

20.201 Mechanisms of Drug Action

The Liver and Metabolism

September 30, 2005

Distribution of Chemicals to Liver

- Chemicals entering blood are distributed in the general circulation via the aorta
- Chemicals enter various organs
- Focus now on liver

• Liver anatomy

- ~ Largest organ and gland (1.5 kg)
- ~ Structure: lobes (2 large - R and L; 2 small - caudate, quadrate)
- ~ Blood supply: portal blood flow, 80%; hepatic artery, 20%; outflow into vena cava
- ~ Bile duct/gall bladder: bile secreted into bile duct/gall bladder; then into duodenum

• Liver function

- ~ major metabolic organ in body
- ~ significant route of xenobiotic excretion
- ~ exocrine gland: albumin, clotting factors (prothrombin, fibrinogen, factors 7,9,10) lipoproteins, bile
- ~ storage organ: carbohydrate (glucose buffer), lipids (TG's), blood (up to 1 L reservoir)
- ~ metabolic functions: gluconeogenesis, amino acid deamination/urea formation, cholesterol synthesis, fatty acid oxidation

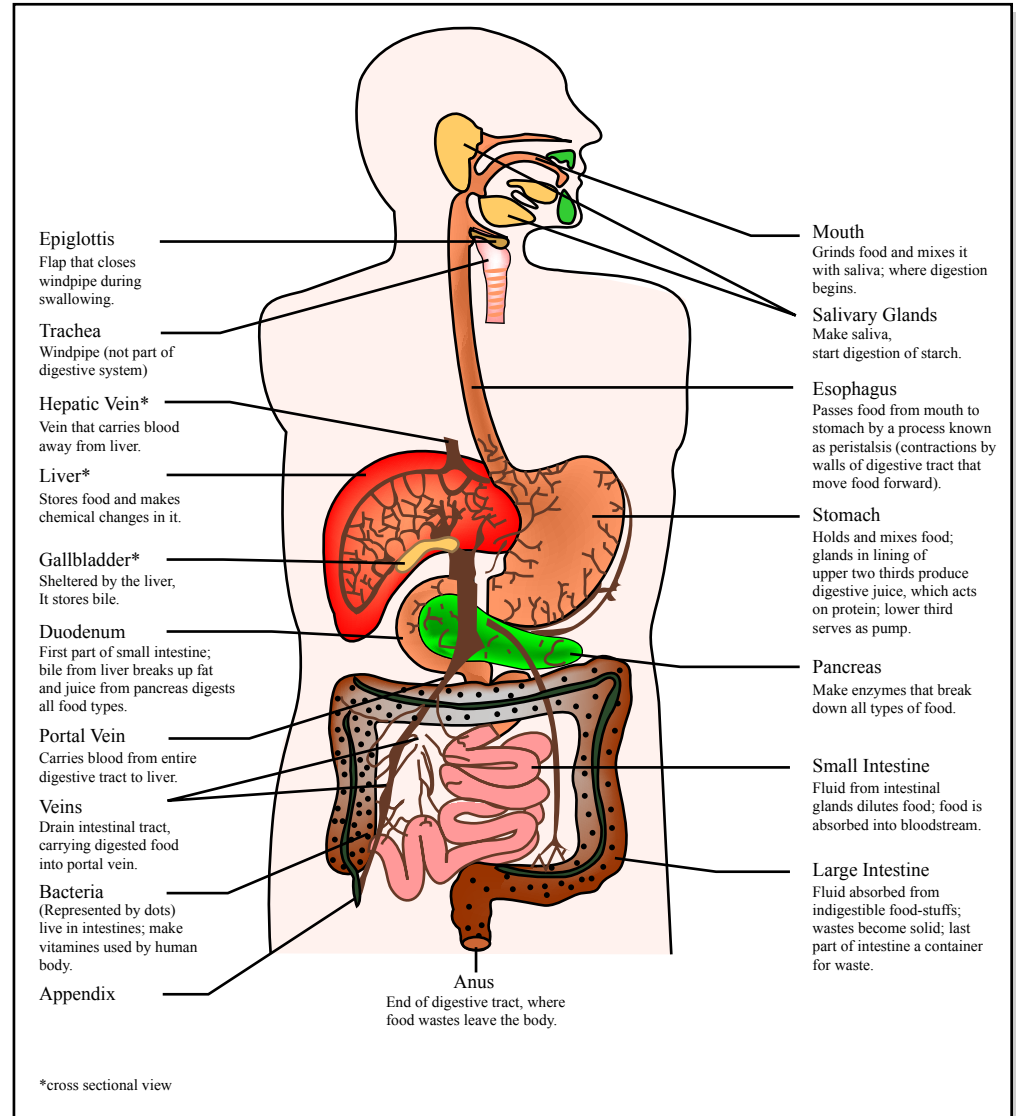


Figure by MIT OCW.

- Unique circulation of blood from gut to liver: all venous blood from stomach and intestines proceeds via portal vein directly to liver.
- Poses problem for development of orally-active drugs: can achieve nearly complete removal of drug by metabolism in one pass through the liver.

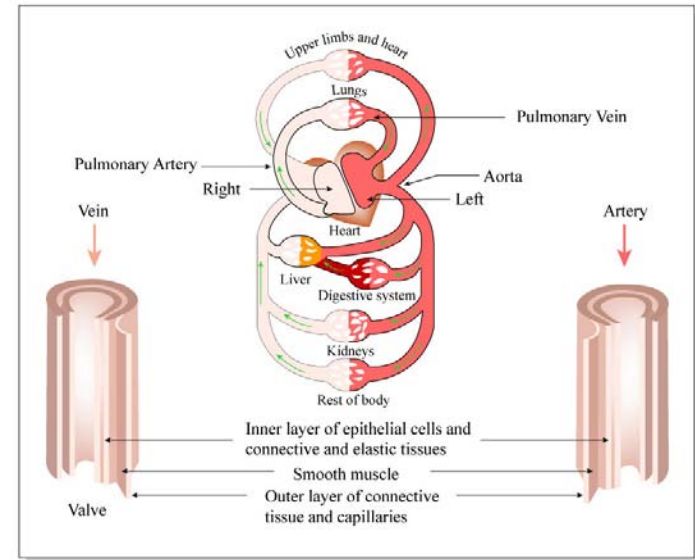


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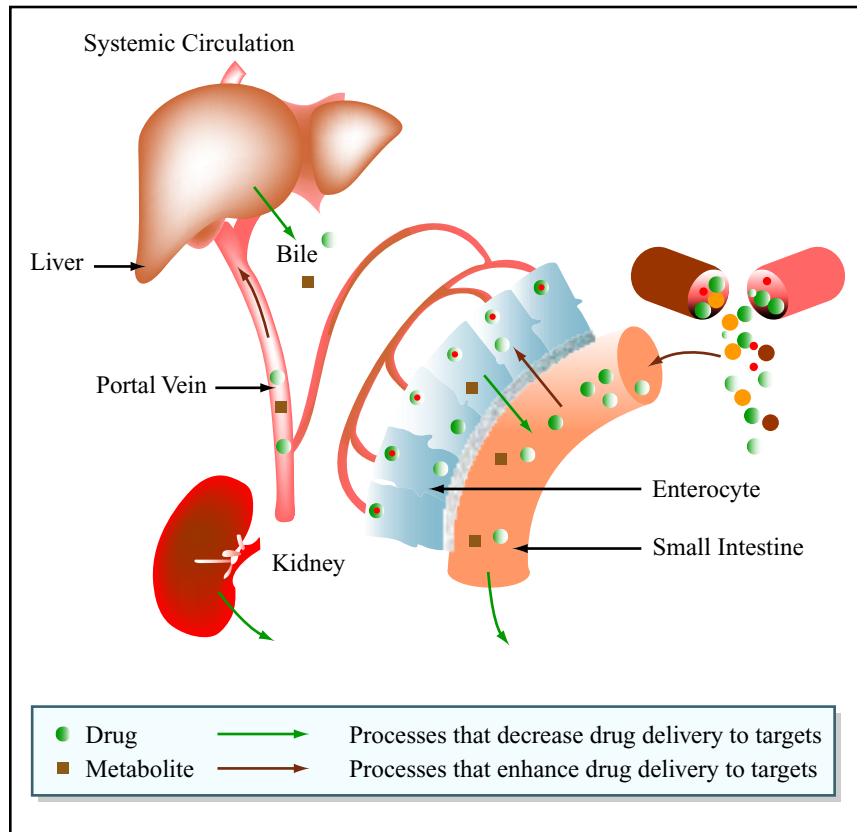


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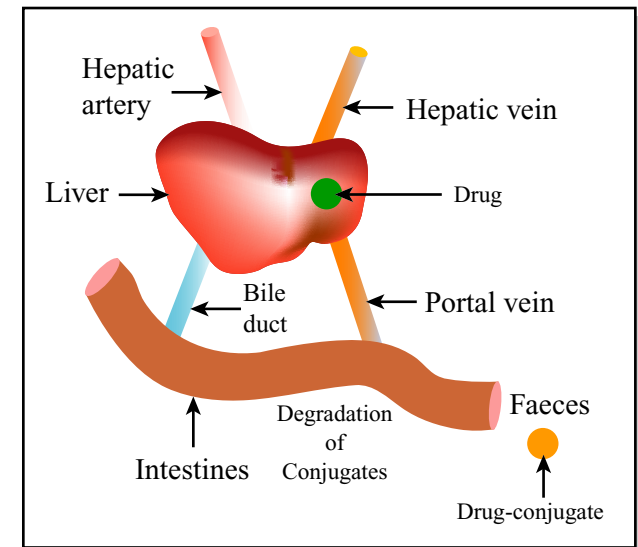


Figure by MIT OCW.

The Liver and Metabolism

- Major sites of metabolism
 - ~ All cells capable of metabolism;
 - ~ Main metabolic tissues include:
 - liver (hepatocytes)
 - kidney (proximal tubule epithelium)
 - lung (Clara cells, type II pneumocytes)
 - intestine (epithelial lining)
 - skin (epithelial cells)
 - testes (sertoli and seminiferous tubule cells)
 - gut flora (rivals liver in metabolic capacity)
 - ~ Major extra-hepatic sites of metabolism are routes of entry/exit!!!
- General function of metabolism: convert water insoluble chemicals into soluble forms
- Two types of metabolic reactions: Phase I and Phase II

BEST RESOURCE FOR THE CHEMISTRY AND BIOLOGY OF XENOBIOTIC

METABOLISM: Chapter 6 in "Casarette and Doull's Toxicology: The Basic Science of Poisons" edited by Curtis Klassen. 6th Edition. McGraw-Hill Medical Publishing, NY, 2001. This book is available in the Science Library.

- ~ Liver divided into 50-100,000 lobules: structure follows function
- ~ Lobule: central vein bounded by portal triads: portal venule, hepatic arteriole, bile ductule
- ~ Can also divide into acini: 3 zones of hepatocytes between central vein and triad
- ~ Hepatocytes (main epithelial cell of liver)
- ~ Sinusoids: capillary spaces between plates; leaky capillaries
 - 1) Large diameter (40 mm vs. usual 0.08 mm) causes reduced blood flow
 - 2) Space of Disse: between endothelial cell and hepatocyte
 - 3) Kupfer cells: liver-bound macrophages
 - 4) Ito cells: synthesize collagen; vitamin A storage
- ~ Blood flows from portal triad to central vein
- ~ Functional/biochemical organization

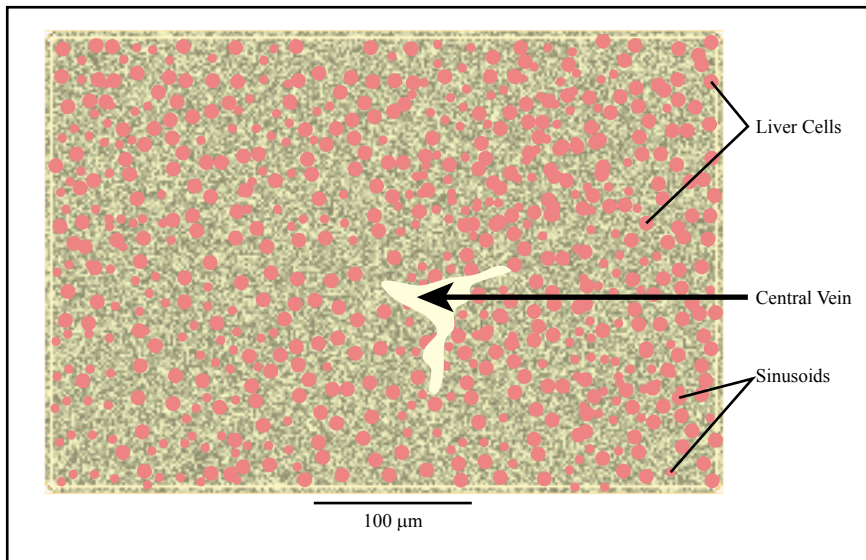
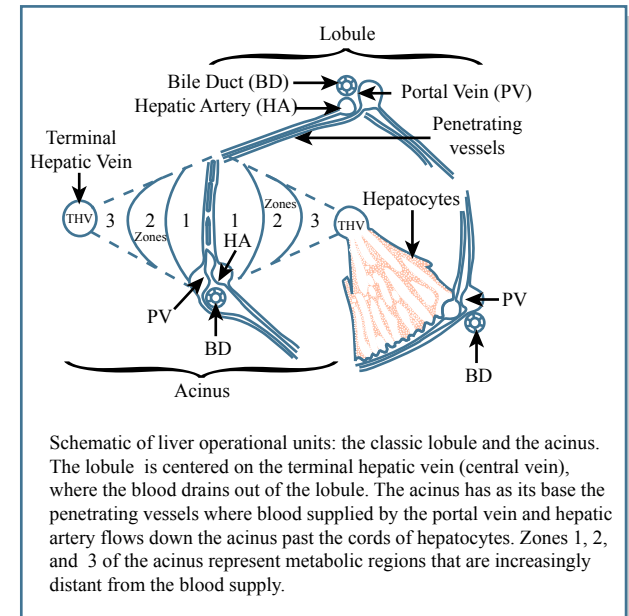


Figure by MIT OCW.



Schematic of liver operational units: the classic lobule and the acinus. The lobule is centered on the terminal hepatic vein (central vein), where the blood drains out of the lobule. The acinus has as its base the penetrating vessels where blood supplied by the portal vein and hepatic artery flows down the acinus past the cords of hepatocytes. Zones 1, 2, and 3 of the acinus represent metabolic regions that are increasingly distant from the blood supply.

Figure by MIT OCW.

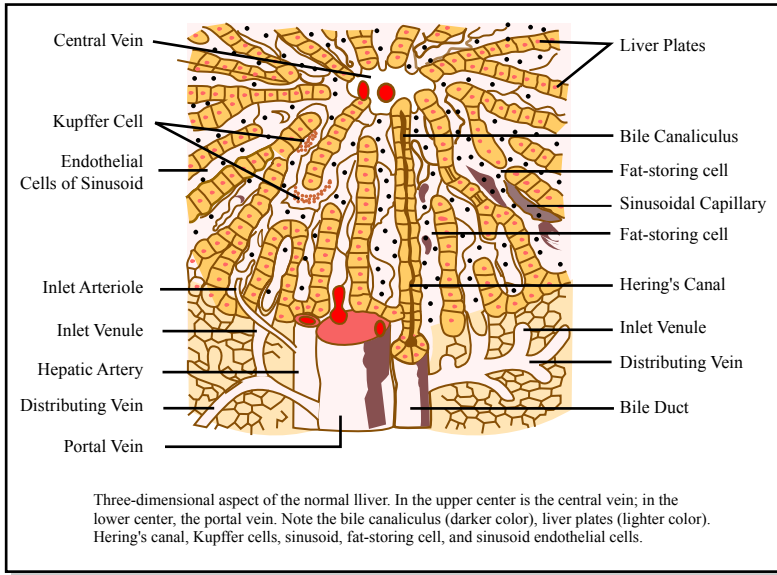


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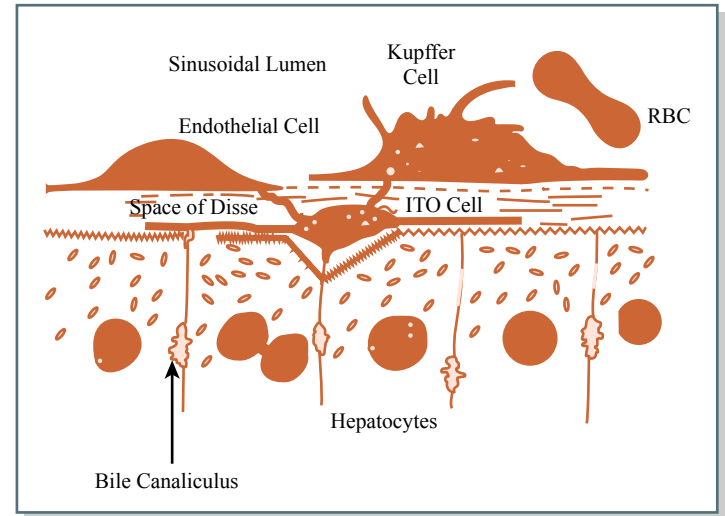


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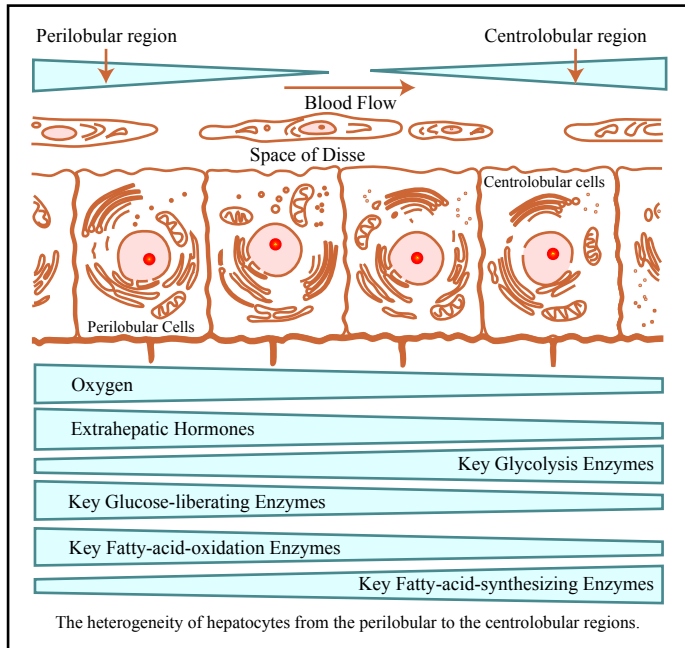


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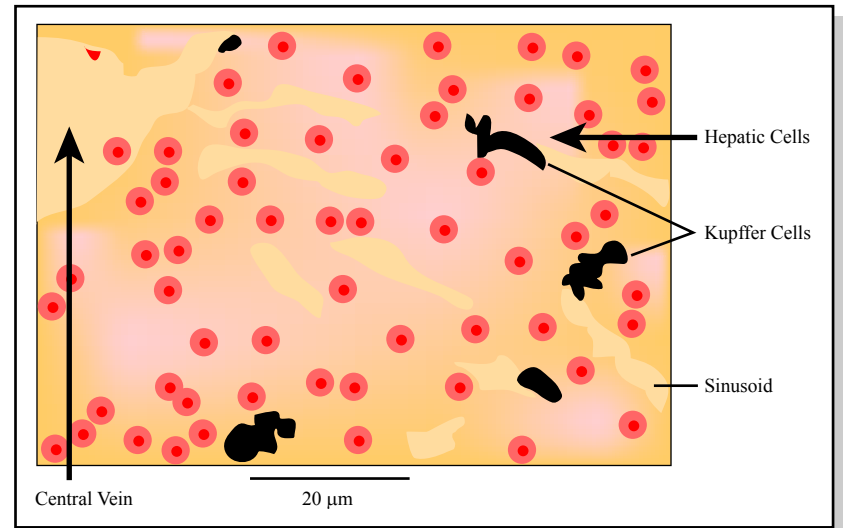


Figure by MIT OCW.

Locations of metabolic enzymes in cells

| REACTION | ENZYME | LOCALIZATION |
|---|--------------------------|---------------------------------|
| PHASE I | | |
| Hydrolysis | Carboxylesterase | Microsomes, cytosol |
| | Peptidase | Blood, lysosomes |
| Reduction | Epoxide hydrolase | Microsomes, cytosol |
| | Azo-and nitro-reduction | Microflora, microsomes, cytosol |
| | Carbonyl reduction | Cytosol |
| | Disulfide reduction | Cytosol |
| | Sulfoxide reduction | Cytosol |
| Oxidation | Quinone reduction | Cytosol, microsomes |
| | Reductive dehalogenation | Microsomes |
| | Alcohol dehydrogenase | Cytosol |
| | Aldehyde dehydrogenase | Mitochondria |
| | Aldehyde oxidase | Cytosol |
| | Xanthine oxidase | Cytosol |
| | Monoamine oxidase | Mitochondria |
| | Diamine oxidase | Cytosol |
| | Prostaglandin H synthase | Microsomes |
| | Flavin-mono-oxygenases | Microsomes |
| | Cytochrome P450 | Microsomes |
| PHASE II | | |
| | Glucuronide conjugation | Microsomes |
| | Sulfate conjugation | Cytosol |
| | Glutathione conjugation | Cytosol, microsomes |
| | Amino acid conjugation | Mitochondria, microsomes |
| | Acylation | Mitochondria, cytosol |
| | Methylation | Cytosol |
| General Pathways of Xenobiotic Biotransformation and their Major Subcellular Location | | |

- Metabolic enzymes located in cytosol, smooth endoplasmic reticulum (SER) and other subcellular structures
- Location often reflects solubility of substrate: lipophilic substrates metabolized in membranes of SER

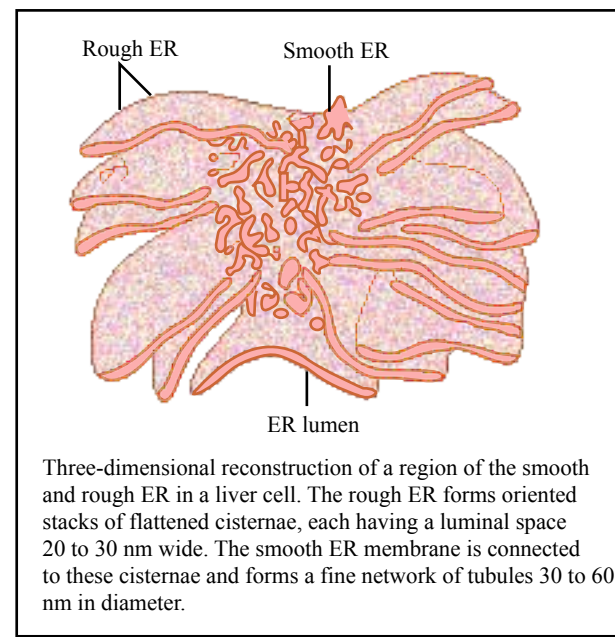


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