Al-Mustaqbal University College
Department of Pharmacy
General Toxicology
4th stage
Lecture: 5

Toxic Response on Liver

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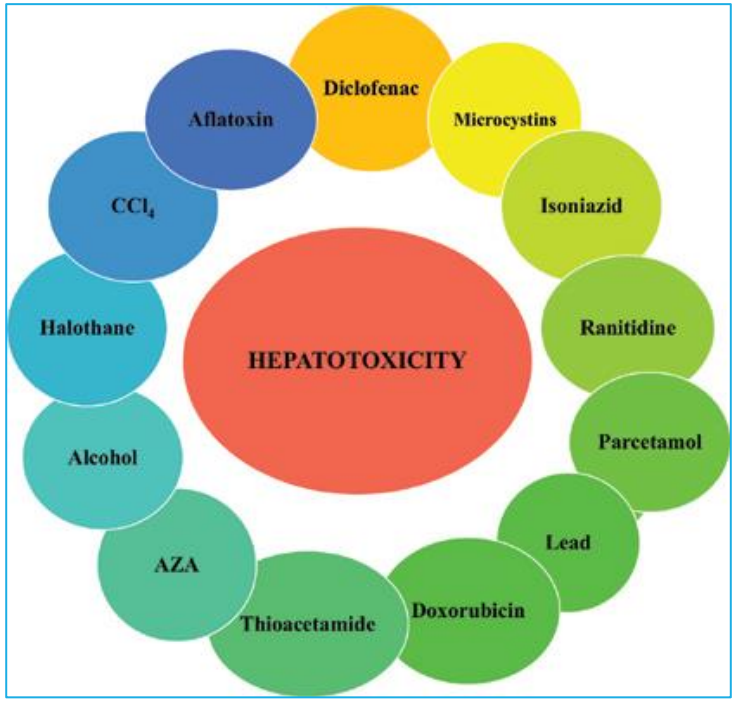
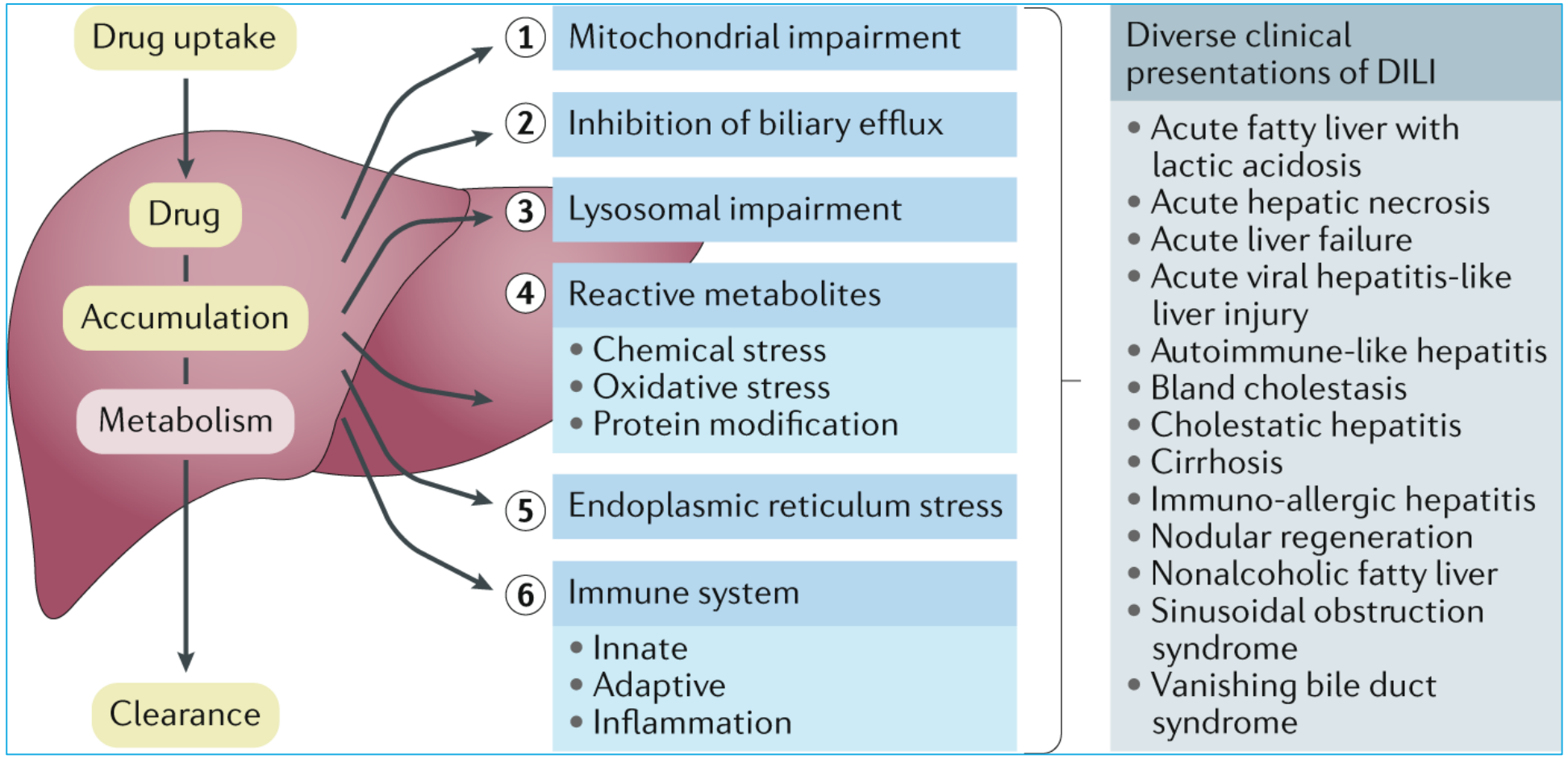
Hepatotoxicity

✓**Liver injury** can arise from exposure to many types of chemicals, including drugs, environmental pollutants, occupational chemicals, plant toxins, and others.

✓Major **adverse responses** of the liver include steatosis (fatty liver), cell death, cholestasis, vascular damage/ dysfunction, fibrosis, and cancer.



Hepatotoxicity



Hepatotoxicity

- ✓The specific response of the liver to a chemical insult depends on the intensity and duration of the exposure and the cell population(s) affected.
- ✓Mild stresses may cause reversible cellular dysfunction and can prompt a reparative response.
- ✓However, sufficient acute exposure to many chemicals can result in serious liver injury and irreversible dysfunction.

1. Cell Death

✓**Cell death from chemical exposure is known to occur by several different molecular pathways.**

✓**Resulting modes of cell death include:**

1. **Oncotic necrosis**
2. **Apoptosis**
3. **Pyroptosis**
4. **Necroptosis**

Oncotic necrosis

✓**It is often referred to simply as "necrosis," characterized by:**

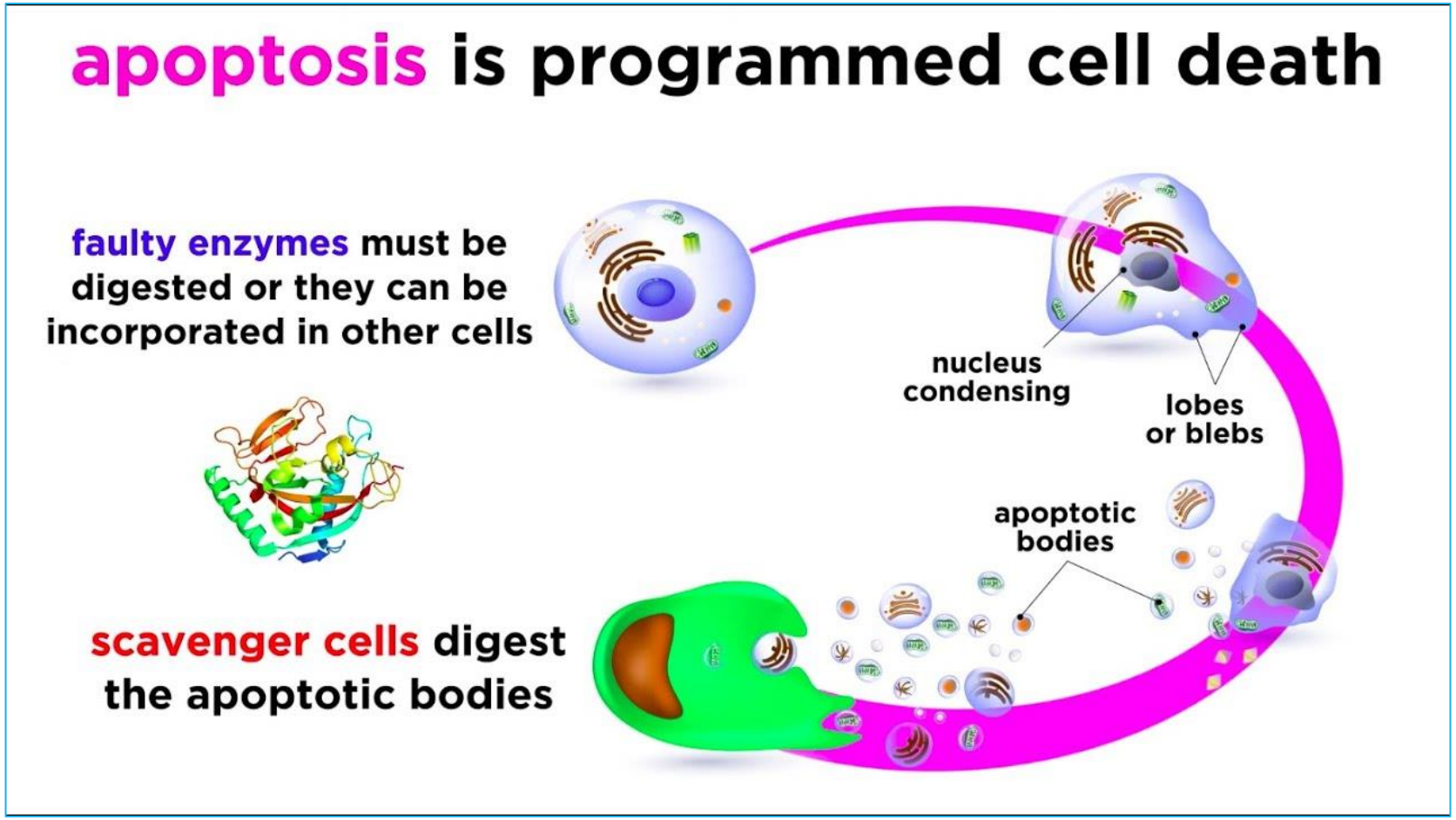
1. **Cell swelling**
2. **Leakage of cellular contents**
3. **Nuclear disintegration (karyolysis)**
4. **Influx of inflammatory cells**
5. **Cell contents released during oncotic necrosis include intracellular enzymes such as ALT and AST which appear in the plasma and are used as biomarkers of hepatocellular injury**

Apoptosis

✓**It is a programmed cell death characterized morphologically by:**

1. **Cell shrinkage**
2. **Chromatin condensation**
3. **Nuclear fragmentation**
4. **Formation of membrane-bound cell fragments termed "apoptotic bodies"**

Apoptosis


apoptosis is programmed cell death
faulty enzymes must be digested or they can be incorporated in other cells
nucleus condensing
lobes or blebs
apoptotic bodies
scavenger cells digest the apoptotic bodies

Apoptosis

- ✓**Because the apoptotic bodies are phagocytosed and digested by Kupffer cells or other neighbouring cells, apoptosis is often not accompanied by an inflammatory response.**
- ✓**The pathway to apoptosis involves activation of caspase enzymes that results in the cleavage of nuclear DNA.**

Pyroptosis

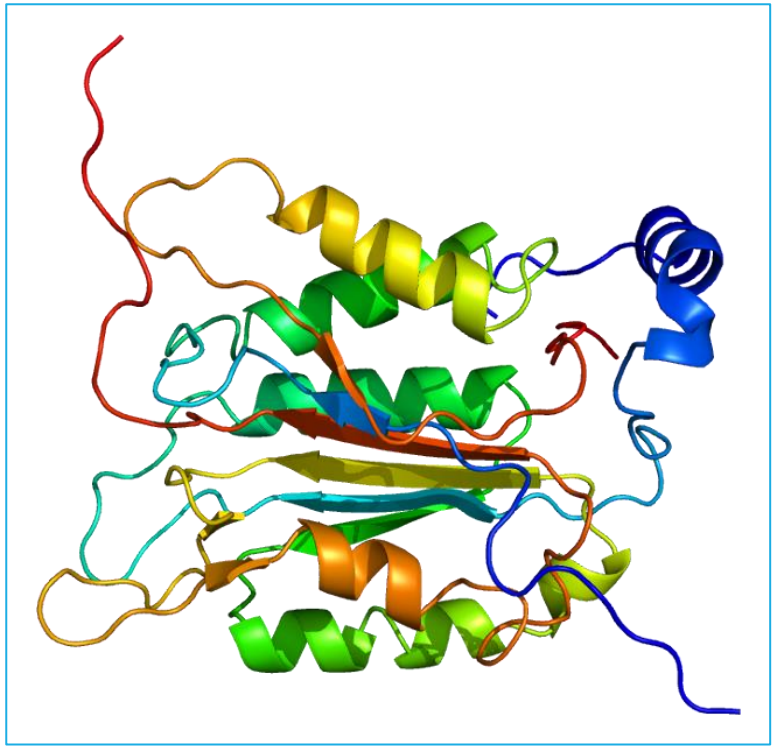
- **Pyroptosis** represents a form of cell death that is **triggered** by **pro-inflammatory** signals and associated with **inflammation**.

- This type of cell death is seen **primarily** in inflammatory cells such as macrophages and may be **triggered** by **bacterial** or **pathogen** infections.

Pyroptosis

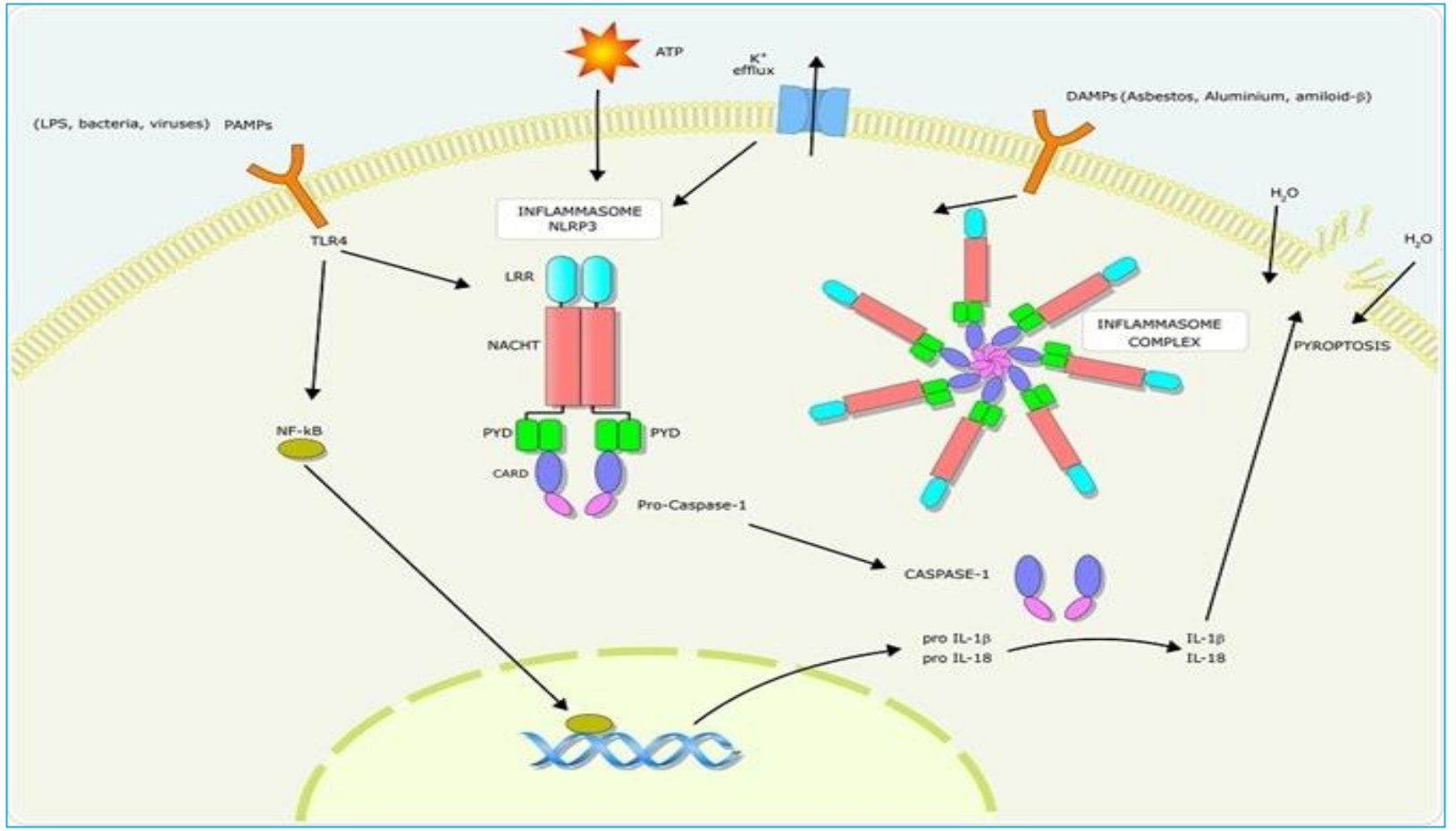
✓A **cardinal** feature of pyroptosis is the requirement for **caspase-1 activation**.

✓**Caspase-1** is responsible for the **maturation** of proinflammatory cytokines such as interleukin-1 beta (IL-1β) and IL-18 through **inflammasome-dependent pathways**.



Structure of Caspase-1

Pyroptosis


ATP
K+ efflux
(LPS, bacteria, viruses) PAMPs
DAMPs (Asbestos, Aluminium, amiloid-β)
INFLAMMASOME NLRP3
TLR4
LRR
NACHT
PYD
PYD
CARD
NF-kB
Pro-Caspase-1
CASPASE-1
INFLAMMASOME COMPLEX
H2O
H2O
PYROPTOSIS
pro IL-1β
pro IL-18
IL-1β
IL-18

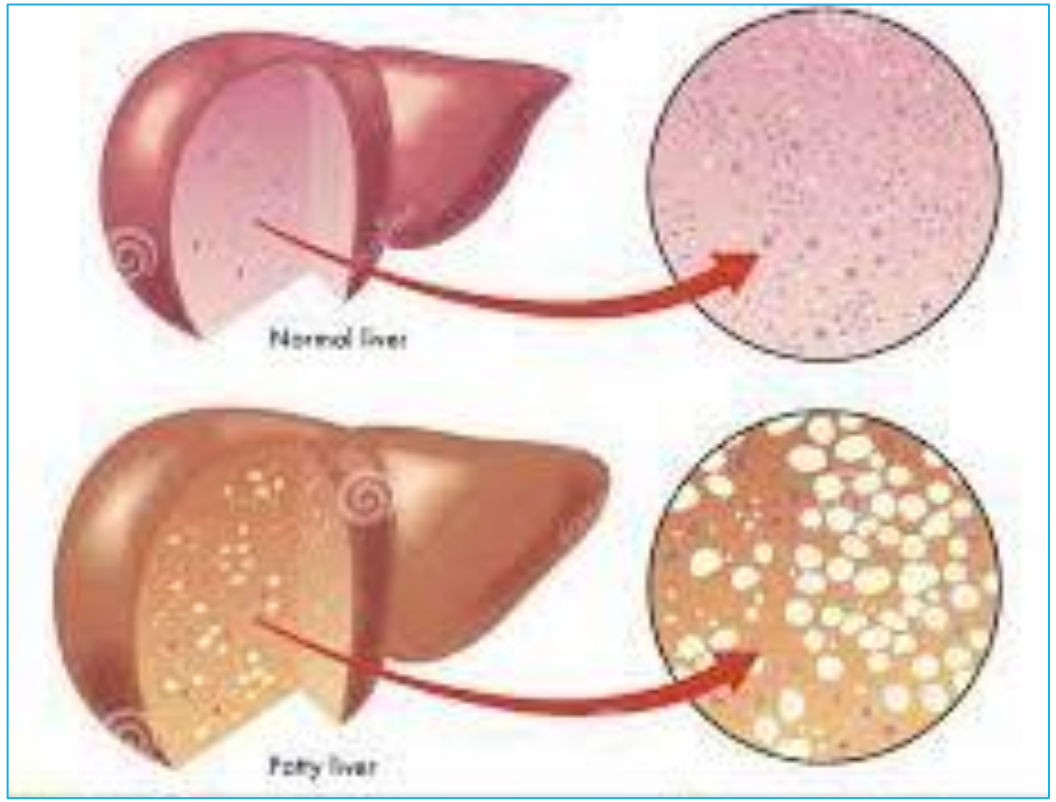
Necroptosis

- ✓**Necroptosis** represents a process of a **regulated version** of the **necrotic cell death** pathway.
- ✓As was the case with necrotic cell death, necroptosis is also **caspase-independent**.
- ✓However, in a manner **analogous** to apoptosis, necroptosis is **triggered** by the binding of **TNF-α and Fas ligand** to their respective cell surface receptors.

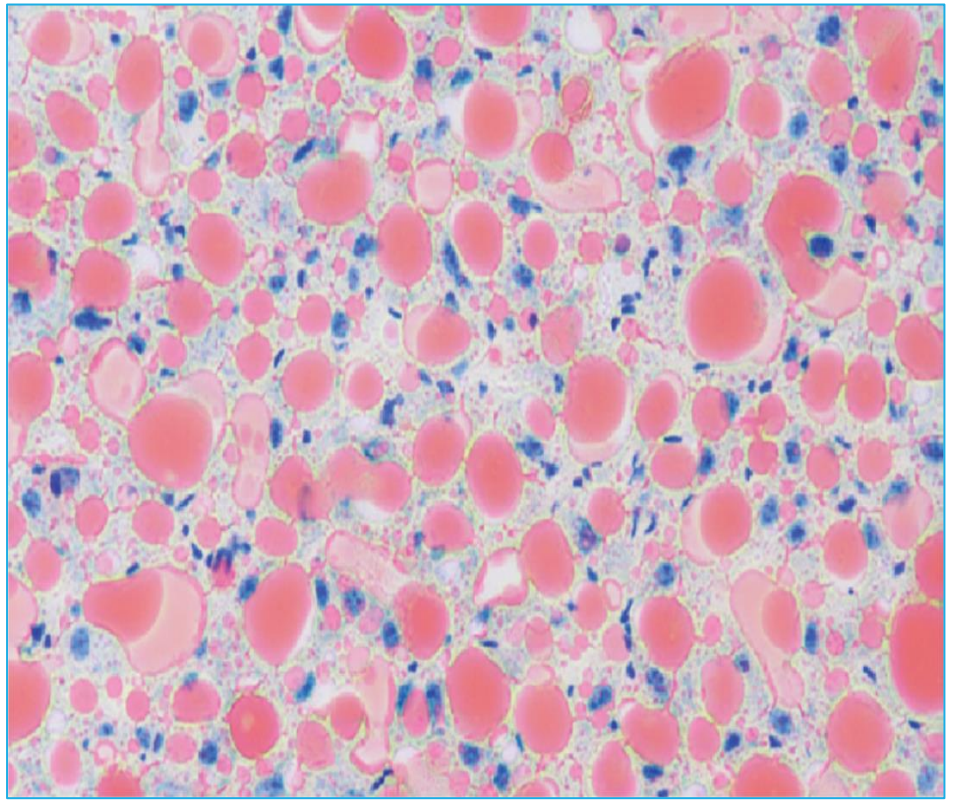
2. Fatty Liver (Steatosis)

- ✓**Fatty liver** (steatosis) is defined as an **appreciable increase in lipid** (mainly triglyceride) content of HPCs.
- ✓**Histologically**, HPCs containing **excess** fat appear to have many rounds and empty **vacuoles**.
- ✓The **accumulation** of these vacuoles can **displace** the **nucleus** to the periphery of the cell.
- ✓ Based on the **size** of the fat droplets, one can distinguish between **macrovesicular** (large droplets) and **microvesicular** (small droplets) steatosis.

2. Fatty Liver (Steatosis)



Fatty liver (steatosis)



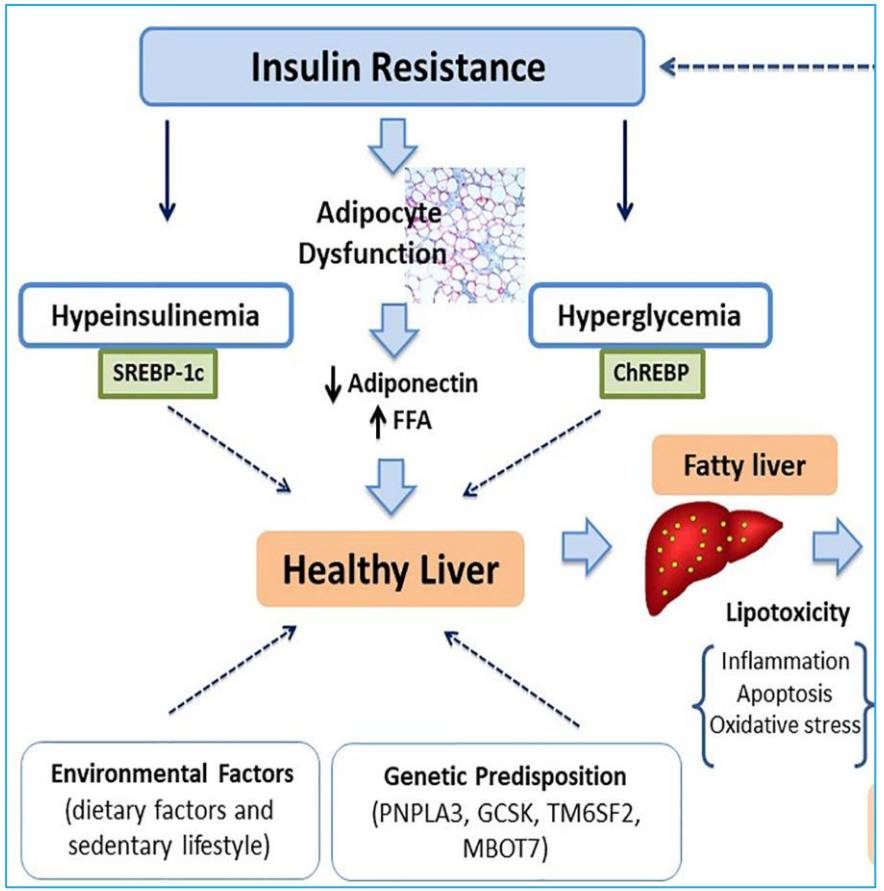
Macrovesicular Steatosis, Nuclei are stained blue

2. Fatty Liver (Steatosis)

- ✓**Steatosis occurs commonly from moderate alcohol consumption and other factors; it is reversible and probably harmless if the stimulus for it is temporary.**
- ✓**When accompanied by inflammation can lead to steatohepatitis.**
- ✓**Steatosis can progress to life-threatening chronic liver damage, fibrosis (e.g., cirrhosis), and hepatocellular carcinoma.**

2. Fatty Liver (Steatosis)

- ✓The most common **cause** of hepatic steatosis is **insulin resistance** associated with **obesity** and a **sedentary** lifestyle.
- ✓Some **chemicals** that produce steatosis associated with lethality include <u>ethanol, valproic acid, fialuridine, carbon tetrachloride, ethionine, and cycloheximide</u>.



3. Canalicular Cholestasis

- ✓**It is defined as a decrease in the rate of bile formation or an impaired secretion of specific solutes into bile.**
- ✓**Cholestasis is characterized biochemically by elevated serum levels of compounds normally concentrated in bile, particularly bile salts and bilirubin.**

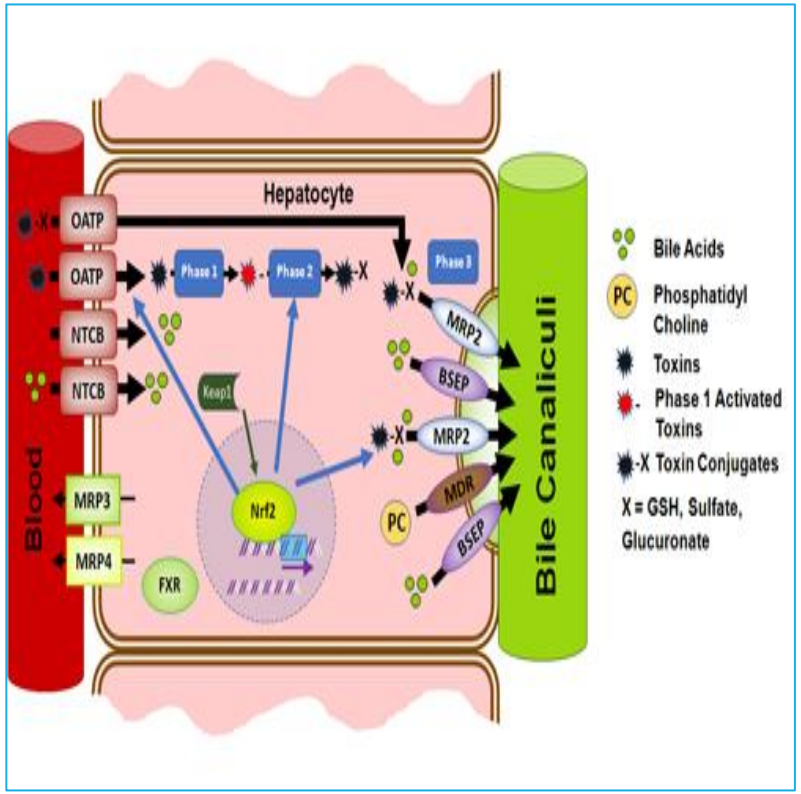
3. Canalicular Cholestasis

- ✓When biliary excretion of the yellowish bilirubin pigment is impaired, it accumulates in the skin and eyes, producing jaundice.
- ✓Additionally, excess bilirubin increases in urine, which becomes darker yellow or brown.

3. Canalicular Cholestasis

✓**Some drugs that cause cholestatic injury, such as rifampicin, bosentan, and troglitazone, directly inhibit the bile salt export pump (BSEP) and can thereby lead to the accumulation of bile acids.**

✓**Estrogen and progesterone metabolites also inhibit BSEP from the canalicular side after excretion.**



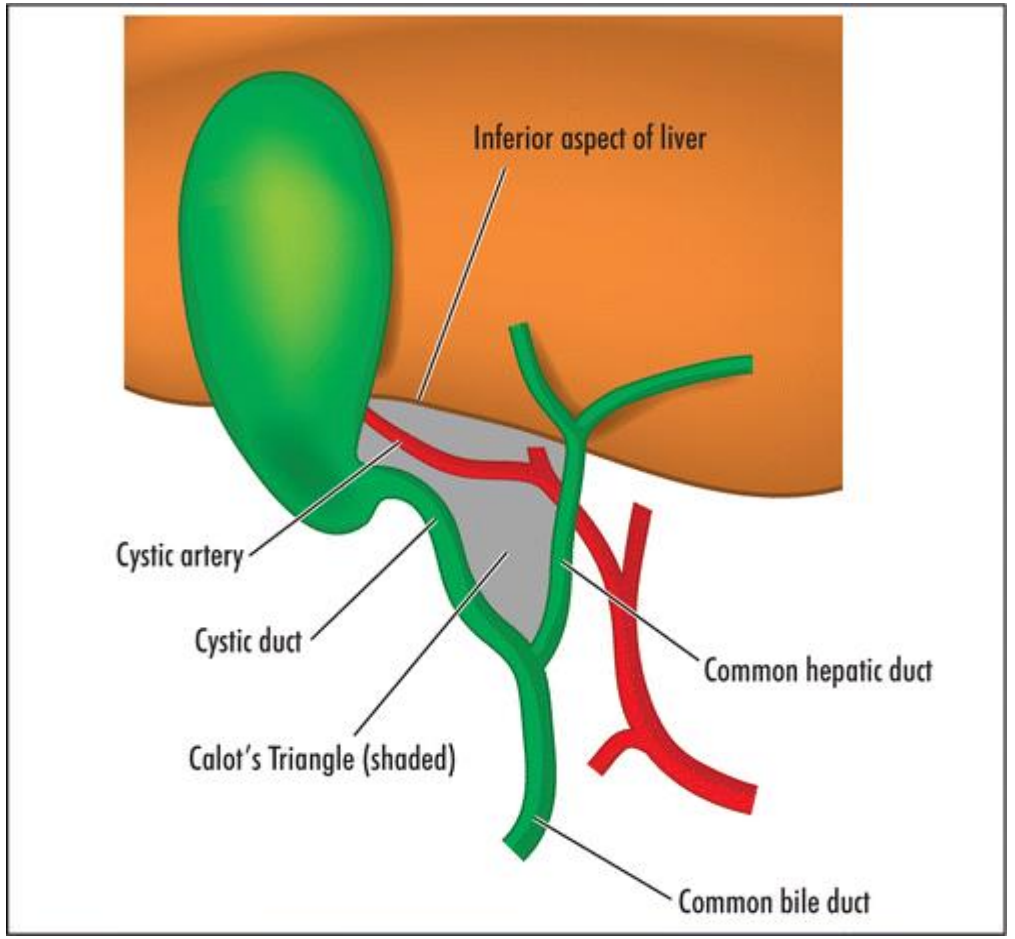
4. Bile Duct Damage

- ✓It is a form of damage to the intrahepatic bile ducts also called cholangiodestructive cholestasis.
- ✓A useful biochemical index of bile duct damage is a sharp elevation in serum of alkaline phosphatase (ALP).
- ✓In addition, serum levels of bile acids and bilirubin are elevated, as observed with canalicular cholestasis.

4. Bile Duct Damage

✓**Initial lesions** following a single exposure to cholangiodestructive chemicals include:

1. **Swollen** biliary epithelium
2. **Debris** of damaged cells within ductal lumens
3. **Inflammatory** cell infiltration of portal tracts



4. Bile Duct Damage

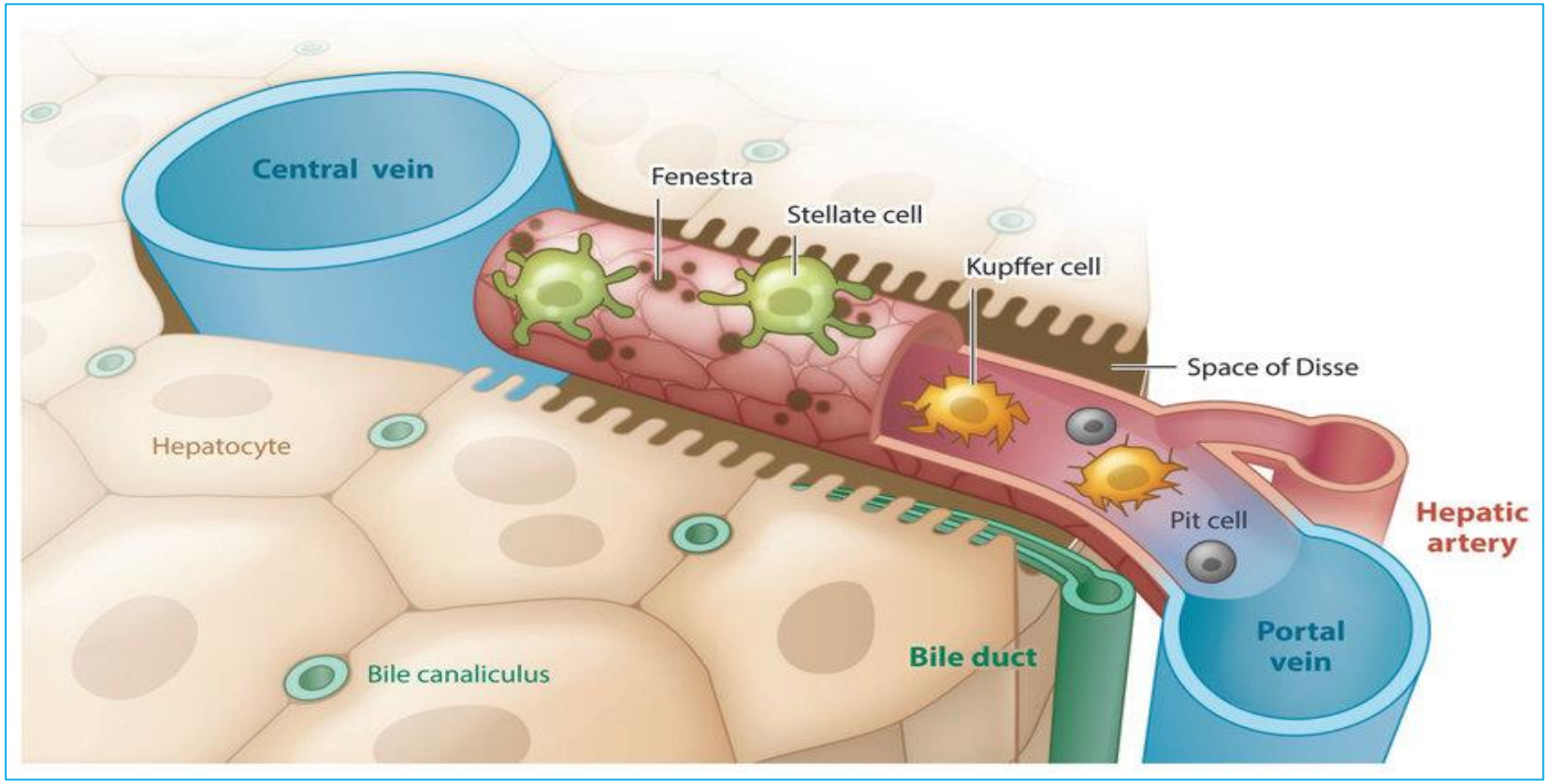
✓**Bile duct damage has been reported in patients receiving:**

1. **Antibiotic**
2. **Anabolic steroids**
3. **Contraceptive steroids**
4. **The anticonvulsant carbamazepine**

5. Sinusoidal Endothelial Cell Damage

- ✓ **The sinusoid is essentially a specialized capillary lined with endothelium with numerous fenestrae (holes) that allow for high permeability.**
- ✓ **The functional integrity of the sinusoid can be compromised in two ways, by dilation or blockade of its lumen and by the destruction of sinusoidal endothelial cells (SECs).**

5. Sinusoidal Endothelial Cell Damage



Schematic of the hepatic sinusoid

5. Sinusoidal Endothelial Cell Damage

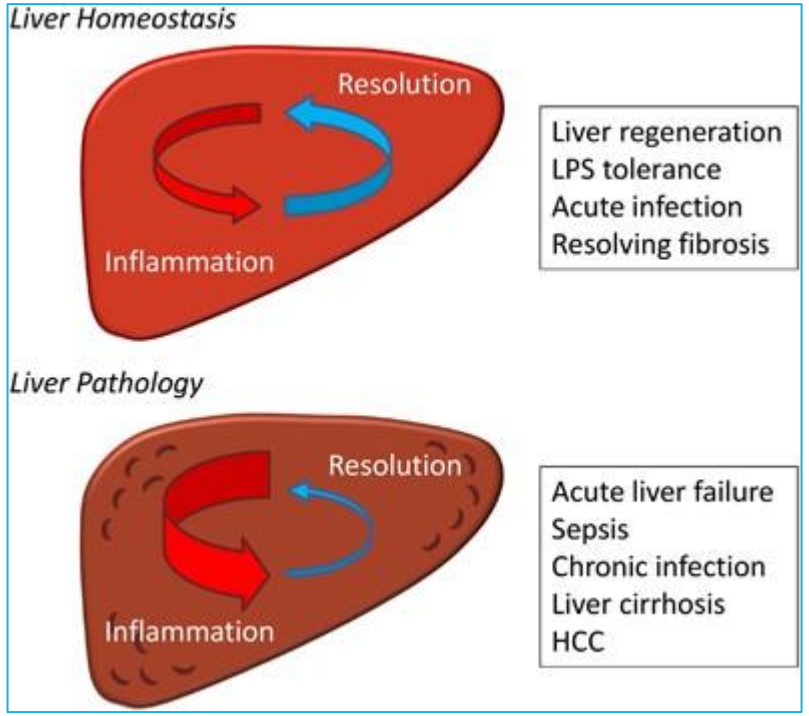
- ✓**Dilation** of the sinusoid occurs when the downstream flow of blood is **impeded**.
- ✓The **rare condition** of primary dilation, known as **peliosis hepatis**, has been associated with exposure to **anabolic steroids** and **danazol**.
- ✓**Blockade** can occur when the **fenestrae enlarge** to such an extent that **red blood** cells become **caught in them**.

5. Sinusoidal Endothelial Cell Damage

- ✓**Gaps** between endothelial cells occur after **exposure** to acetaminophen, galactosamine/endotoxin.
- ✓A **consequence** of SEC injury is the **loss of barrier function** with extensive blood **accumulation** in the liver **parenchyma** (i.e., hemorrhage).
- ✓**Pyrrolizidine** alkaloid plant toxins can result in **SEC destruction** and sinusoidal obstruction.

6. Inflammation

- ✓**Inflammation** occurs in many organs as a **response** to **injury** that entails **activation** of **innate immunity**.
- ✓In the **liver**, the inflammatory response involves **circulating** blood cells as well as the **resident** cell.
- ✓ **Activated coagulation** and **complement** cascades are also **components** of an **acute** inflammatory response.



6. Inflammation

- ✓ **The activation of resident macrophages (Kupffer cells), NK, NKT cells, and innate lymphoid cells play a major role in liver inflammation.**

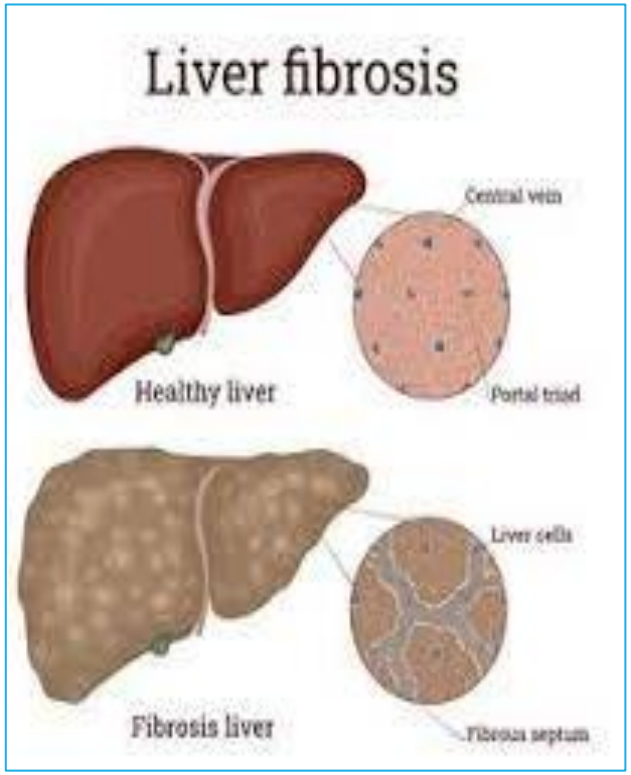
- ✓ **Additionally, the accumulation and activation of blood-borne cells including platelets, neutrophils, lymphocytes, and monocytes within the damaged liver are well-recognized features of hepatotoxicity produced by many chemicals.**

Regeneration and Repair

- ✓The liver has a high capacity to restore lost tissue and function by regeneration.
- ✓Loss of HPCs due to hepatectomy, either after surgical resection in human patients or modelled by major removal of the liver (e.g., 70%) in rodents, triggers proliferation of all mature liver cells.
- ✓This process is capable of restoring the original liver mass.

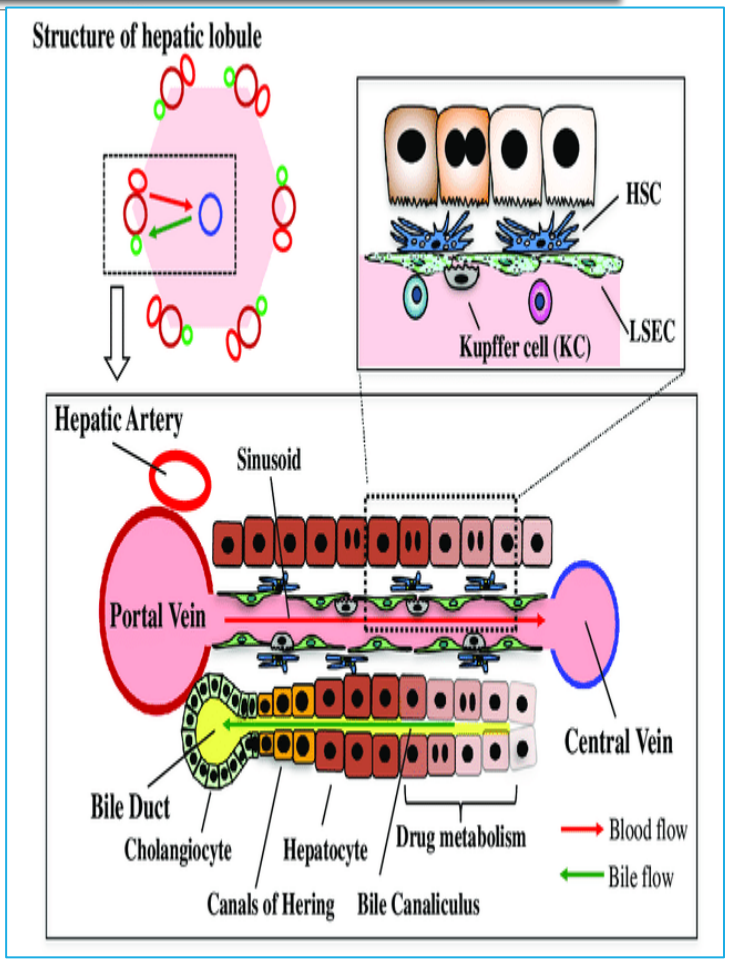
Fibrosis

- ✓Hepatic **fibrosis** (scarring) occurs in response to **chronic liver injury** that **overwhelms** the capacity of the organ to **repair**.
- ✓It is **characterized** by the **accumulation** of excessive fibrous tissue, specifically **fibril-forming collagen types I and III**, and a **decrease** in normal plasma membrane **collagen type IV**.



Fibrosis

- ✓Fibrosis can develop around central veins, portal tracts, or within the space of Disse.
- ✓This progressive collagen deposition, marked by interconnecting fibrous scars, alters the architecture of the liver.
- ✓Fibrosis can progress to cirrhosis and the liver has the limited residual capacity to perform its essential functions.



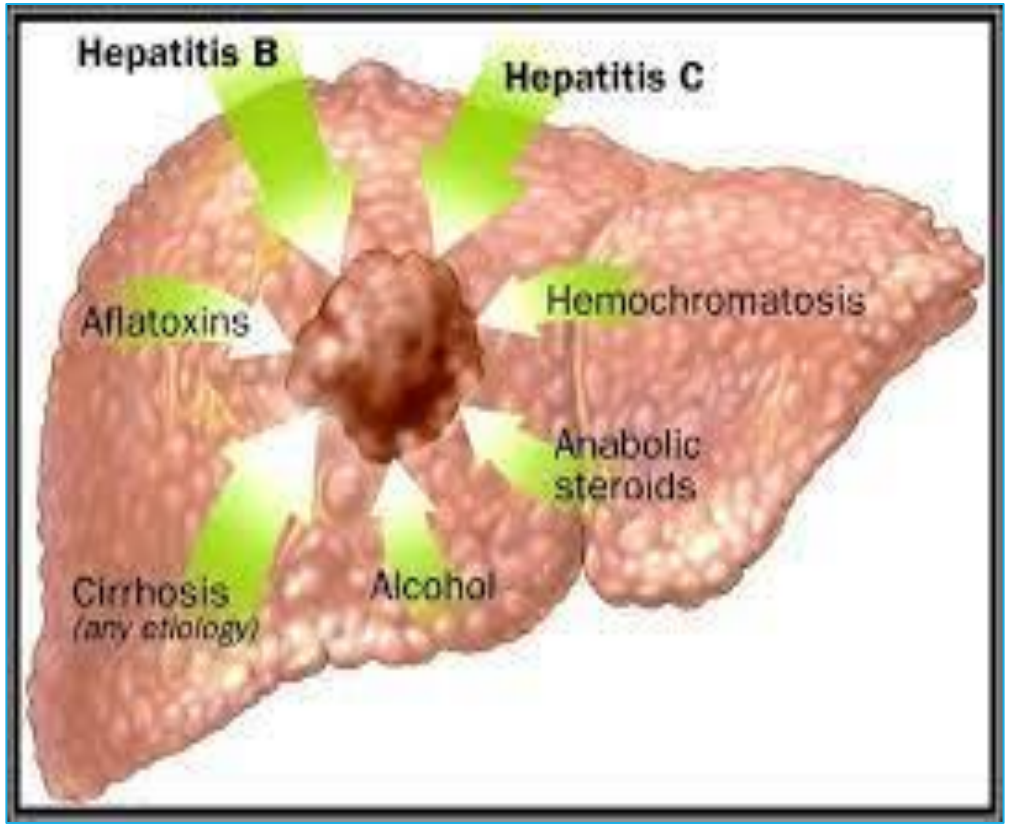
Fibrosis

- ✓The **primary** cause of hepatic fibrosis/cirrhosis in humans worldwide is **viral hepatitis**.
- ✓However, **biliary obstruction** and **steatohepatitis** are of growing public health importance for the development of hepatic **fibrosis**.
- ✓Repeated exposure to carbon tetrachloride, thioacetamide, aflatoxin, and other chemicals has been associated with hepatic **fibrosis**.

Liver Cancers

- ✓**Chemically induced neoplasia can involve tumors that are derived from HPCs as well as other cell types within the liver.**
- ✓**Hepatocellular cancer has been linked to chronic abuse of androgens, alcohol, and consumption of aflatoxin-contaminated diets.**
- ✓**In addition, viral hepatitis, metabolic diseases such as hemochromatosis, α1-antitrypsin deficiency, and nonalcoholic steatohepatitis are major risk factors for hepatocellular carcinoma.**

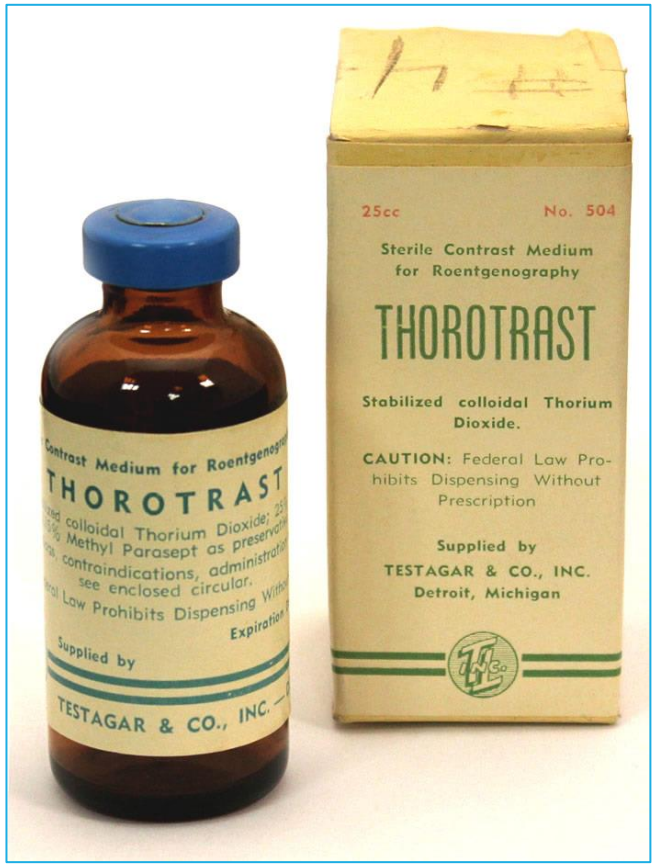
Liver Cancers



Causes of liver cancer (hepatocellular carcinoma)

Liver Cancers

- ✓Exposure to **radioactive thorium dioxide** used as a contrast medium for radiology (**Thorotrast**) has been linked to tumors derived from HPCs, sinusoidal cells, and bile duct cells (**cholangiocarcinoma**).
- ✓The compound **accumulates** in Kupffer cells and **emits radioactivity** throughout its extended half-life.



THANK YOU
FOR YOUR ATTENTION