Toxic Responses Of The Liver

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INTRODUCTION TO THE LIVER

- Major target organ of many toxins
- Understanding of hepatotoxicity:

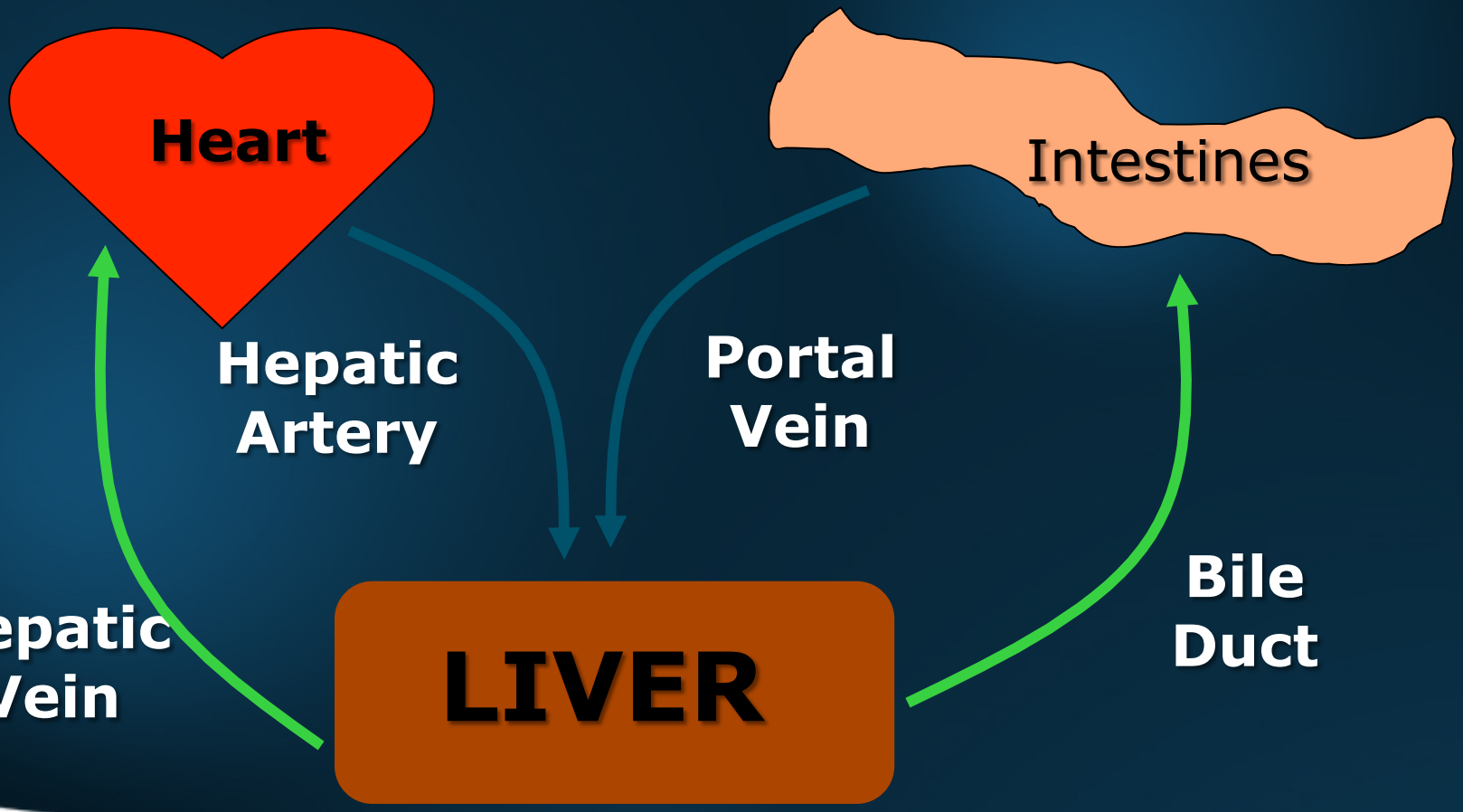
  (1) MAJOR FUNCTIONS OF THE LIVER
  (2) ITS STRUCTURAL ORGANISATION
  (3) BILE FORMATION

(1) LIVER FUNCTIONS

- **Complex organ – many vital functions:**
  - Carbohydrate/Fat/Protein metabolism
  - Drugs & hormone metabolism
  - Immunologic function
  - Bilirubin formation and excretion

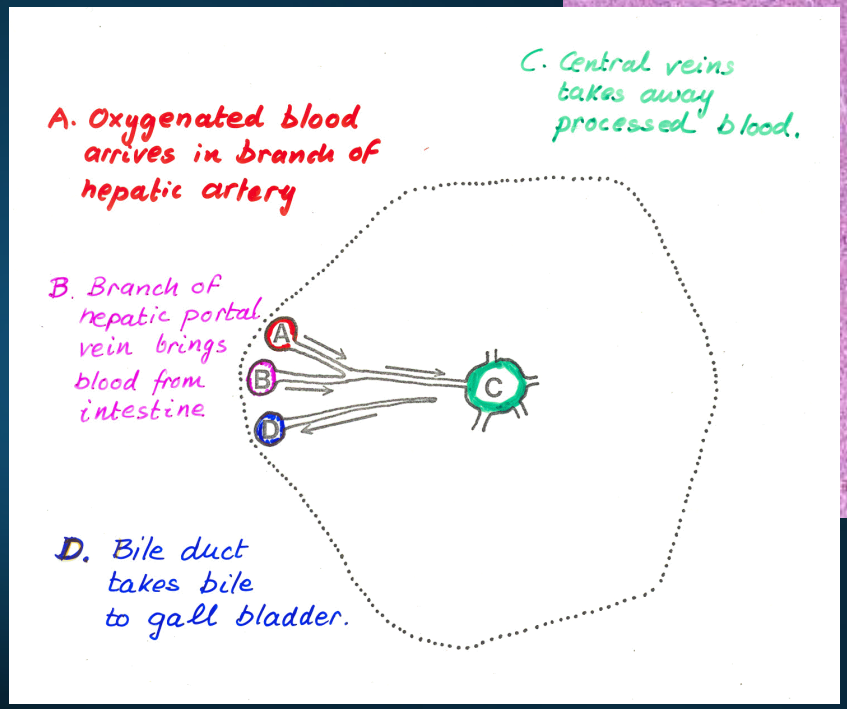
(2) STRUCTURAL ORGANISATION

KEY ROLE IN INTERMEDIARY METABOLISM



The lobule

Anatomical view from periphery to central vein



The acinus

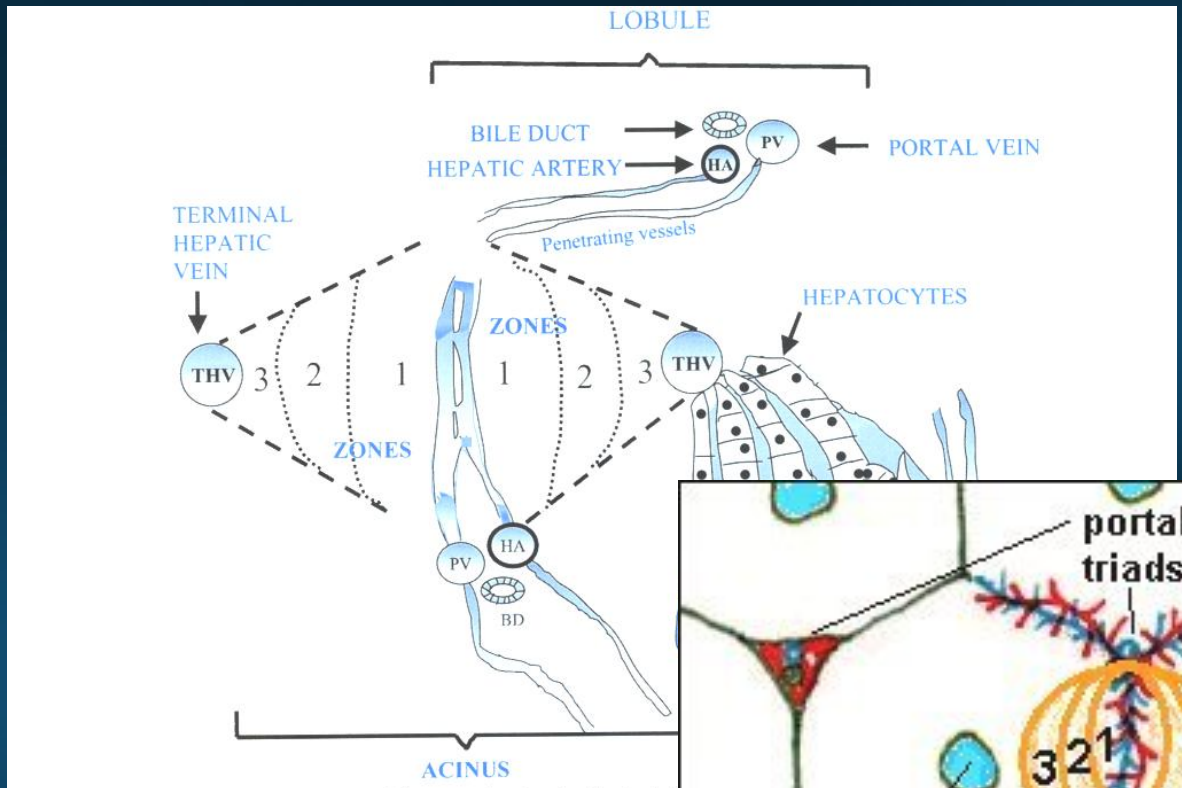
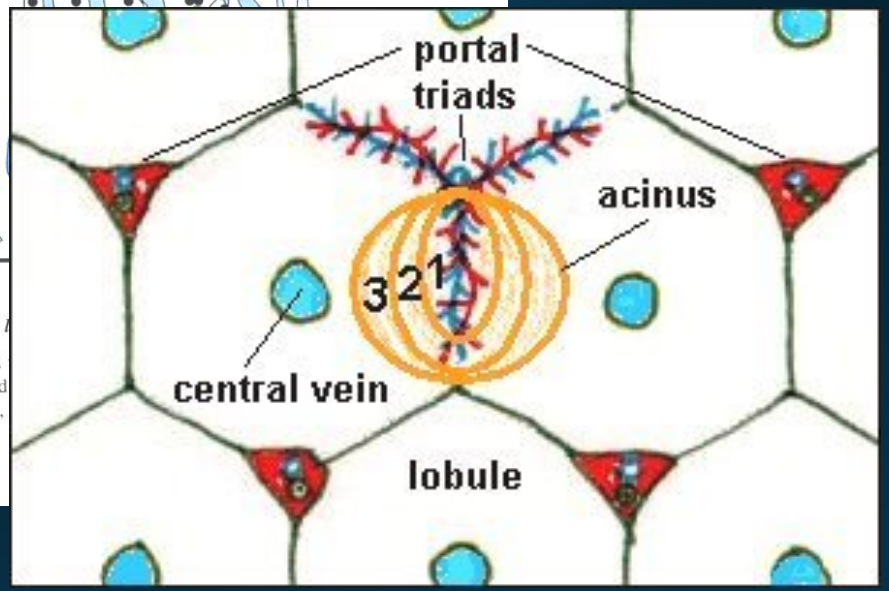
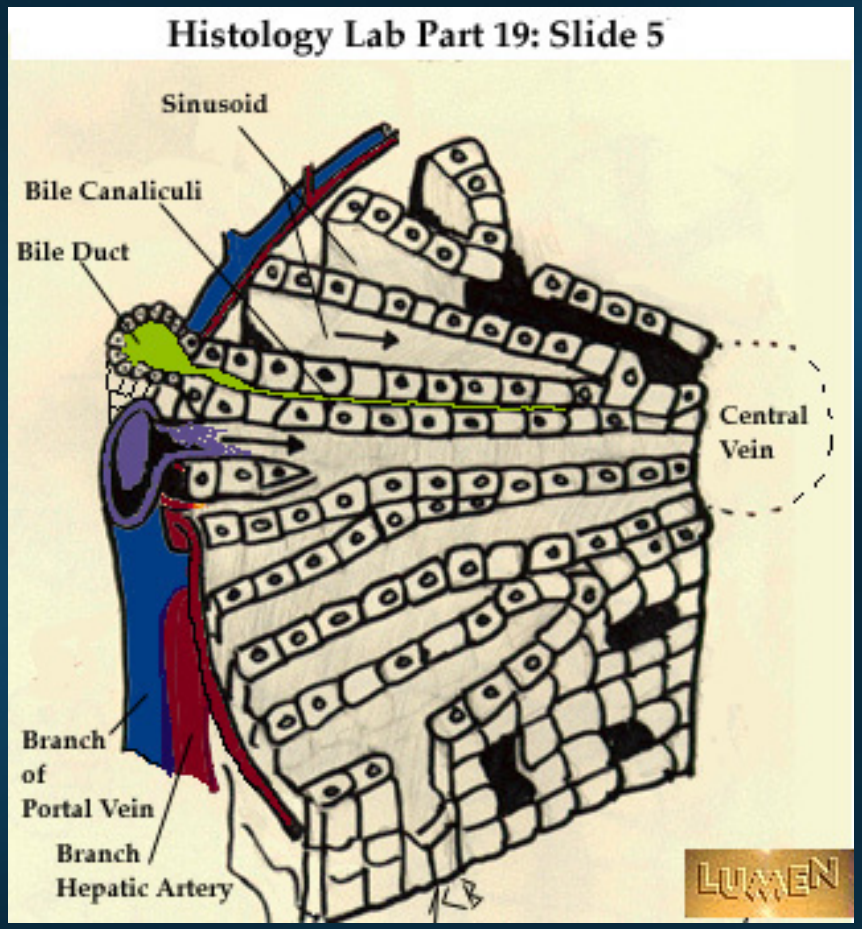


Figure 13-2. Schematic of liver operational units, the classic l

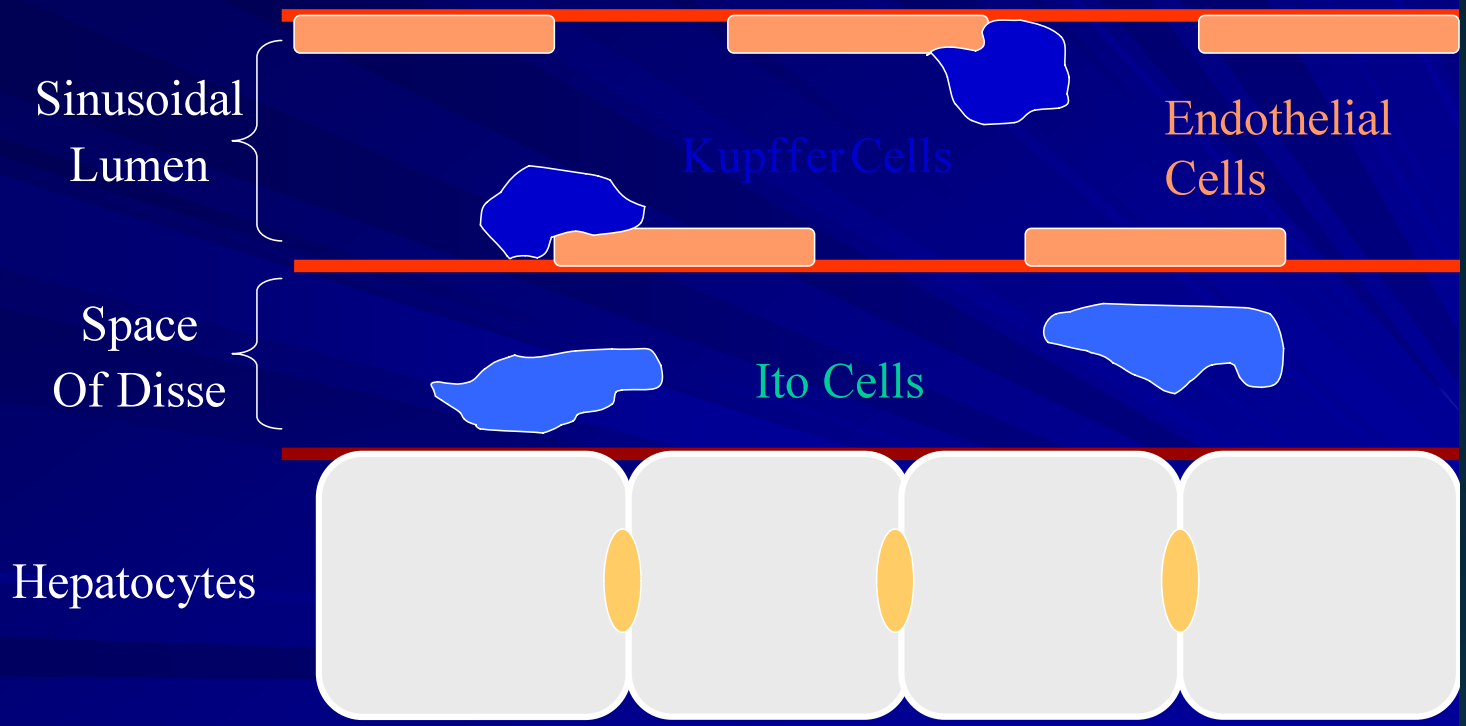
The lobule is centered around the terminal hepatic vein (central
The acinus has as its base the penetrating vessels, where blood
flows down the acinus past the cords of hepatocytes. Zones 1,
gions that are increasingly distant from the blood supply.



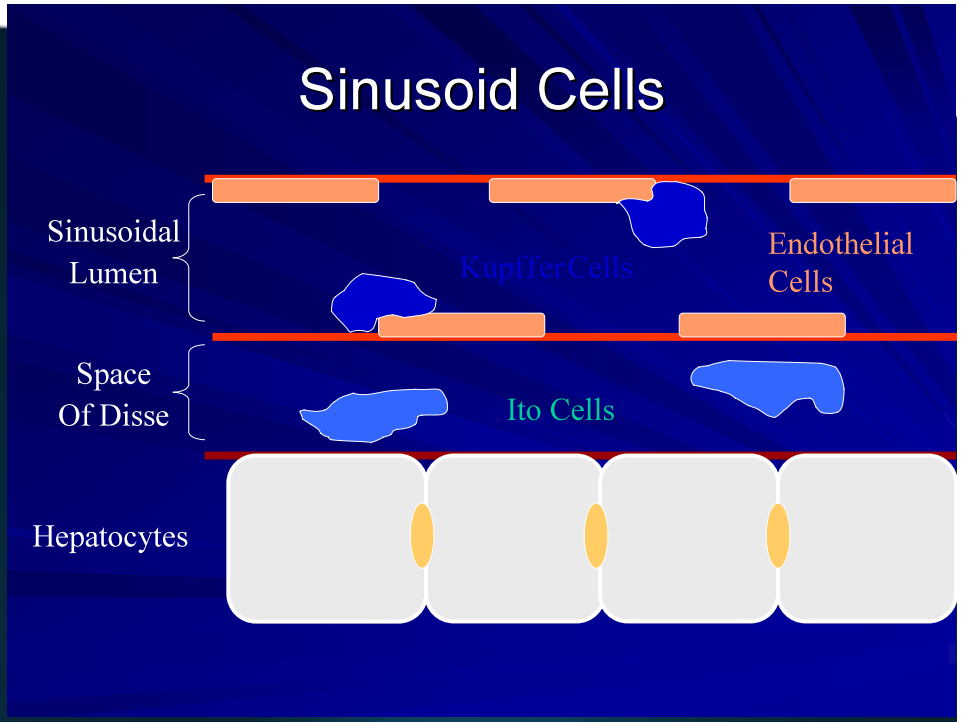
Sinusoids


Histology Lab Part 19: Slide 5
Sinusoid
Bile Canaliculi
Bile Duct
Central Vein
Branch of Portal Vein
Branch Hepatic Artery
LUMEN

Sinusoid Cells

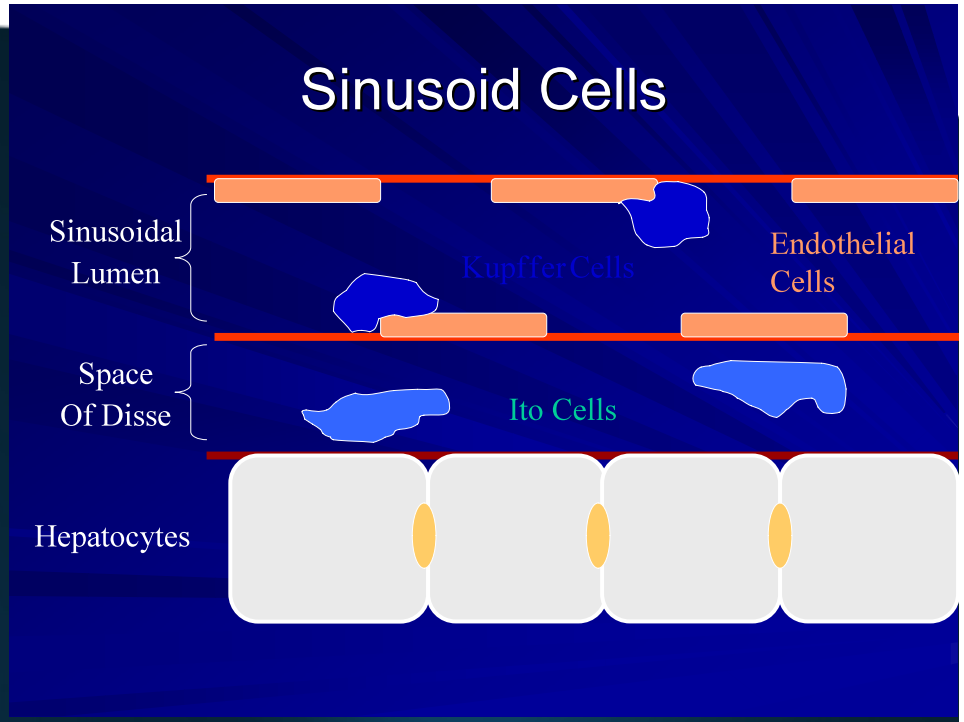


Endothelial Cells



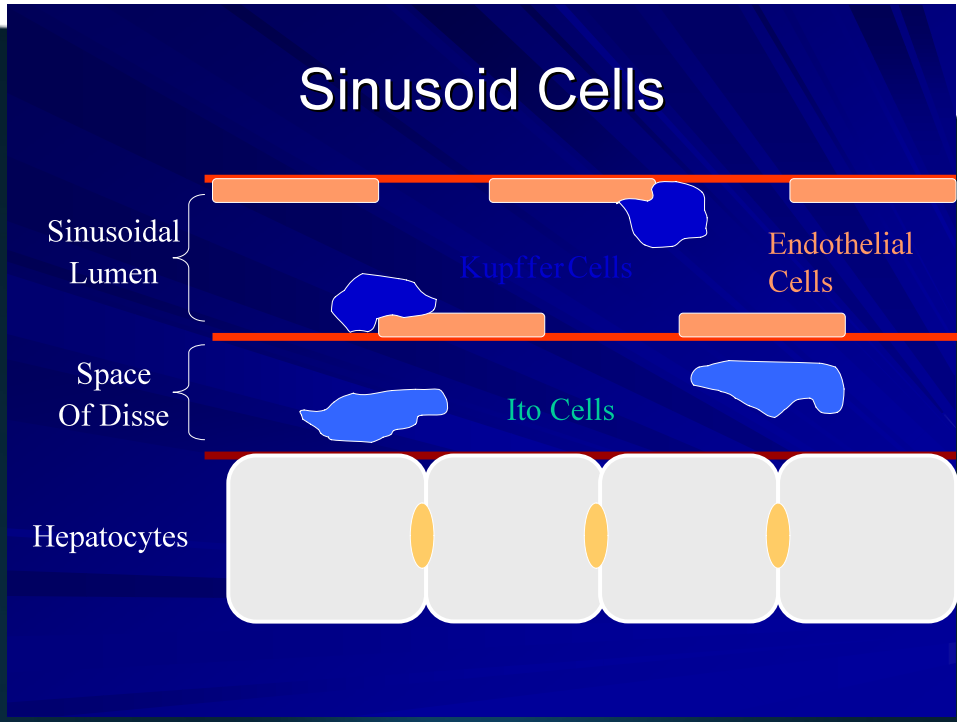
Fenestrated endothelium
Separated from hepatocytes by Space of Disse
Semipermaeable membrane – materials exchange
Lipoprotein metabolism – process LDL, HDL, VLDLs
Antigen presentation

Ito Cells



Stellate cells
Differentiate into myofibroblasts
Cytokine secretion
Secrete ECM proteins

Kupffer Cells



Non-specific host defence
Inflammation/Phagocytosis
Antigen presentation
Cytokine secretion
Senescent and damaged RBCs
Tumour cell surveillance

(3) BILE FORMATION

- Composed of bile salts, glutathione, phospholipids, cholesterol, bilirubin, organic anions, proteins, metals, ions, xenobiotics

- Bile formation essential for:
  - Lipid uptake from small intestines
  - Protection of small intestine from oxidative injury
  - Excretion of endogenous and xenobiotic compounds

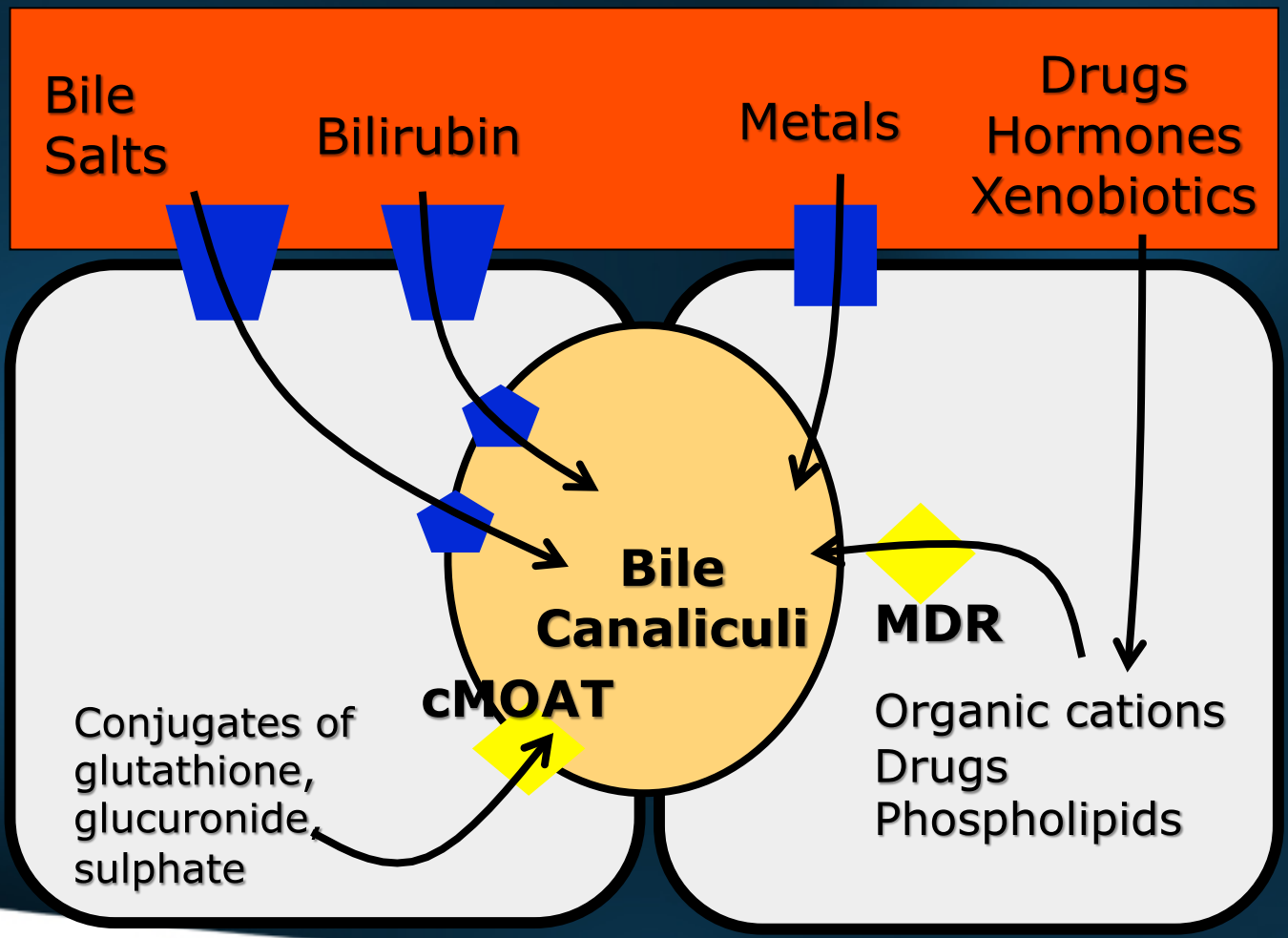
Bile Excretion

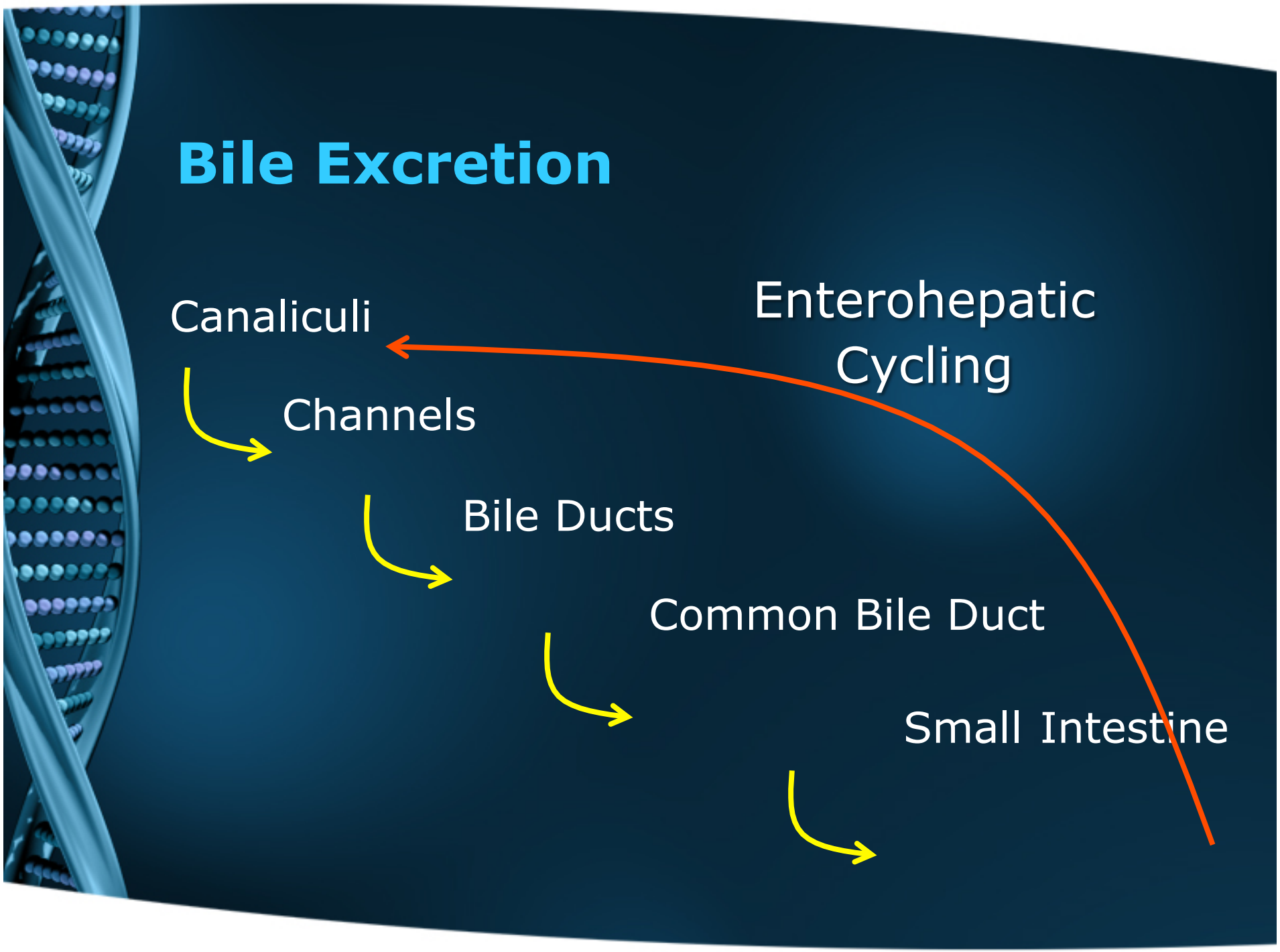
- Driving Force of Bile Formation -
  - Active Transport of Bile Salts
- ATP-dependent exporters
  - MDR (multiple-drug resistance)
  - cMOAT (canalicular multiple organic ion transporter)

Bile Excretion

- Metals Added
    - Diffusion v receptor
    - Excretion by lysosomes
    - Cu, Mn, Cd, Se, Au, Ag, As

Bile Formation




Bile Excretion
Canaliculi
Channels
Bile Ducts
Common Bile Duct
Small Intestine
Enterohepatic Cycling

FACTORS INVOLVED IN LIVER INJURY

Susceptible because of:

- **ANATOMY:**
  - Considerable cardiac output
  - Unusual sinusoidal architecture
- **LOCATION:**
  - 1st organ perfused by things absorbed from GIT
- **FUNCTION:**
  - Primary organ involved in biotransformation

BIOACTIVATION & DETOXIFICATION

Cyt P450 (centrilobular)

Oxidation/reduction/hydrolysis

PHASE I

Xenobiotic → Reactive intermediate

Glutathione/transaminases (periportal)

Conjugations

PHASE II

→ Stable metabolite

Bioactivation

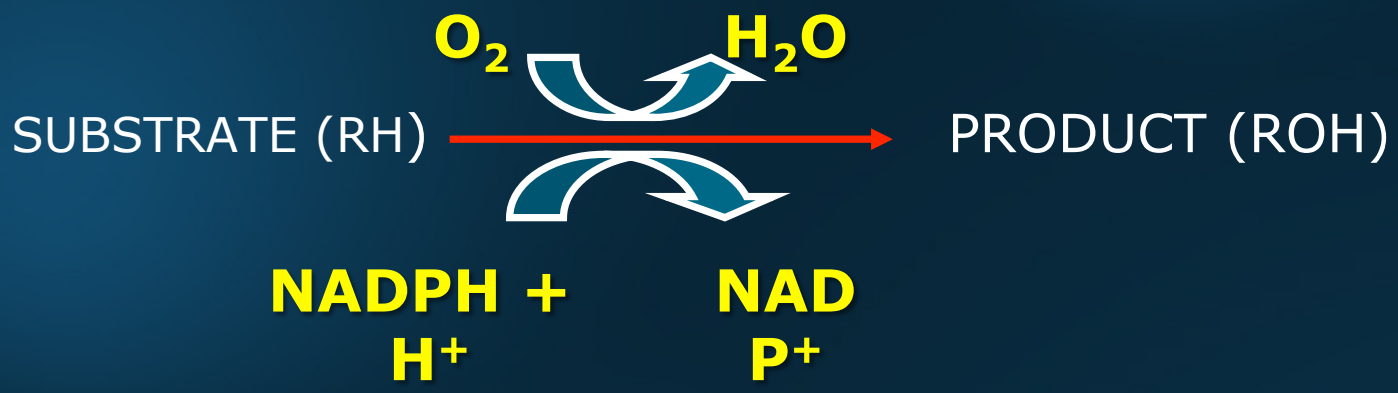
- **Ethanol**
  - EtOH → acetaldehyde
    (rapidly by alcohol dehydrogenase)
  - Acetaldehyde → acetate
    (slowly by aldehyde dehydrogenase)
  - Polymorphisms in Asian people
    - More "fast" & less "slow" → Build-up of acetaldehyde

Bioactivation

Cytochrome P450 is a Haem-containing protein

The basic reaction that it catalyses is monooxygenation:

- one atom of O_2 is incorporated into a substrate (RH)
- the other is reduced to water using NADPH:



Cytochrome P450 Enzymes

A superfamily of enzymes in the SER with wide substrate specificity – a major group responsible for drug metabolism

Important Points to Remember:

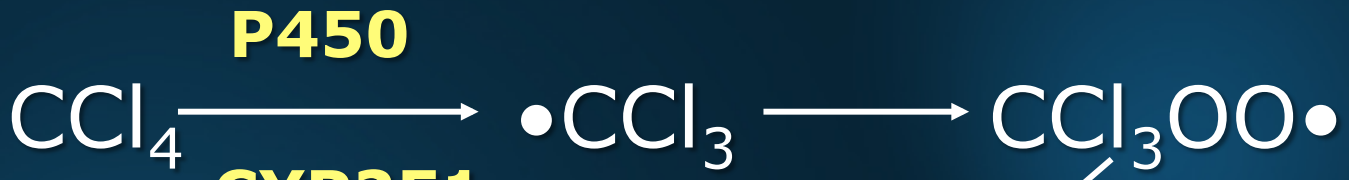
- Each isozyme can metabolise MANY different drugs
- Many drugs can be metabolised by more than one isozyme

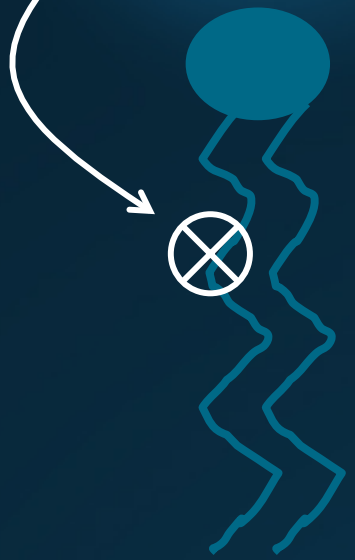
- Few compounds are conjugated directly, so PHASE I metabolism is a very important line of defence

- Unfortunately Cyt p450 can → reactive oxygen compounds that are hepatotoxic (esp CYP2E1 & CYP3A)

Bioactivation

Carbon Tetrachloride





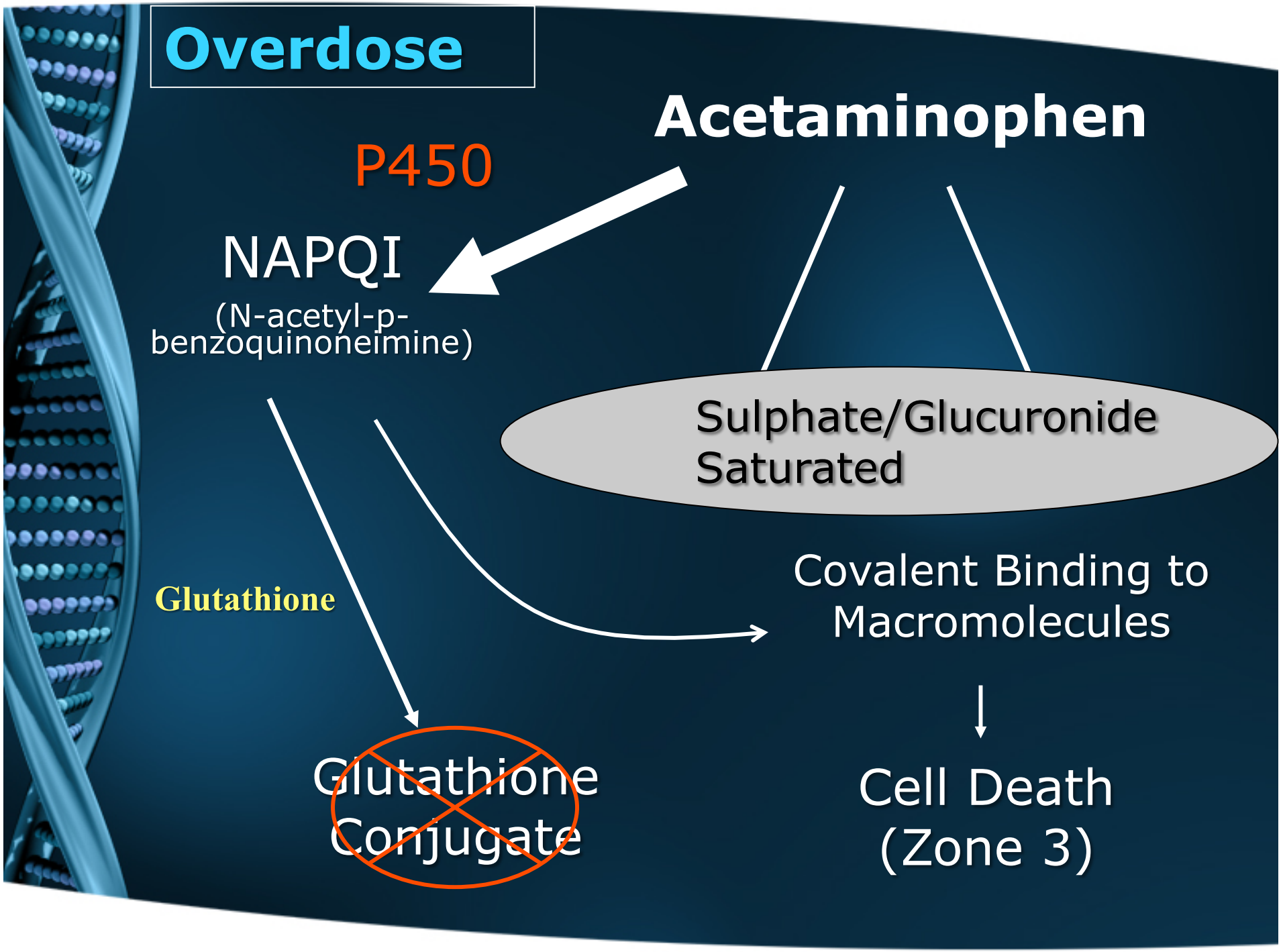
Lipid peroxidation of fatty acid

Bioactivation

- Acetaminophen
  - 1st introduced into clinical medicine late 1900s – "back door" - no formal preclinical animal toxicity studies
  - Attracted little attention and was soon forgotten
  - Potential hepatotoxicity was not suspected until the first clinical reports of severe and fatal liver damage following OD in 1960s
  - Species differences in its metabolic activation
  - Paracetamol is involved in 15 to 30% of deliberate self-poisonings in UK

Acetaminophen

- Glutathione-S-transferase is important
- Uses glutathione as a cofactor
- Acetaminophen metabolite conjugated by Glutathione
- Toxicity only revealed when GSH levels depleted to a certain level due to:
  - Overdose
  - Fasting


Overdose
Acetaminophen
P450
NAPQI
(N-acetyl-p-benzoquinoneimine)
Sulphate/Glucuronide Saturated
Glutathione
Covalent Binding to Macromolecules
Glutathione Conjugate
Cell Death (Zone 3)

Sinusoidal Cells in Liver Toxicity

- Kupffer cells/Ito cells become activated after exposure to toxins
- Kupffer cells can be activated by Vit A
  - This then enhances acute toxicity of CCl_4
- Activated Kupffer cells produce reactive oxygen species & reactive nitrogen species

Mechanisms of Liver Damage

- **Cell skeleton**
  - Microcystin:
    - Covalently binds to cytoskeletal proteins
    - Leads to hyperphosphorylation reactions
    - Microtubular scaffolding collapses, resulting in deformation of hepatocyte

Mechanisms Of Liver Damage

- **Cholestasis**
  - Toxins can inhibit bile formation by various mechanisms
    - Transporter/Export function
    - Tight junction leakage
    - Concentration of reactive substances

Mechanisms

- **Mitochondrial Damage**
  - **Toxins can:**
    - **Inhibit mitochondrial DNA synthesis**
    - **Lead to free radical production by effects on electron transport chain**

Response To Damage

- In general, tissues respond similarly:
  - Inflammation
  - Degeneration / Necrosis
  - Recovery/Proliferation/Malignancy

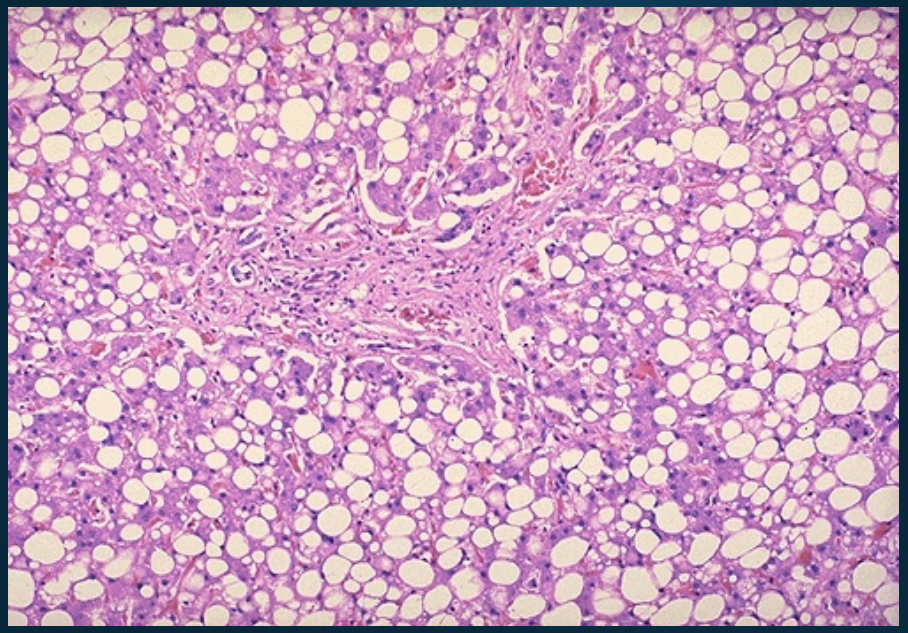
Types Of Liver Injury

- Response of liver to injury relates to:
  - Degree & duration of the insult
  - Cell population affected
- Types of injury include:
  - Fatty change
  - Hepatocellular death
  - Canalicular cholestasis
  - Bile duct damage
  - Sinusoidal damage
  - Cirrhosis
  - Neoplasia

Fatty Change

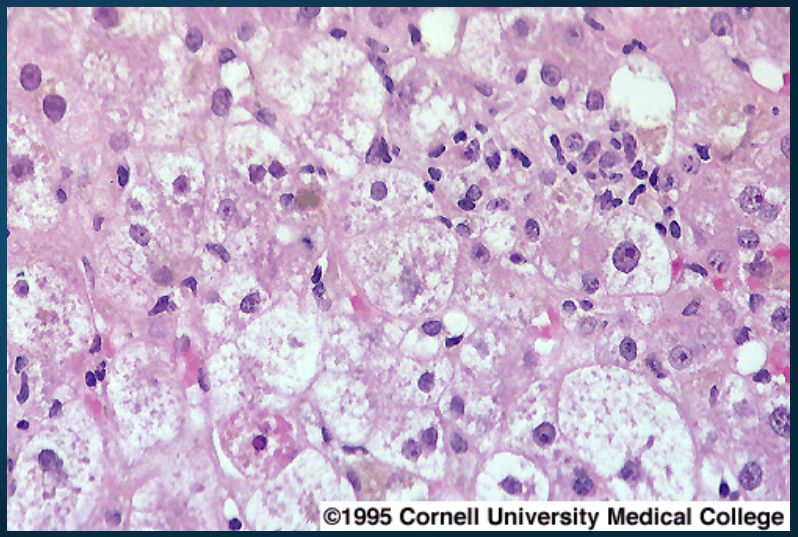
- Increased lipid in hepatocyte cytoplasm
- Due to altered lipid metabolism
- Common with acute toxins
- Potentially reversible
- Most common cause is alcohol

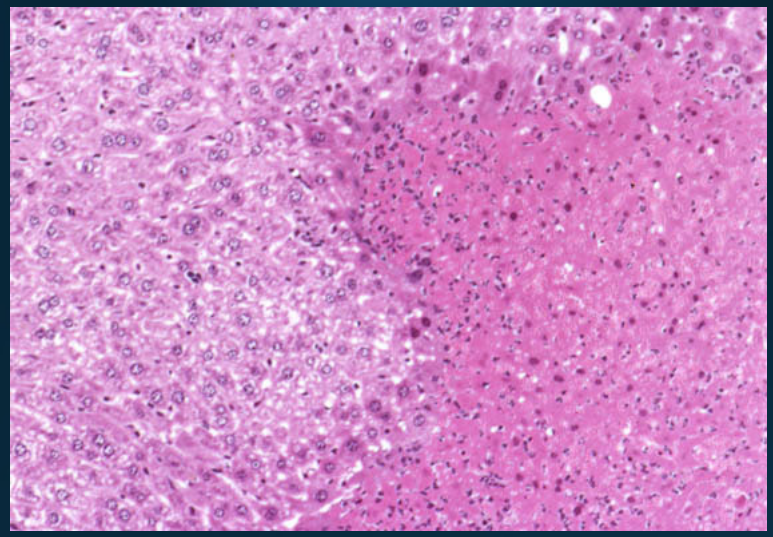
Fatty Change



Cell Death

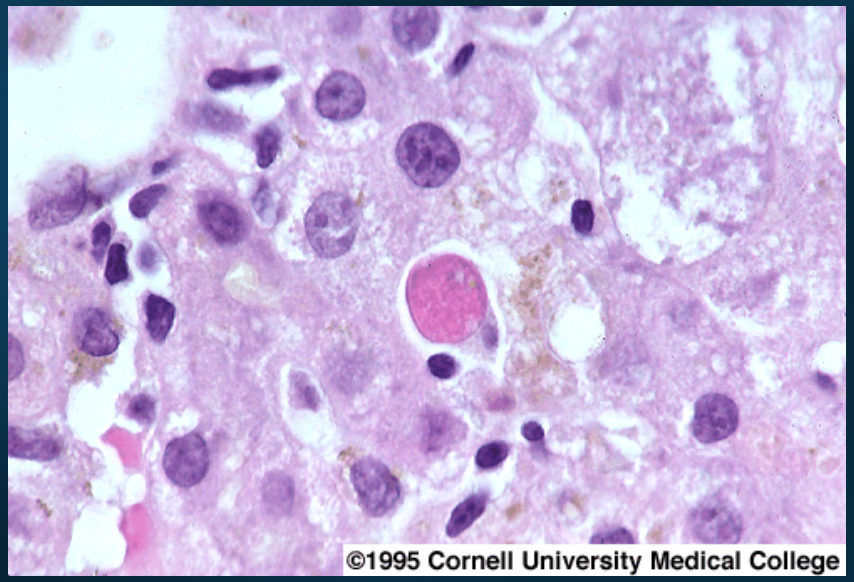
- Necrosis (Eg/ due to acetaminophen)
  - Cell swells
  - Leakage of cytoplasm
  - Nuclear disintegration





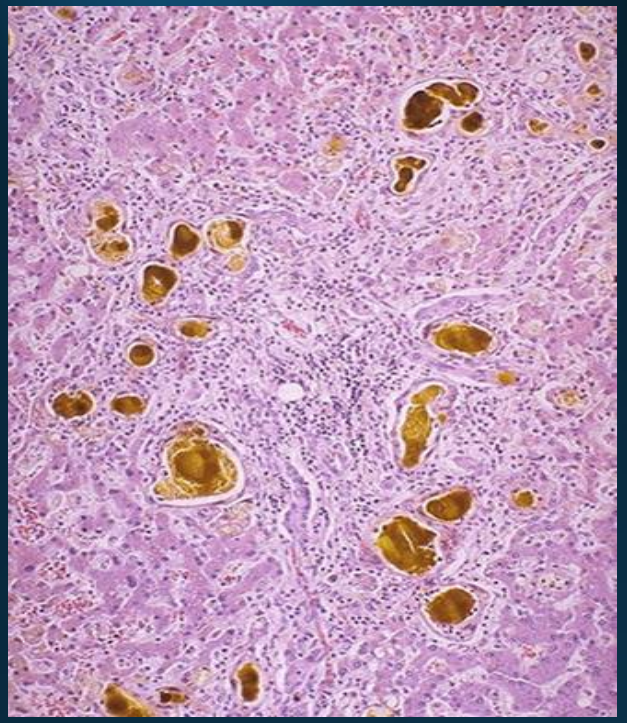
Apoptosis

- Features
  - Cell shrinkage
  - Nuclear fragmentation
  - Formation of apoptotic bodies
  - Usually no/minimal inflammation



Cholestasis

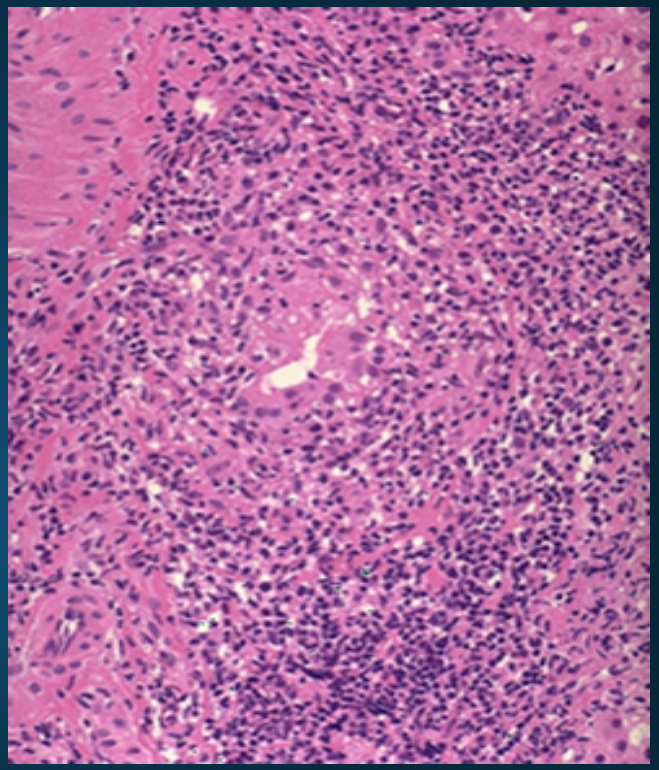
- Reduced formation/secretion of bile
  - Leads to accumulation of things like bilirubin that are normally excreted in bile
  - Results in icterus
- Offending drugs:
  - Cyclosporin
  - Oestrogens

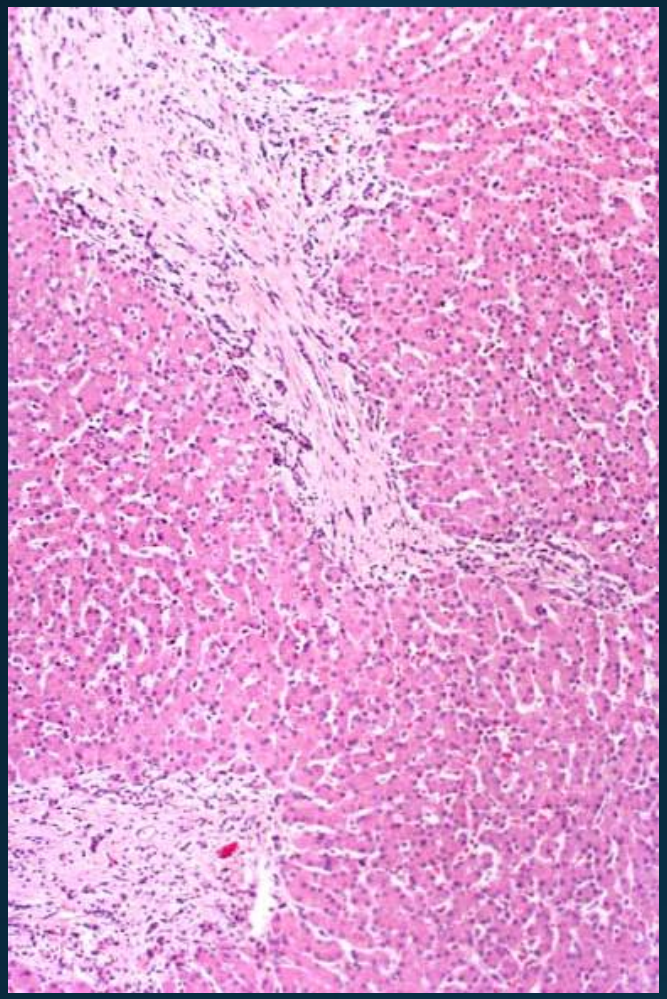


Bile Duct Damage

- Cholangiodestructive cholestasis
- Increased serum activity of gamma glutamyltransferase (GGT)
- Bile duct epithelial damage →
  - Necrosis, Inflammation, Fibrosis
  - Bile duct hyperplasia
  - Bile duct loss (Vanishing bile duct syndrome)

Biliary Inflammation & Fibrosis

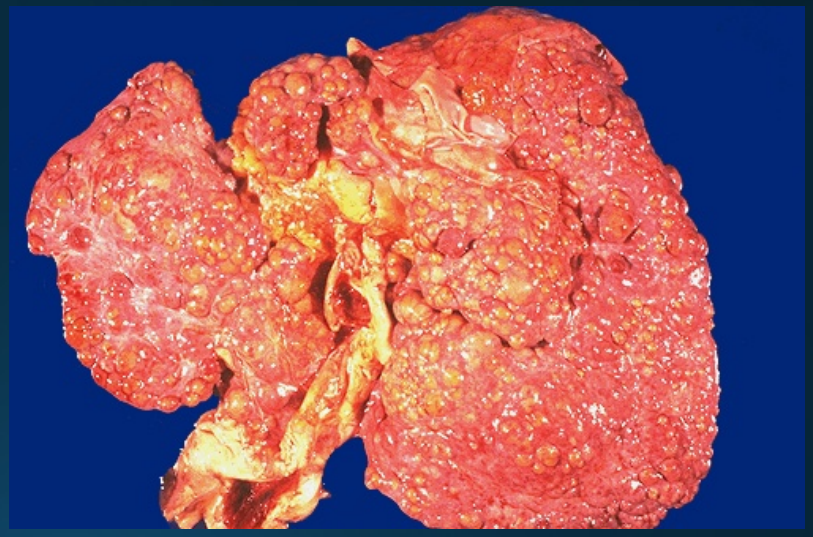


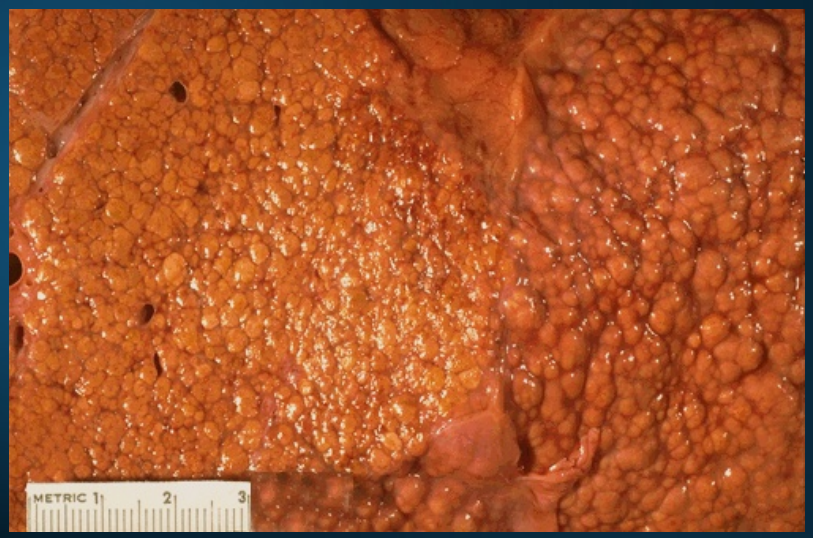


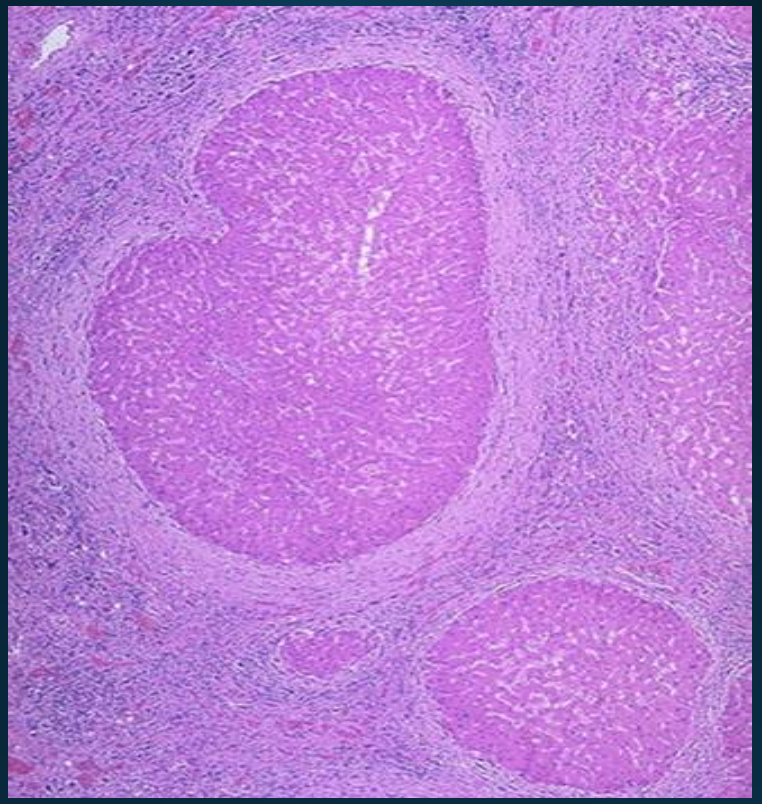
Cirrhosis

- Progressive liver injury – chronic action
- Necrotic areas replaced by fibrous tissue
- Result of repetitive injury of liver cells
- Associated with alcohol abuse

Cirrhosis



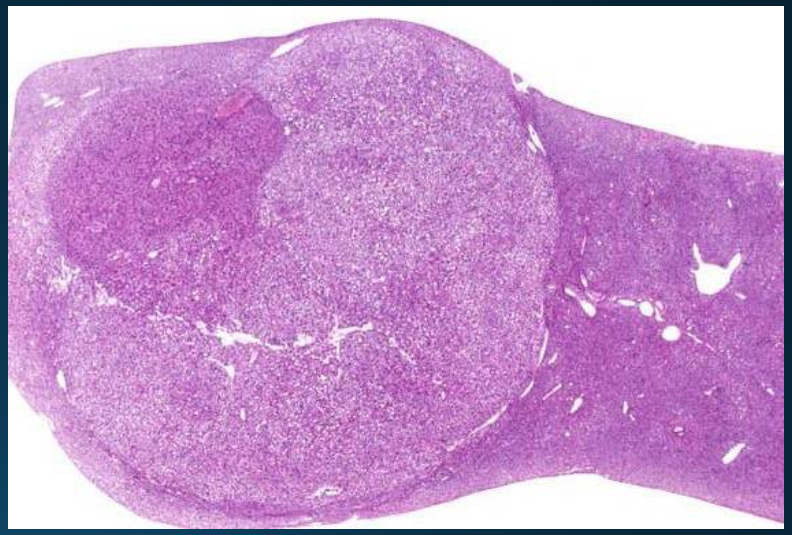


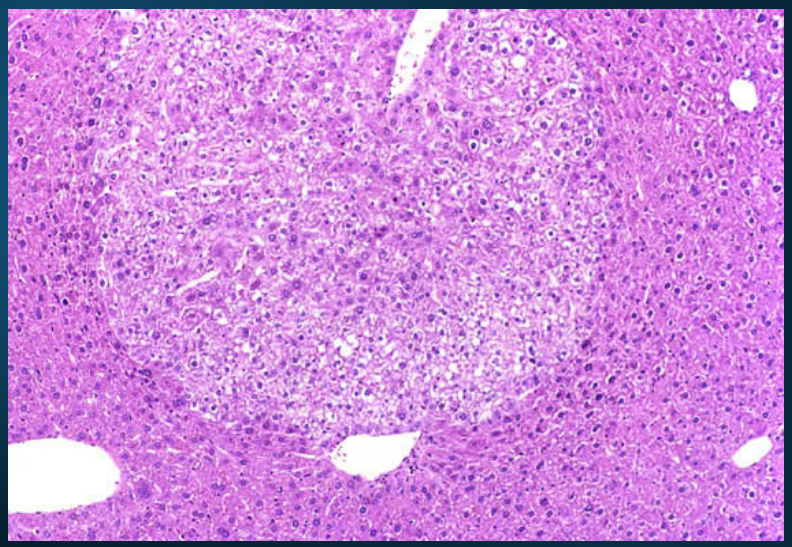


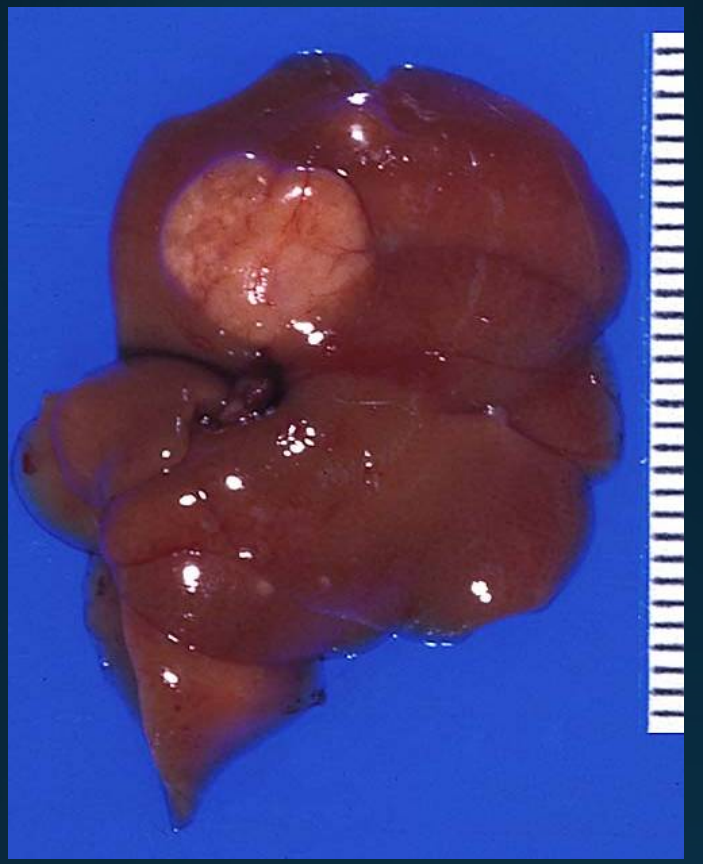
Neoplasia

- Primary neoplasms arise from cells in the liver
  - Hepatocytes
  - Bile duct epithelium
- Secondary neoplasms arise from cells outsideliver
  - Invasion
  - Metastasis
- Aflatoxins
  - Result in hepatocellular carcinoma

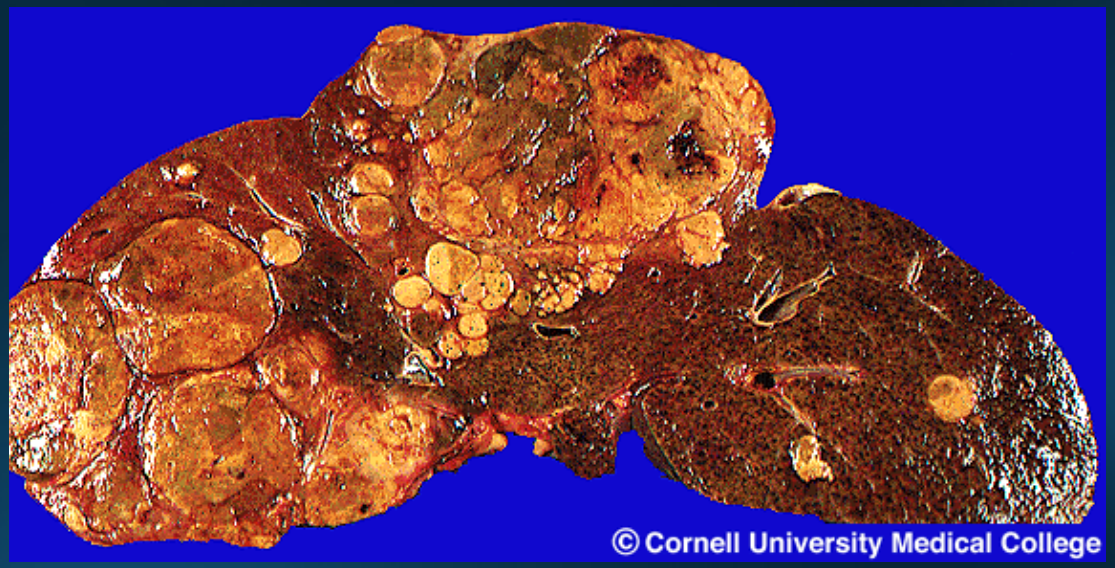
Hepatocellular adenoma

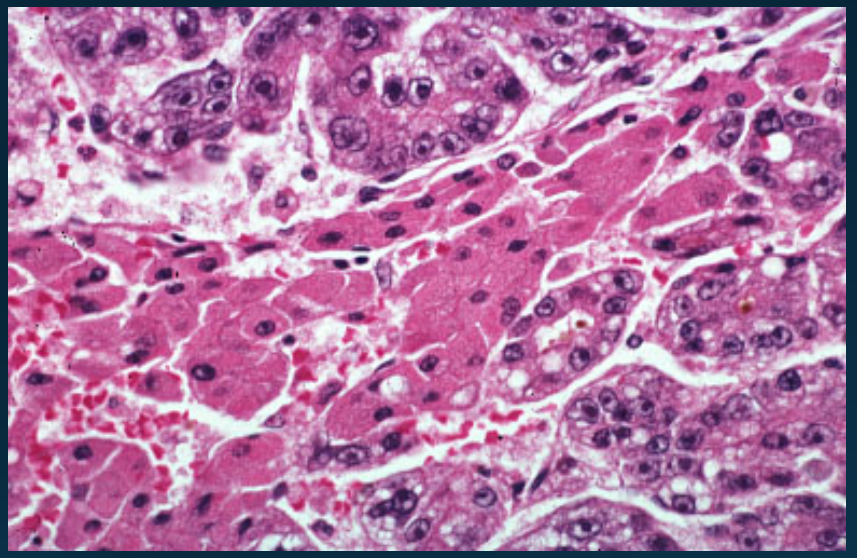




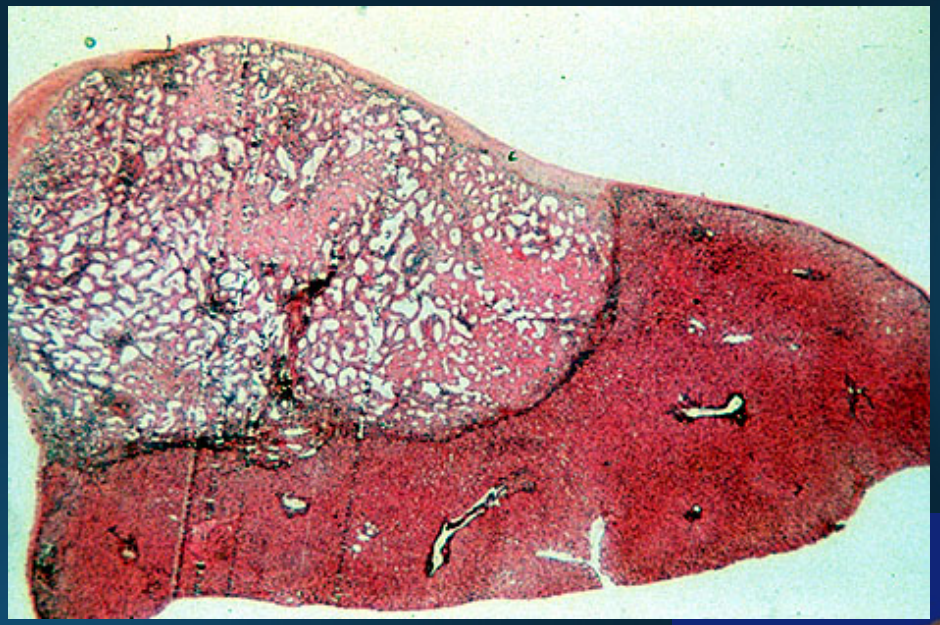


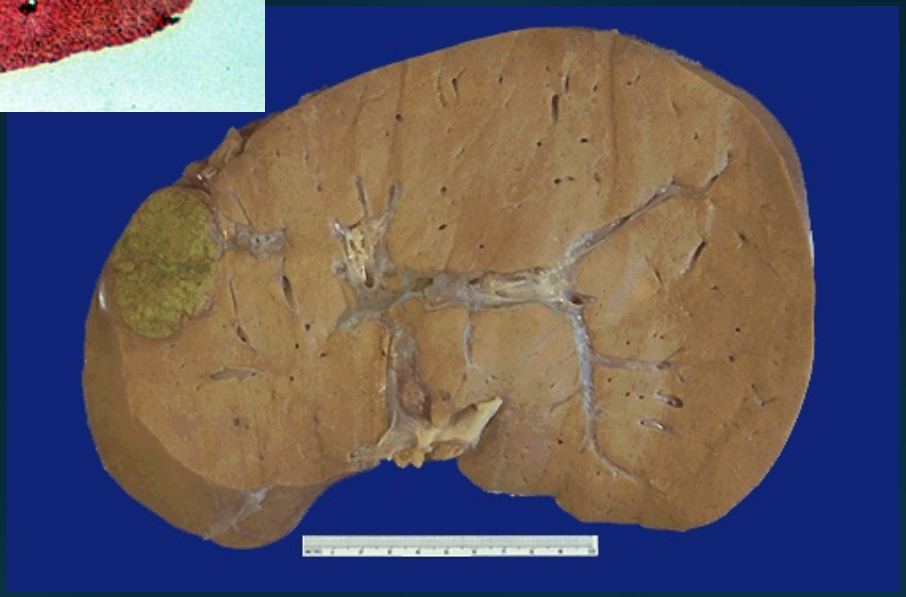
Hepatocellular carcinoma



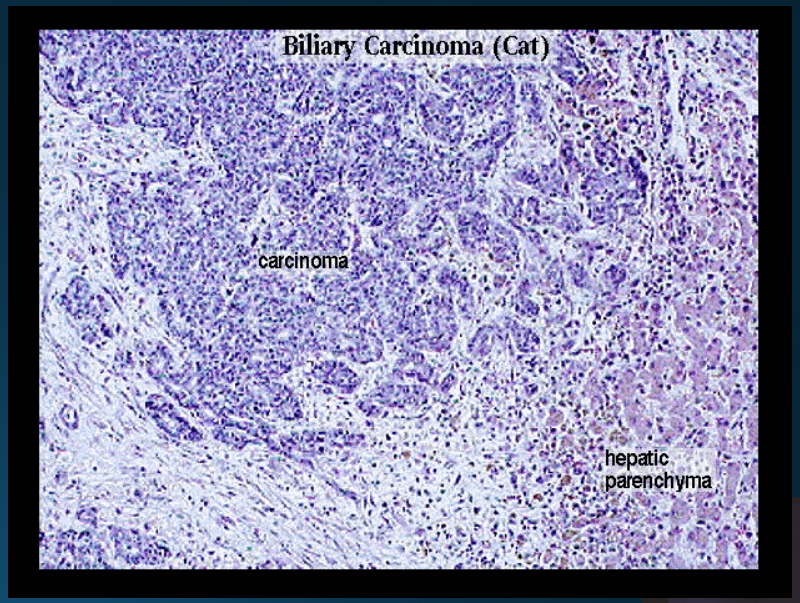


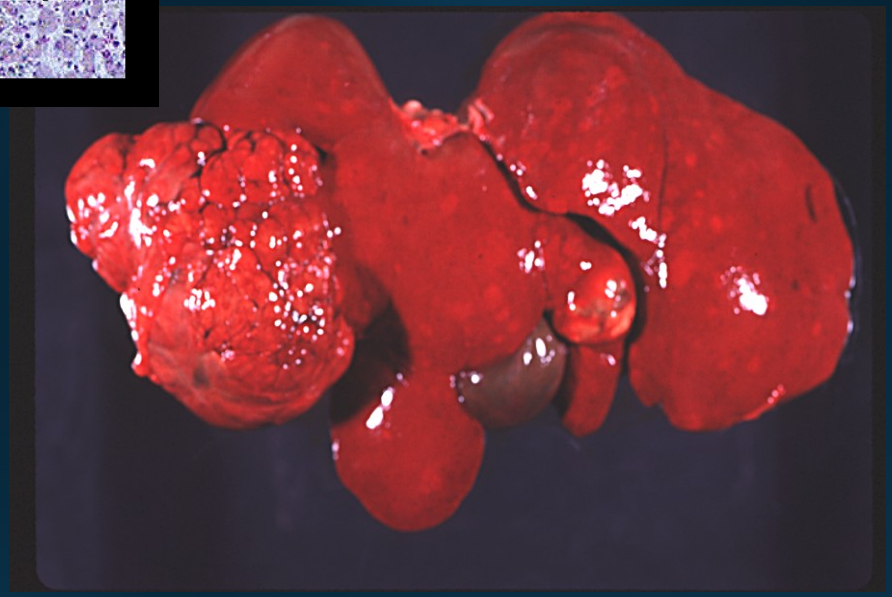
Bile Duct Adenoma





Bile Duct Carcinoma





In Summary

- The liver is a metabolically important organ
  - Biosynthesis
  - Nutrient metabolism
  - Detoxification & biotransformation
- But remember its Achilles heel effect
  - High cardiac output & optimum anatomic location
  - Biotransformation can produce toxic substances
  - Enterohepatic circulation leads to re-exposure

Thank You!