Al Mustaqbal University College
Department of Pharmacy
4th stage
Toxicology

Lect. 3

Systemic Toxicology of liver

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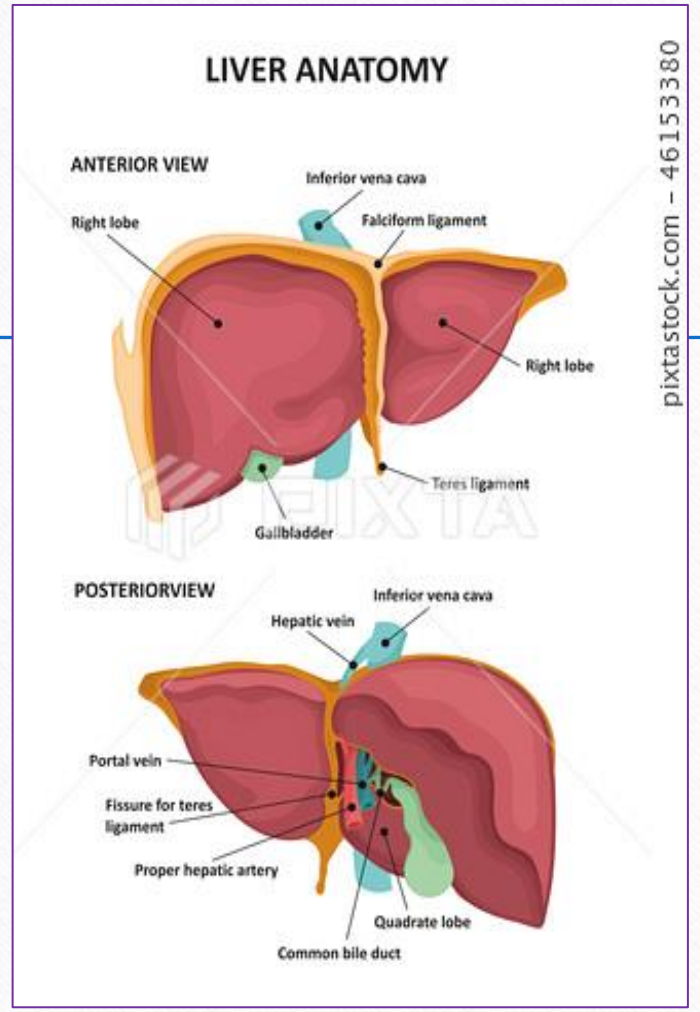
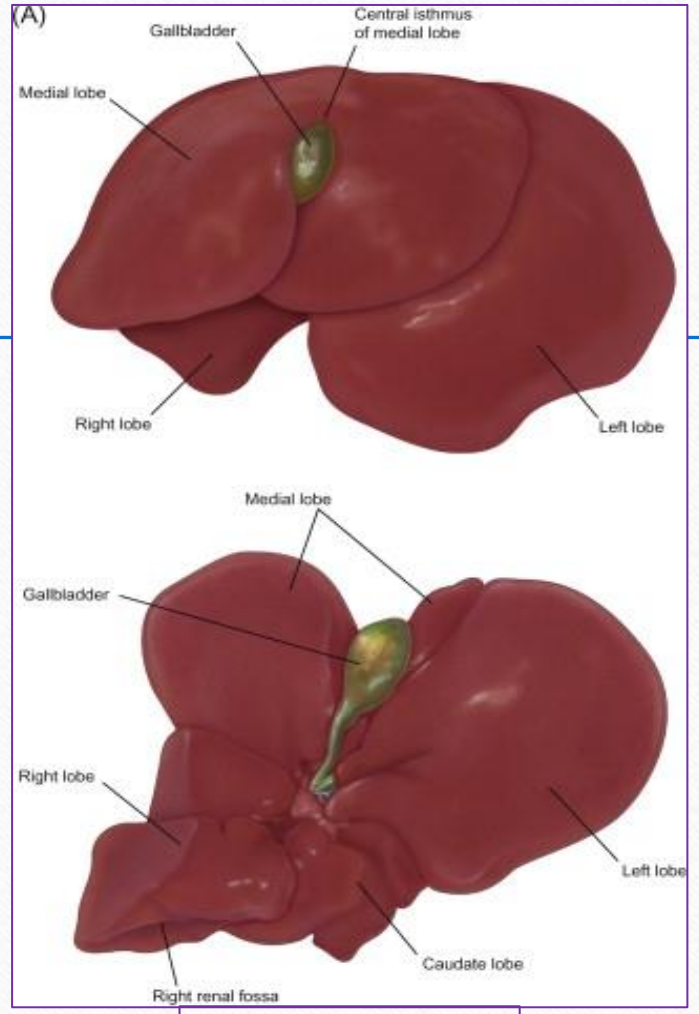
LIVER ANATOMY AND PHYSIOLOGY

- Livers of mammals typically have two (humans) or more (rodents) lobes into which blood vessels enter and exit.

- The liver is unusual among organs in that it has a dual blood supply, As is typical of other organs.



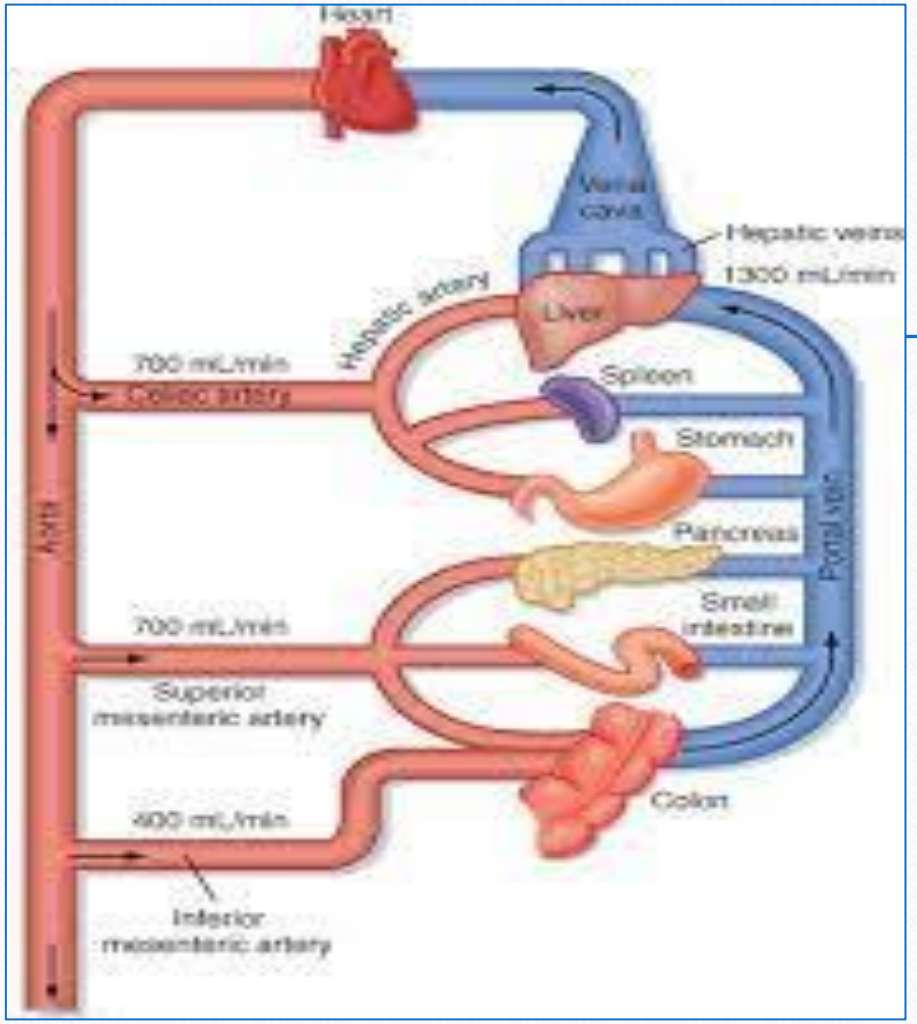
Human liver

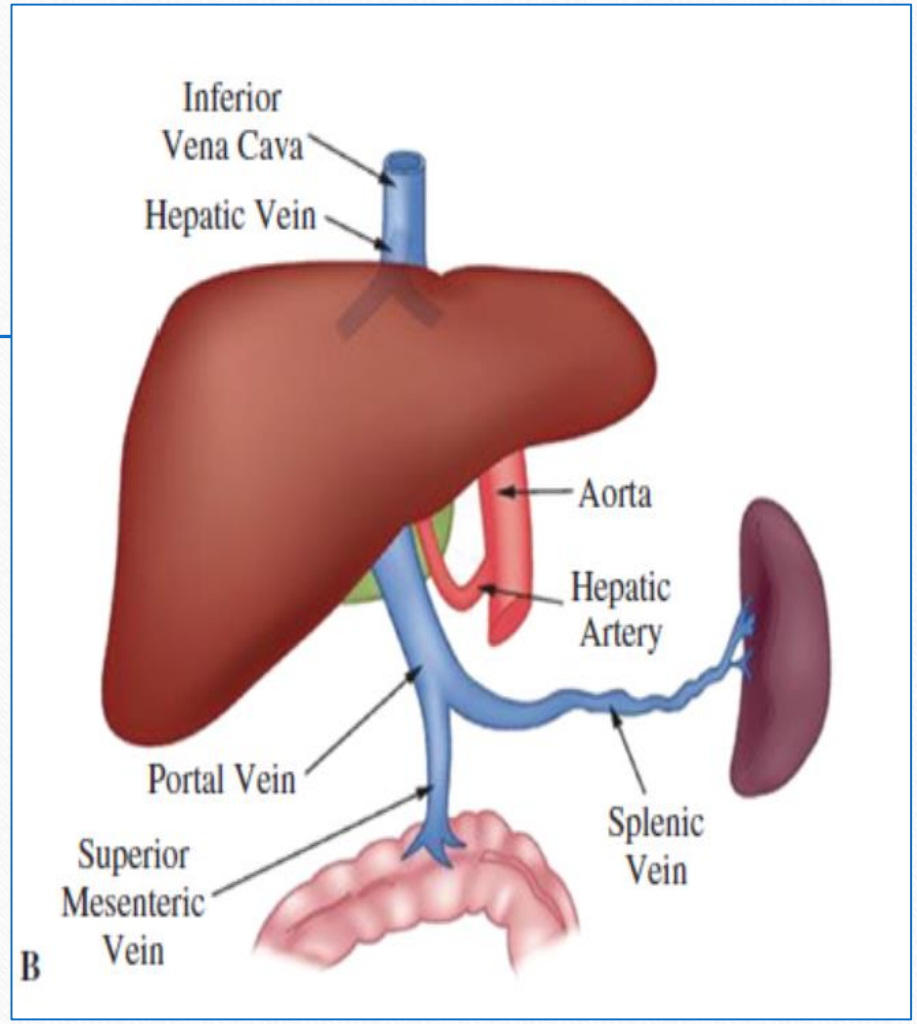


Mouse liver

LIVER ANATOMY AND PHYSIOLOGY

- The liver has an arterial supply via the hepatic artery, which provides a minority of blood entering the liver (about 1/3 in humans, less in rodents).
- The major blood supply to the liver arises from the hepatic portal vein, which comprises venous drainage from the stomach and intestine.





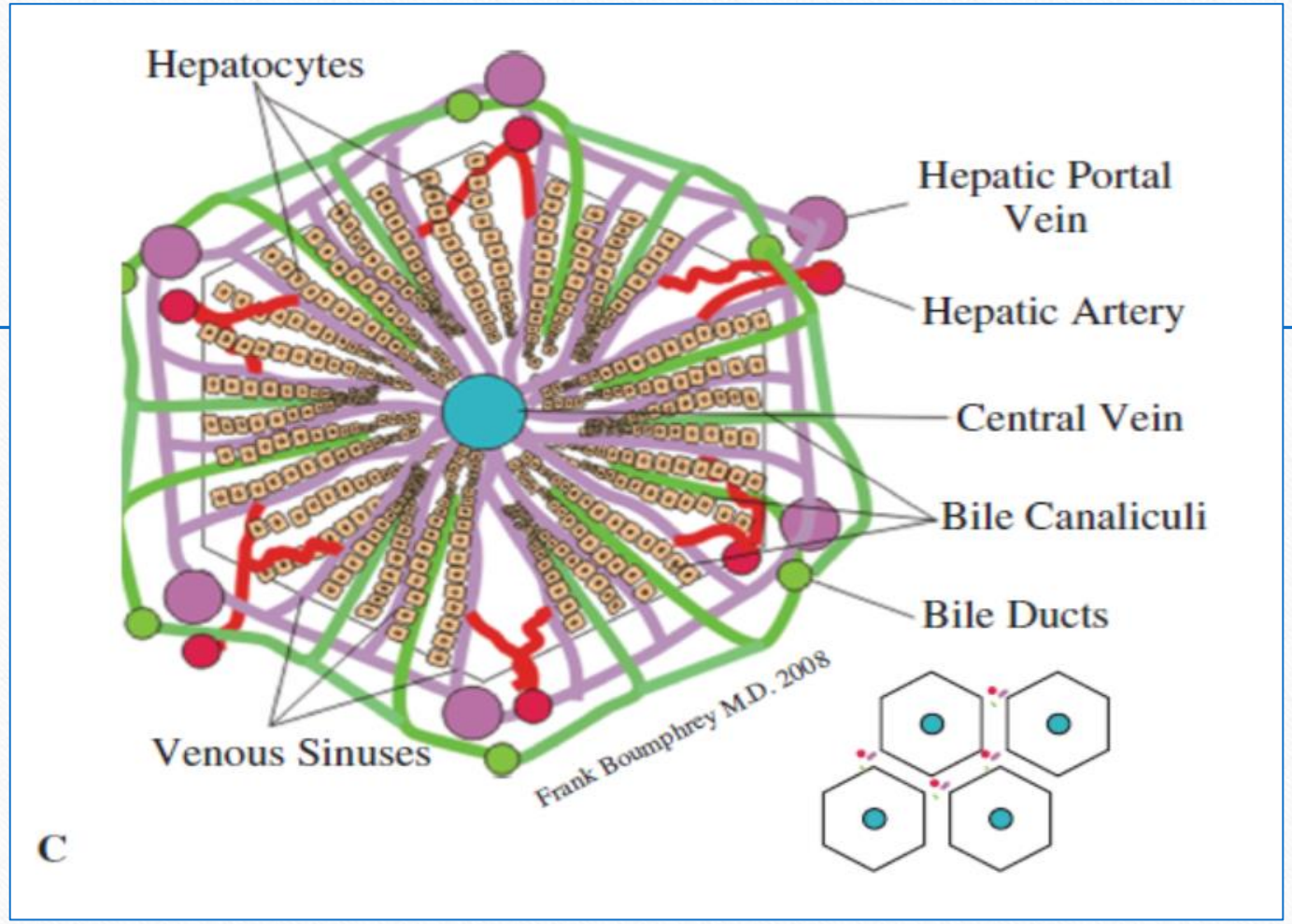
Dual blood supply of liver

LIVER ANATOMY AND PHYSIOLOGY

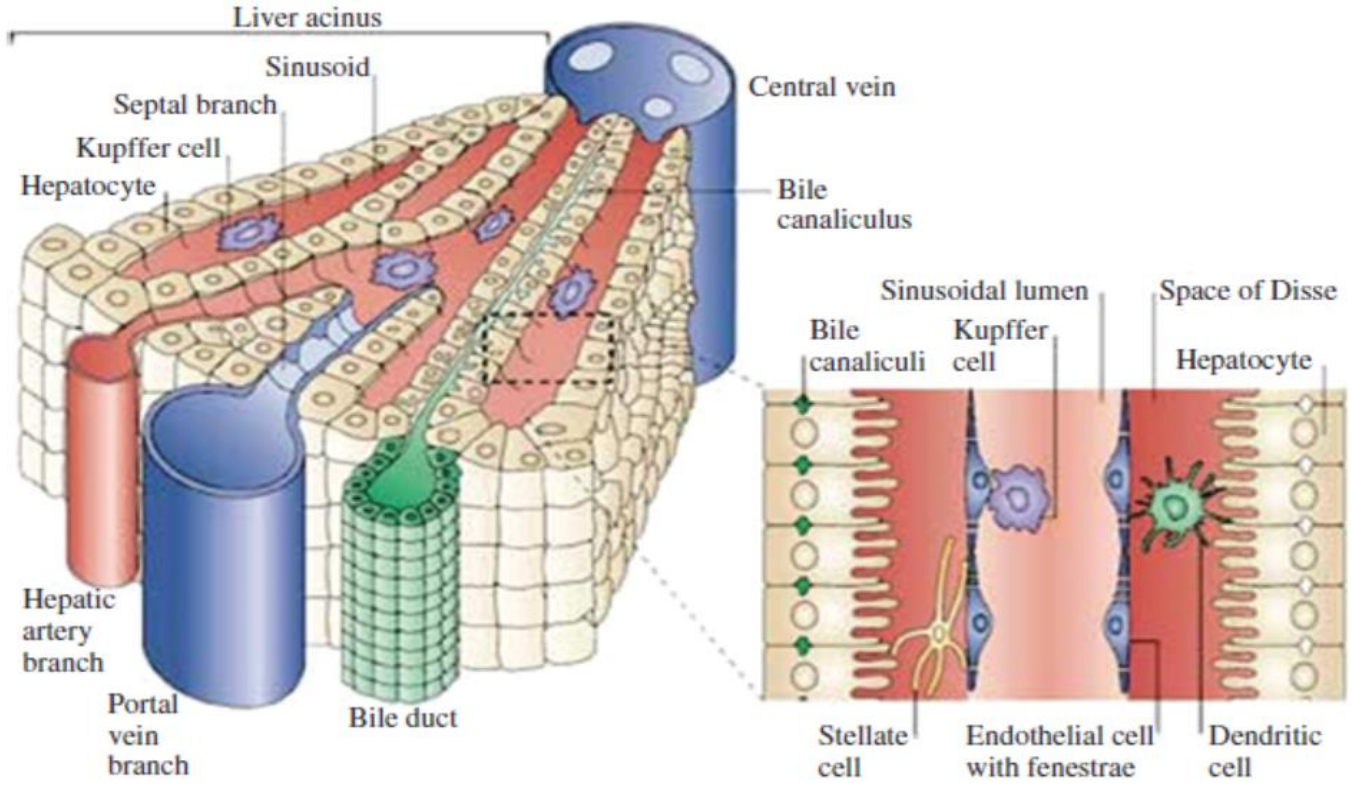
- This unique anatomy positions the liver to have first contact with food-borne xenobiotic agents absorbed into the blood from the gastrointestinal (GI) tract.
- It also means that the liver receives blood from which much oxygen has been removed after nourishing the GI tract.

LIVER ANATOMY AND PHYSIOLOGY

- According to the classical lobular concept, the liver is organized into hexagonal lobules that
- Each lobule is oriented around a central vein (also known as a terminal hepatic venule).
- At the corners of the lobule are portal triads (also known as portal tracts).
- As the name implies, each of these contains a branch of the portal vein (portal venule), a hepatic arteriole, and one or more small bile ducts



The structure of the liver lobule



The structure of the liver acinus

LIVER ANATOMY AND PHYSIOLOGY

- Keeping in mind this general structure, the lobule is viewed as having three regions known as:

1. Periportal (nearest portal triad),
2. Centrilobular (surrounding the central vein),
3. Midzonal (between periportal and centrilobular).

General Functions of Liver

1. **Processing of foods** (Monosaccharides → glycogen or energy, Gluconeogenesis, Lipids → processing, energy)
2. **Synthesis of circulating lipids & Protein** (e.g., albumin, coagulation, and complement factors, lipoproteins)
3. **Uptake of dietary lipids** (e.g., cholesterol) and **vitamins** from blood
4. **Degradation of cholesterol and steroids** & **Ammonia detoxification** (urea formation)

General Functions of Liver

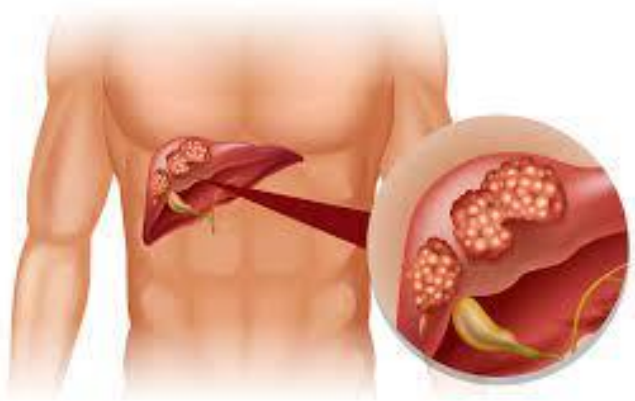
5. Heme synthesis & Iron reutilization
6. Elimination of bilirubin & bacterial products from blood
7. Xenobiotic metabolism (drugs, food-borne agents, etc.)
8. Excretion via biliary tract (drugs, metals, etc.)

LIVER RESPONSES TO CHEMICALS

- **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.

LIVER RESPONSES TO CHEMICALS

- *Inflammation and proliferative* repair play important and sometimes *dichotomous* roles in determining *outcome* of exposure to *hepatotoxicants*.



LIVER RESPONSES TO CHEMICALS

- 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.

LIVER RESPONSES TO CHEMICALS
1·Cell Death

Cell death from chemical exposure is known to occur by several different molecular pathways that mainly include:

1·Oncotic necrosis

2·Apoptosis

3·Pyroptosis

4·Necroptosis

LIVER RESPONSES TO CHEMICALS
1·Cell Death

Oncotic necrosis:

- Often referred to simply as "necrosis," is characterized by cell swelling, leakage of cellular contents, nuclear disintegration (karyolysis), and an influx of inflammatory cells·
- Cell contents released during oncotic necrosis include intracellular enzymes such as alanine aminotransferase (ALT) and aspartate amino transferase (AST), which appear in the plasma and are used as biomarkers of hepatocellular injury

LIVER RESPONSES TO CHEMICALS
1·Cell Death

Apoptosis:

- It is characterized morphologically by cell shrinkage, chromatin condensation, nuclear fragmentation, and formation of membrane-bound cell fragments termed "apoptotic bodies·"
- Because the latter are phagocytosed and digested by Kupffer cells or other neighboring cells, apoptosis is often not accompanied by an inflammatory response·

LIVER RESPONSES TO CHEMICALS
1·Cell Death

Pyroptosis

- It represents a form of cell death that is triggered by proinflammatory signals and associated with inflammation·
- This type of cell death is seen primarily in inflammatory cells such as macrophages and may be trigged by bacterial or pathogen infections·

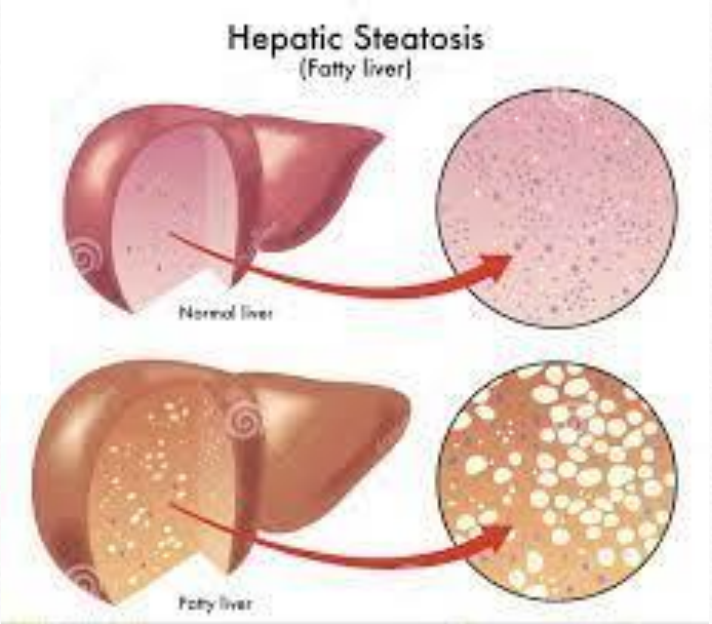
LIVER RESPONSES TO CHEMICALS
1·Cell Death

Necroptosis

- It is a programmed form of necrosis, or inflammatory cell death·
- In contrast to , necrosis that is associated with unprogrammed cell death, it resulting from cellular damage or infiltration by pathogens·

LIVER RESPONSES TO CHEMICALS
2. Fatty Liver (Steatosis)

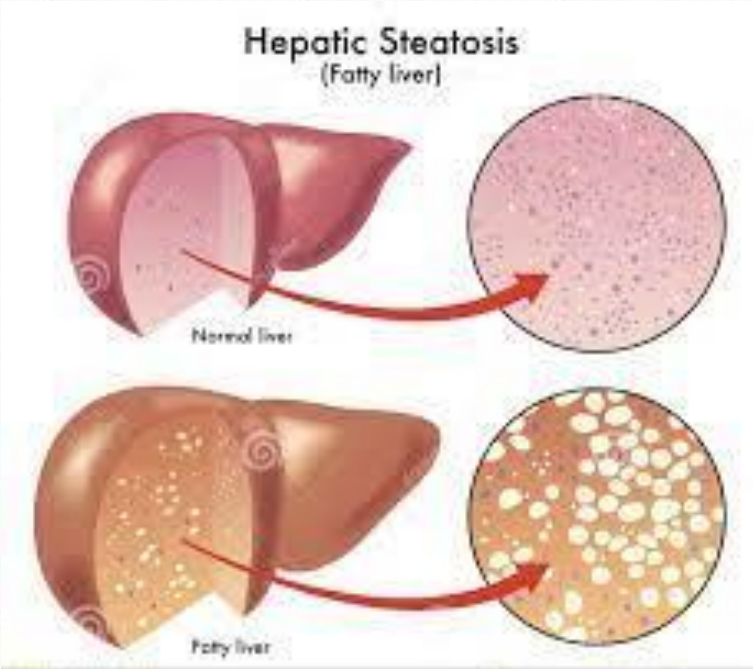
- **Fatty liver (steatosis)** is defined as an **appreciable increase in lipid** (mainly triglyceride) content of HPCs.
- Steatosis occurs commonly from **moderate alcohol consumption** and other factors and is **reversible** and probably **harmless** if the **stimulus for it is temporary**.



LIVER RESPONSES TO CHEMICALS
2. Fatty Liver (Steatosis)

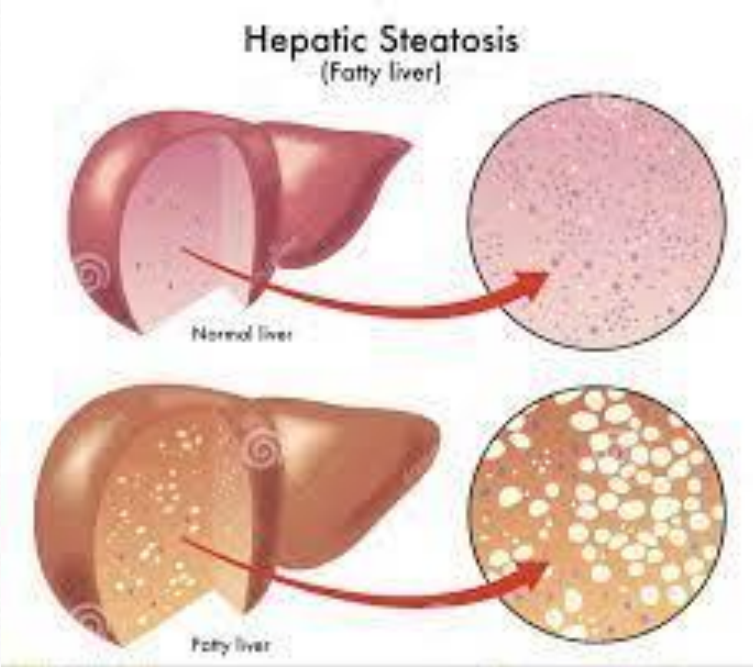
- However, livers with steatosis are more susceptible to additional insults, such as from hepatic ischemia or hepatotoxicants

- Perhaps more importantly, persistent steatosis appears to be a precursor to serious liver disease.



LIVER RESPONSES TO CHEMICALS
2. Fatty Liver (Steatosis)

- When accompanied by inflammation (i.e., steatohepatitis), steatosis can progress to lifethreatening chronic liver damage, fibrosis (e.g., cirrhosis), and hepatocellular carcinoma.



LIVER RESPONSES TO CHEMICALS
2. Fatty Liver (Steatosis)

Among chemicals that produce steatosis associated with lethality include:

1. The antiepileptic drug valproic acid,
2. The antiviral drug fialuridine ,
3. The solvent carbon tetrachloride ,
4. Protein synthesis inhibitors such as ethionine, puromycin, and cycloheximide.

LIVER RESPONSES TO CHEMICALS
3. Canalicular Cholestasis

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

LIVER RESPONSES TO CHEMICALS
3. Canalicular Cholestasis

- When biliary excretion of the yellowish bilirubin pigment is impaired, it accumulates in skin and eyes, producing jaundice.
- Additionally, excess bilirubin increases in urine, which becomes darker yellow or brown.
- Many different types of chemicals, including metals, hormones, and drugs, can cause cholestasis.

LIVER RESPONSES TO CHEMICALS
4. Inflammation

- In the liver, the inflammatory response involves:

1. Circulating blood cells as well as the resident cell types
2. Activated coagulation and complement cascades
3. Alterations in microvascular function are also components of an acute inflammatory response.

LIVER RESPONSES TO CHEMICALS
4. Inflammation

- The activation of resident macrophages (Kupffer cells), NK, NKT cells, and innate lymphoid cells plays 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.

LIVER RESPONSES TO CHEMICALS
4. Inflammation

- Acute inflammatory responses participate in the removal of damaged tissue and in the initiation of liver repair.
- However, under certain circumstances, inflammatory cells and their products can aggravate existing liver injury by release of cytotoxic mediators or indirectly by release of cytokines or other mediators that activate intracellular cell death signaling pathways in liver cells

Regeneration and Repair

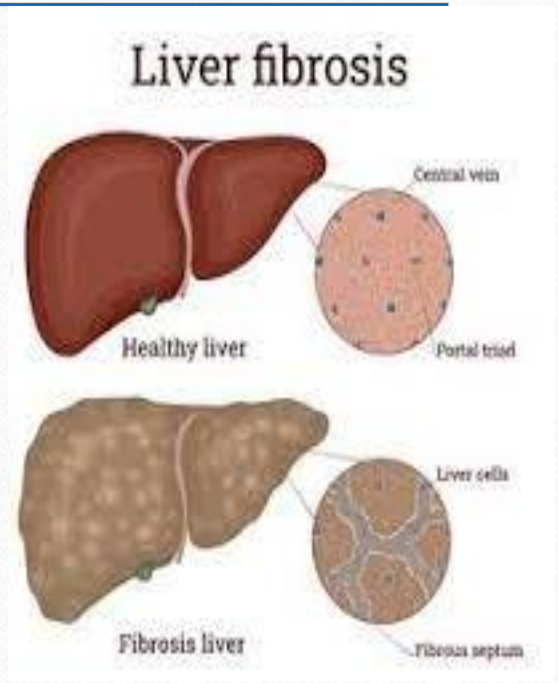
- The liver has a high capacity to restore lost tissue and function by regeneration.
- Loss of HPCs due to hepatectomy, either after surgical resection in human patients or modeled by major removal of liver (e.g., 70%) in rodents, triggers proliferation of all mature liver cells.
- This process is capable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

Regeneration and Repair

- The mechanisms critical for restoring liver mass are not entirely understood.
- HPCs are normally quiescent, that is, they are in GO phase of the cell cycle. So In order to proliferate, they need to enter the cell cycle.
- This process is initiated by cytokines (TNF-α, IL-6), which prime HPCs to respond to essential growth factors such as HPC growth factor (HGF) and transforming growth factor-α (TGF-α).

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

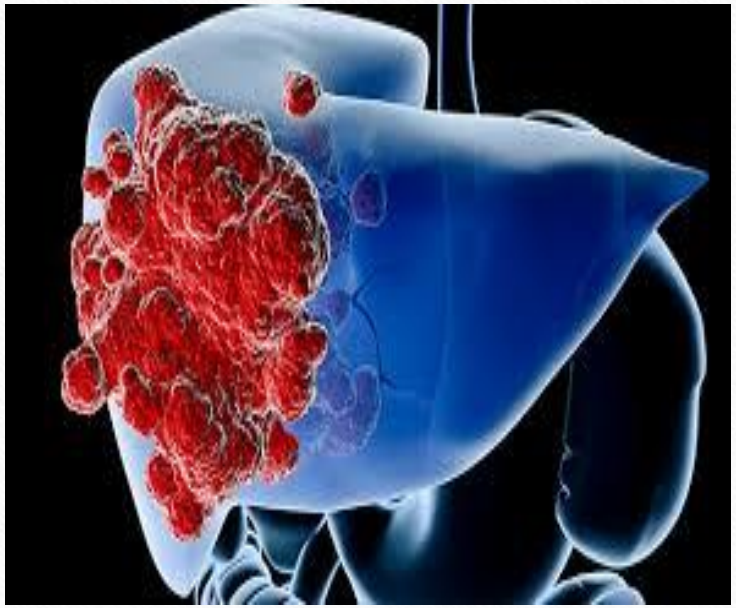


Fibrosis

- Fibrosis can develop around central veins, portal tracts, & other area.
- This progressive collagen deposition, marked by interconnecting fibrous scars, alters the architecture of the liver.
- When the fibrous scars subdivide the remaining liver mass into nodules of regenerating HPCs, fibrosis has progressed to cirrhosis.
- During cirrhosis the liver has limited residual capacity to perform its essential functions.

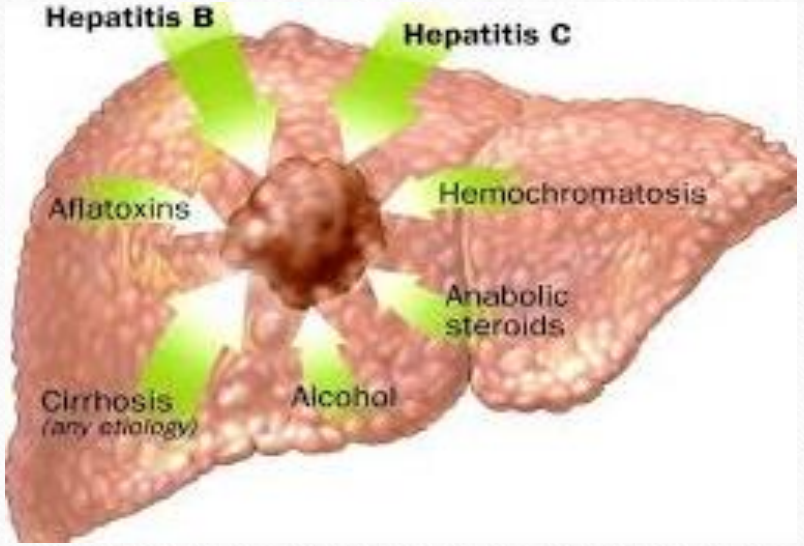
Liver Cancers

- 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.



Liver Cancers

- In addition, viral hepatitis, metabolic diseases such as hemochromatosis, α1-antitrypsin deficiency, and nonalcoholic steatohepatitis are major risk factors for hepatocellular carcinoma.




DONE !
Thank you for listening