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INTRODUCTION TO GENERAL PHARMACOLOGY

PHARMACOKINETIC PROCESSES

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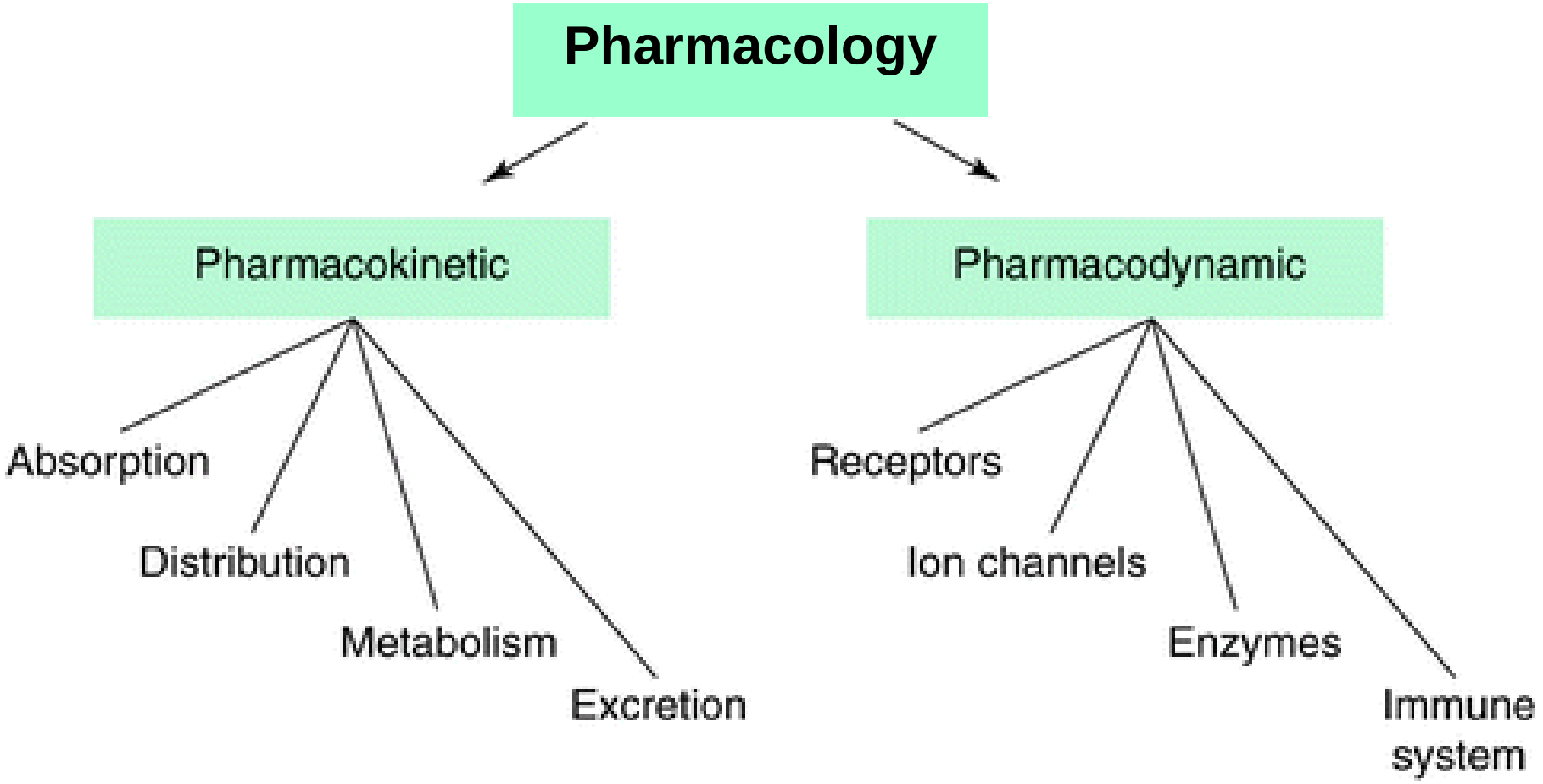
Pharmacology as Scientific Discipline



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Pharmacogenetics

- Study of ***genetically determined differences*** of physiological and biochemical functions of the organism, which could be revealed based on ***drugs effects***

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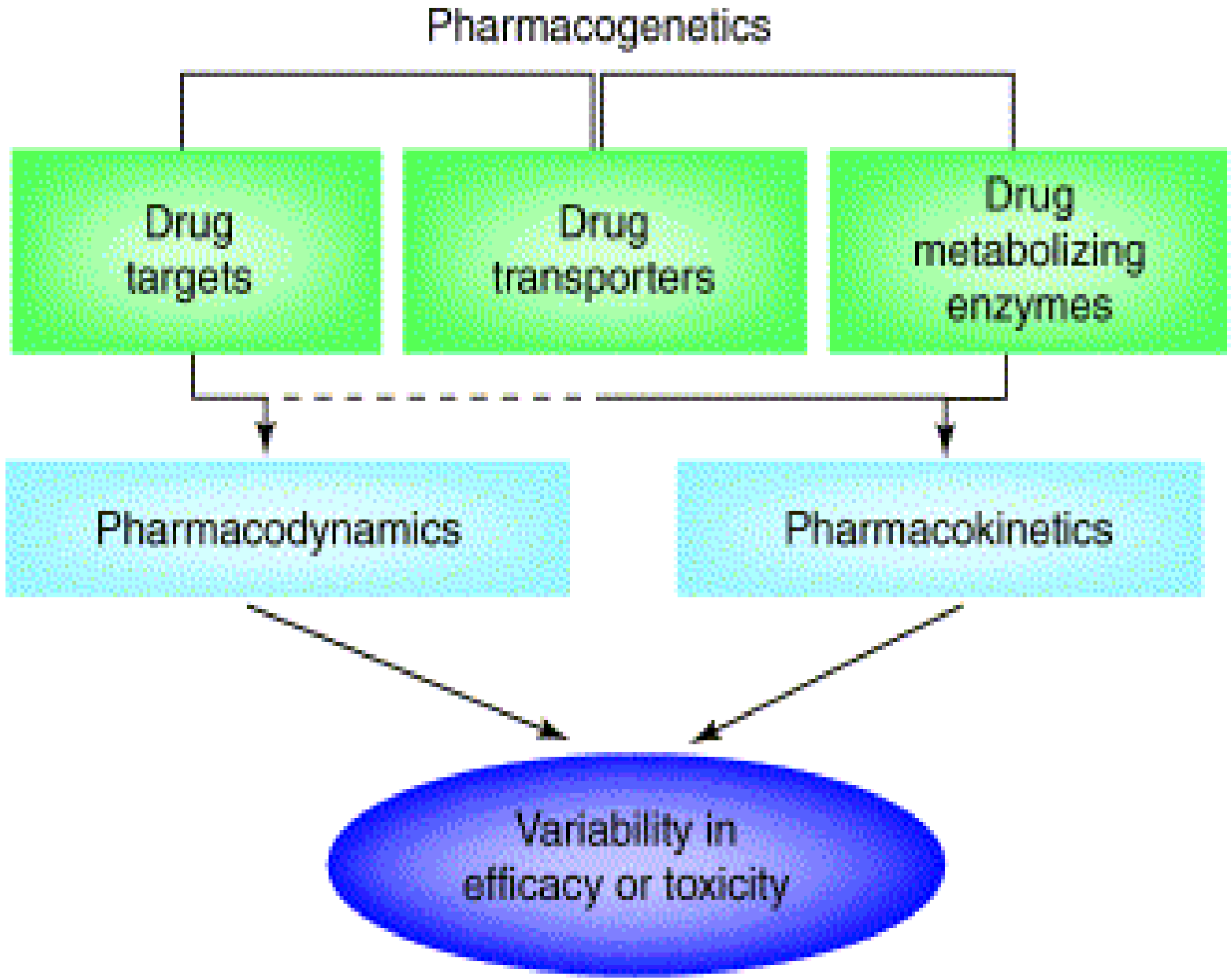

TRENDS in Genetics

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Definitions

- Pharmacokinetics
- Pharmacokinetic processes
- Pharmacokinetic parameters
- Pharmacokinetic analysis

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Pharmacokinetics

- Deals with the study of the processes:

  Absorption, Distribution,

  Metabolism, Excretion

  of drugs, and relationship with effects of medications

  (therapeutic, toxic)

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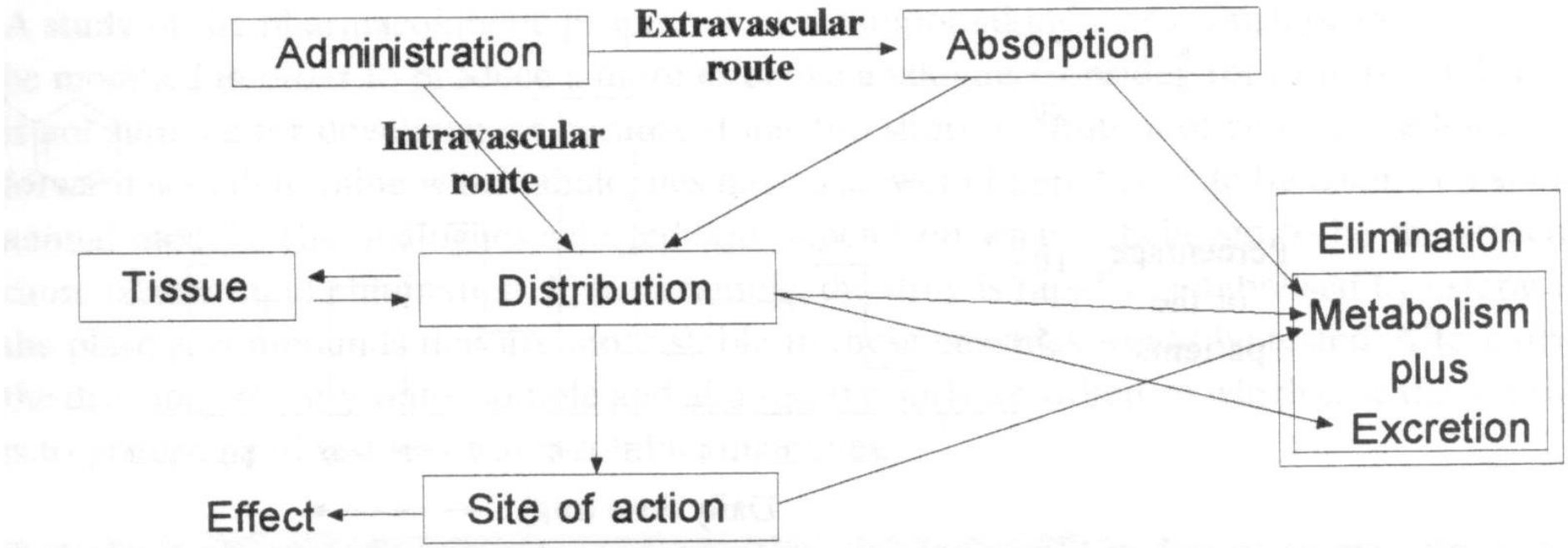
Pharmacokinetic processes



The general stages and their relationships in the life cycle of a drug after administration.

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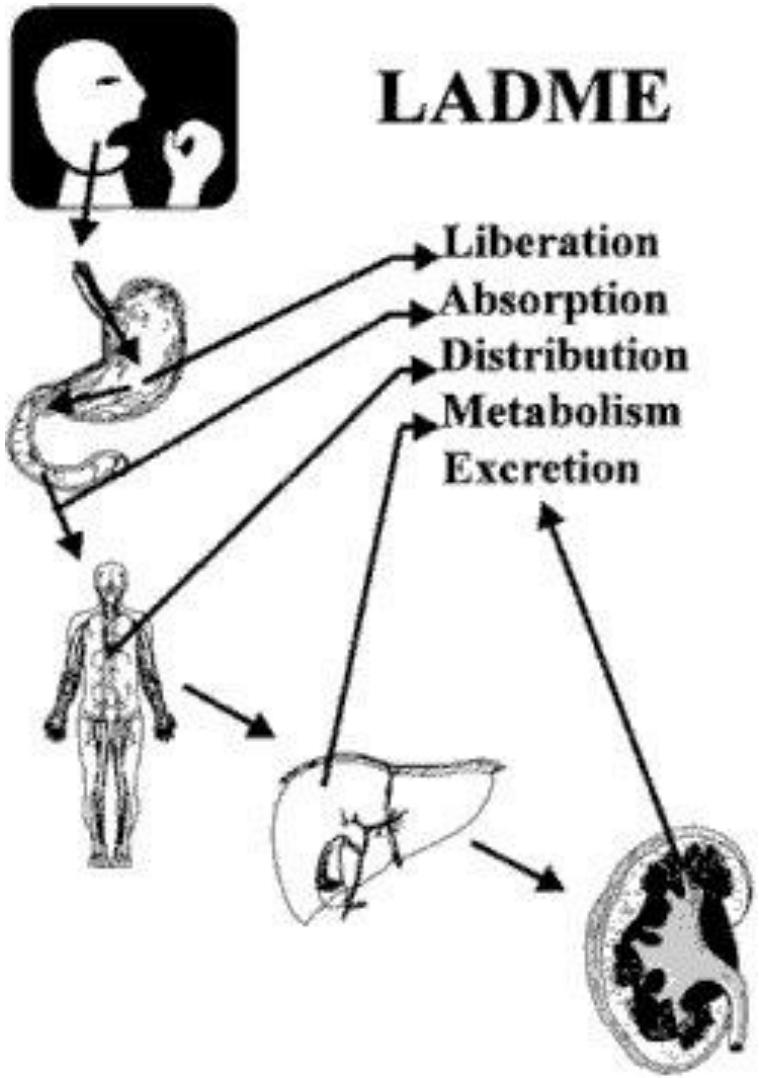
Pharmacokinetic processes



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Time aspect of the PK processes

- Usually follow LADME, but **never** separately !!!
- Coincide – one could start during other still runs
- e.g.: SR tab – core continuously release active substance, but formerly absorbed part is simultaneously eliminated from the organism

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Pharmacokinetic parameters

- Important tool to get information about ***drug motion*** in organism

- Allow to predict the ***time course*** of drug concentrations, and to design appropriate ***dose scheme***

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Pharmacokinetic parameters

- Volume of Distribution (V_d)
- Total Clearance (Cl)
- Bioavailability (F)
- Half-Life ($t_{1/2}$)
- Area Under the Curve (AUC)
- Absorption rate constant (k_a),
  Elimination rate constant (k_{el})

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Types of PK parameters

– *Primary*: changes depend on physiolog. parameters – e.g. blood flow, proteins bound, glomerular filtration

- Volume of Distribution (Vd)
- Clearance (CL)

– *Secondary*: depend on primary parameters

- Half-Life ($t_{1/2}$)
- Area Under the Curve (AUC)
- Bioavailability (F)

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Pharmacokinetic analysis

- **Compartmental Model**
  - *central compartments* (blood, organs with good blood supply – lungs, liver, kidney)
  - *peripheral compartments* (muscles, skin, fat...)
- **Non-compartmental Model**
  - quantification of PK parameters with the physiological importance (Cl, Vd, $t_{1/2}$)

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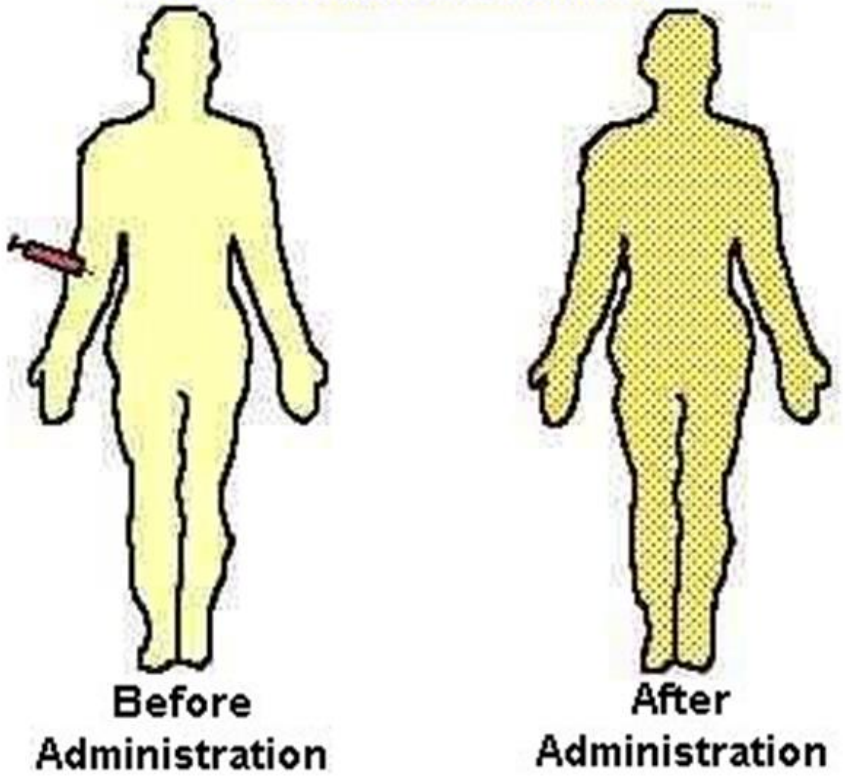
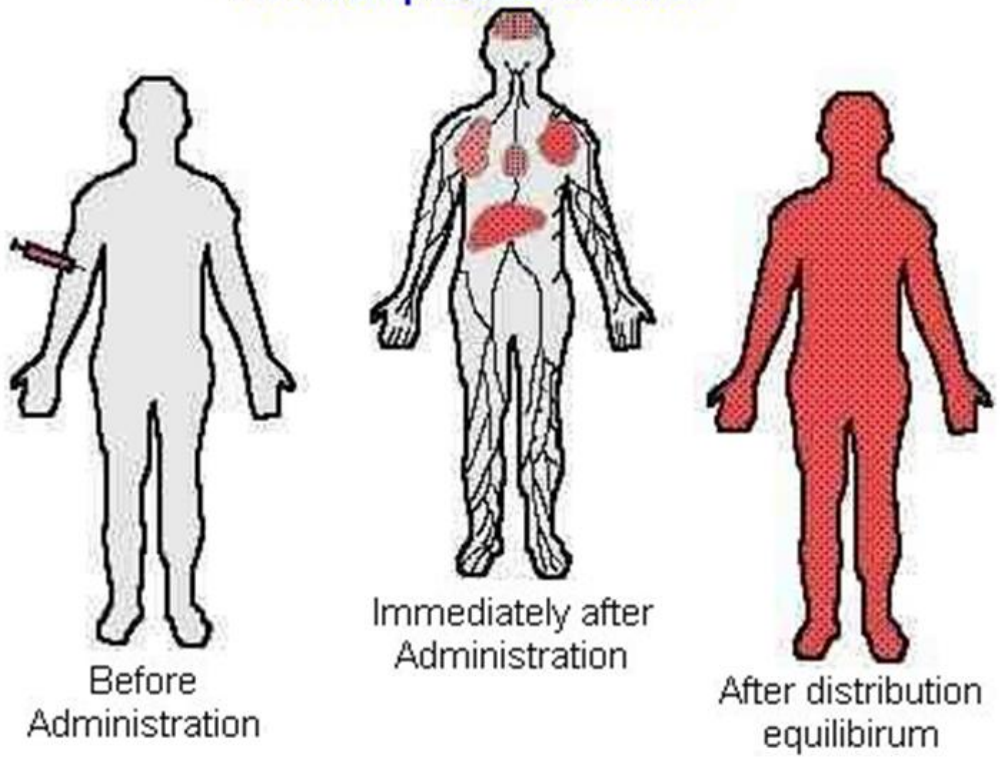
One compartment model



Two compartment model



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Pharmacokinetics

- *Linear* – **independent** of dose;

  linear relation between dose and amount of excreted compound

  (*1st Order Kinetics*)

- *Non-linear* – **dependent** of dose;

  at initial phase relation could be linear, but after capacity of system is exceeded kinetics become non-linear

  (*Ø Order Kinetics*)

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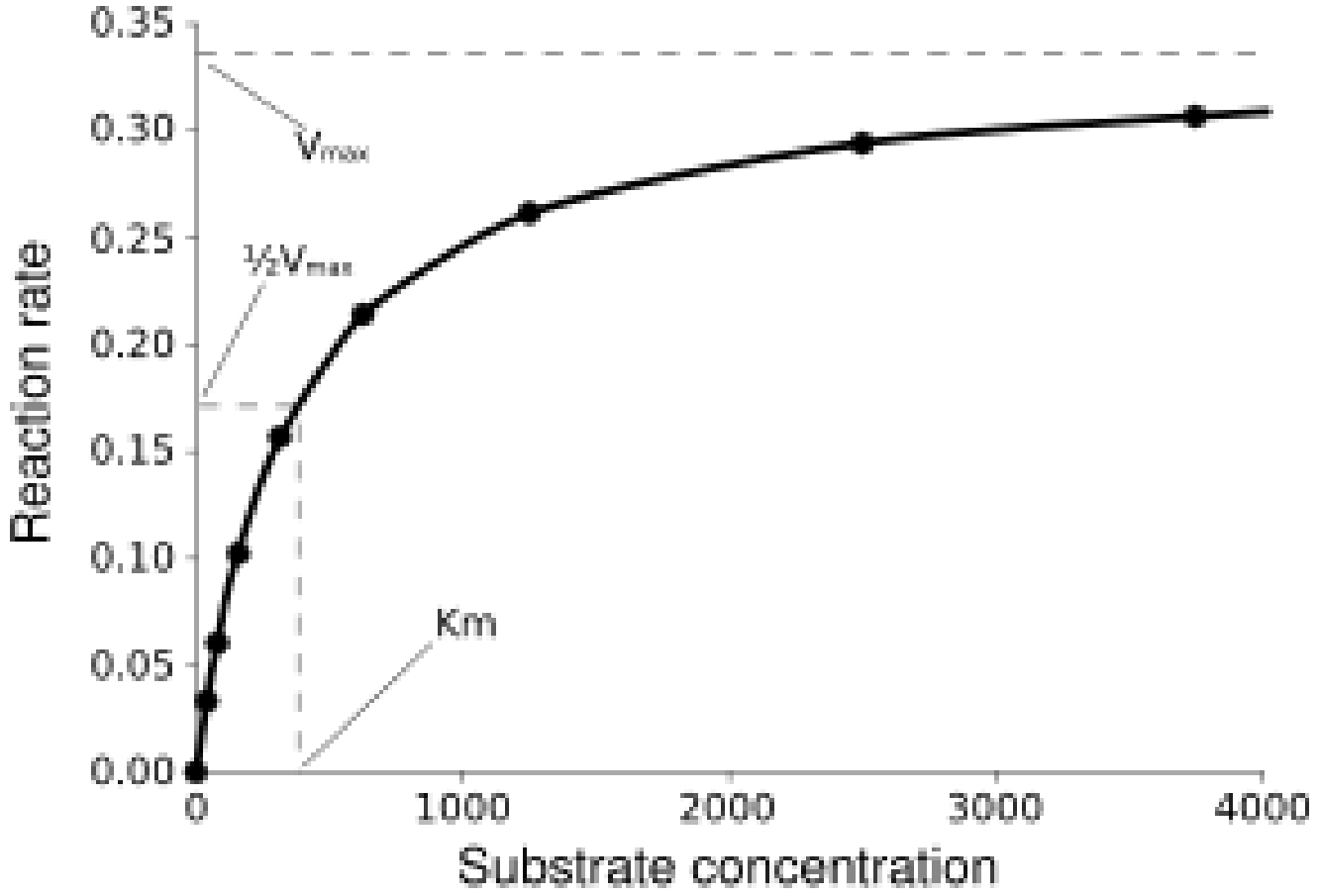
Non-linear Pharmacokinetics

Saturation enzyme curve (relation between substrate concentration and enzymatic rate)



Routes of Drug Administration

- **Local :**
  - solution, emulsion, suspension, powder, ointment
  - on skin, mucous membrane, body cavities (intraocular, intraarticular, intrathecal…)

- **General :**
  - enteral (into the intestinal tract)
    - *per os* (*p.o.* – orally)
    - *per rectum*
  - parenteral (bypasses the GIT)

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Parenteral Application

- intravenous - *i.v.*
- intraarterial - *i.a.*
- intramuscular - *i.m.*
- subcutaneous - *s.c.*
- sublingual
- on skin
- on nasal mucous membrane
- inhalant

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General Administration (whole body)

– **Enteral - *per os***

Factors influencing drug absorption administered p.o.:

- Stomach pH, Drug Form (enterosolvent)
- Food
- GIT motility
- GIT function – stomach and bile acid, pancreatic and gut juice
- Stasis in *vena portae*
- Drug interactions

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General Administration (whole body)

- **Enteral - *per rectum***

  - Usage of suppository for both local and systemic effect

  - Fast onset of the effect (cca in 15 min)

  - Must not irritate rectum mucouse membrane

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General Administration (whole body)

- **Parenteral**
- ***i.v.*** - inj., inf. – Drug (isotonic, apyrogenic, sterile solution) goes to circulation almost immediately
- ***i.a.*** – similar to i.v., except: D level can be quickly set in target structure of some organ (e.g. RTG contrast subst. to see part of arterial bloodstream; 5-FU into *a. hepatica* to affect hepatic cancer)
- ***i.m.*** - inj. - sterile solution, suspension, emulsion
- ***s.c.*** - inj., implanted tbl.

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General Administration (whole body)

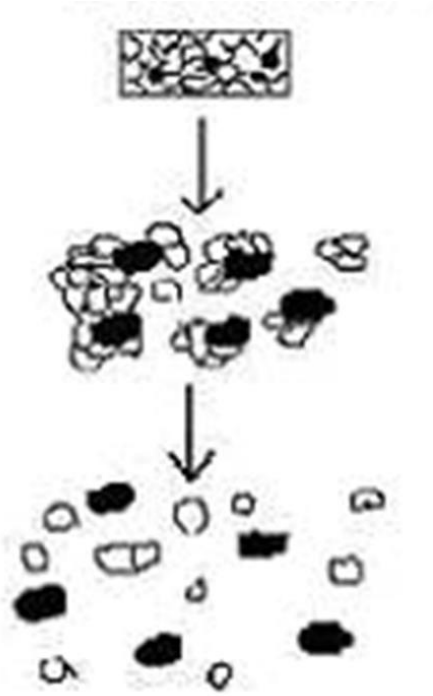
- **Parenteral**

- **Sublingual** - (drops, tbl.) for lipophilic D, penetrate to system bloodstream; no first pass ef.
- **Intrabucal** - between cheek and gingiva
- **Transdermal** – only lipophilic D, slow penetration of small amount
- **Intranasal** - peptide hormones, calcitonine, ADH. Inactivation in GIT is bypassed
- **Inhalant** – fast absorption due to diffusion

PK processes - LIBERATION

- Required for biological effects

- Dependently on DF we can observe :
  - **disintegration** to small parts
  - **dispersal** to particles of undiluted Dg
  - **dissolution** of solid particles in the digestive fluid



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ABSORPTION

- Drug penetration through lipoid CM and pores to blood and lymphatic stream

- D penetrates membranes through
  - *more cellular layers* (skin, vagina, cornea)
  - *one layer* (enterocytes, renal tubules cells)

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ABSORPTION

Effect of physico-chemical properties

- Absorption is facilitated by:

  low Mr; absence of electric charge; lipophility; strong blood flow; and appropriate degree of permeability

- Compounds:
  - hydrophilic
  - lipophilic
  - amphiphilic

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ABSORPTION

- *Bloodstream vs. Local*

  (local anesthetics; SM as decongestants; inhalation broncholytics)

- Process is realized by the following :
  - passive diffusion
  - filtration
  - active transport

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Passive Diffusion

- Most important for majority of D
- Small intestine is the major site of most D absorption due to the large absorption area
- pH is important factor

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How pH affects absorption

- Drugs are weak acids or weak bases

- Environment pH determines degree of ionization of weak acids and bases by *Henderson–Hasselbalch equation*:

$$\log \left(\frac{\text{protonised form}}{\text{non-protonised form}} \right) = \text{pH} - \text{pKa}$$

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Filtration

- Important for absorption of small drug molecules, soluble in H_2O (e.g. urea, LMW sugars) in small intestine

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Active transport

- For drugs similar to substances having physiological transport in human body (Aminoacids, Glucose, Fat)

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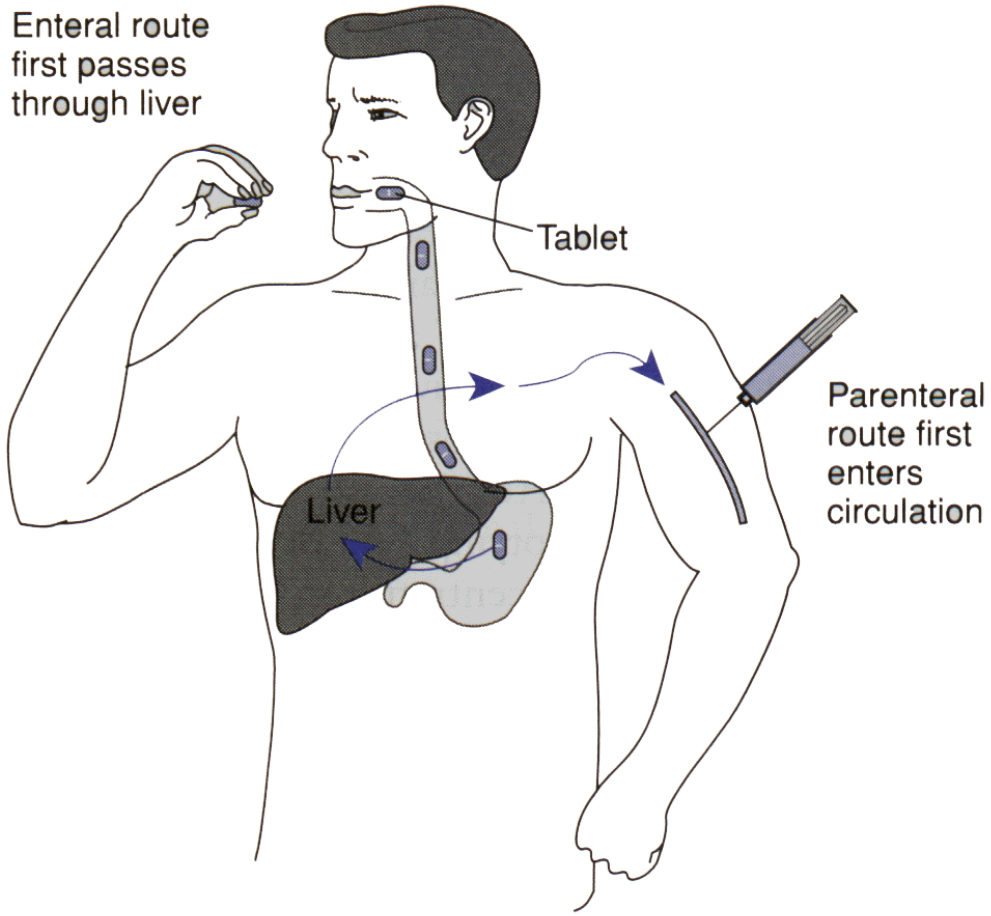
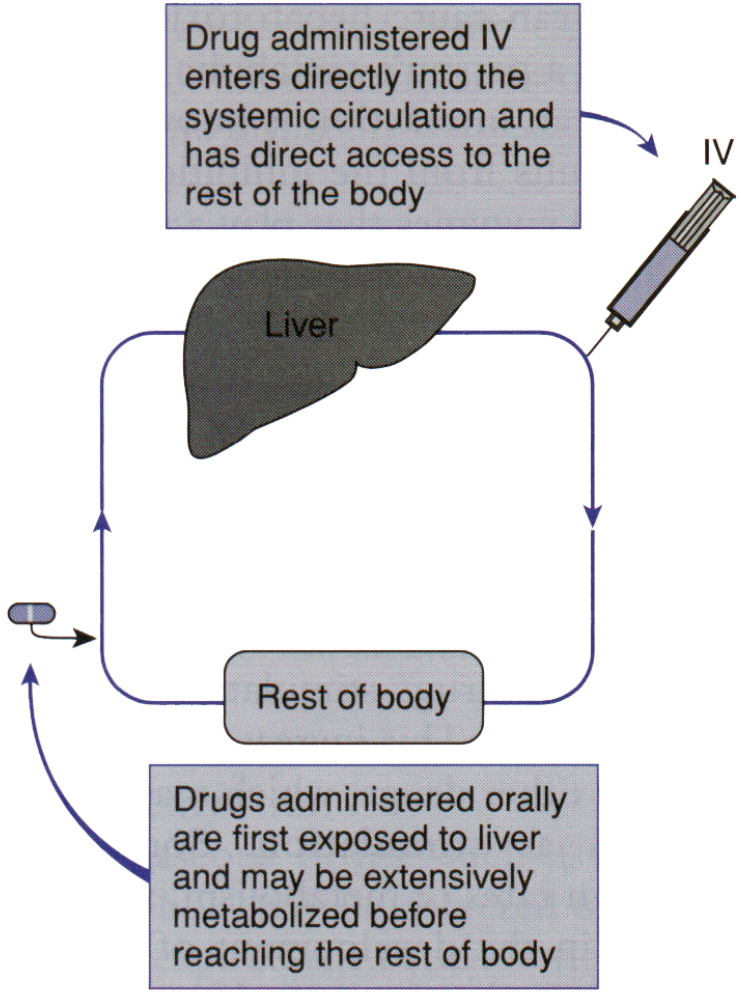
First Pass Effect

– **Often inactivates D or decreases concentration (βSL; morphine; petidine; imipramine; salicylates; nitroglycerin; βSM salbutamol)**





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Biological membranes

- Continuous lipid double layer with various membrane proteins incorporated

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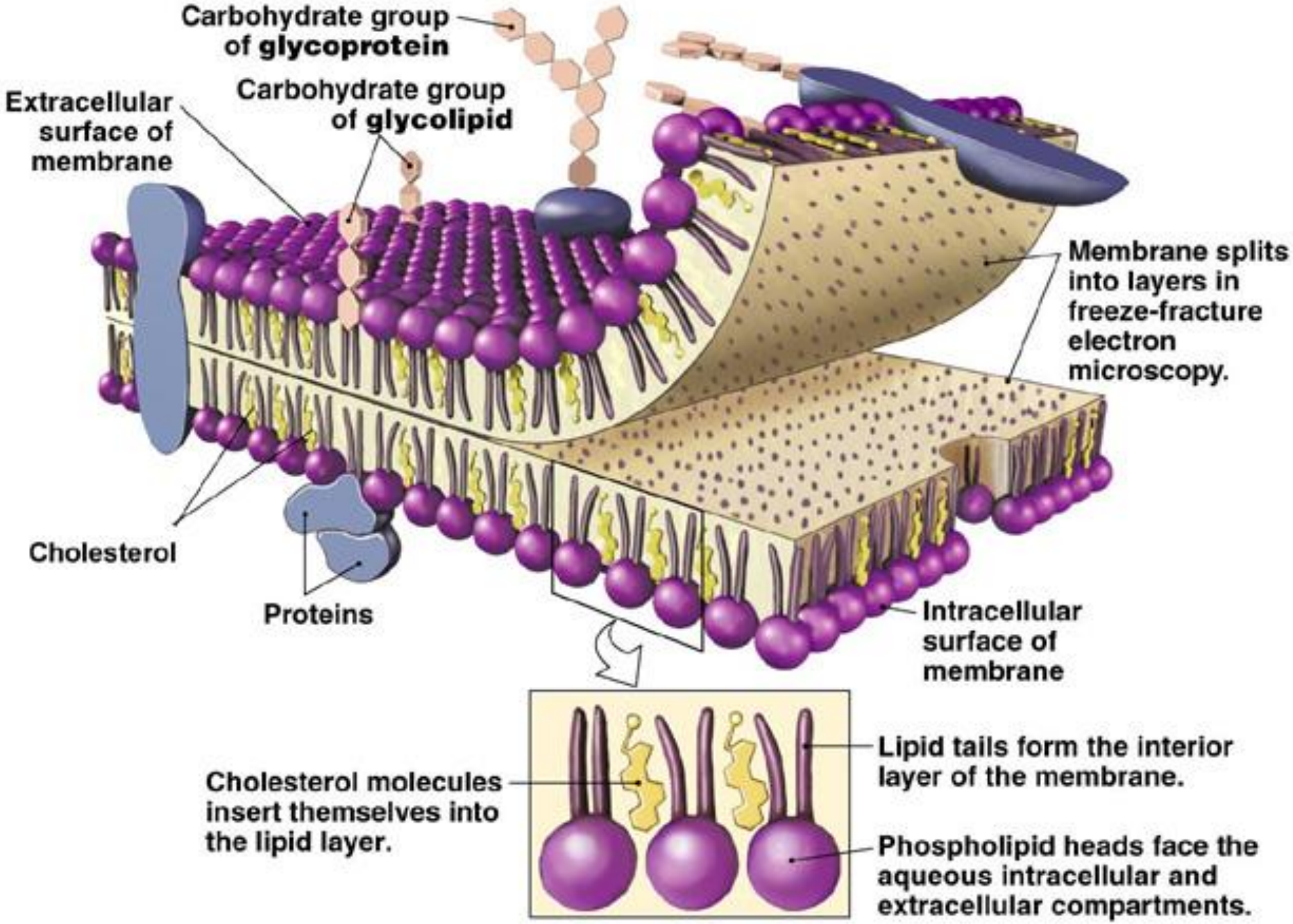

Fig. 3-4

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Transport across membranes

- **Passive Transport** (**LAZY**!)
  - Diffusion of lipid soluble substances
  - Protein channels
  - Facilitated transport

- **Active Transport** (**HARD WORK**!)
  - Transport against gradients
  - Active, co-transport, counter transport

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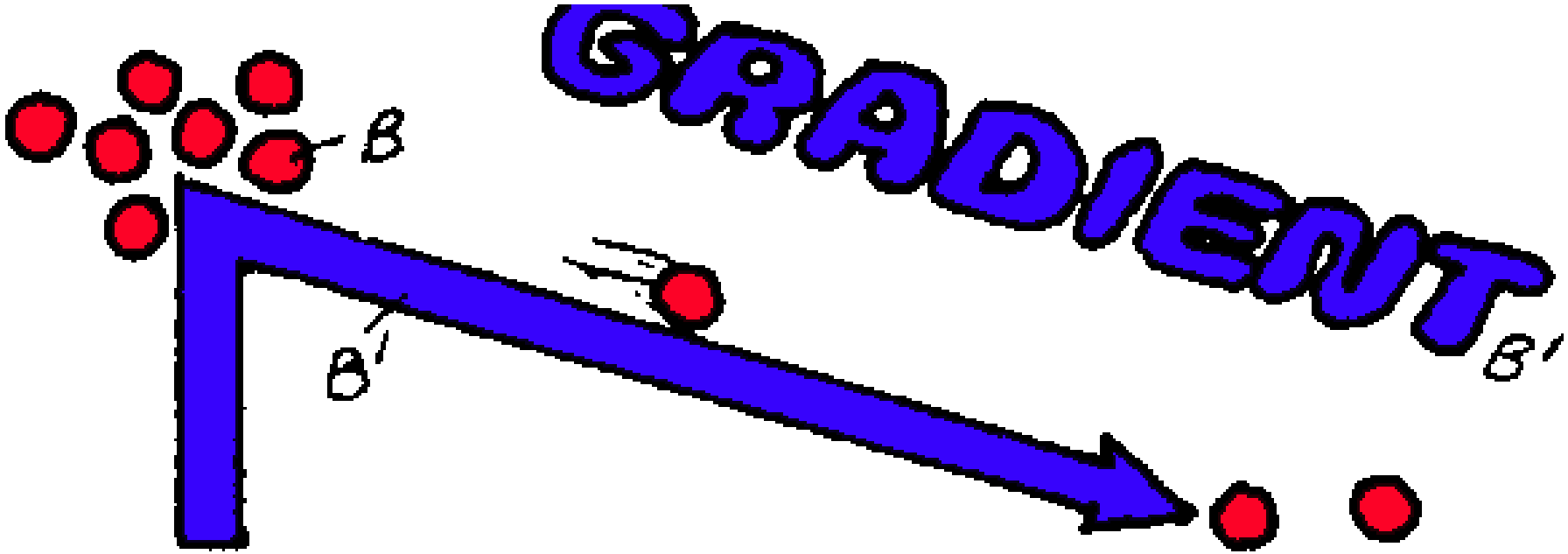
PASSIVE Diffusion

- Movement from an area of high concentration to low concentration



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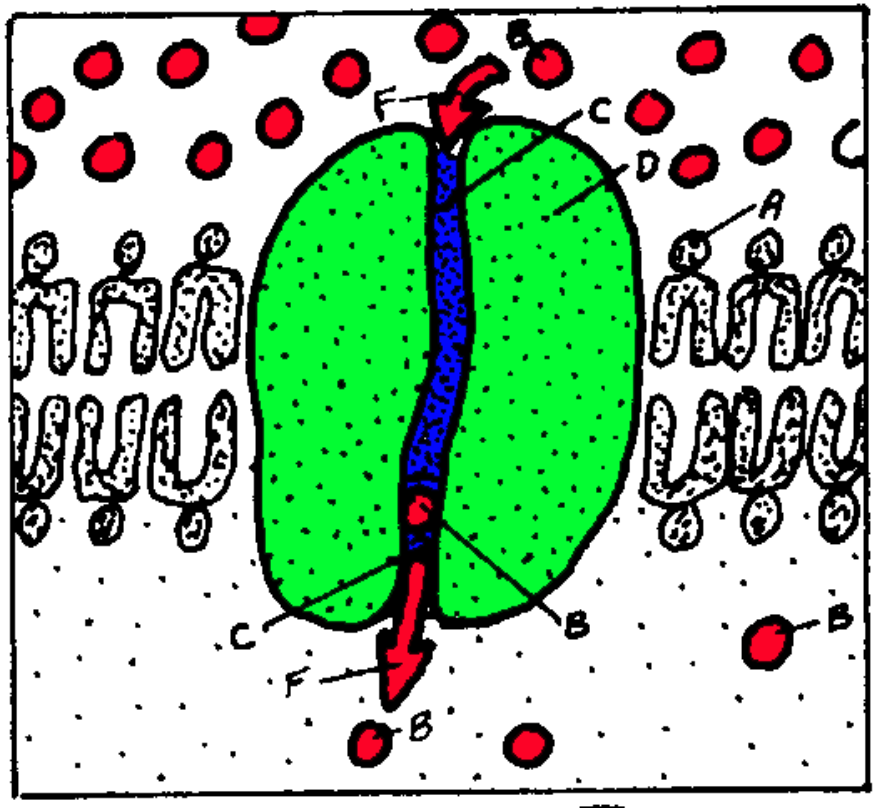
PASSIVE Protein Channel

- Protein channels in the membrane allow certain drugs to pass through



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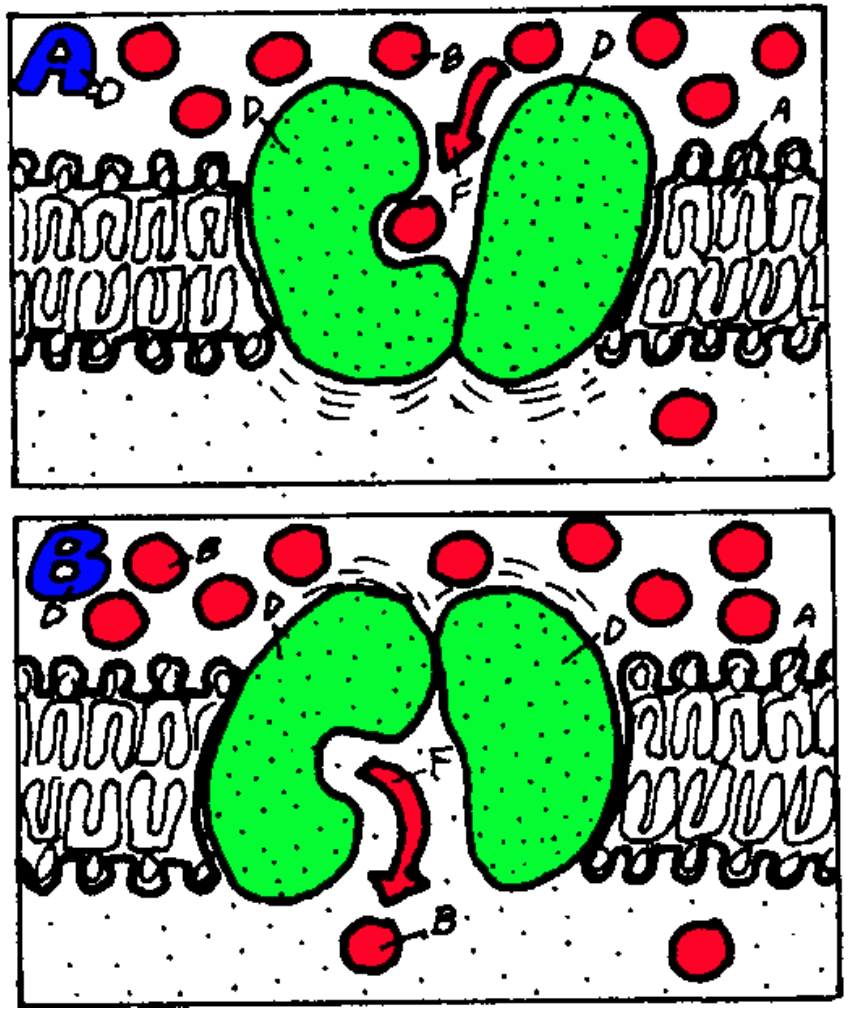
PASSIVE Facilitated Transport

- "Conformational help" from a protein
- Binding site exposed



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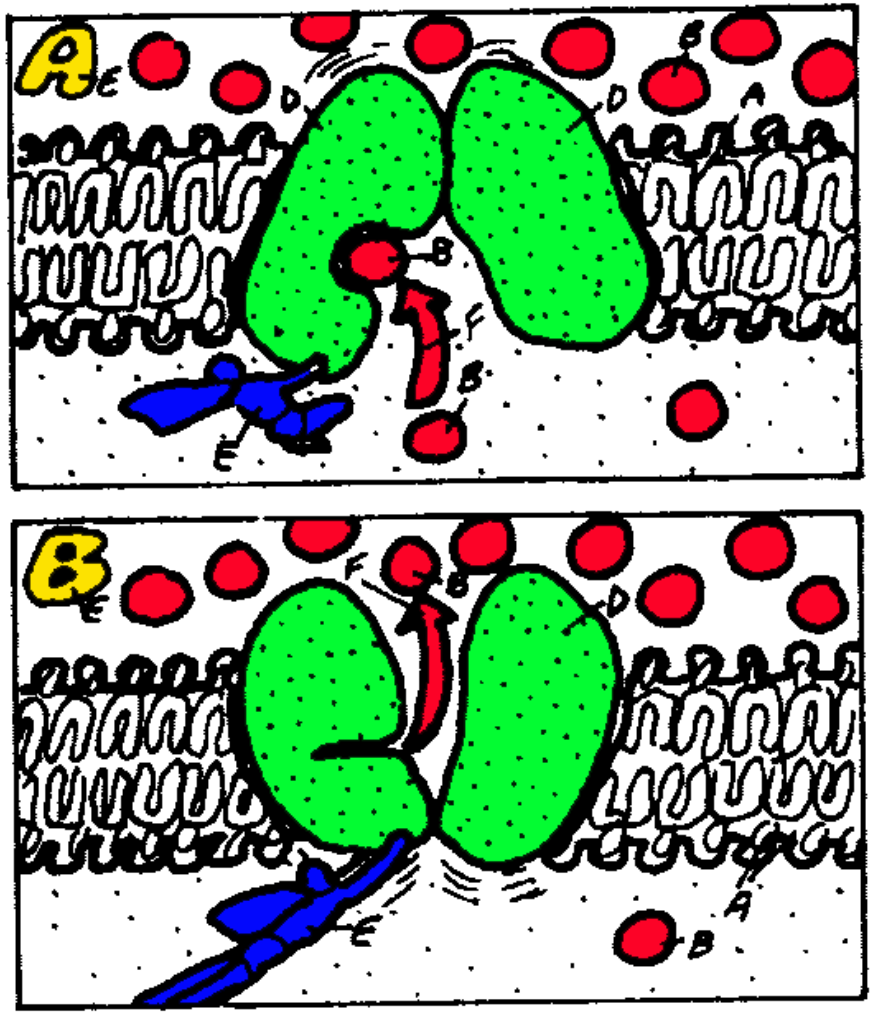
ACTIVE transport

- Molecules move uphill (towards higher concentration)

- Transporting the protein using **energy**!!!



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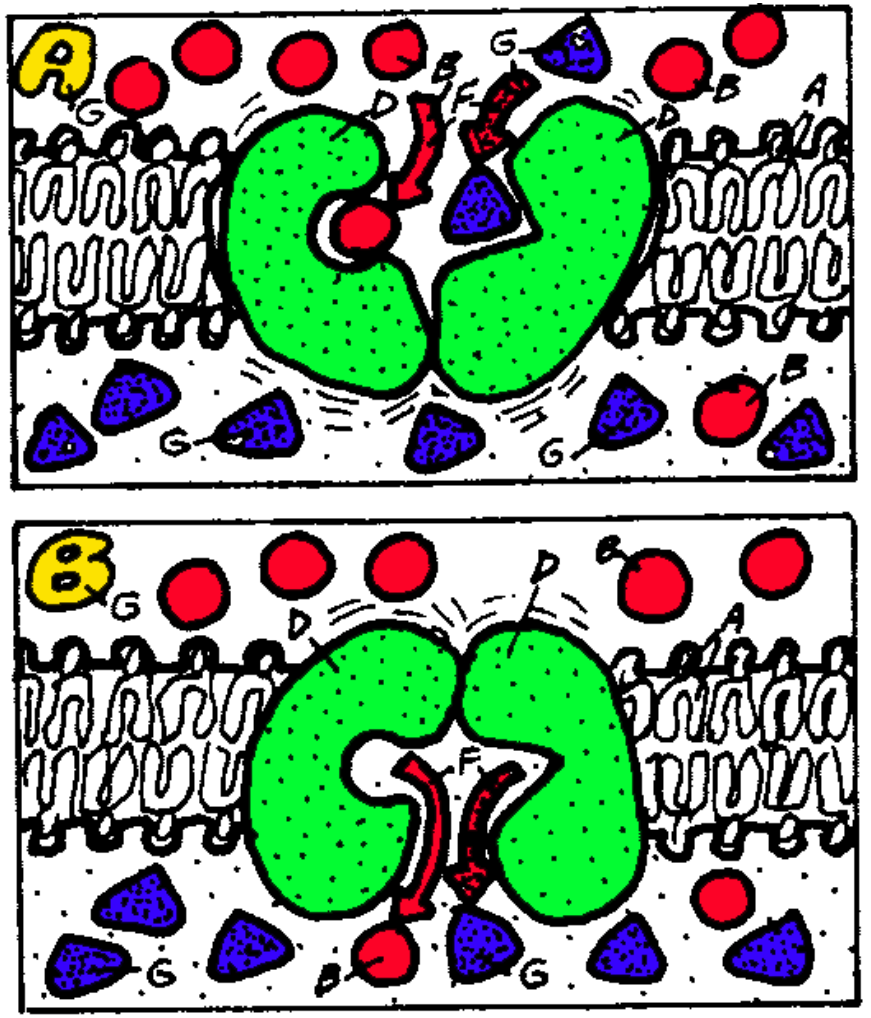
CO-transport

- One molecule goes downhill
- The other (the one that needs to be transported) goes uphill

Cotransporters can be classified as *symporters* and *antiporters* depending on whether the substances move in the same or opposite directions.



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DISTRIBUTION

- Process by which D administered into organism travels from intravascular into extravascular area

- Both-side transport of D from systemic circulation into various organs, tissue, and body fluids

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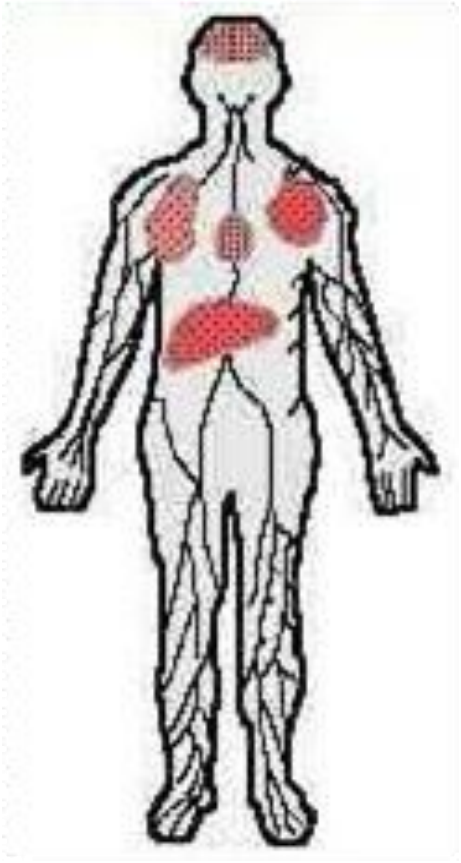
Central compartment

– Hypothetic area, where D after administartion is distributed first

Organ	Perfusion rate (ml/min/g tissue)	% cardiac output
bones	0.02	5
brain	0.5	14
fat	0.03	4
heart	0.6	4
kidney	4.0	22
liver	0.8	27
muscles	0.025	15
skin	0.024	6



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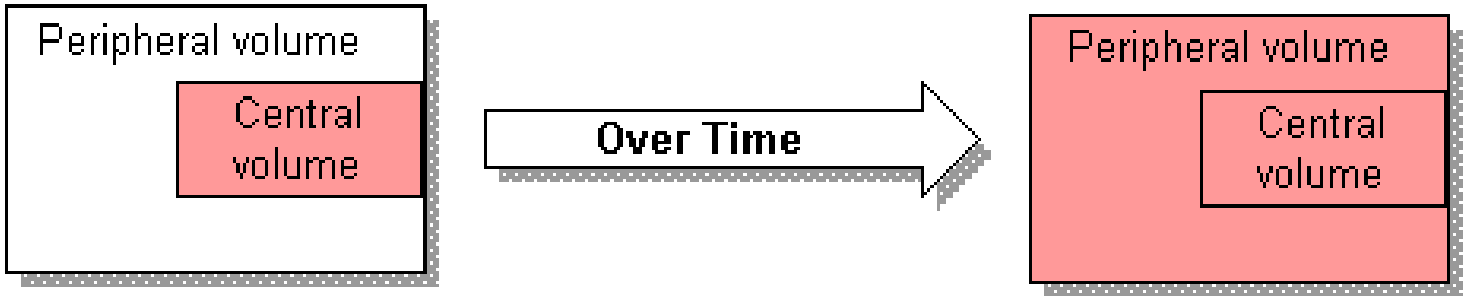
Tissue (peripheral) compartment

- Summary of all tissue out of central compartment
- All peripheral tissue are NOT homogeneous

Drug distribution into compartments in time:



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Transport proteins

- High % bond reduces extravascular D distribution
- Albumine is MOST IMPORTANT
  - Qualitative viewpoint (binds most D with various structure)
  - Quantitative viewpoint (50% of total proteins)

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Differences in transport proteins bonds

Drug	% bond
caffeine	10
digoxin	23
gentamycine	50
teophylin	15
fenytoin	87
verapamil	90
diazepam	96
warfarin	>99

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METABOLISM

- Metabolism = change = biotransformation
- Several possible outcomes – activate, inactivate, maintain activity
- Most common = inactivate, make more polar
- Sometimes metabolites with qualitatively different toxic or side effects

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DRUGS	EFFECT OF METABOLISM	
	BEFORE	AFTER
80% of all drugs	**ACTIVE**	**INACTIVE**
Azathiprine *Cyclophosphamide*	**INACTIVE** (prodrug)	**ACTIVE**
Phenytoin	**ACTIVE**	**TOXIC METABOLITE** **Antigen** **Carcinogen** **Cytotoxin**
Diazepam	**ACTIVE**	**ACTIVE**

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P450 Enzyme System – Induction

- Cytochrome P450
  - Found in the liver, GI tract
  - In smooth endoplasmic reticulum

- Cyt P450 **induction** (increase activity)
  - Most common way: increase production of enzyme
  - Eg. *Phenobarbital*

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P450 Enzyme System – Inhibition

- P450 3A4 present in GIT
- Responsible for 1st pass MTB of some D
- GRAPEFRUIT JUICE inhibits P450 3A4
- Cyclosporins, statins metabolized by this enzyme
- Levels in serum are ELEVATED!

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EXCRETION

– Basic part of kidney is **nephron**:

- *Glomerular filtration*:
  D with Mr < 25 kD

- *Tubular secretion*: active, needs E and transporters

- *Passive reabsorption*: diffusion of lipophilic molecules back to blood

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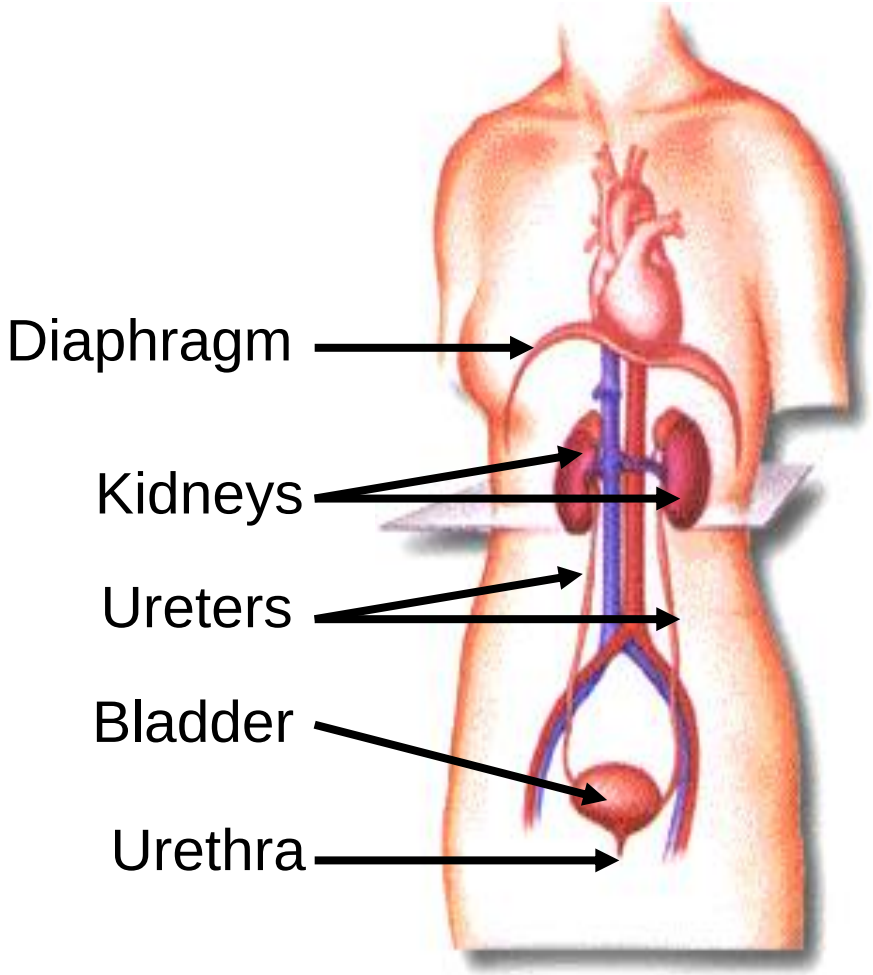
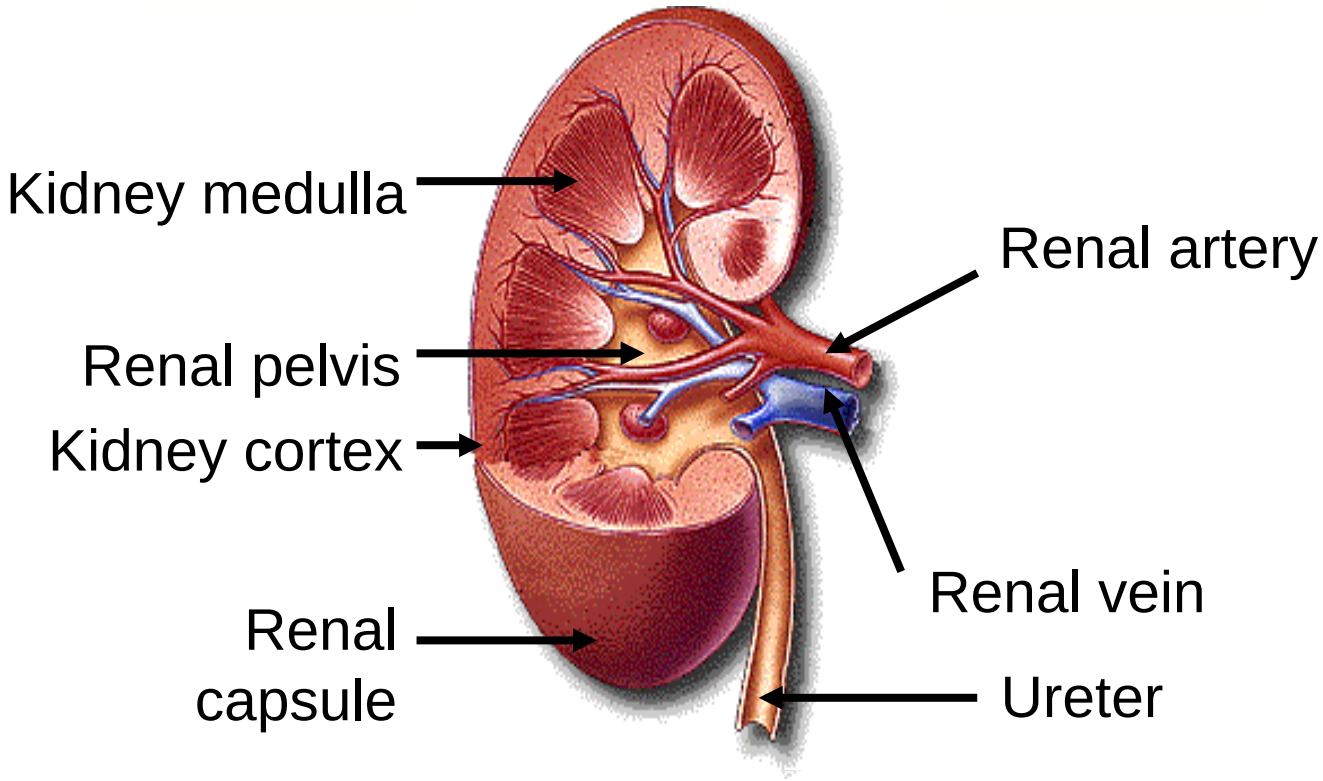
Kidney





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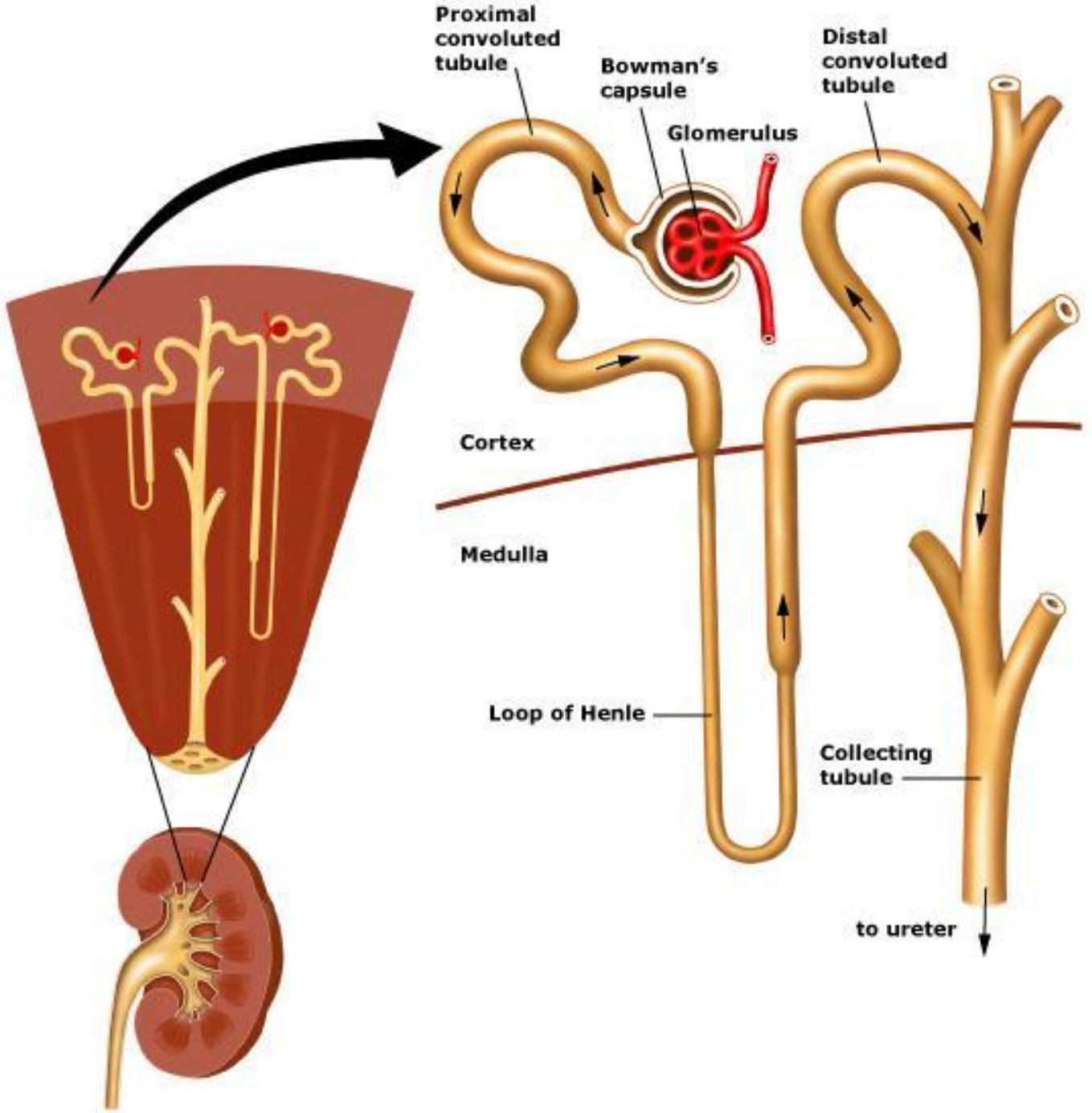
Proximal convoluted tubule
Bowman's capsule
Glomerulus
Distal convoluted tubule
Cortex
Medulla
Loop of Henle
Collecting tubule
to ureter

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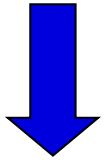
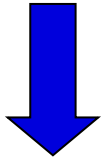
Glomerular filtration

- Albumine size is cca 67 kDa



- Drugs bonded to proteins does NOT go to urine



- Time of D remains in organism is extended

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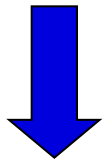
Tubular reabsorption

- Drugs with high level of liposolubility are reabsorbed passively back to systemic circulation



- Excretion is delayed

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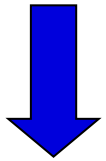
Bile excretion

- Enterohepatal circulation extends stay of drug in organism



- Prolongation of drugs effect
  (MTX, indometacine)

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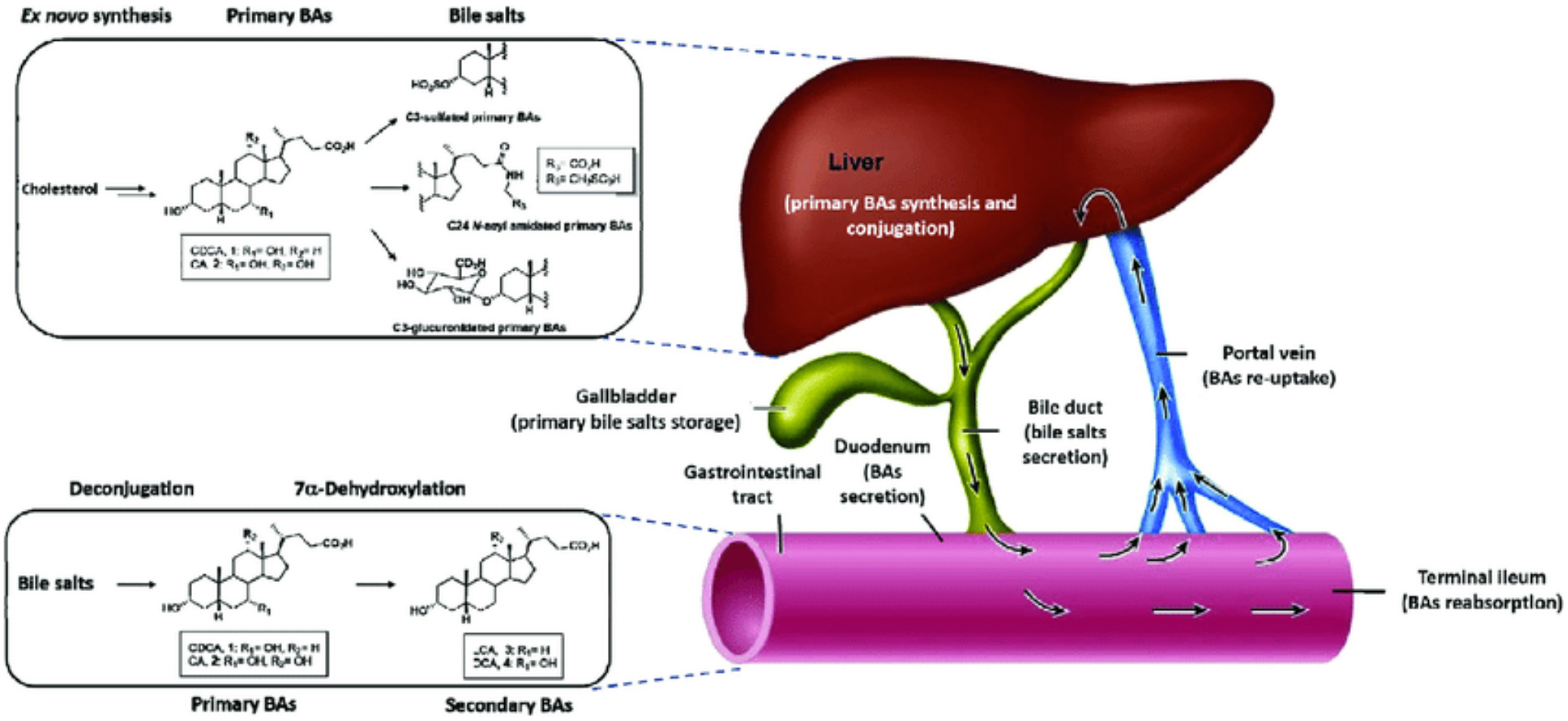
Enterohepatic circulation



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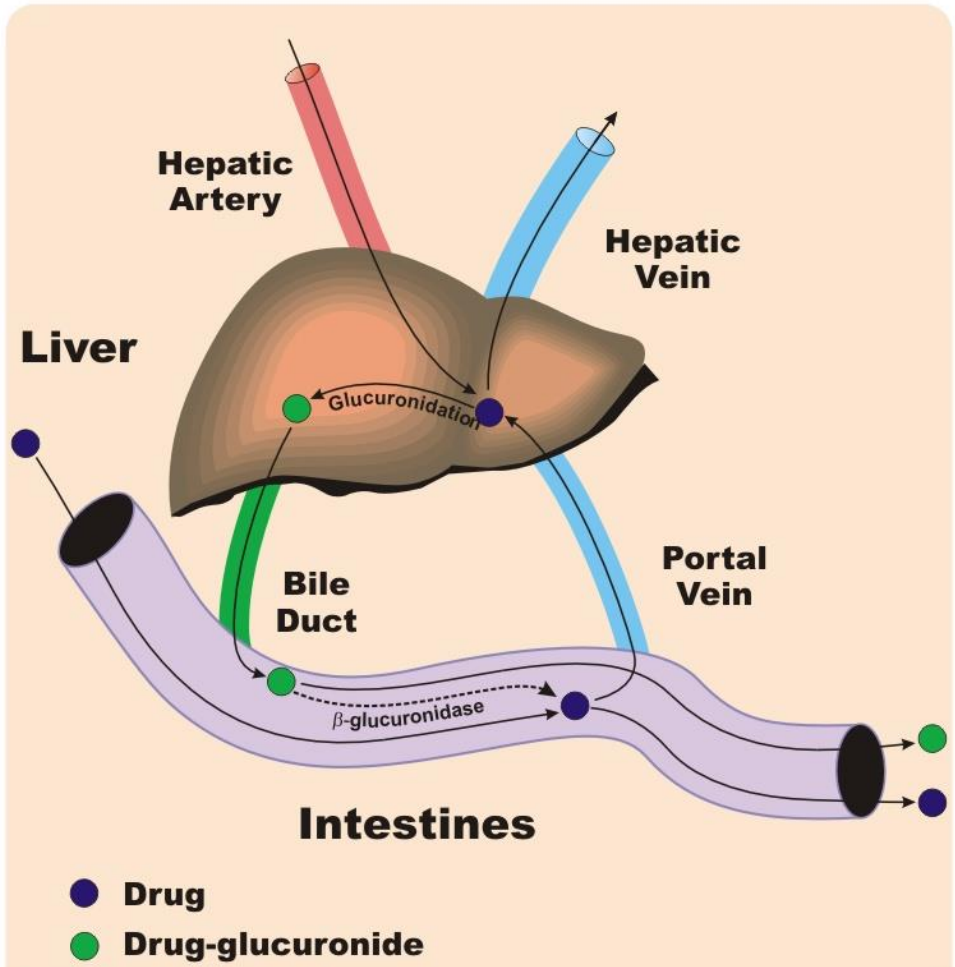
Enterohepatic Recirculation



Drugs entering the liver via the portal vein (from the intestine) or via the hepatic artery (from the general circulation) may be glucuronidated. The glucuronide metabolite reenters the intestine via the bile duct, destined to be excreted in feces.
Beta-glucuronidase produced by intestinal microflora enzymatically removes the glucuronide portion of the metabolite reforming the original drug, which again reenters the liver via the portal vein to start the process again.

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Other routes of drugs excretion from organism

- stool (could be high during diarrhea)
- lungs (vaporous drugs, e.g.systemic anesthetics)
- sweat, salivas (important for TDM)
- excretion into breast milk

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Thank you
for your attention

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