Pharmacokinetics

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Recommended lectures

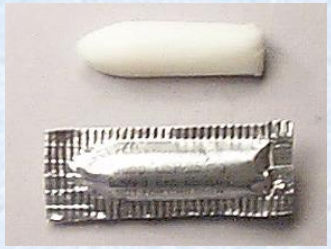
- S. G. Gilbert: A small dose of toxicology (Taylor &Francis, 2005)
- M. J. Neal: Medical Pharmacology at a Glance (8th edition, Wiley, 2016)
- Gyires Klára, Fürst Zsuzsanna (szerk.): A farmakológia alapjai (Medicina, 2011)

- Written exam at the end of the semester

Drug administration types

Local

- Skin
- Mucosa
- Eye

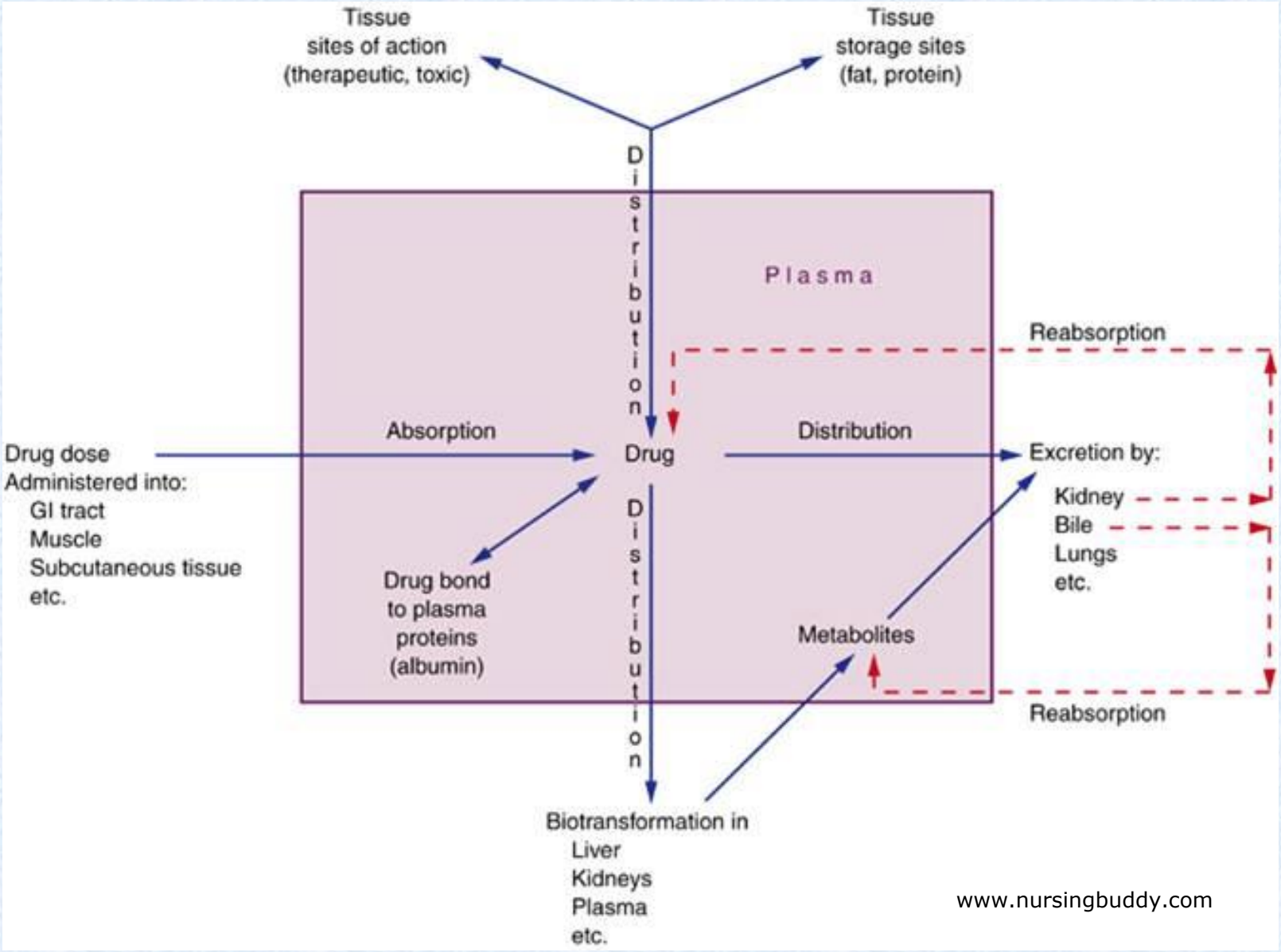


Systemic

- Enteral
  - Oral
  - Sublingual
  - Rectal

- Parenteral
  - Intravenous
  - Subcutaneous
  - Intramuscular
  - Intraperitoneal
  - Inhalation
  - Percutaneous

Fate of drugs in the body



Fate of drugs in the body

ADME: absorption, distribution, metabolism, elimination

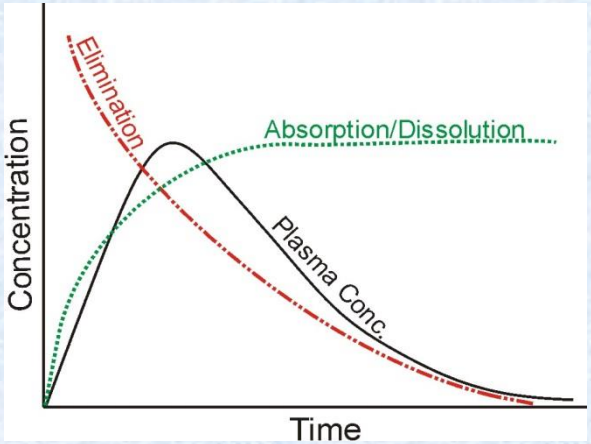
Biological effect correlates with concentration in blood

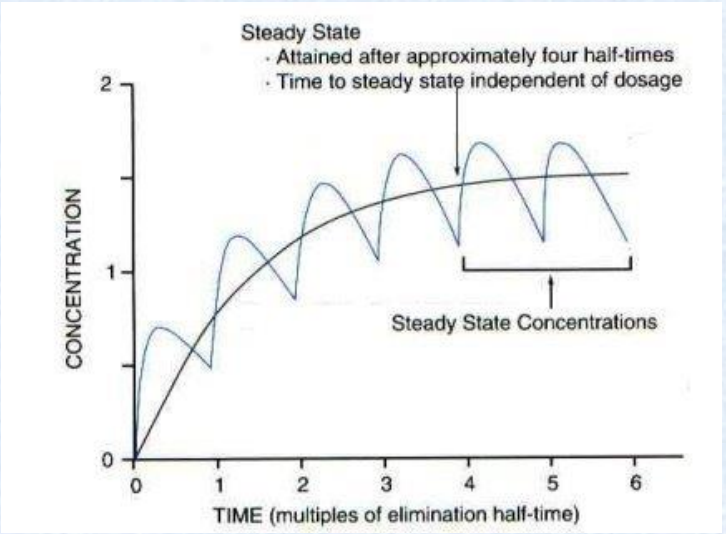
Drugs: xenobiotics

Therapeutic effect ⟷ toxic side effect

ADME parameters are very important for drug effect, primordial research area in drug development

ADME parameters determine the necessary frequency of drug administration

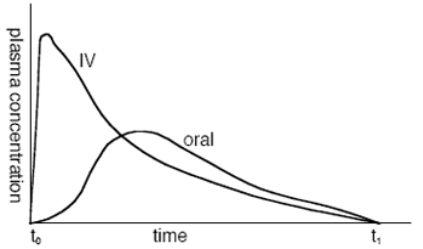




Absorption

Absorption: process during which the substance enters the systemic blood vessels

Influenced by: - route of administration (i.v. bypasses absorption barriers, sublingual, rectal bypasses first-pass metabolism…)



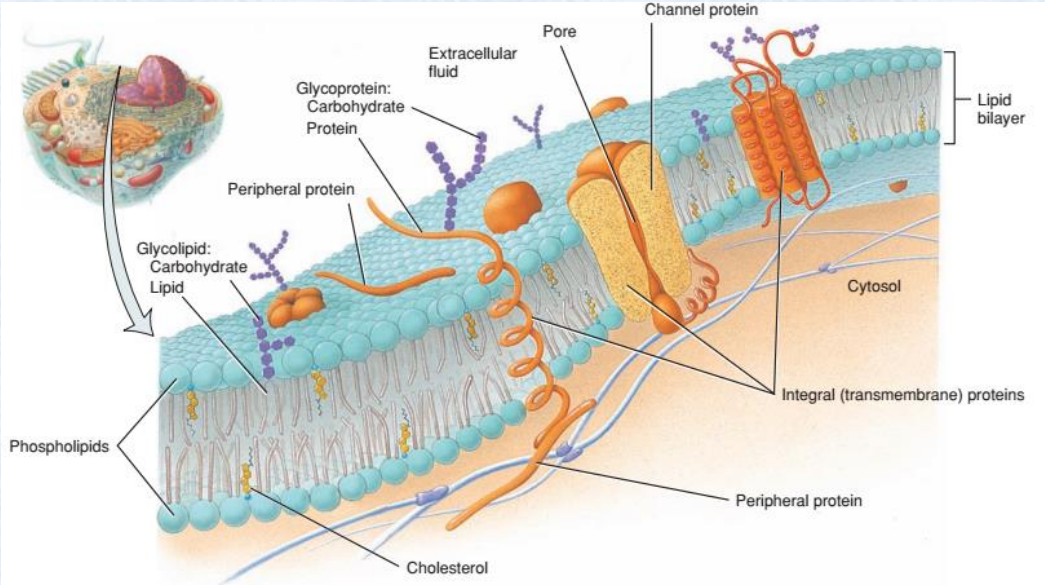
- formulation of the drug, resistance to gastric acid, enzymes
- size of the molecule
- solubility of the molecule (hydrophilic/lipophilic)
- pH of the environment → ionic /nonionic form
- intestinal motility, fullness of stomach…

Translocation through barriers

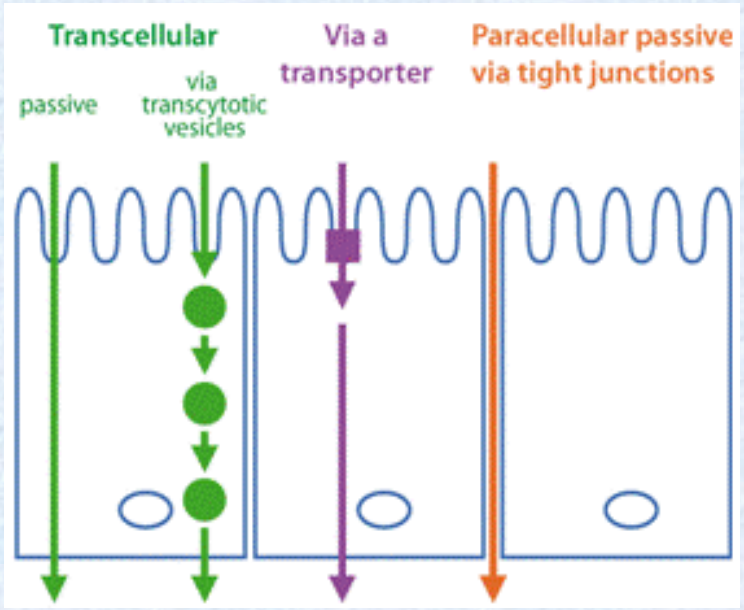
Cell membranes: lipid barriers

- Diffusion trough intercellular space
- Through plasma membranes

- Passive diffusion
- Endocytosis
- Transporter/carrier



Tortora & Derrickson, 2012



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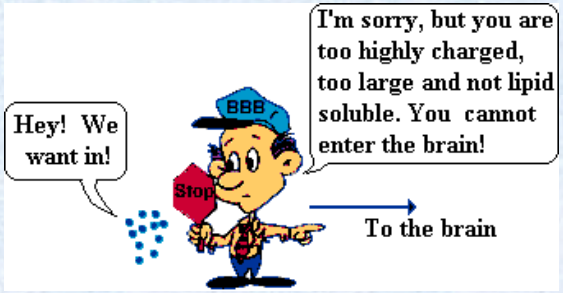
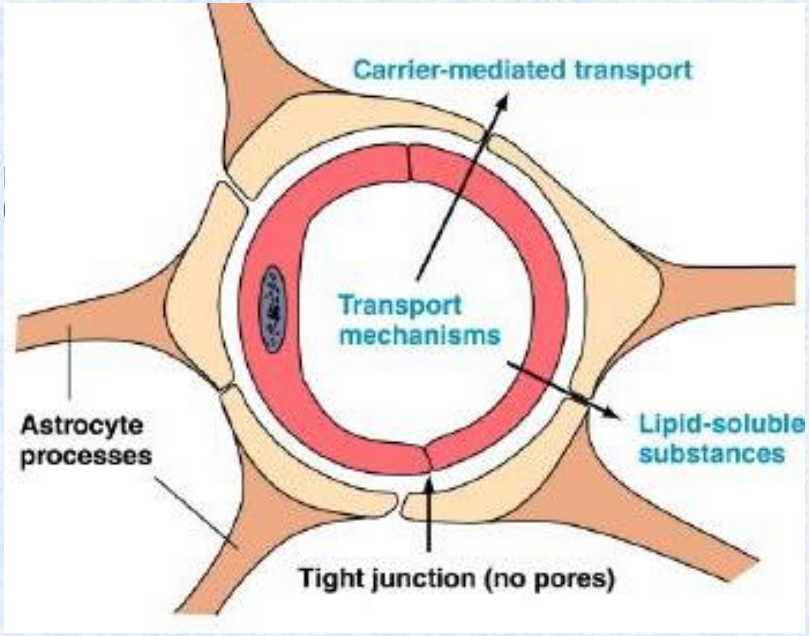
Absorption barriers

Tight junctions between cells – diffusion between cells not possible, only through endothelium



- Blood-brain barrier
- Placental barrier – small lipophilic molecules cross, foetus insufficient metabolism, may accumulate



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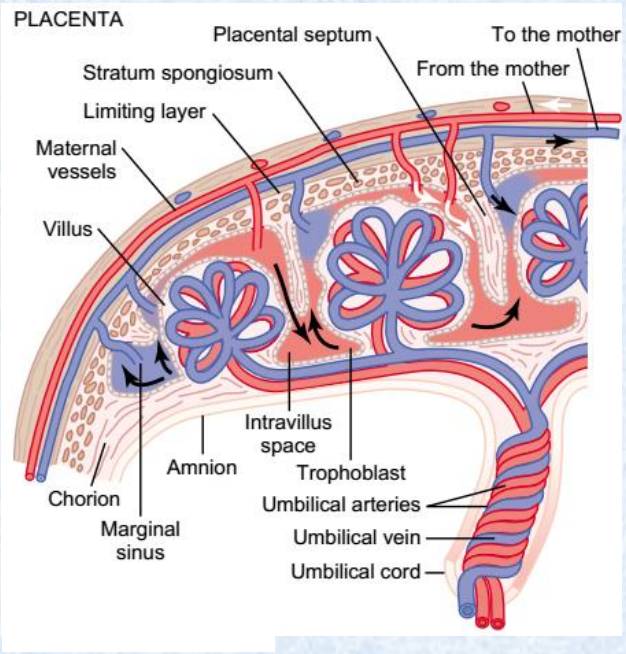
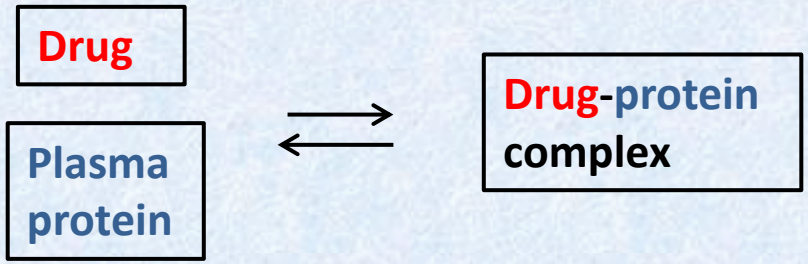


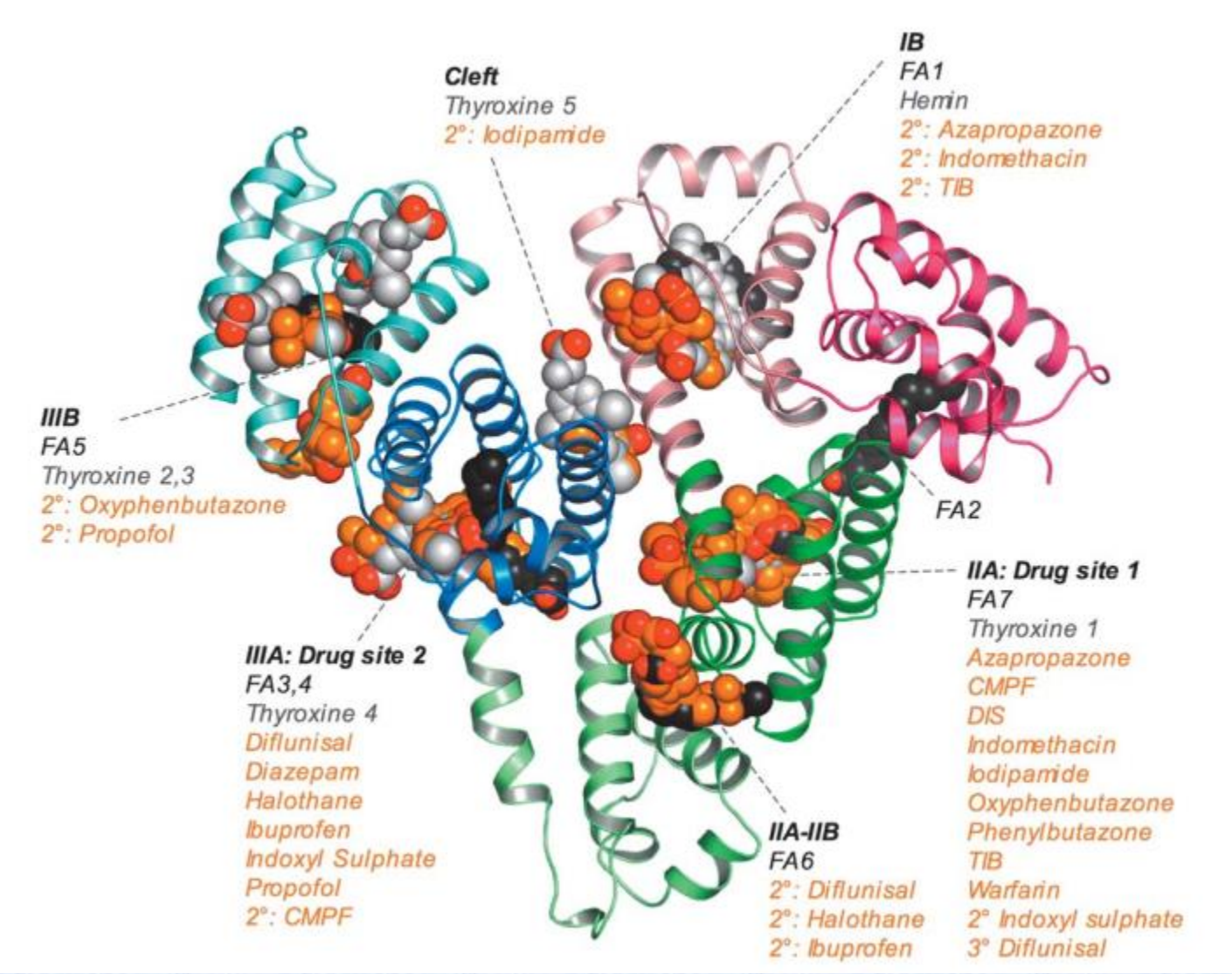
Guyton, 2006

Binding to plasma proteins

- Albumins, globulins, transferrin etc. (endogenous ligands: fatty acids, hormones, hemoglobin metabolites…)
- Protein bound drug ineffective
- "Store", prolongation of effect, slower metabolism, elimination
- Nonspecific binding, competition between drugs (displacement)
- Warfarin anticoagulant – 97% bound to protein!
- Decrease of blood plasma protein level (malnutrition, liver disease), renal disease may increase free drug concentration



Binding to albumin

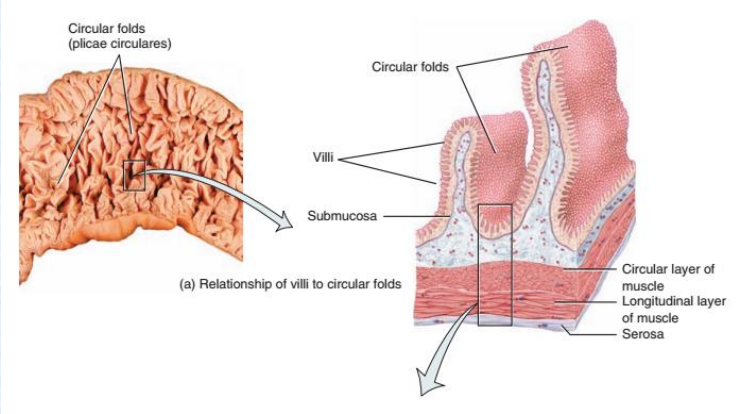


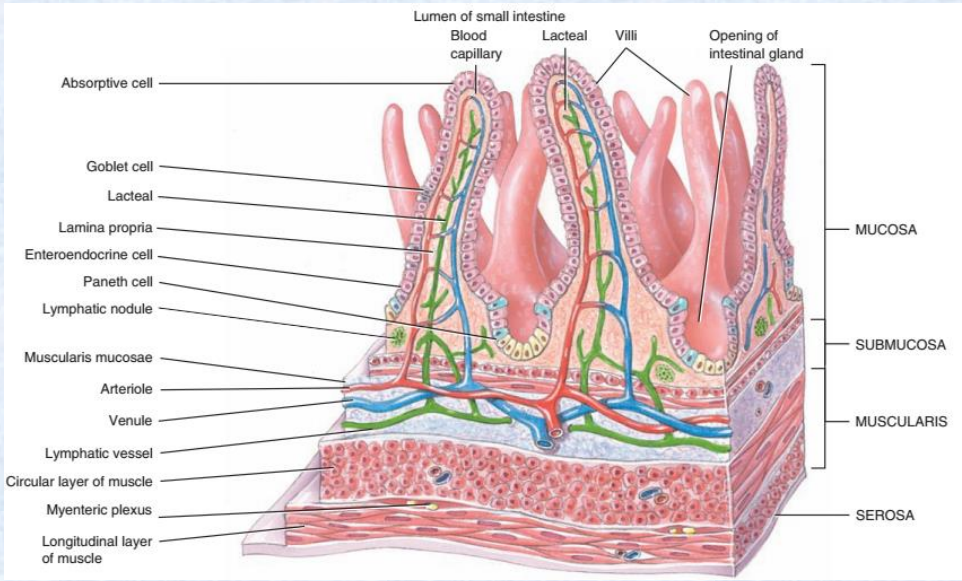
Ghuman et al. 2005

Oral administration

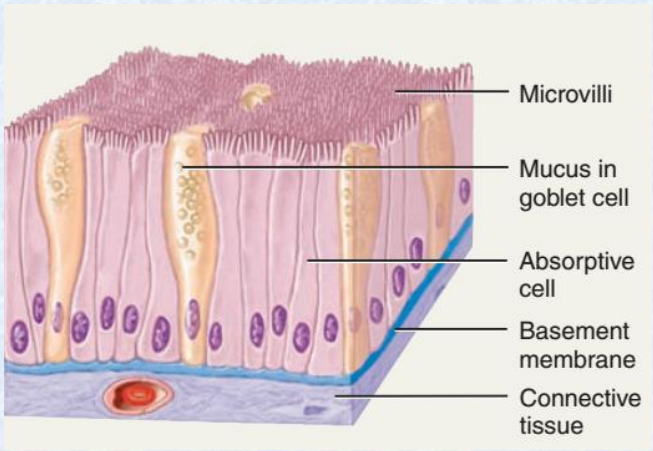
Absorption usually from small intestine (~nutrients)

Absorption from stomach – caffeine, ethanol





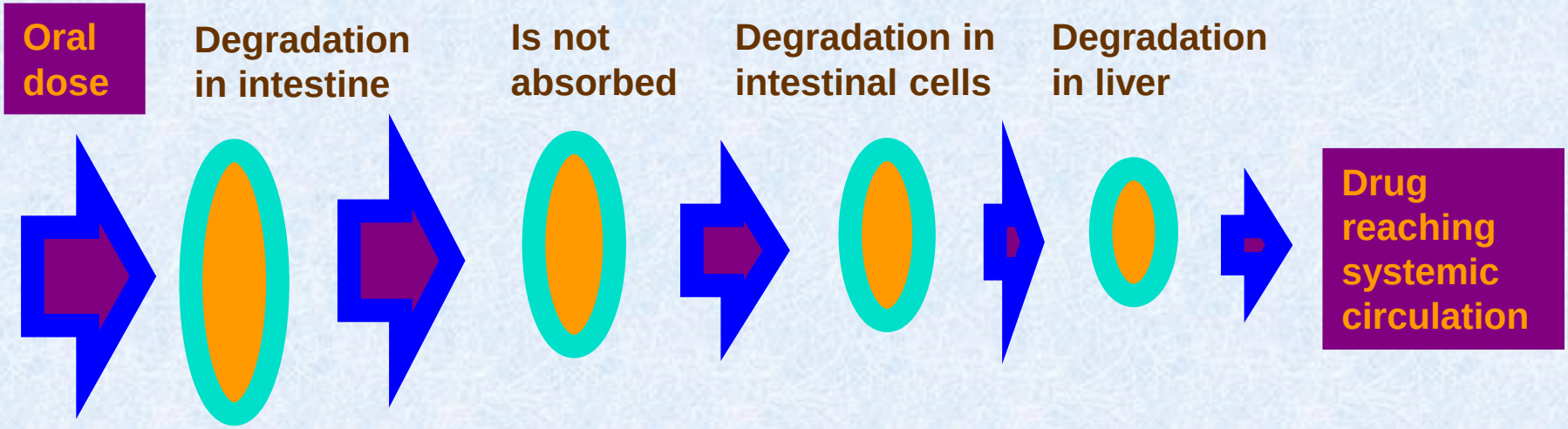
Tortora Derrickson 2012



Bioavailability

Bioavailability – fraction of administered drug reaching systemic circulation (0-1)

Intravenous injection: bioavailability=1 (100%)



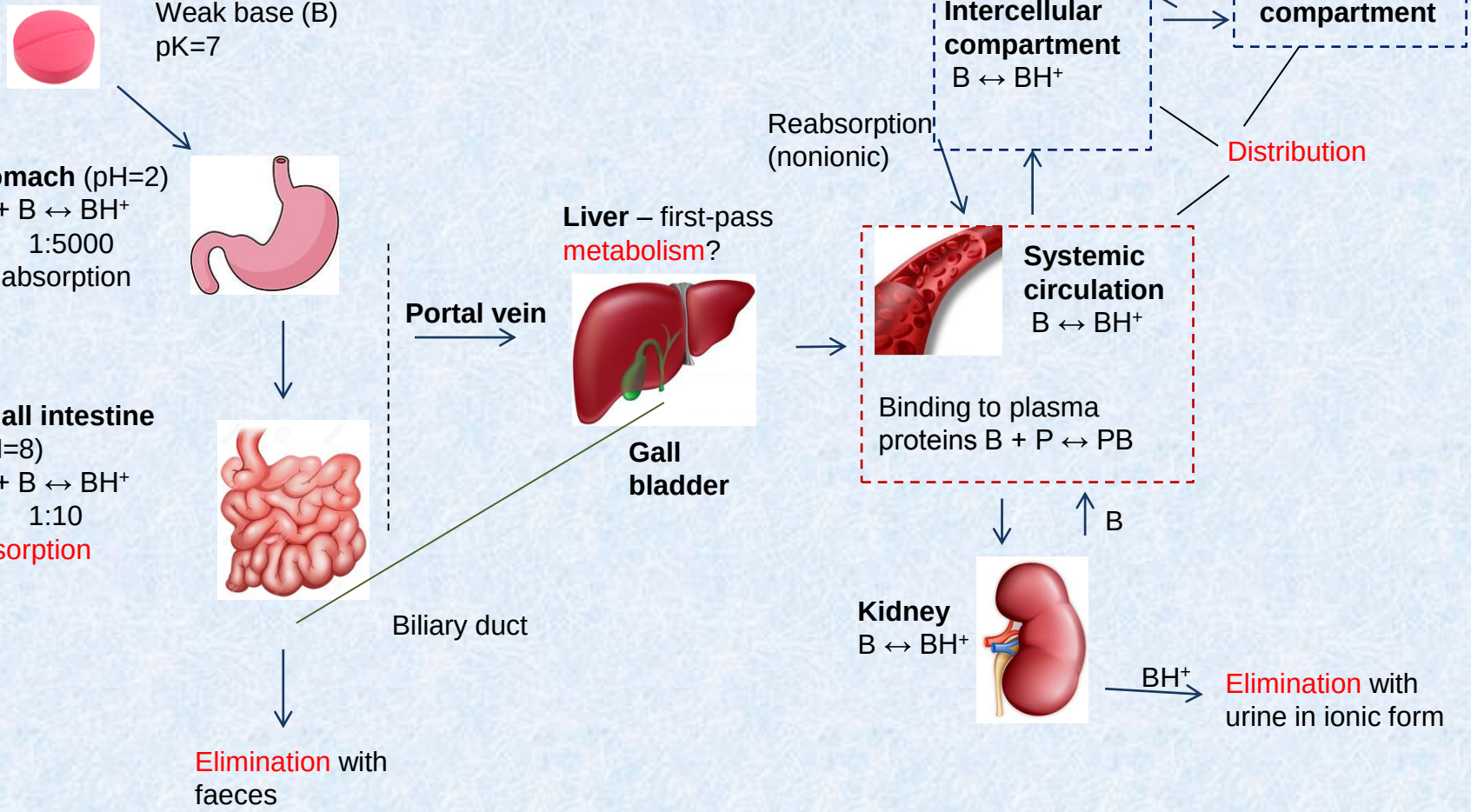
Distribution

Distribution between the different compartments of the body.

Blood ↔ intercelllular (interstitial) space ↔ intracellular space

- Lipophilic substances pass easily into the cell.
- Ionic substances usually stay in intercellular space.
- Substances with strong plasma protein binding/big molecules stay in blood.
- Lipophilic agents may accumulate in brain, fat tissue (e.g. pesticides, other pollutants).

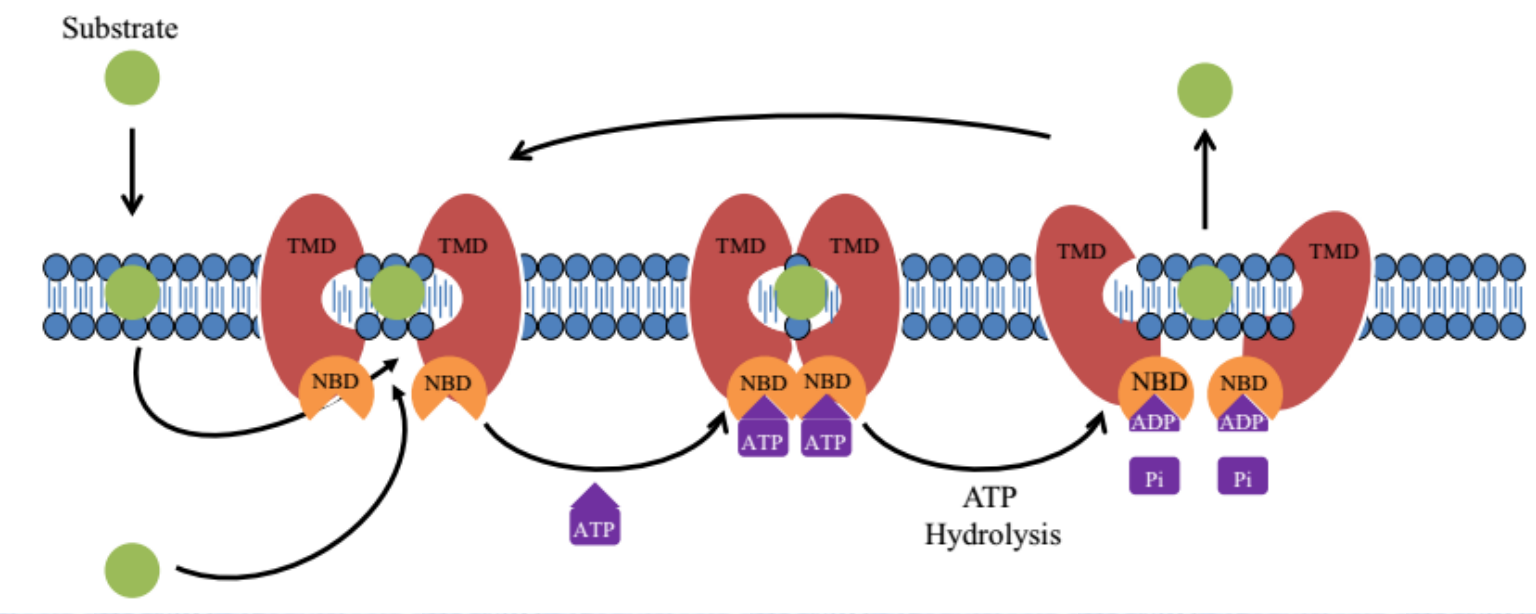
Fate of drug depending on pH



Neal, 2016

Multidrug transporters

- ATP binding cassette (ABC) transporters, pumps (active trp.)
- Multidrug transporters – MDR, MRP protein families
- Expressed at "pharmacological barriers" (intestine, kidney, bile canaliculi, BBB…)
- Multidrug resistance phenotype – MDR overexpression
- Wide range of hydrophobic compounds, xenobiotic protection



Chen et al. 2016

Metabolism

Metabolism (biotransformation): process during which the body modifies a substance molecule to render it less toxic/more easy to eliminate (metabolites as active as drug: diazepam→ oxazepam,

pro-drug: levodopa → dopamine)

Liver enzymes

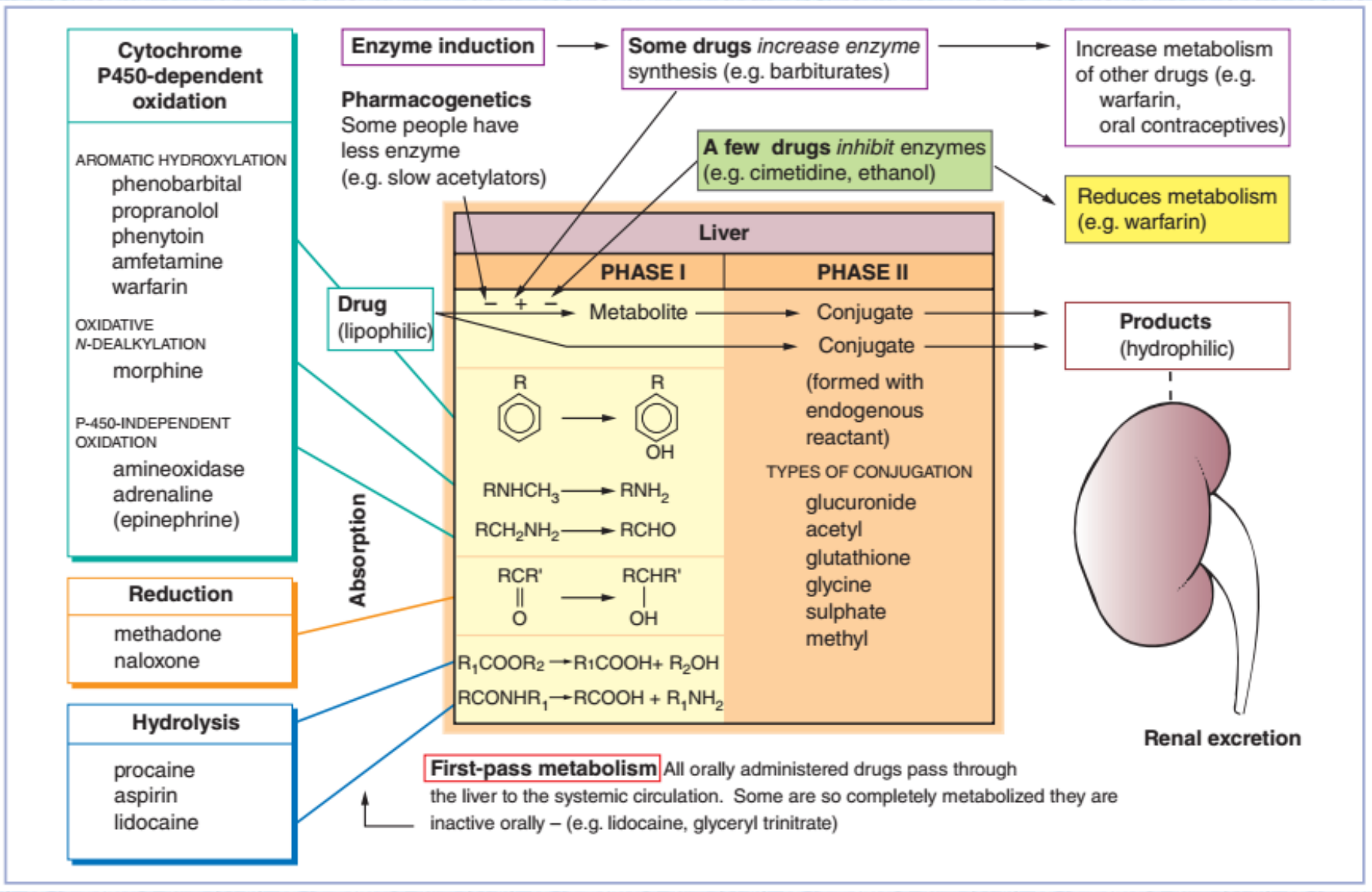
Phase I → more polar metabolite

- Oxidation – cytochrome P450 superfamily
- Hydrolysis
- Reduction

Phase II → more hydrophilic metabolite

- Conjugation with endogenous compounds (glucuronide, acethyl-, methyl-, sulphate-…)

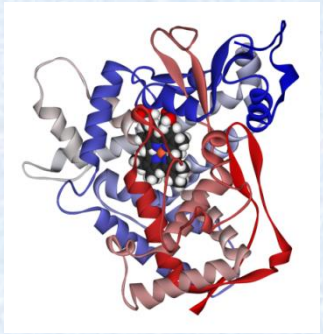
Metabolism



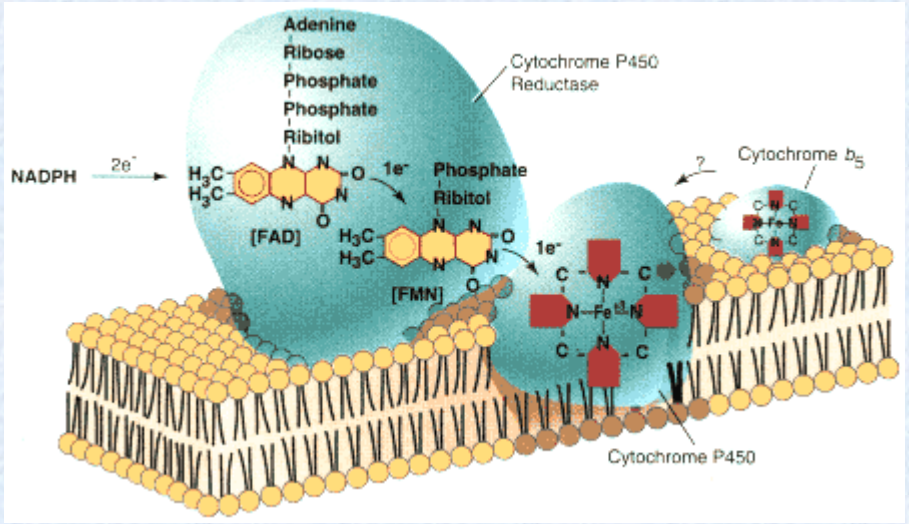
Neal, 2016

CYP450 enzymes

- Cytochrome P450 superfamily (a dozen enzymes of CYP1, CYP2, CYP3 families responsible for 70-80% of drug metabolism, most important: CYP3A)
- MFO: mixed function oxidase complex, microsomal membrane (smooth endoplasmic reticulum)
- Weak substrate specificity, >60 reactions catalysed
- Hem cofactor
- Human liver > 40 isoforms



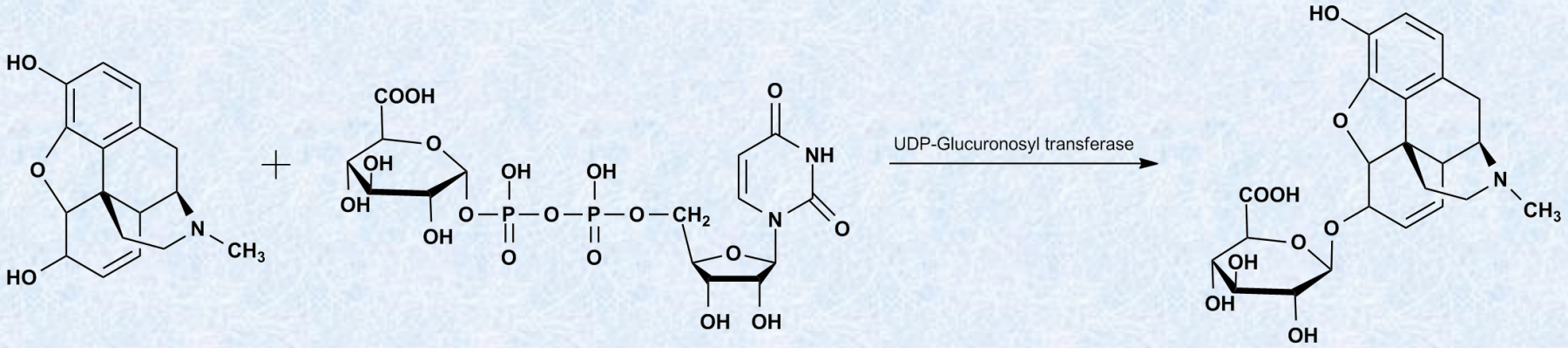
Wikipedia.org



lion.freeoda.com

Glucuronide conjugation

- Catalysed by enzymes
- Fast, common reaction in hepatocytes
- Same drug molecule can conjugate to several glucuronides
- Metabolite mostly (but not always!) inactive
- Low in neonates and children (rather sulphatation)



Morphine

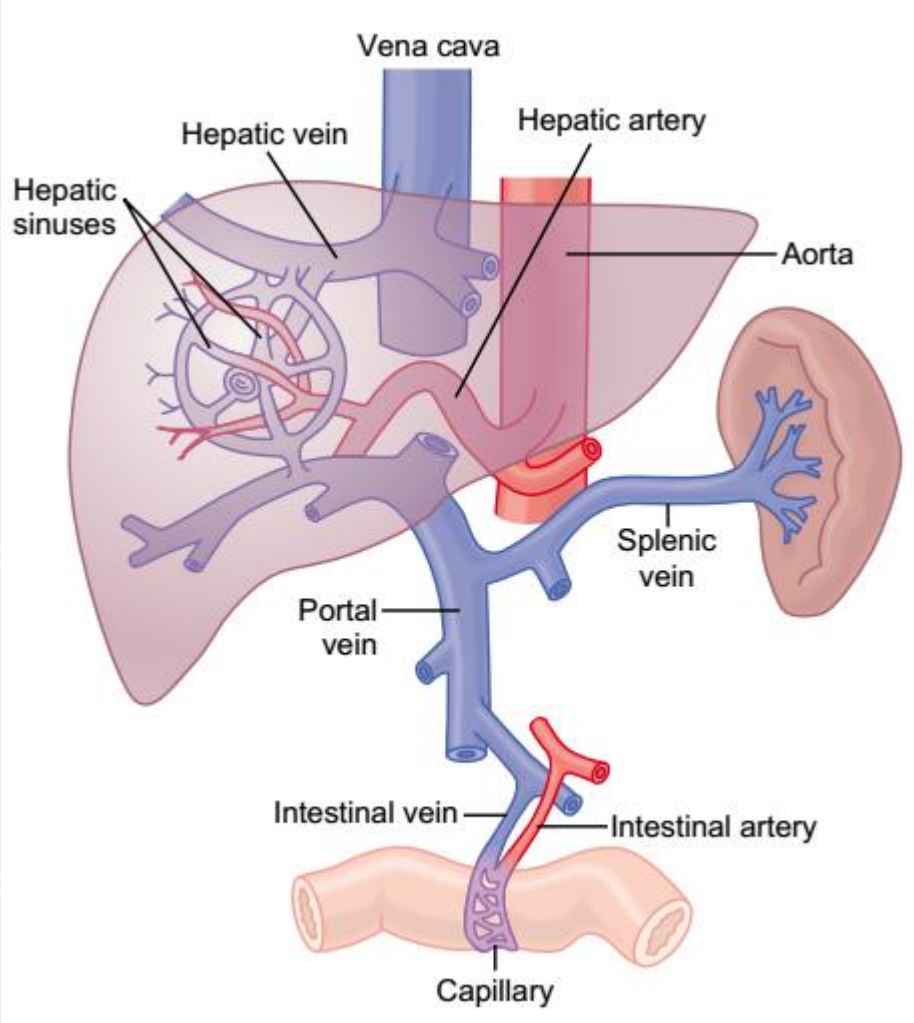
UDP-Glucuronic acid

Morphine-6-glucuronide

First-pass metabolism

- Anatomical basis: capillaries of small intestine → portal vein → liver
- Extensive metabolism in liver/intestine

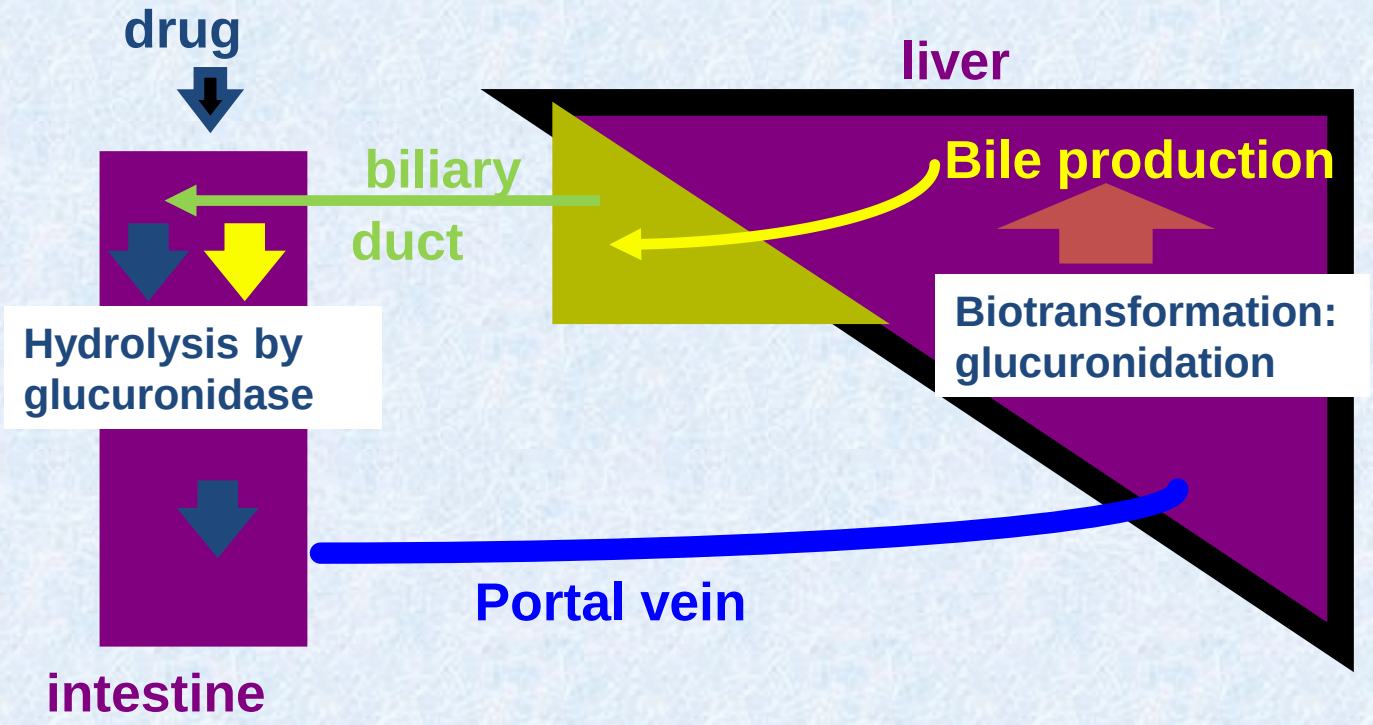
e.g. lidocaine, morphine



Guyton, 2006

First-pass metabolism

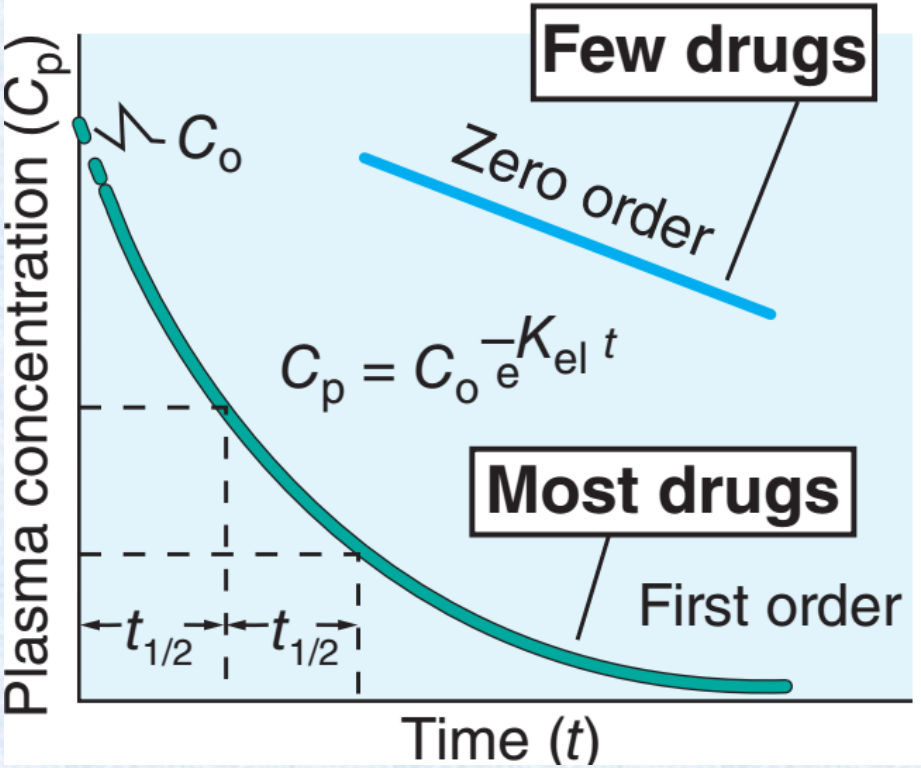
Enterohepatic recirculation



Elimination

Elimination: substance is degraded or leaves the body.

Half-life ($t_{1/2}$): time taken for a substance to reduce its blood level by half.

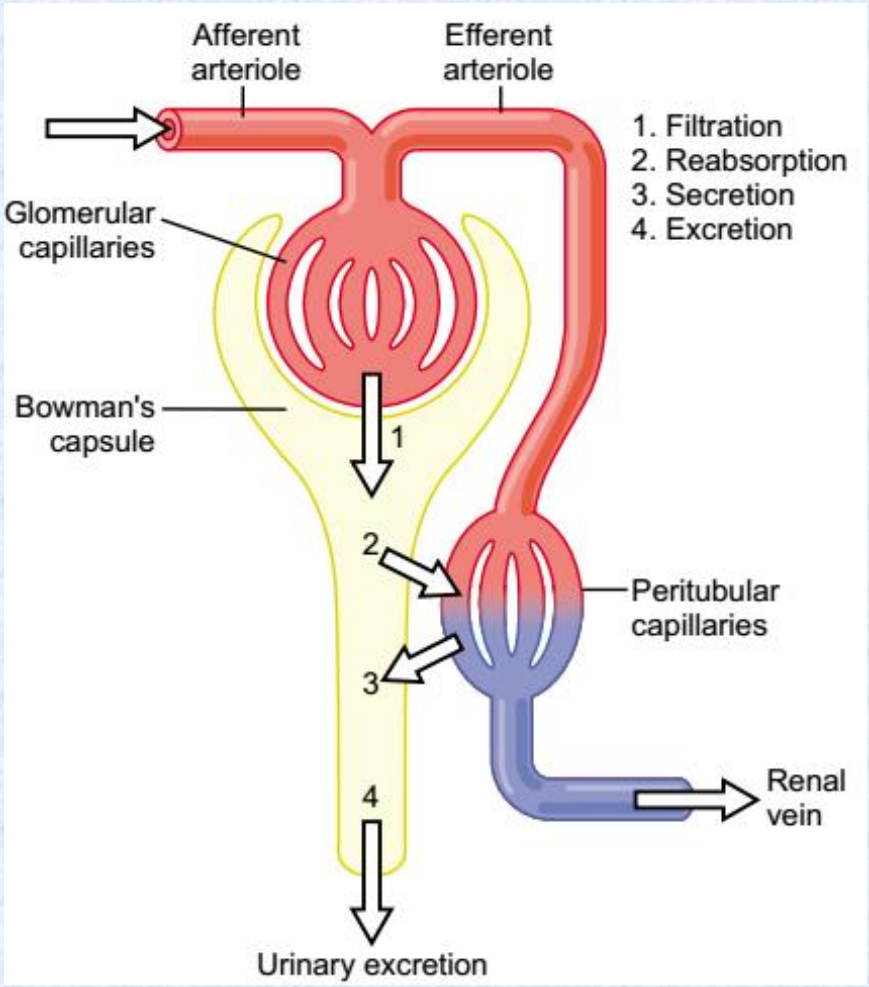


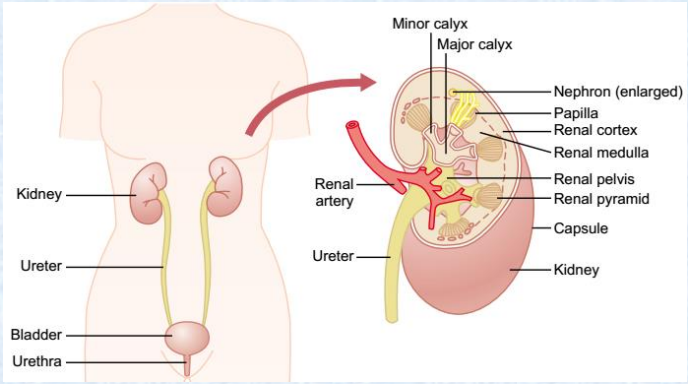
Neal, 2016

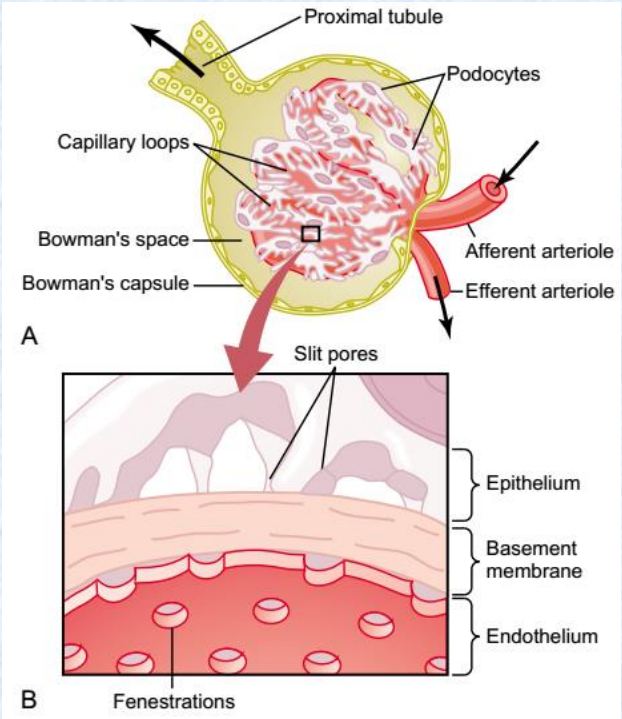
- First-order elimination kinetics: elimination rate proportional with concentration.
- Zero-order elimination kinetics: elimination rate not proportional with concentration, saturation of an eliminating process.

Elimination

Excretion via kidney







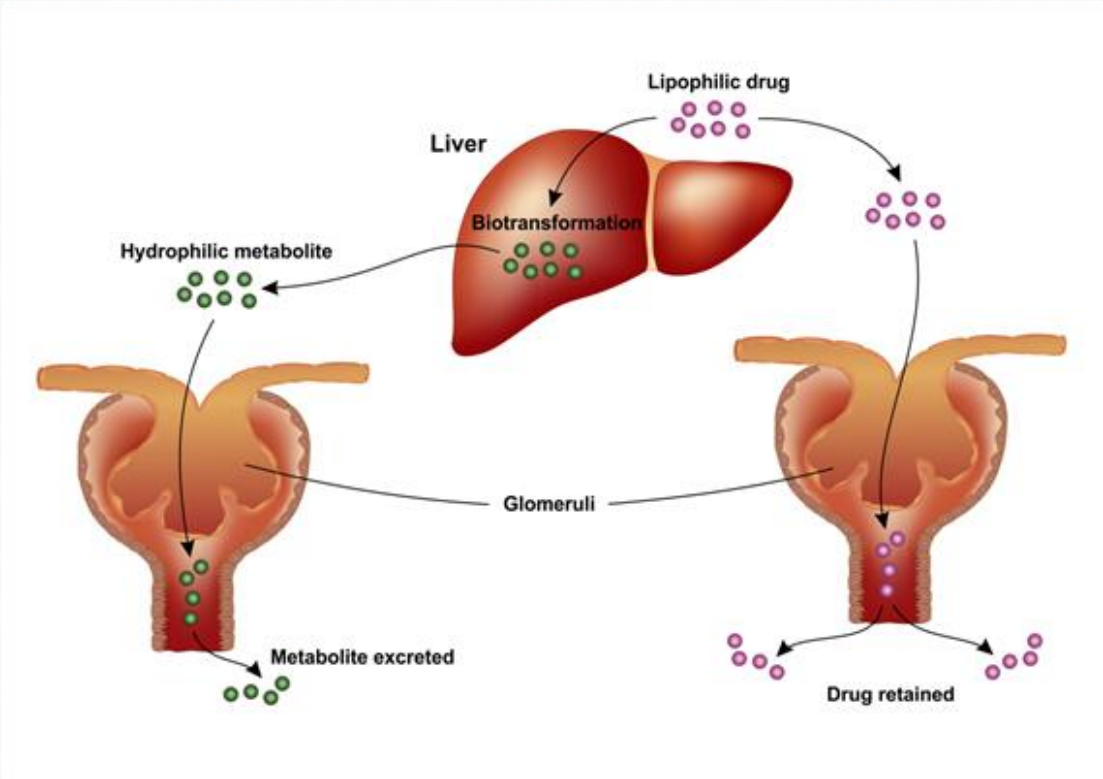
Guyton, 2006

Elimination

Excretion via kidney

Small hydrophilic drugs/metabolites

Age: 65 years, GFR ↓ by 30%, every year 1-2% ↓

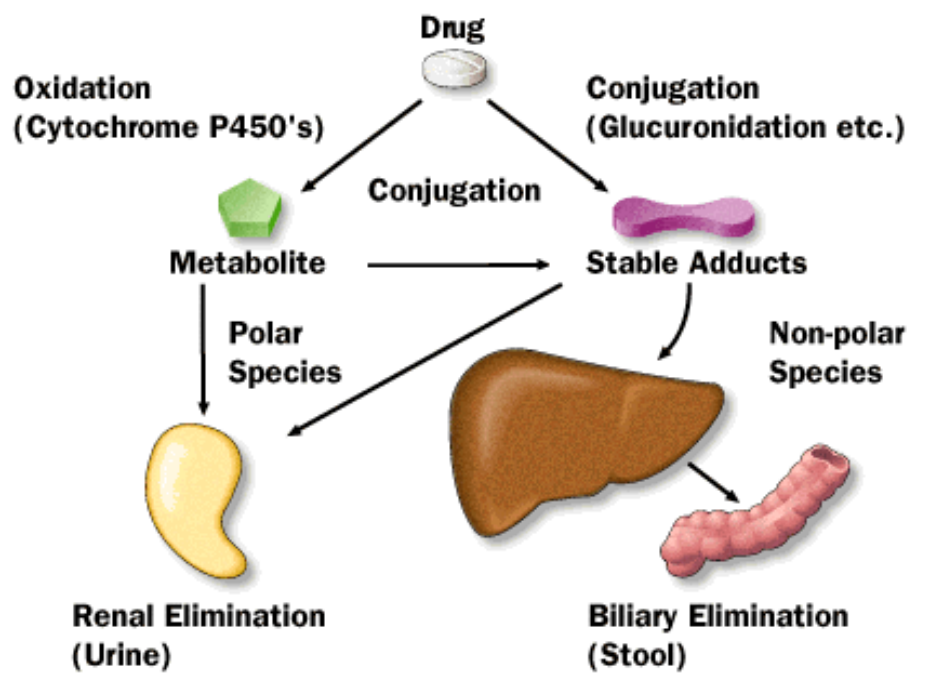


Balogh et al 2011 Molecular Diagnostics

Elimination

Other organs

- Bile and faeces
- Lungs: volatile substances (alcohol test)
- Skin: sweat glands, mammary glands!



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