LADME system

Distribution

Distribution

- Definition

Distribution is the the API's movement to the tissues from the sytemic circulation.

Distribution

- Distribution is influenced by
  - **Permeability of capillaries**
  - **Perfusion of tissues, speed of perfusion**
  - **Protein binding of API's**
  - **Differences in local pH**
  - **Type of transport mechanisms**
  - **Permeability of different membranes**

Distribution

- Characteristics
  - **API's can accumulate in different amount in different organs, tissues**
  - **Selective accumulation depends on the histological and chemical construction of the tissues and the blood perfusion of the tissue**

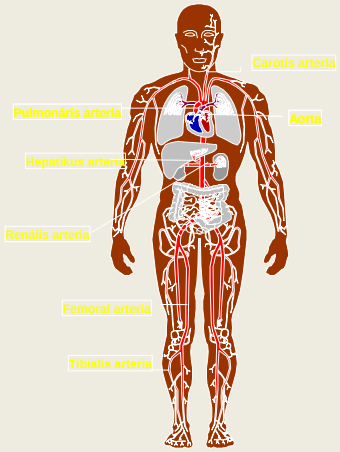
Distribution

- Characteristics

  - **Inner wall (endothel) of capillaries' (excepting CNS's endothel) construction is loose, API's of definite MW can filtrate through its pores into the interstitial space.**

  - **Permeability of capillaries especially in the liver and kidneys is high.**

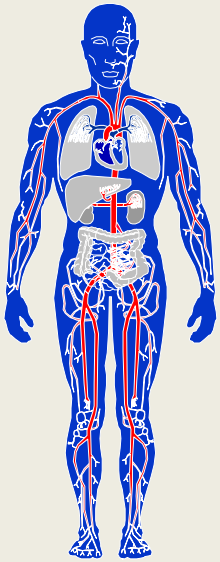
Distribution



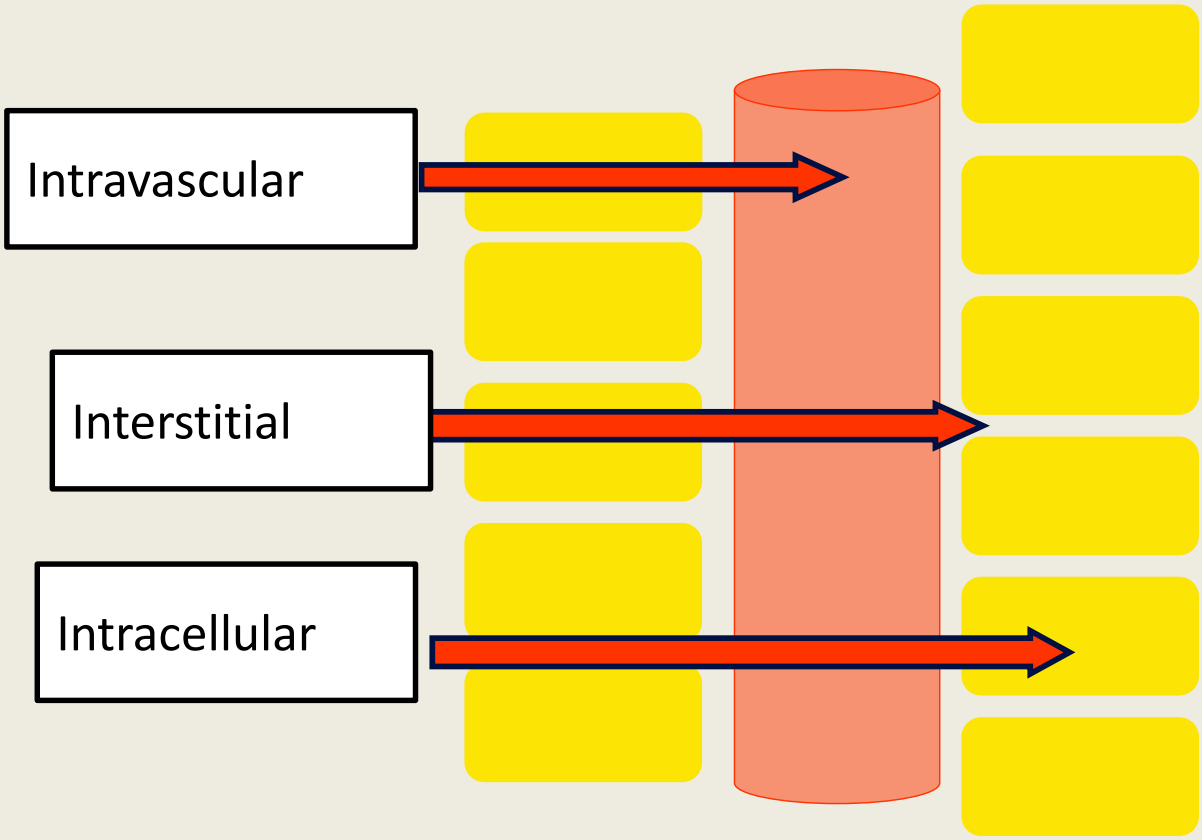
- Characteristics
  - Speed of distribution

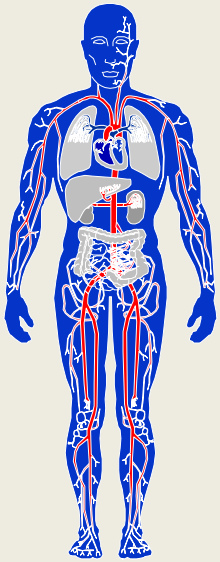
- Speed of equilibrium is different in different tissues
  - Central compartment (heart, liver, lungs, kidneys)
  - Peripheral compartment (muscle, skin, fat)
  - Deep peripheral compartment (bones)

Volume of distribution



Water compartments





Water compartments

Water content of the body: 60%
In case of a 70 kg person there is 42 l water

Total water content (42 l)

- 2/3 → **Intracellular (28 l)**
- 1/3 → **Extracellular (14 l)**
  - **Intravascular (6 l)**
    - **plasm (3 l)**
    - **+**
    - **corpuscles (3 l)**
  - **+**
  - **Extravascular (interstitial) (8 l)**

Volume of distribution

- API first moves into the systemic circulation during the absorption.
- During the final equilibrium of the API, it disspates in the body's different tissues/organs, which volume together is the volume of distribution (V_d).

Volume of distribution

- Volume of distribution is not necessarily related with the borders of tissues or organs.

Calculation of volume of distribution (V_d)

$$V_d = \frac{D}{C}$$

V_d	virtual volume of distribution
D	administered dose
C	measured API concentration

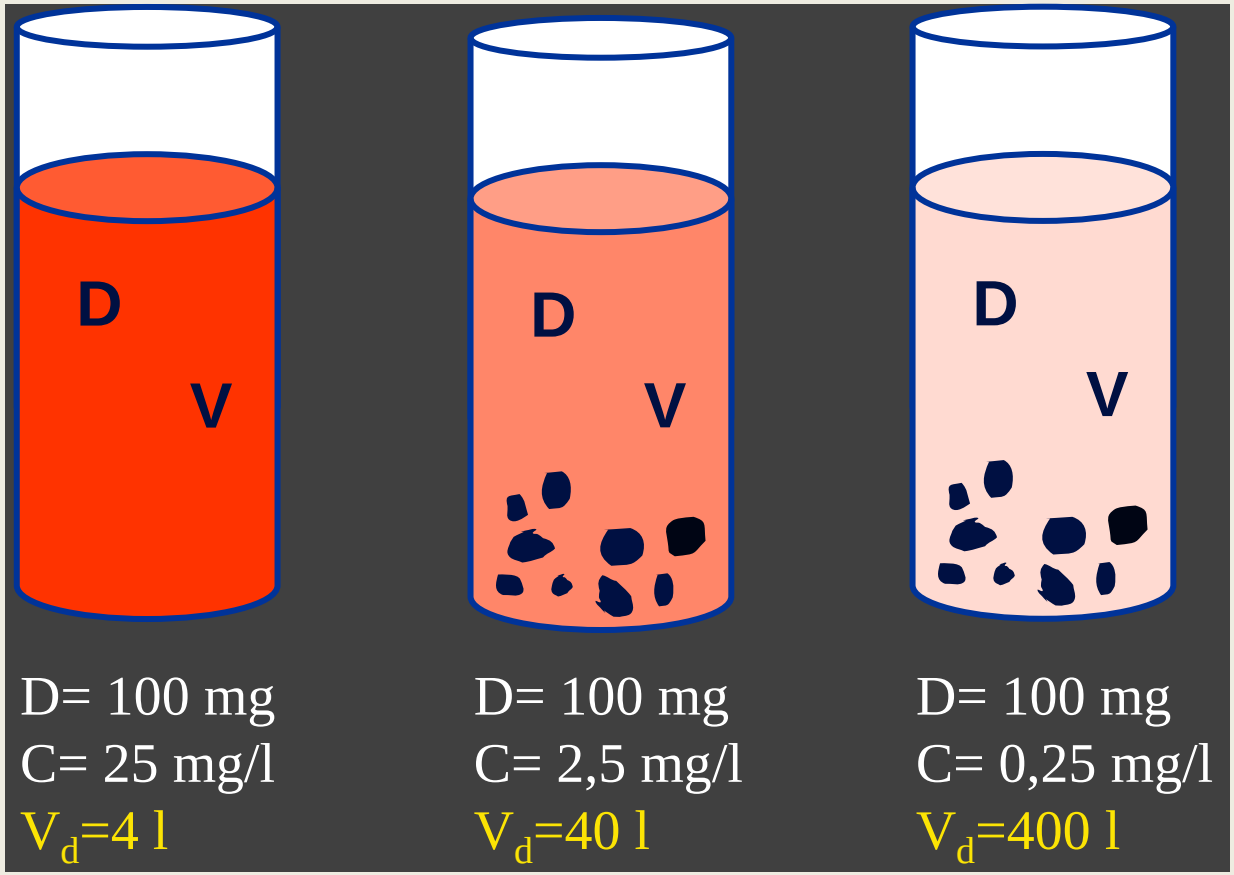
Place of the measurement (C) is usually the vascular compartment (veins).

Volume of distribution

- **Protein binding model**

API's bound to the plasm proteins are practically invisible for the body.

$$V_d = \frac{D}{C}$$



Volume of distribution

- V_d depends on the
  - Body weight
  - Body composition (fat, muscle, etc.)
  - Physico-chemical properties of the API
    - » pK_a, MW, solubility
  - Tissue protein binding
  - Plasm protein binding

Volume of distribution (litre)

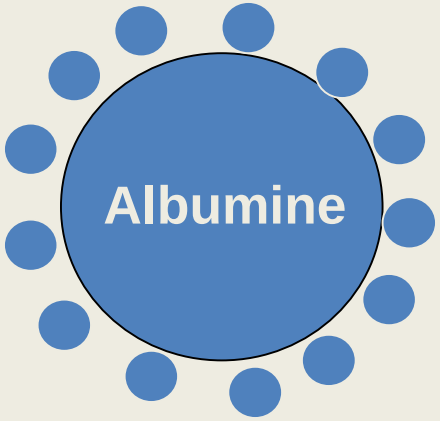
70 kg person

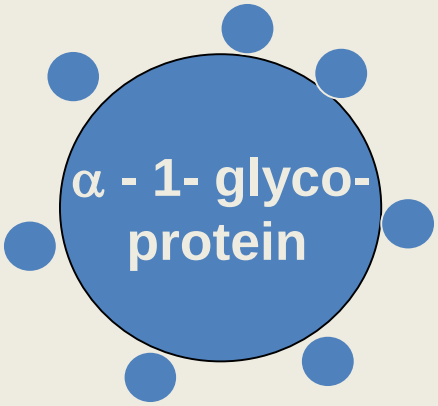
API	V (litre)	Notes
Warfarine	7	Small Vd. Mainly plasm, few amount in tissues.
Sulfisoxazole	11,2	
Gentamycine	16	
Teophylline	35	Medium Vd. Same amount in plasm and tissues.
Cimetidine	140	
Diazepam	170	
Digoxine	490	Great Vd. Mainly in tissues, few in plasm.
Mianserine	910	
Quinacrine	50000	

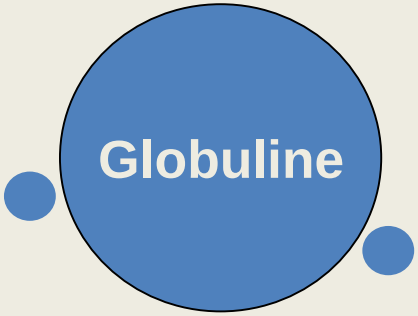
Distribution

- Characteristics
  - **API's bind to the plasm proteins in a reversible way. The most important plasm proteins are:**
    - **albumine,**
    - **globulines,**
    - **ceruloplasmine,**
    - **glycoproteins,**
    - **alpha- and beta-lipoproteins,**
    - **transferrine**

Distribution







4g/100ml

Weak acids, neutral APIs

40 - 100mg/100ml

Weak bases

Very small conc.

Pharmacokinetics
Absorption

Dose: **50 mg** coated tablet is taken, then in 20-60 minutes:

Plasma concentration max: **3,8 µmol/l**
50% - first pass effect

Distribution

Diclofenac's **99,7% binds to plasm proteins!**

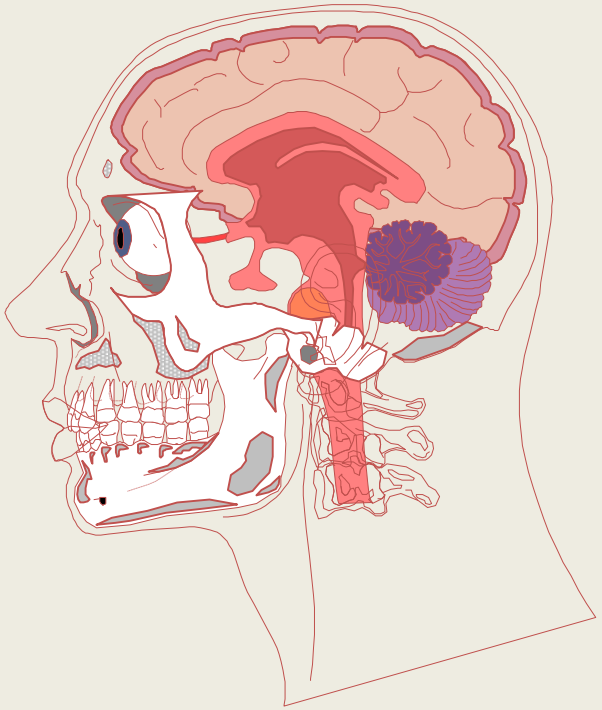
Distribution

- **CNS**

•Tight junctions

Blood-brain barrier:

- **antibiotics in case of meningitis**
- **dopamin administration in parkinsonism**

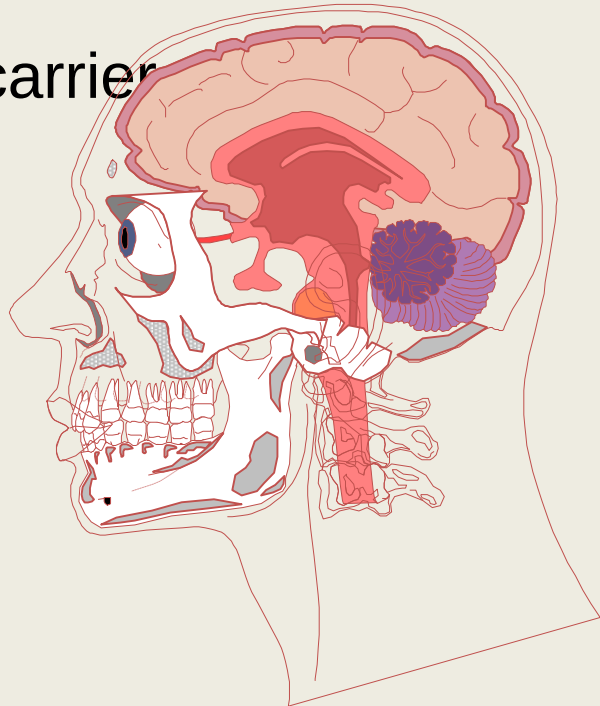


Distribution

- **CNS**

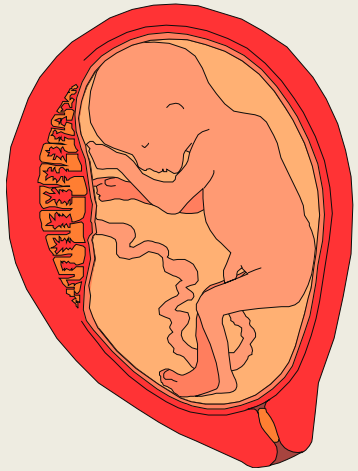
  - DMSO accelerates penetration

  - hiperosmolar concentration
    Application of mannitol to increase methotrexat penetration
    - using prodrugs, like dihdropiridine carrier

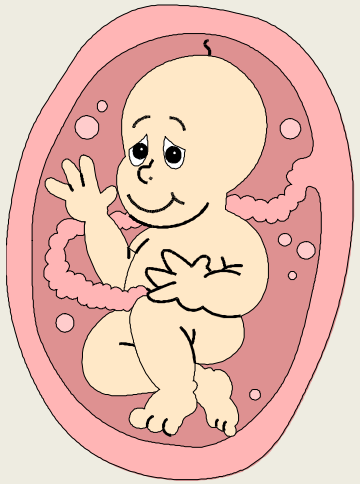


Distribution

- **placenta transfer**

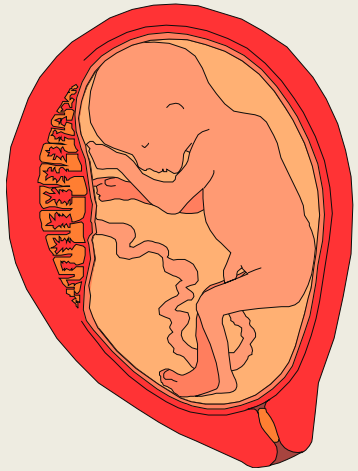


Drugs applied during the pregnancy can harm the embryo.



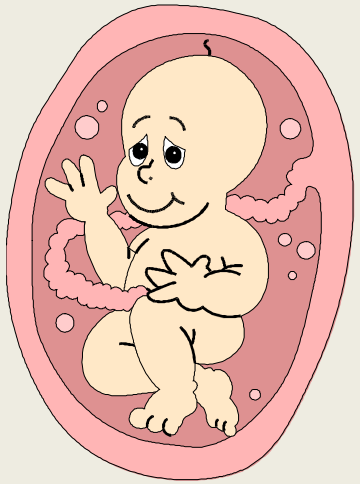
Distribution

- placenta transfer



High lipid solubility helps the penetration through the placenta:

- sulphonamides, barbiturates narcotics, analgesics, steroids



Well-known teratogen APIs

- Thalidomide (1956) – against flu' and as a sedative agent
- Teratogen side effect was discovered in 1960 (limb reduction, GI and CV disorders)

Well-known teratogen APIs

- Isotretinoine – spontaneous abortion, CV disorders, small ears, hydrocephalus

Pregnancy

- FDA
  - A – safe drugs (human/animal experients)
  - B – do not cause teratogenity in animals, human – n.d.
  - C – no experiences in humans or animals
  - D – teratogenity is proved, but it can be applied considering the risk/benefit
  - X – teratogenity is proved, but risk/benefit should be considered; likelyhood of risk is higher

Metabolism

Metabolism

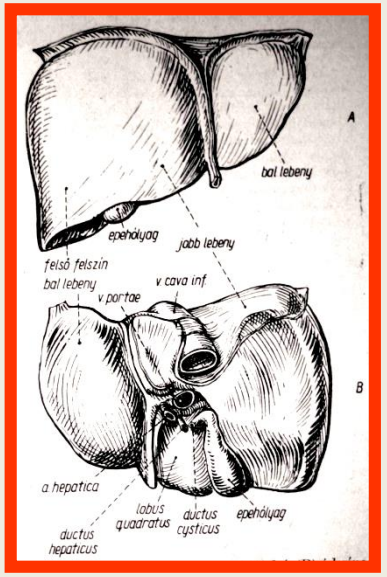
- Drugs are foreign substances for the body (xenobiotics) what should be eliminated.

Metabolism

- metabolism accelerates the excretion, because the polarity of the metabolites increase

- during the metabolism, APIs lose or decrease their effect or increase in effect can be observed. In this case we can talk about prodrugs or active metabolites.

Metabolism



- metabolism can increase the toxicity of the API

- liver plays the main role in the metabolism, other organs: lungs, kidneys, skin have secondary role.

Enzyme induction

(1) Phenobarbitale (PB) type

(2) Polycyclic (PC) aromatic type

(3) Ethanol type

(4) Glucocorticoid type

(5) Autoinductors – carbamazepine, cyclophosphamide

Enzyme inhibition

Allopurinol, cimetidine, carbidopa

Stereoselective metabolism

R - warfarin - quicker elimination
S - warfarin - 5 x effective

l - hexobarbital - quicker elimination
d- hexobarbital

R- ibuprofen
S- ibuprofen - 160 x effective

I. phase metabolism

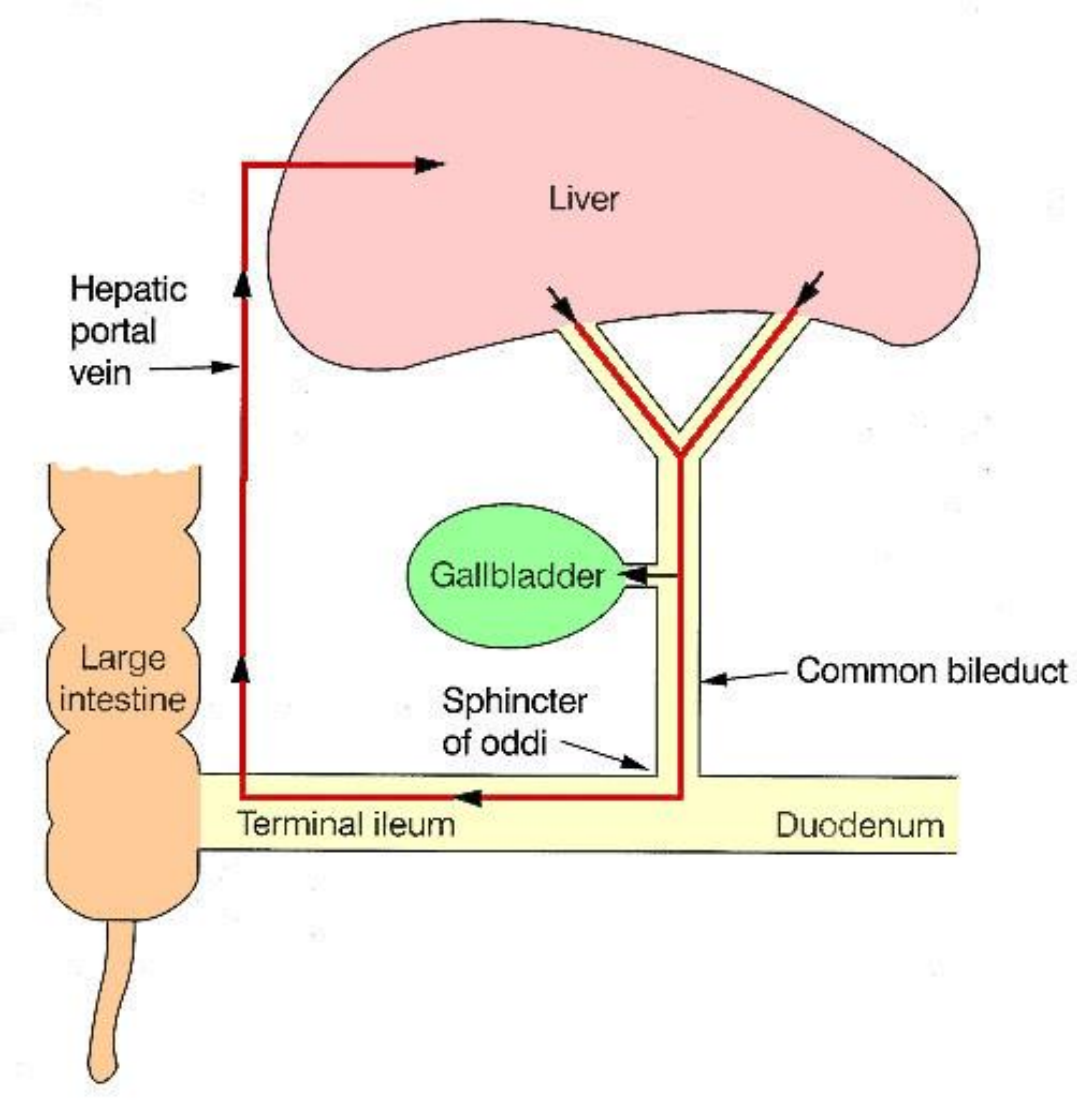
- microsomal oxidation
- non microsomal oxidation
- reduction
- hydrolysis
- hydratation
- isomerisation
- various reactions

II. phase – conjugation

- These reactions increase the water solubility of the metabolites of the I. phase reactions, thus accelerating the last step of LADME system, the excretion.

- e.g.: glucuronide conjugation

Enterohepatic circulation



LADME SYSTEM

EXCRETION

University of Pécs

Institute of Pharmaceutical Technology and Biopharmacy

Elimination

- Definition:
  - Elimination contains processes that reduce the concentration of the API in the fluid compartments of the body and the API becomes inactive.

Excretion

Definition:

Excretion is a process that evacuates both the unmetabolised API and its metabolites from the body.

Excretion

Characteristics

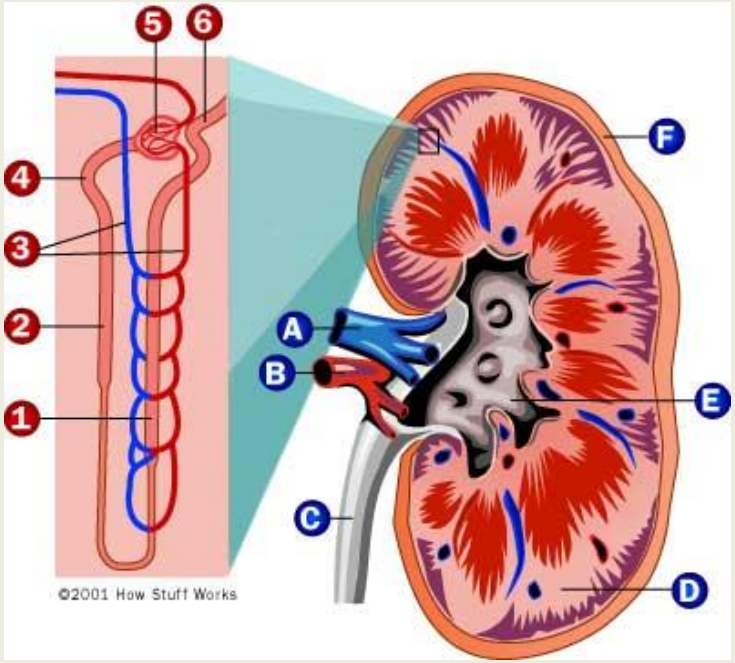
- APIs and metabolites have to cross membranes similarly to the absoprtion, thus the same physico-chemical characters influence the excretion and the absorption.

- In case of exretion the role of the active transport is much higher than in case of absoprtion.

- The kidney is the key organ for the excretion, important role has the bile, smaller roles: lungs, salivary glands, sweat glands and mammary glands.

Kidney

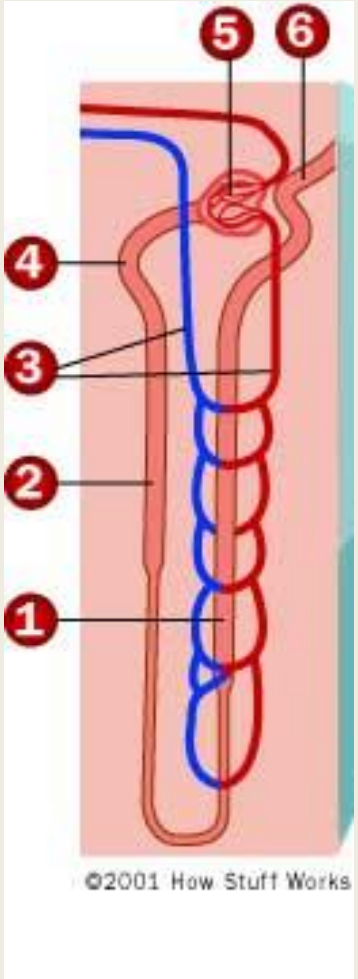
- Microscopical investigation shows a complex vascularisation and tubular structure which constitutes the kidney's basic structural unit called: nephron.



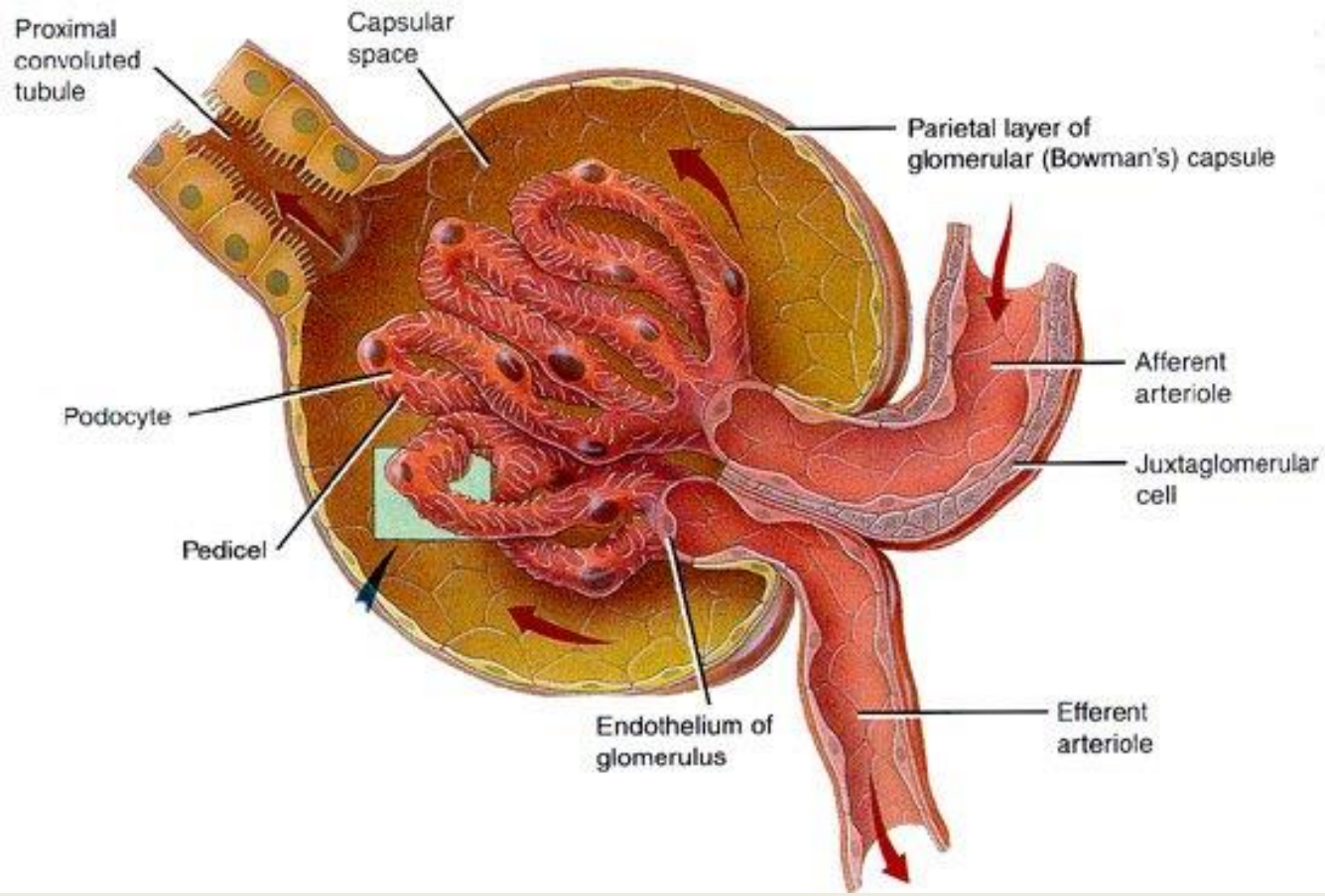
Nephron

- The nephron begins with the glomerulus which is sorrounded by a double layer capsule called Bowman's capsule. Bowman's capsule continues in the tubular structure.

- The glomerulus and Bowman's capsule is called together the Malpighi-body.



Malpighi body



Excretion via kidneys

- Glomerular filter only allows molecules to be filtered below 5.000 dalton, between 5.000 and 50.000 it is restricted, above 50.000 it is impossible.

- Molecular weight of the smallest protein is around 70.000 dalton.

- Only free circulating APIs (not bound to proteins) can be filtered glomerulally.

Excretion

Excretion via kidneys

- pH of the urine in the tubules (which is between pH 4.5-8) influences the API's reabsoprtion.

- Acidic pH inhibits, alkalic pH increases the reabsoprtion of alkalic APIs. This phenomenon is used in the practice when applying **NH_4Cl** to enforce the urination of overdosed alkalic compounds.

- Urination of overdosed acidic compounds can be enforced by **$NaHCO_3$**.

Urinary acidifiers

- Ammonium-chloride
- Salicylates
- Ascorbic acid
- Cyclamate

Urinary alkalizers

- Sodium-bicarbonate
- Antacids
- Acetazolamide
- Sodium glutamate
- Thiazide-type diuretics

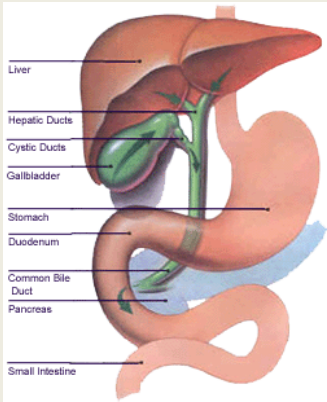
Excretion

Excretion via the bile

- Daily arounf **1 l bile** is excreted in the duodenum. Molecules with molecular weight higher than **1000 do not excrete via bile.**
- **Enterohepatic circulation**
- Substances that increase the secretion of the bile, also increase the excretion of APIs.

Excretion via the bile

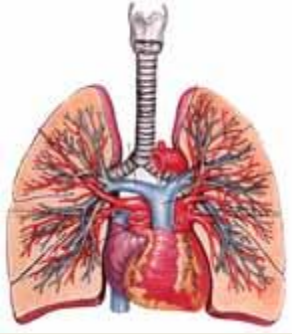
- Substances containing **–OH and/or =O groups** in heterocyclic compounds, also molecules containing **sugar** can be excreted via the bile.



Substances excreted via the bile

- **Bile acids**
- Ionised fraction of penicillin
- Steroid hormones (partially)
- **Tetracyclines**
- Streptomycine
- **Erythromicine**
- **Furosemide**
- Quinidine
- Doxorubicine

Excretion



Excretion via lungs

- Gases and other volatile substances and also alcohol can be excreted via lungs. No special transport mechanism exist in the lungs, only the alveolar partial pressure determines the excretion.

- The excretion thus occurs by the rules of passive diffusion.

- Increasing the circulating blood volume or taking deep breath can increase the excretion.

Excretion via humour

- APIs and/or their metabolites can excrete via the sweat, saliva and other humour. In these cases passive diffusion is the power of excretion.

Excretion via the saliva

- **Mercury** (stomatitis mercurialis)
- **Saccharine**
- **Lithium**

- Lots of APIs appear in the saliva in the same concentration as the blood which helps to monitor these substances without blood monitoring.

Excretion via the skin

- **Sodium chloride**, **carbamide (urea)**, **uric acid** are excreted via the skin in the sweat

- Other substabces exreted via the skin
  - Bromide salts
  - Essential oils (onion, garlic)

Excretion via breast milk

- Passive diffusion
- pH (milk is more acidic than the blood)
  - Weak bases' concentration is higher in the milk
  - Weak acids' concentration is lower in the milk

Thank you for your attention!