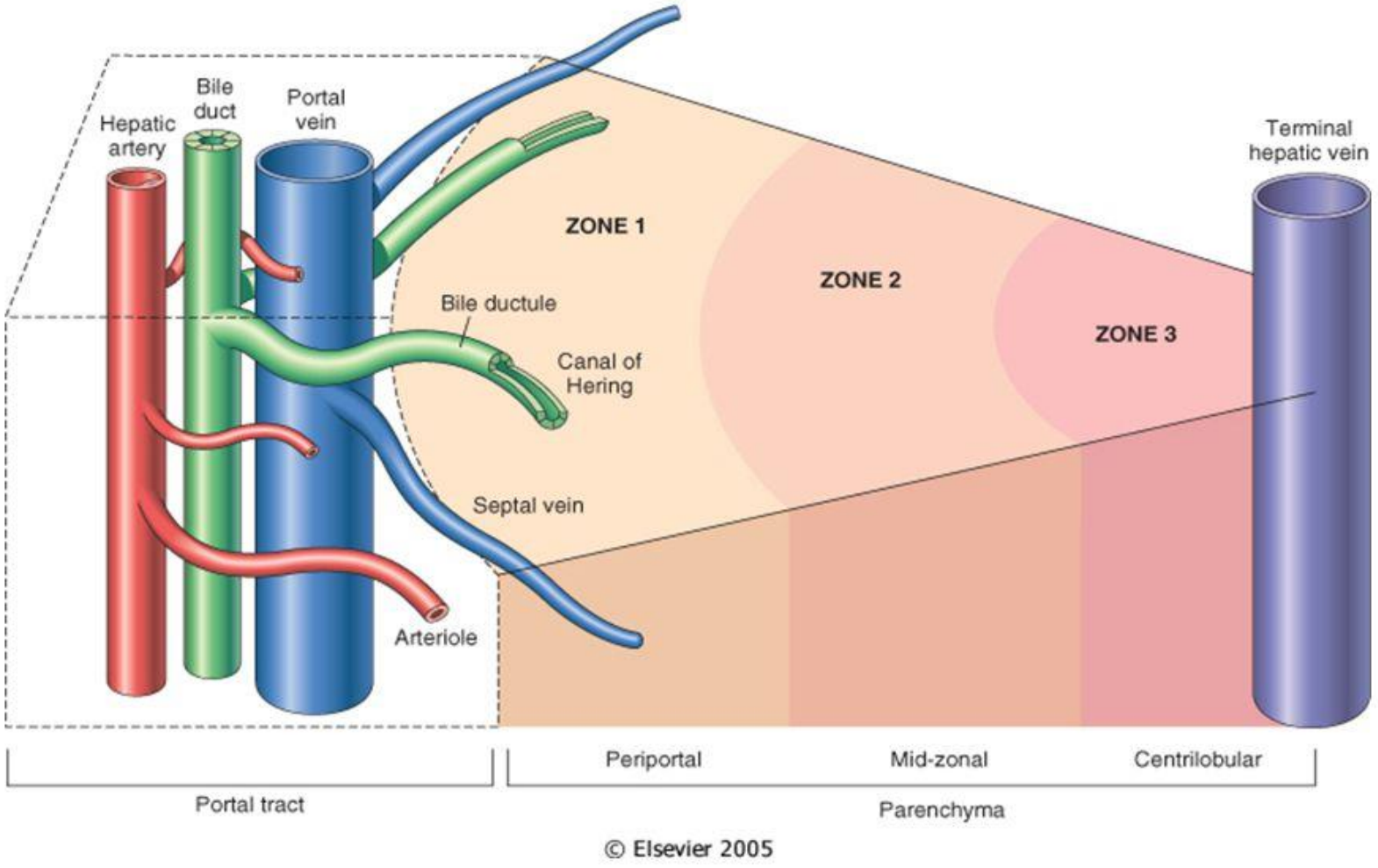
III. **Zone 3**: away from the terminal hepatic vein.



lobule

- They arise from central vein.
- At the corners they have portal triad.(bile duct , portal vein and hepatic artery).
- Consists of three regions:
- **Centro lobular**
- **Midzonal**
- **Periportal.**

Regions of Hepatic Lobule:

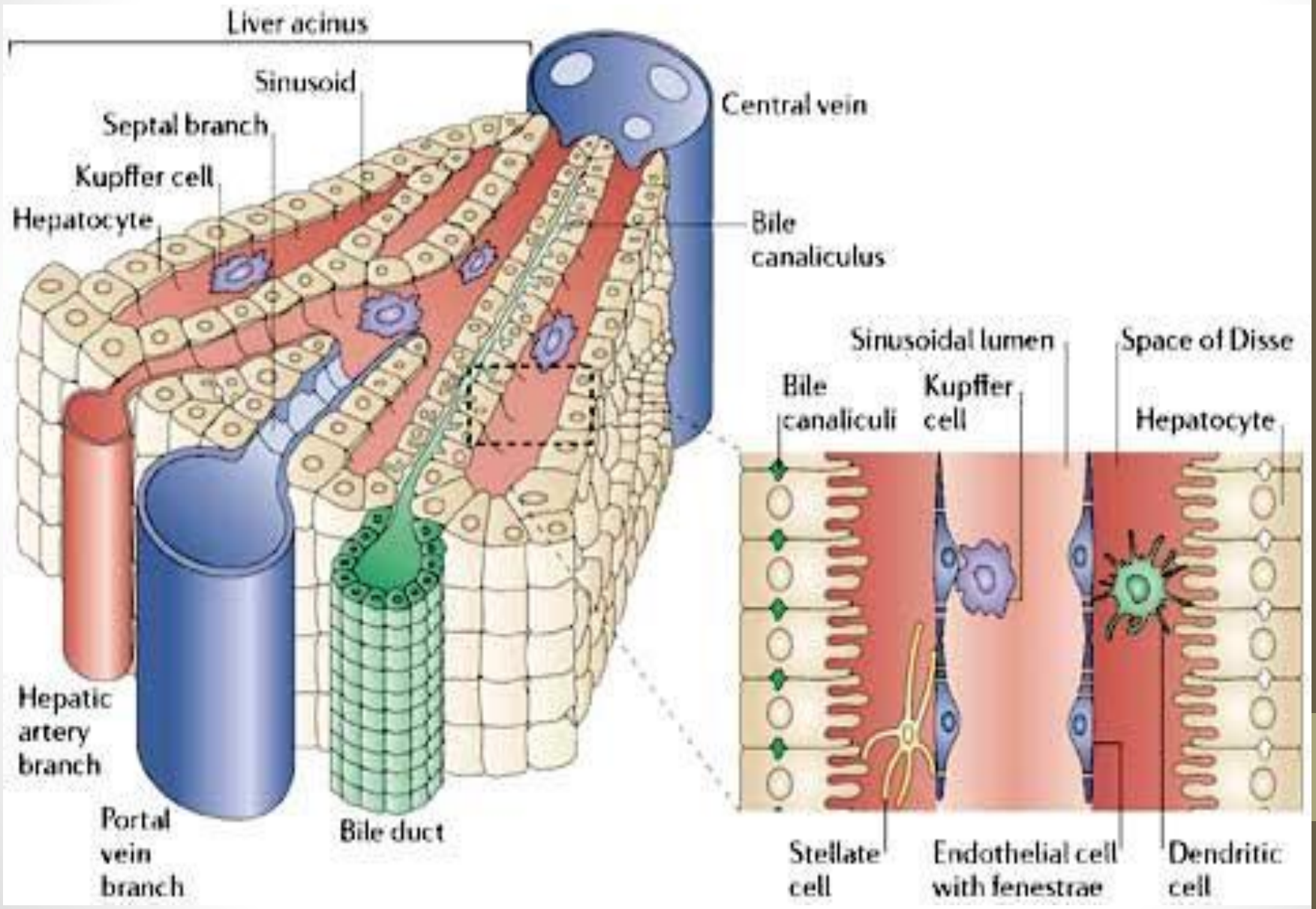


Hepatic Sinusoids:

- They are low pressure vascular channels that receives blood from terminal branches of **hepatic artery** and **portal vein.**
- They are located in the **space of disse** between **sinusoidal endothelial cells** and **hepatocytes.**
- They consist of 3 types of cells:

I. **Endothelial cells** (porous and have scavenging functions)
II. **Kupffer cells** (are macrophages , ingest and degrade particulate matter)
III. **Stellate cells** (site of storage for vitamin A)

Hepatic Sinusoid structure:



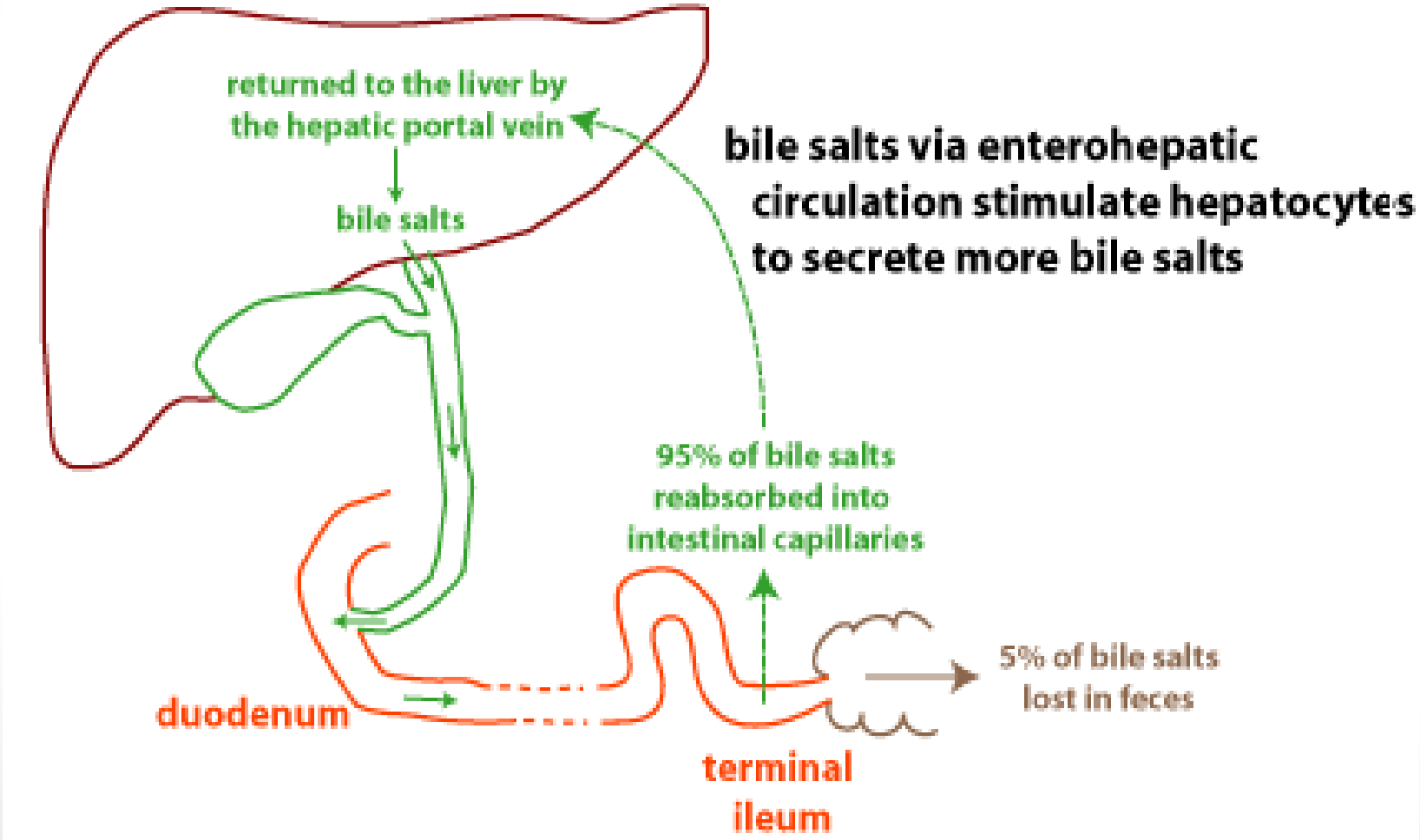
Bile Formation:

- It is a yellow fluid containing **bile acids, glutathione, phospholipids, cholesterol, bilirubin and other organic anions, proteins and xenobiotics .**
- it is essential for :

I. Uptake of lipid nutrient from small intestine.
II. Protection of the small intestine from oxidative insults.
III. Excretion of endogenous and xenobiotics.

- Bile can be stored and concentrated in the gallbladder before its release into the duodenum.

Bile formation release pathway:



Mechanisms and types of toxin-induced injury:

- Responses of liver to toxicant exposure depends on:

1. Intensity of insults
2. No. of cells affected
3. Duration of exposure

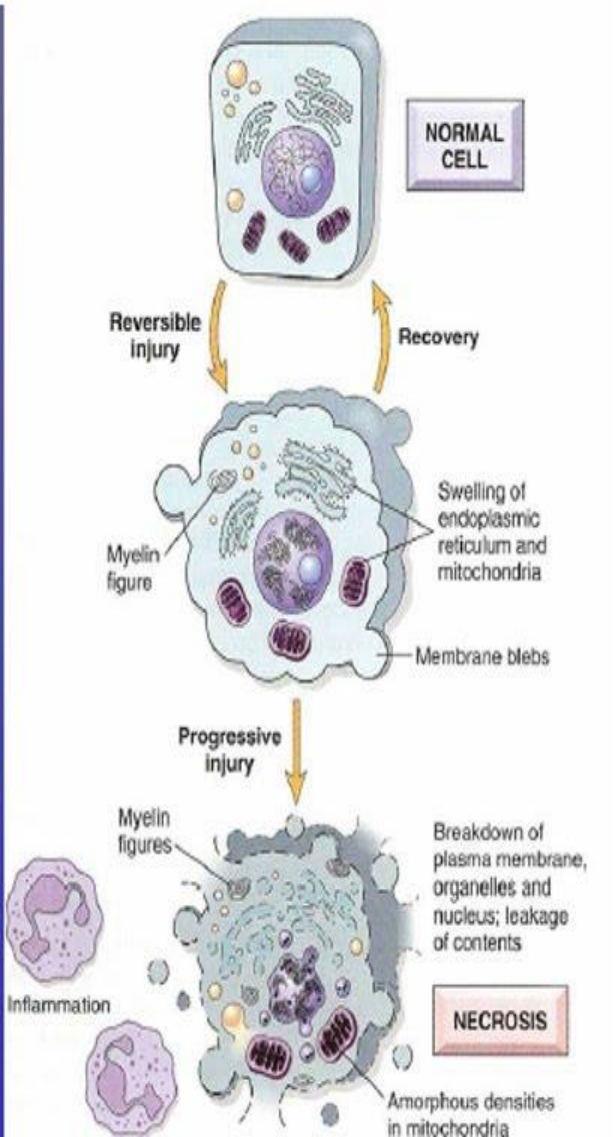
- **Milder stress:** cause reversible dysfuction
- **Acute stress:** leads to necrosis

1. Cell death

Differential features of apoptosis and necrosis	
Apoptosis	**Necrosis**
Affects single cells	Affects groups of neighboring cells
No inflammatory response	Significant inflammatory response
Cell shrinkage	Cell swelling
Membrane blebbing but integrity maintained	Loss of membrane integrity
Increased mitochondria membrane permeability, release of proapoptotic proteins and formation of apoptotic bodies	Organelle swelling and lysosomal leakage
Chromatin condensation and non-random DNA fragmentation	Random degradation of DNA
Apoptotic bodies ingested by neighboring cells	Lysed cells ingested by macrophages

Necrosis

Apoptosis



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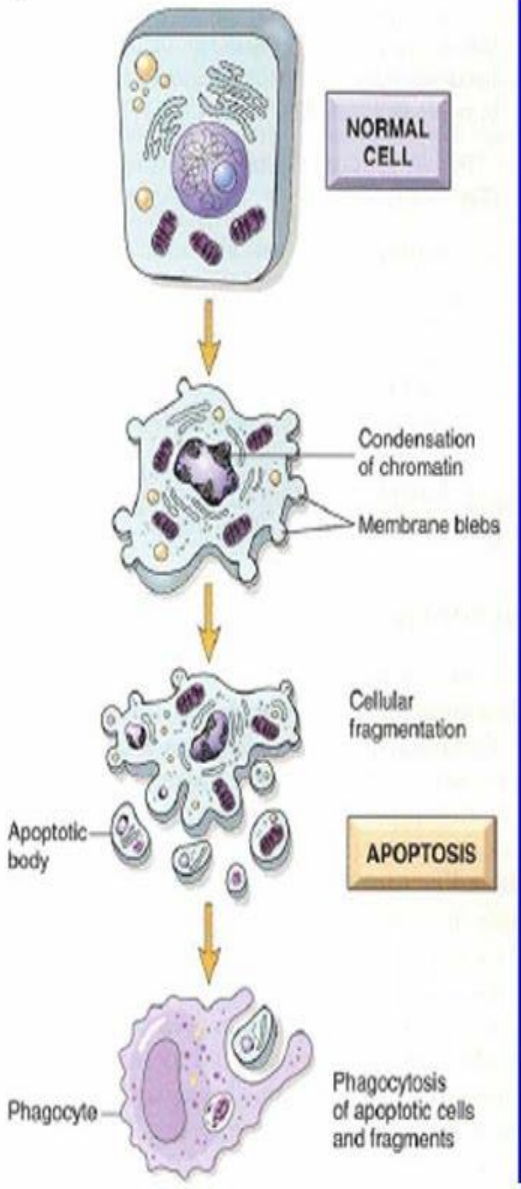


2. Bile duct Damage

- It is called **Cholangio destructive cholestasis.**
- **It leads to:**

➢Elevation in activities of enzymes

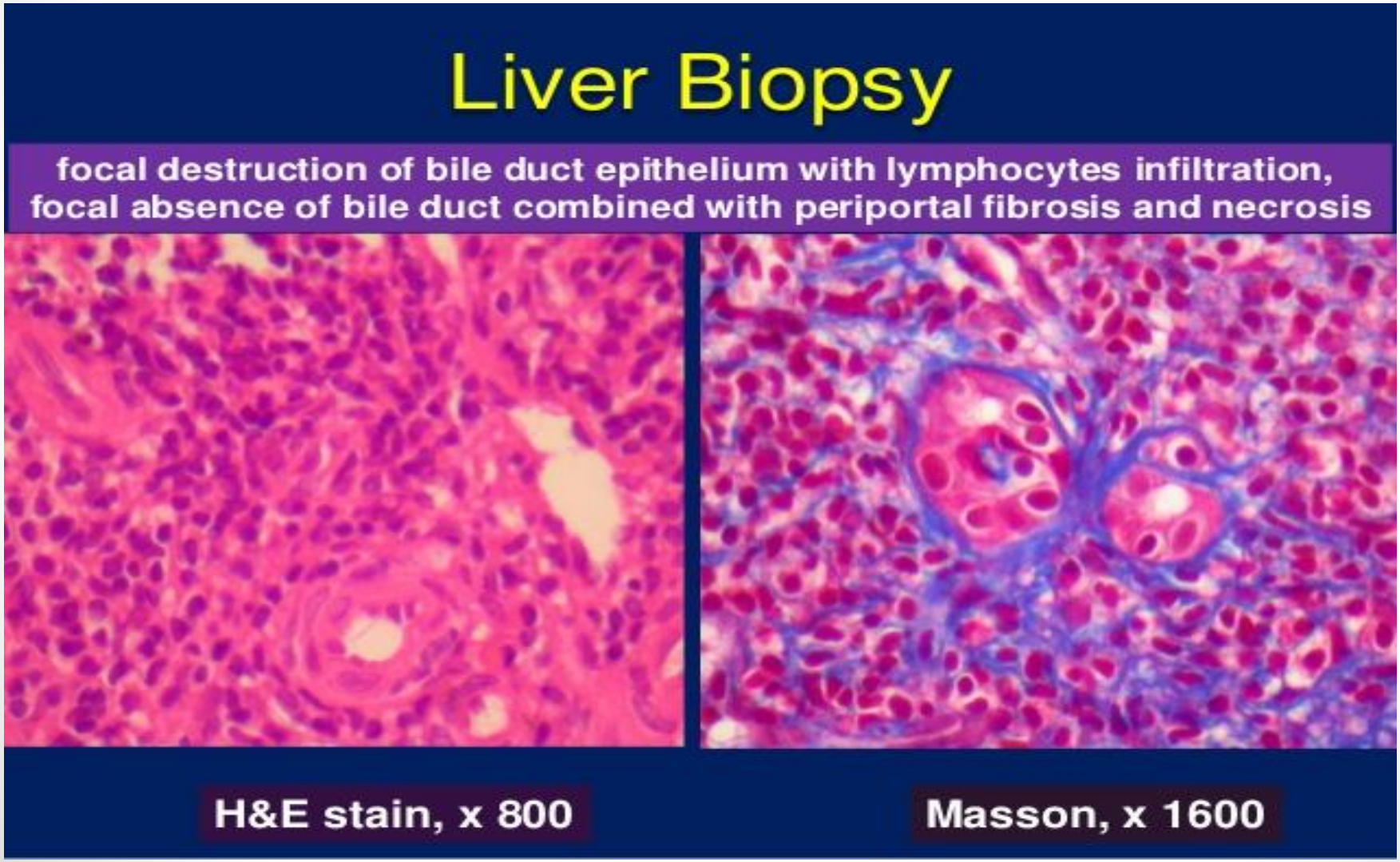
➢Serum level of bile acid and bilirubin rises

➢Initial lesions

➢Inflammation of cells

➢Swollen biliary epithelium which leads to **PBS**(primary biliary cirrhosis).

- In rare cases Permanent damage or even loss of bile ducts occur called **Vanishing bile duct syndrome.**



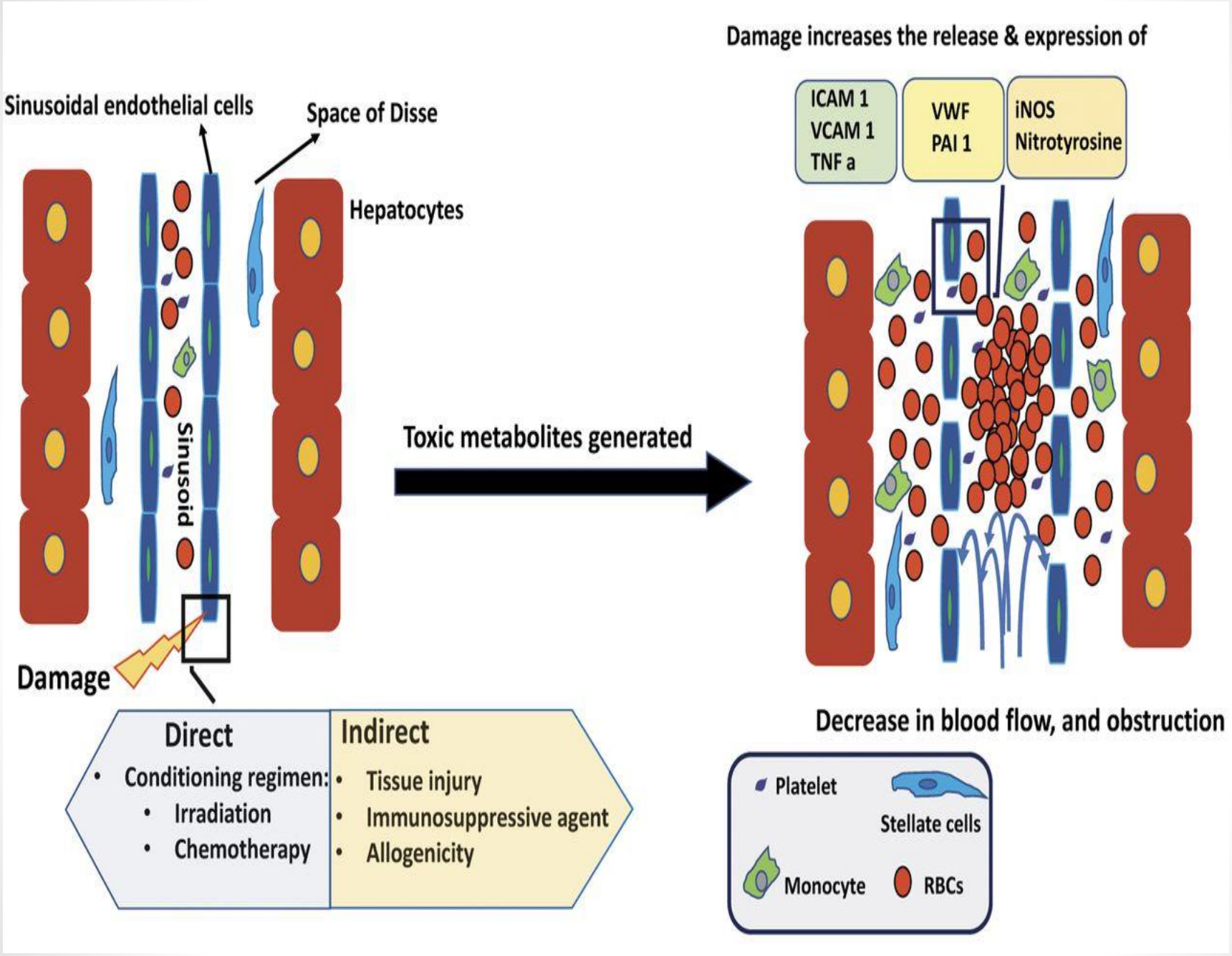
3. Sinusoidal Damage:

- Sinusoidal functional integrity can be compromised by

I. **Dilation**

II. **Blockade** of its lumen by destruction of its endothelial cell wall.

- Dilation of the sinusoid will occur when efflux of hepatic blood is impede leads to **peliosis hepatitis.**
- Loss of barrier due to injury to endothelial cells and accumulation of blood known as **hypovolemic shock.**
- Gaps in sinusoids due to loss of endothelial cells is called **veno-occlusive disease).**


Sinusoidal endothelial cells
Space of Disse
Hepatocytes
Sinusoid
Damage
Toxic metabolites generated
Damage increases the release & expression of
ICAM 1
VCAM 1
TNF a
VWF
PAI 1
iNOS
Nitrotyrosine
Decrease in blood flow, and obstruction
Direct
Conditioning regimen:
Irradiation
Chemotherapy
Indirect
Tissue injury
Immunosuppressive agent
Allogenicity
Platelet
Stellate cells
Monocyte
RBCs

4.Disruption of the cytoskeleton:

- Different toxins disrupt the integrity of hepatocyte cytoskeleton by affecting vital proteins:

I. **Phalloidin** (alter the actin rich web of the hepatocyte cytoskeleton)

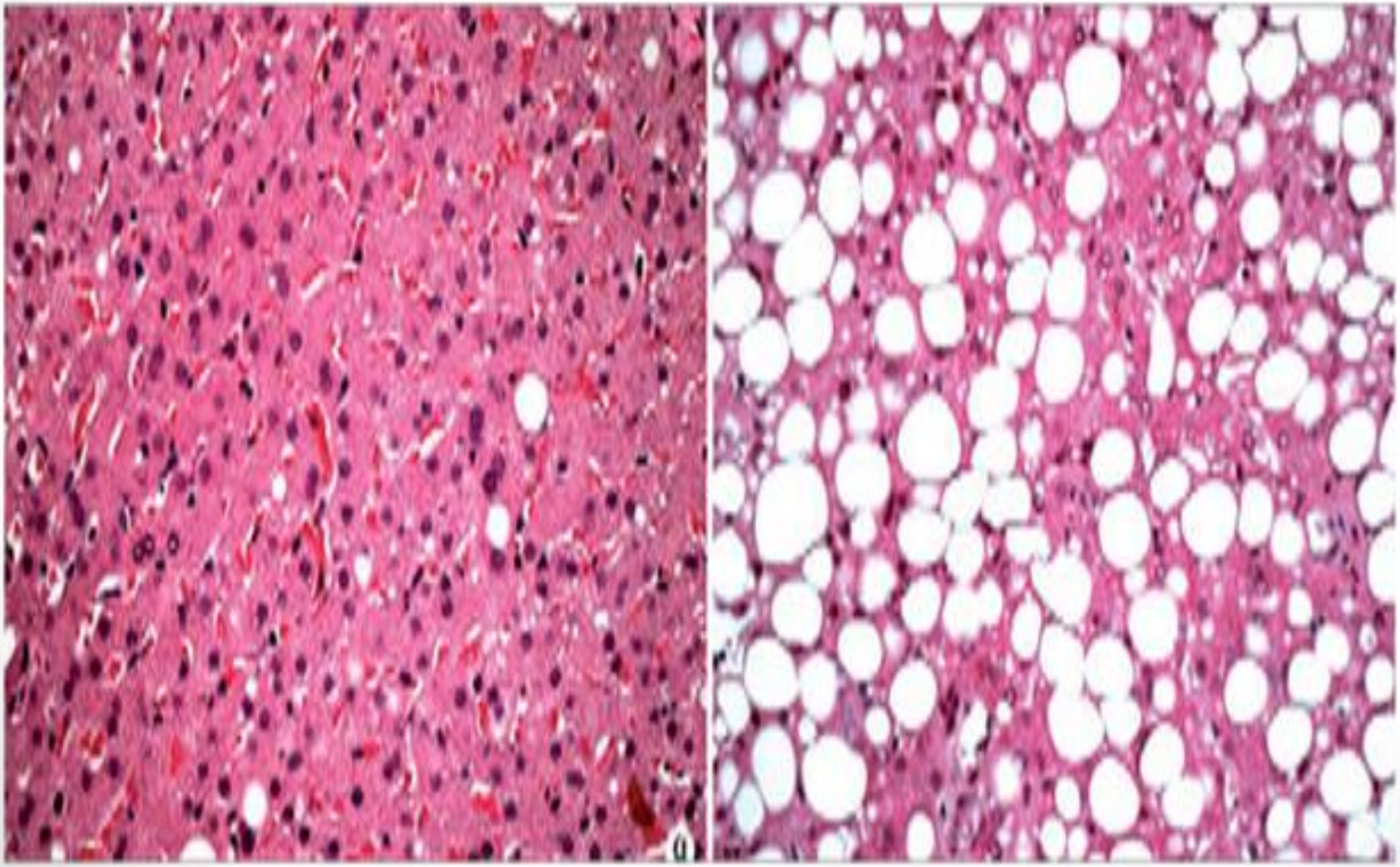
II. **Microcystin** (leads to the hyper phosphorylation of cytoskeleton proteins)

5.Fatty liver(steatosis):

- It includes increase in hepatic lipid content <5% by weight than normal liver.
- Excess fat appear as **round empty vacuoles** that displace the nucleus to periphery of cell.
- **Obesity, sedentary lifestyle, alcohol , drugs and hepatotoxins** are the common causes.
- Based on fat droplets , it is differentiated in :

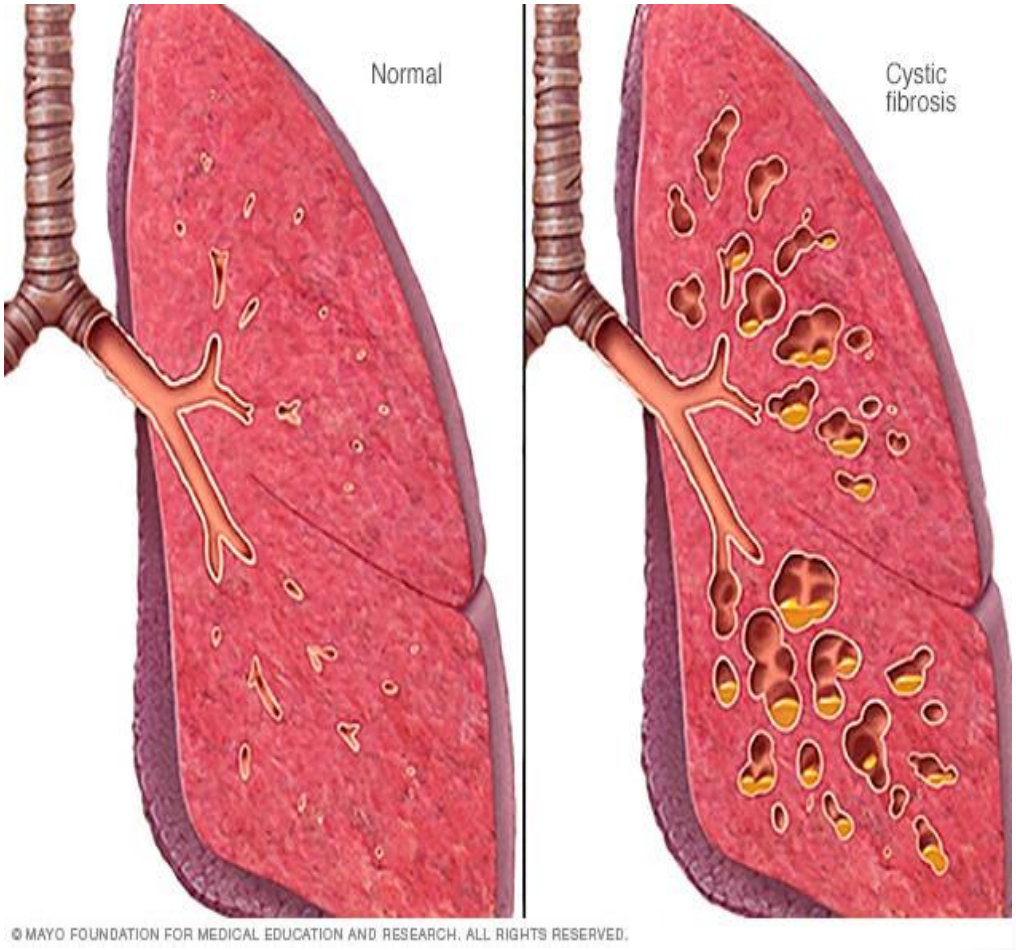
I. **Macrovesicular steatosis**
II. **Microsvesicular steatosis**

Steatosis of Liver:



6.Fibrosis and Cirrhosis:

- **Fibrosis** is formation of large scars tissues in liver.
- It occurs when liver attempts to repair or replace the damaged cells.
- Mainly caused by pollutants , drugs and viral or bacterial infections.

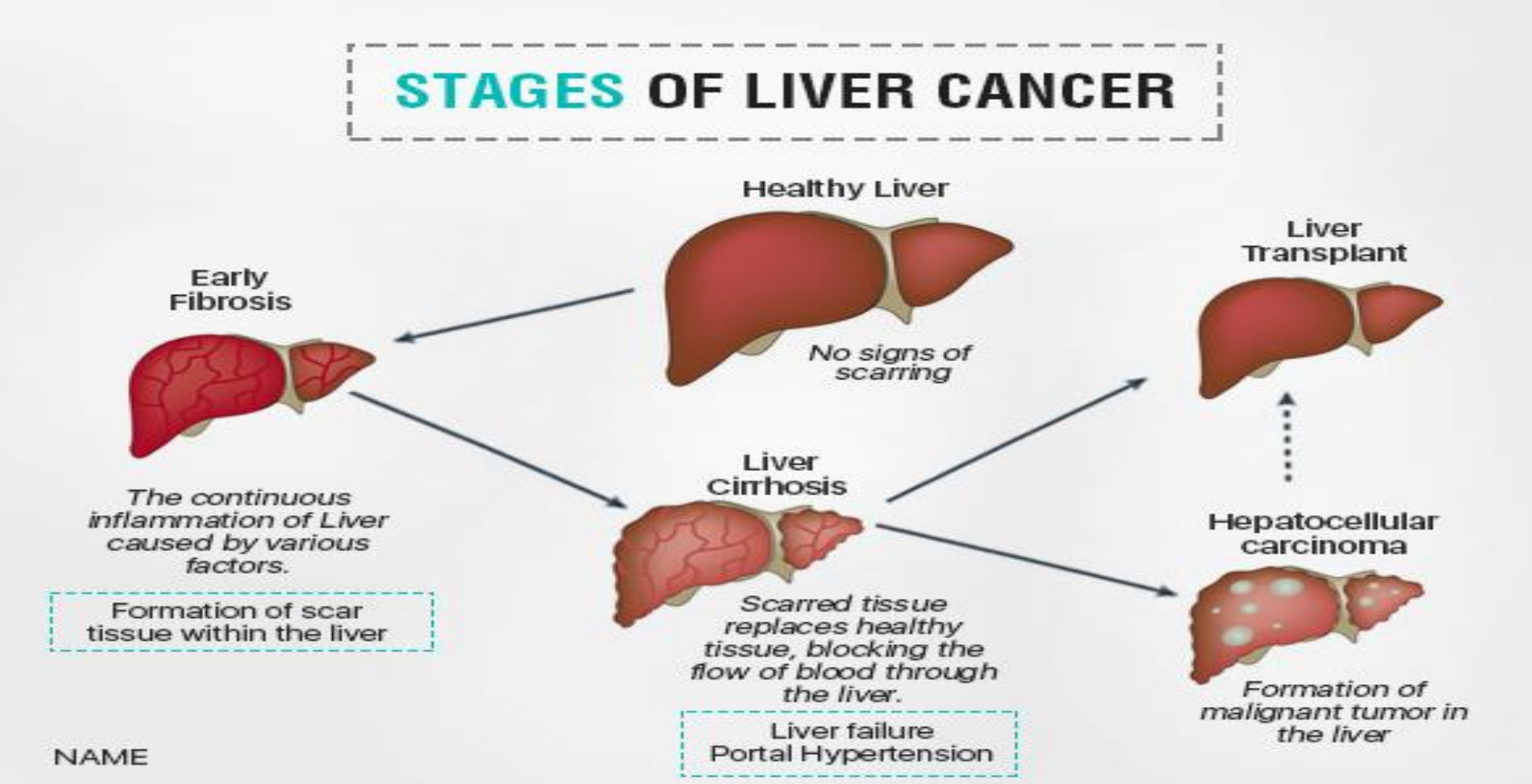


- In **Cirrhosis** Liver does not function properly because normal tissues are replaced by the scar tissues completely.
- Mainly caused by :

I. Alcohol
II. Hepatitis B
III. Hepatitis C
IV. Non-Alcoholic fatty liver disease

7.Tumors:

- The most frequent **malignant** (primary liver cancer) is **Hepatocellular carcinoma HCC**.
- In **benign tumors** there is a mass of abnormal blood vessels called **Hemanginomas.**



Key points:

- **The liver's strategic location between intestinal tract and the rest of the body facilitates its maintenance of metabolic homeostasis in the body.**
- **The liver extracts ingested nutrients, vitamins, metals, drugs, environmental toxicants, and waste products of bacteria from the blood for catabolism, storage, and/or excretion into bile.**
- **Formation of bile is essential for uptake of lipid nutrients from the small intestine, protection of the small intestine from oxidative insults, and excretion of endogenous and xenobiotic compounds.**
- **Cholestasis is either a decrease in the volume of bile formed or an impaired secretion of specific solutes into bile, which results in elevated serum levels of bile salts and bilirubin.**
- **Liver pathophysiology include apoptosis, necrosis , bile duct and sinusoidal damage, disruption of cytoskeleton, fatty liver , fibrosis and cirrhosis and tumors.**