DRUG ABSORPTION
FIRST-PASS ELIMINATION
ENTEROHEPATIC CIRCULATION
&
DRUG DISTRIBUTION

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ADME

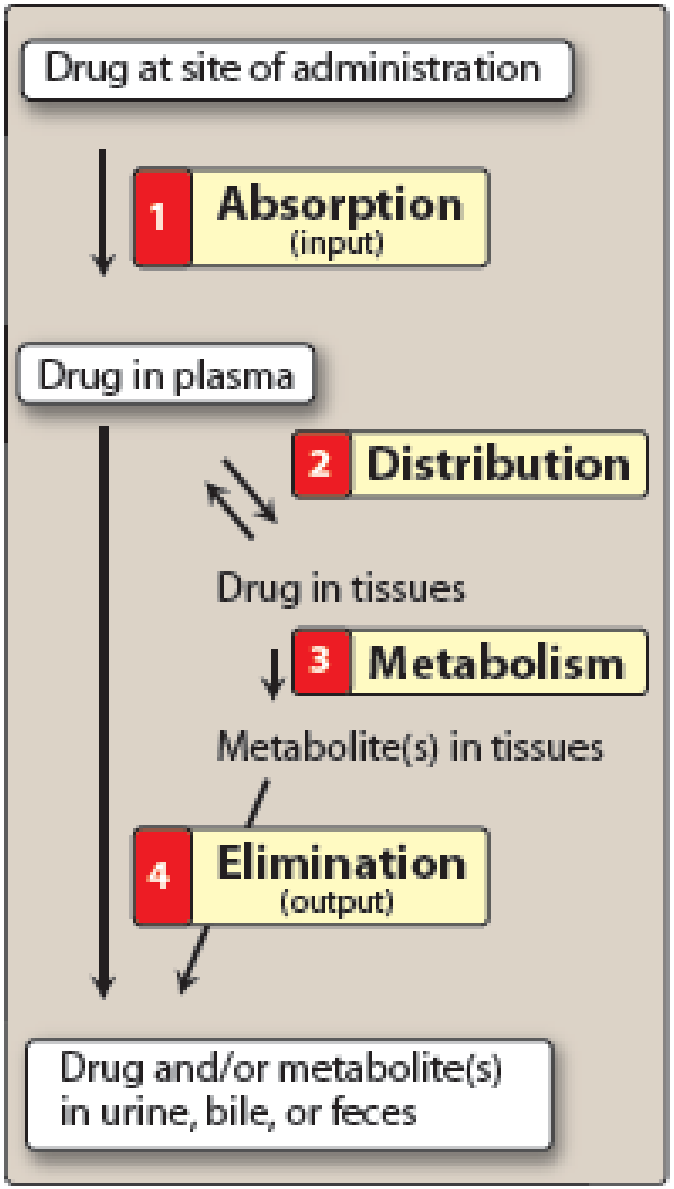
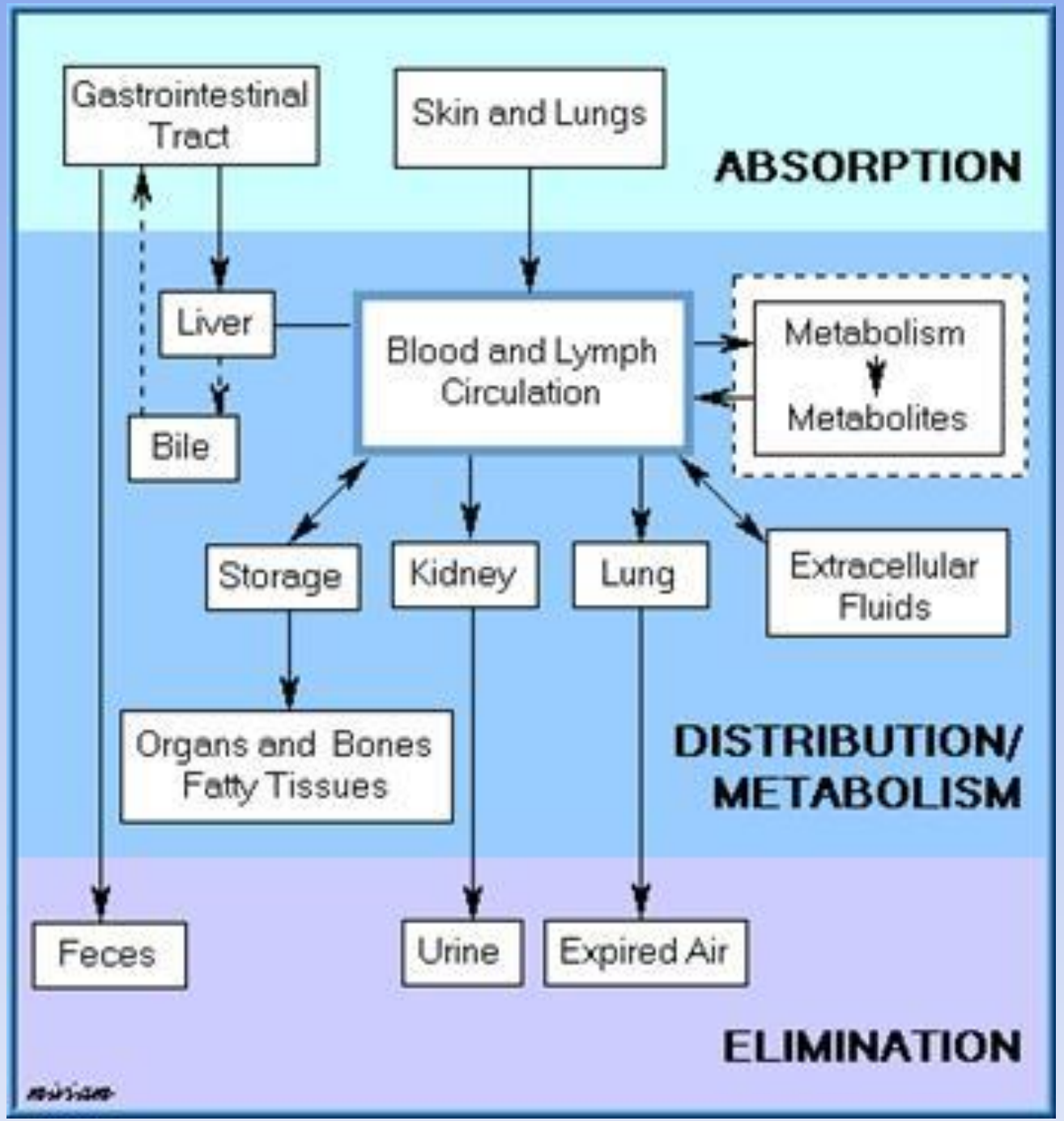
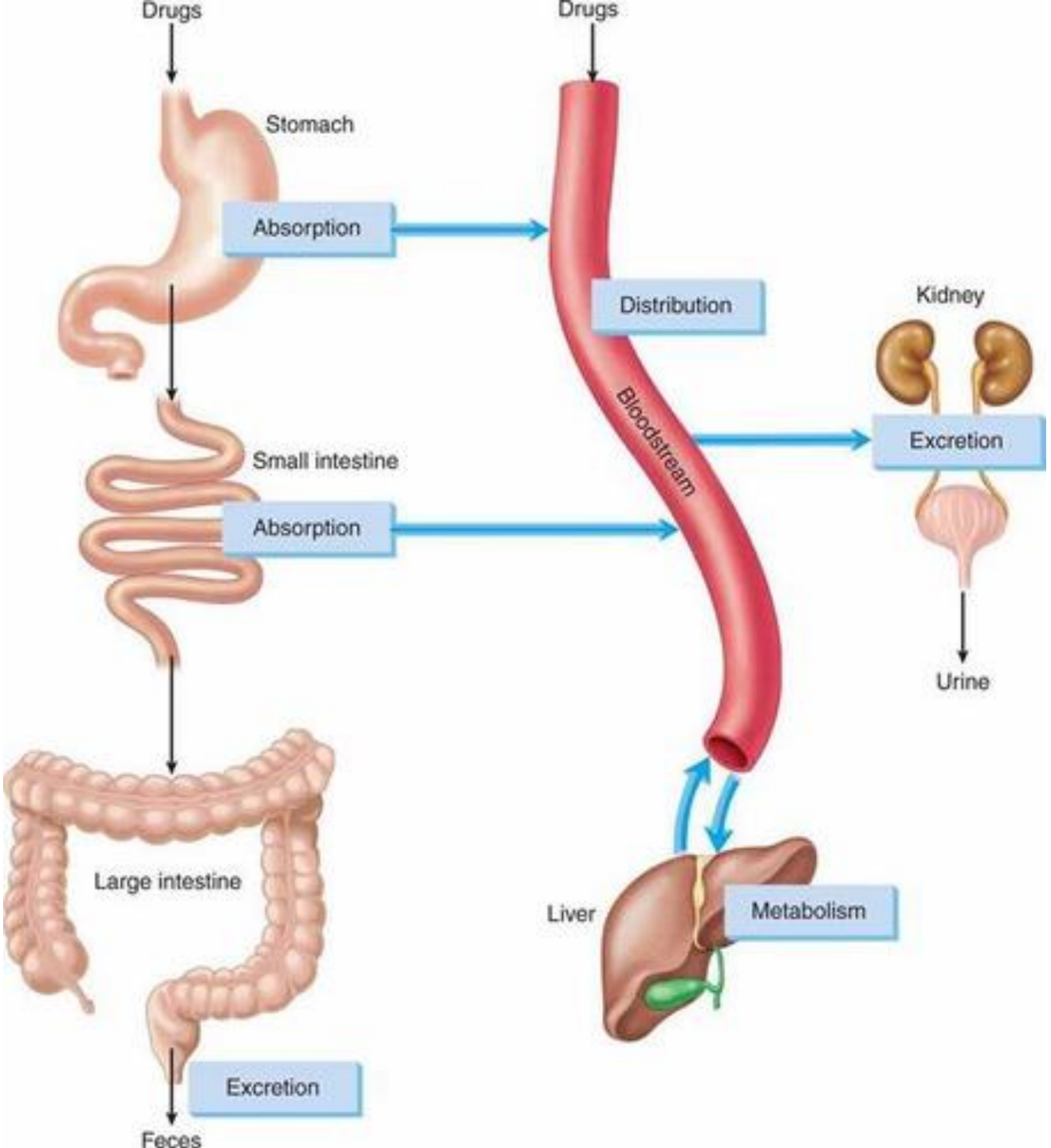


Figure 1.1
Schematic representation of drug absorption, distribution, metabolism, and elimination.


Gastrointestinal Tract
Skin and Lungs
ABSORPTION
Liver
Bile
Blood and Lymph Circulation
Metabolism
Metabolites
Storage
Kidney
Lung
Extracellular Fluids
Organs and Bones
Fatty Tissues
DISTRIBUTION/
METABOLISM
Feces
Urine
Expired Air
ELIMINATION


Drugs
Stomach
Absorption
Small intestine
Absorption
Large intestine
Excretion
Feces
Drugs
Distribution
Bloodstream
Kidney
Excretion
Urine
Liver
Metabolism

ABSORPTION

Definition: Movement of a drug from its site of administration to the systemic circulation

Speed and degree of absorption depend on drug administration route. Ex. IV drug absorption is whole, this means drug reachs to the systemic circulation totally

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(Tedavi açısından oral yolla kullanılan ilaçların absorbsiyonuyla ilgili iki önemli parametre vardır.

1.Absorbsiyon hızı, birim zamanda absorbe olan ilaç miktarıdır. İlac etkisinin başlama süresini belirler

2. Absorbsiyon derecesi yani oranı, ilaç etkisinin ne kadar güçlü olacağını gösterir.)

Movement of Drugs Across Membranes:

Active transport:

- ✓ Involve spesific membrane transport proteins known as drug transporters or carriers------spesific for the substrates
- ✓ Drug molecules bind to the transporter translocated accross the membrane and then released to the other site of the membrane
- ✓ Energy dependent (ex.ATP hydrolysis)
- ✓ Saturable
- ✓ Against an electrochemical gradient

(Aktif transport ilaçları konsantrasyon farkına karşı, yani ilacın düşük konsantrasyonda olduğu bölgeden yüksek konsantrasyonda olduğu bölgeye taşıyabilir.)

Pasive diffusion:

- ✓ This is the ***MOST COMMON mechanism for drug transport***
- ✓ Lipid-soluble drugs permeate across the cell membrane by passive diffusion between the lipid molecules of the cell membrane
- ✓ Not requiring energy
- ✓ Having no saturation
- ✓ Having no carriers
- ✓ Not resisting compatitive inhibition
- ✓ Not effected by physical state of drug

(Bir ilacın pasif difüzyona uğramasını sağlayan güç, bir zarla ayrılan iki vucut boşluğu arasındaki konsantrasyon farkıdır. İlaç yüksek konsantrasyonun olduğu taraftan diğer tarafa geçer.)

Endocytosis (pinocytosis):

- ✓ Drugs of large molecular weight (MW > 900) may enter cells by pinocytosis or phagocytosis.
- ✓ It involves the invagination of a part of the cell membrane and trapping within the cell of a small vesicle containing extracellular constituents. (ex.insulin)

Facilitated Diffusion:

- ✓ No energy dependent
- ✓ Saturable
- ✓ NEVER against an electrochemical gradient
- ✓ selective carrier-mediated.

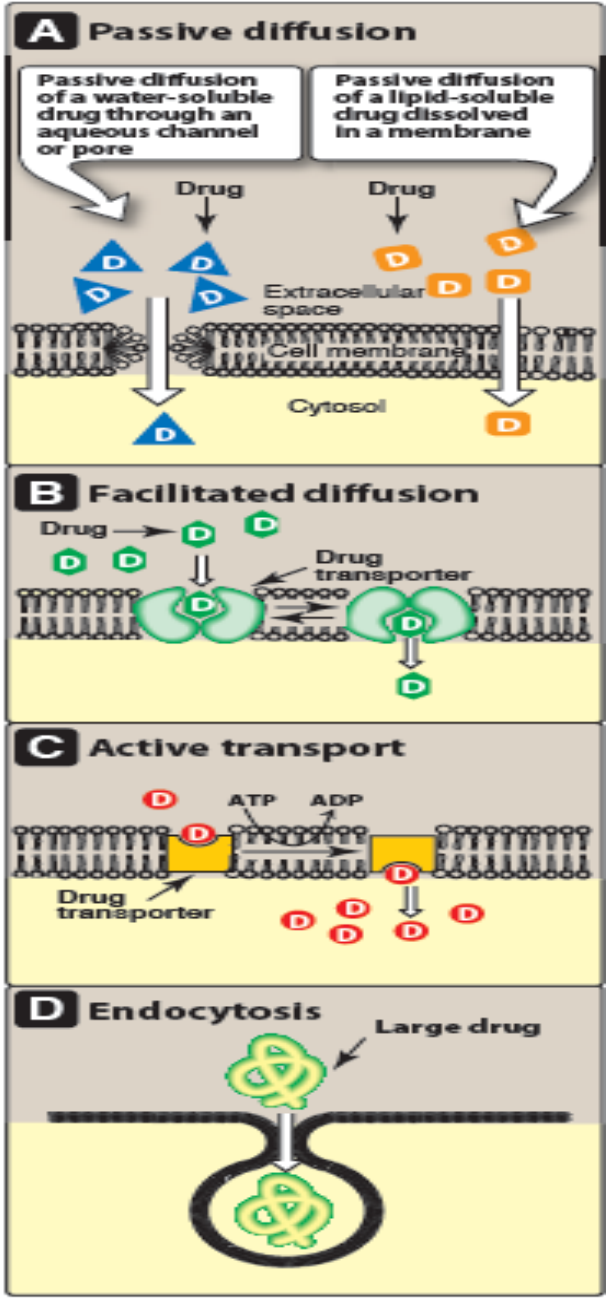
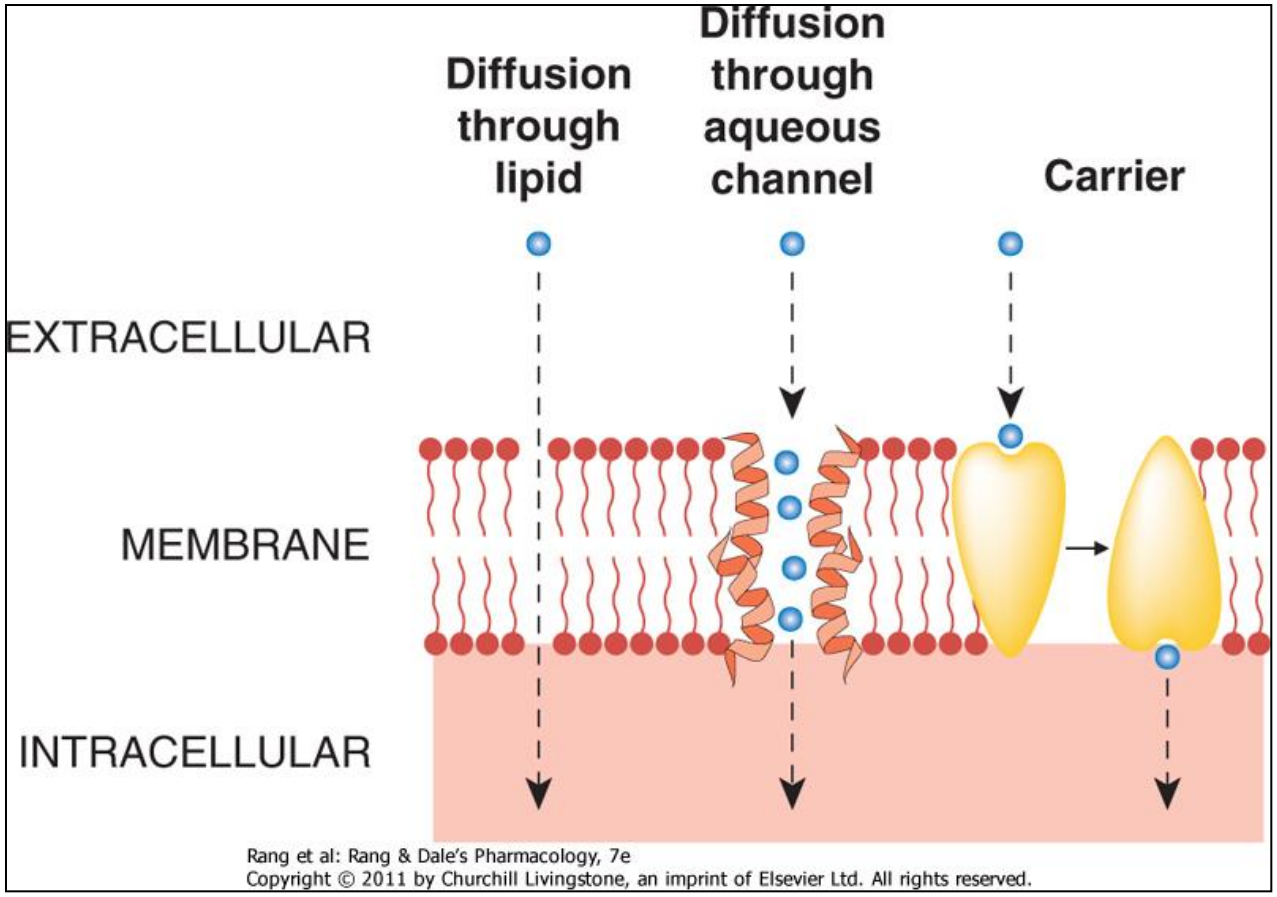
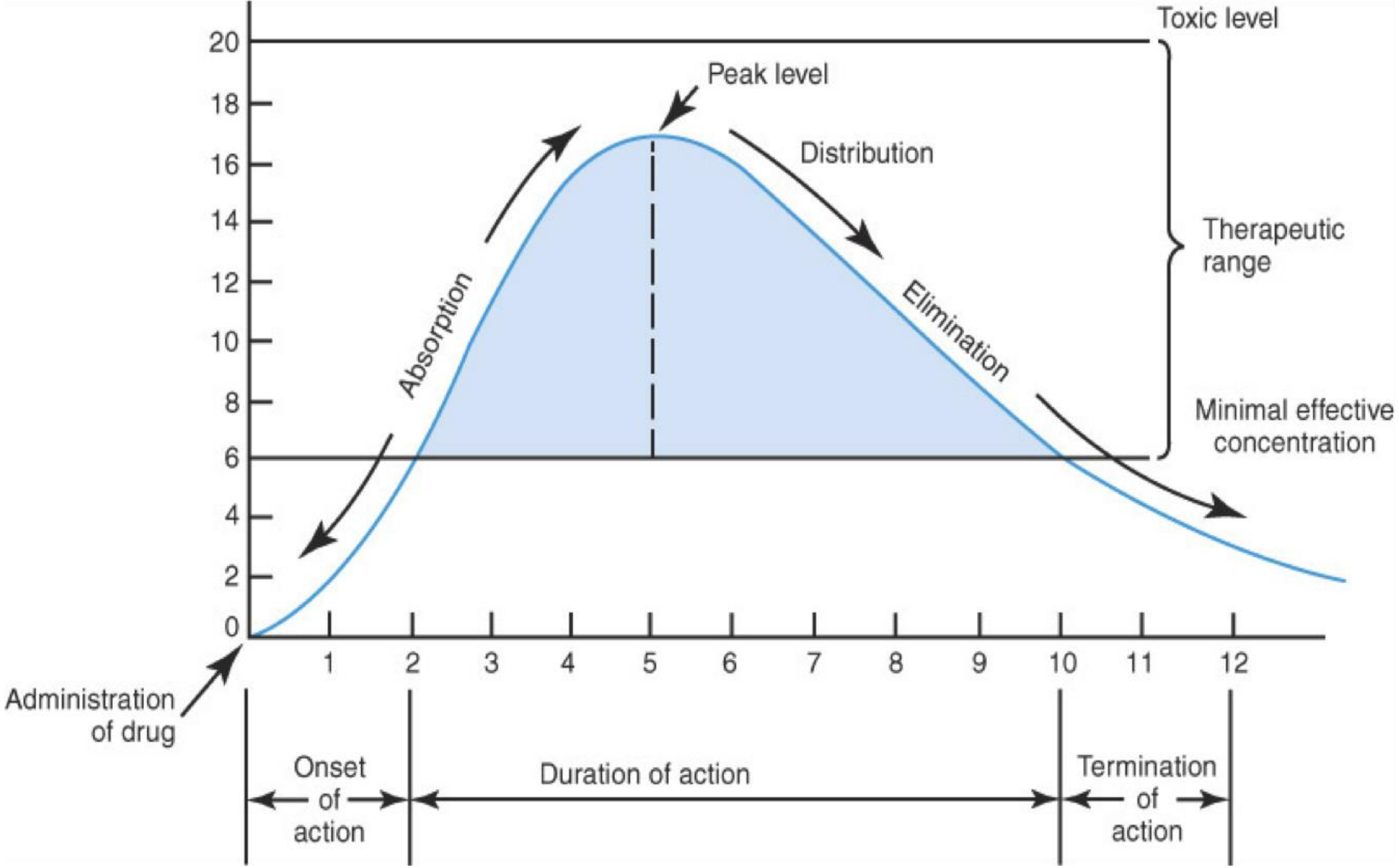


Figure 1.6
Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.





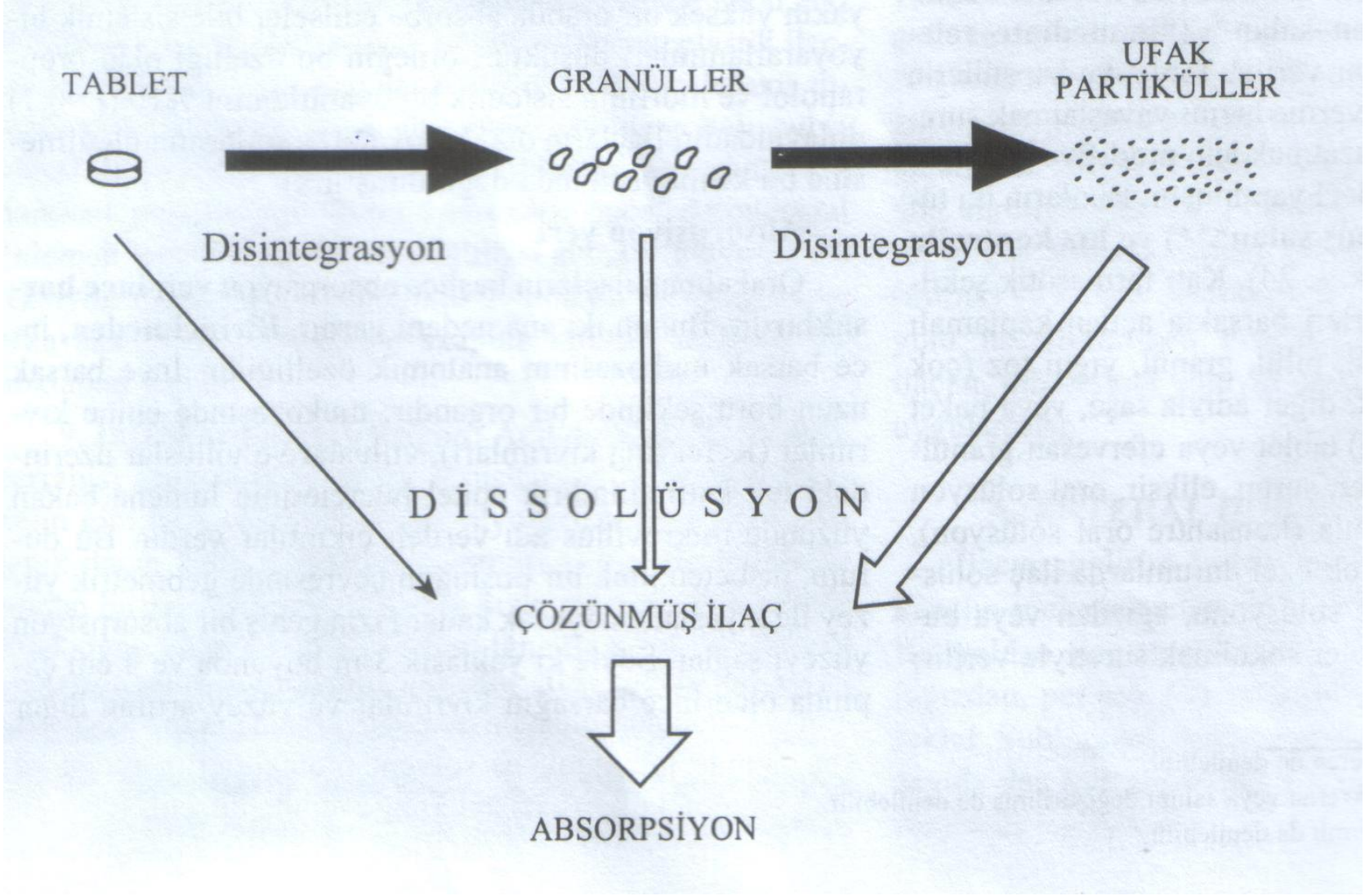
A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters obtained after oral administration of a single dose of drug

Factors affecting absorption:

- ❑ Route of adminitration
- Physical properties-physical state, lipid or water solubility

- ❑ Dosage forms
- Particul size
- Disintegration time and dissolution rate
- Formulation-biopharmaceutics

- ❑ Physiological factors
- Ionization, pH effect *(unionized form penetrates GI mucosa quickly)*
- Presence of food *(the stomach delays gastric emtying so drugs that are destroyed by acid (for ex penicillin) become unavailable for absorption)*
- Presence of other agents
- Diseases *(ex.malabsorption, cirrhosis, biliary obstruction, diarrhoea)*



DISINTEGRATION: DISINTEGRATION
DISSOLÜSYON: DISOLUTION
ÇÖZÜNMÜŞ ILAÇ: DISOLVED DRUG
ABSORPSIYON: ABSORPTION
UFAK PARITIKÜLLER: SMALL PARTICULES
GRANÜLLER: GRANULES

❑*Katı farmasotik şeklindeki ilaçların absorbsiyonundan önce mide-barsak lümeninde 2 önemli fiziksel olayın meydana gelmesi gerekir.*

Farmasotik şeklin ufak taneciklere parçalanması (disintegrasyon)

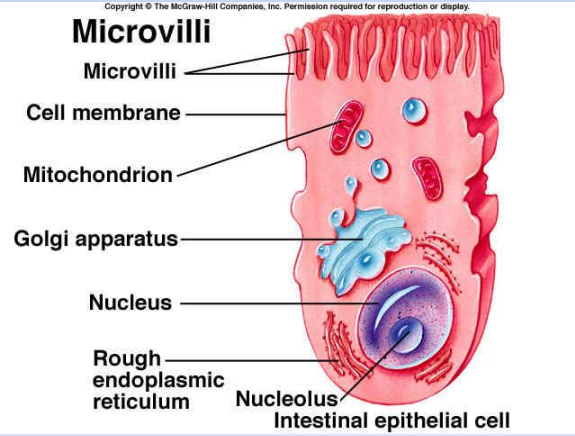
Tanecikler içindeki ilaç moleküllerinin mide veya barsak suyunda çözünmesi (dissolüsyon)

❑*Sıvı farmasotik şekillerdeki ilaçlar (özellikle solüsyonlar) bu aşamalardan geçmediği için gastrointestinal kanaldan daha hızlı ve bazen daha fazla absorbe edilir.*

Absorption of Drugs by the Gastrointestinal Tract:

Epithelial Barriers to Drugs:

Epithelial cells in the GI are joined to one another by occluding zonulae (tight junctions). Drugs must pass through the cells and can not pass around the cells.



Surface Area:

Larger surface areas absorb drugs faster than smaller ones. The gastric mucosa has villi, the small intestines have microvilli. Therefore, the intestines have a much greater surface area than the stomach. Most drugs can be absorbed by the intestines. As a generalization, the presence of food will slow gastric emptying time and will slow the absorption of an orally administered drug.

Also, many drugs slow gastric emptying and may slow the absorption of a second drug.

http://study.com/academy/lesson/villi-fucntion-definition-structure.html

Gastric absorption:

The pH of gastric juice is low. Weak bases will be ionized and will be poorly absorbed. Weak acids will be unionized and will be absorbed well. Furthermore, weak bases--even if they are administered IV—may cross the capillaries and the gastric mucosa and enter the gastric juice where they become ionized and trapped. They may be absorbed later when they reach the intestines.

Intestinal absorption:

The pH of intestinal juice is more basic than gastric juice. Here most weak bases will be unionized and will be readily absorbed. In contrast, most weak acids will be ionized and will be poorly absorbed.

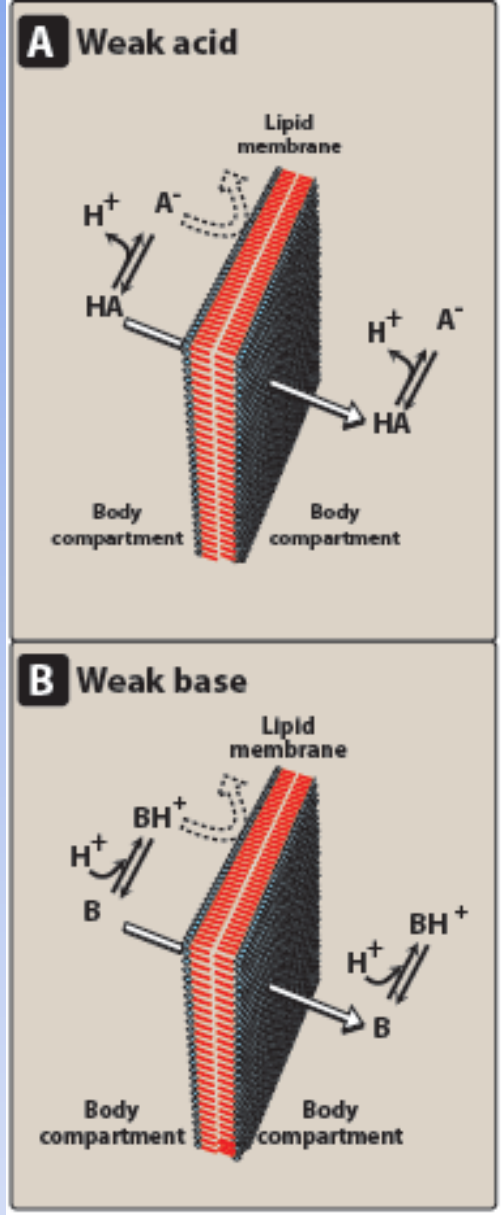


Figure 1.7
A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the non-ionized form of a weak base through a lipid membrane.

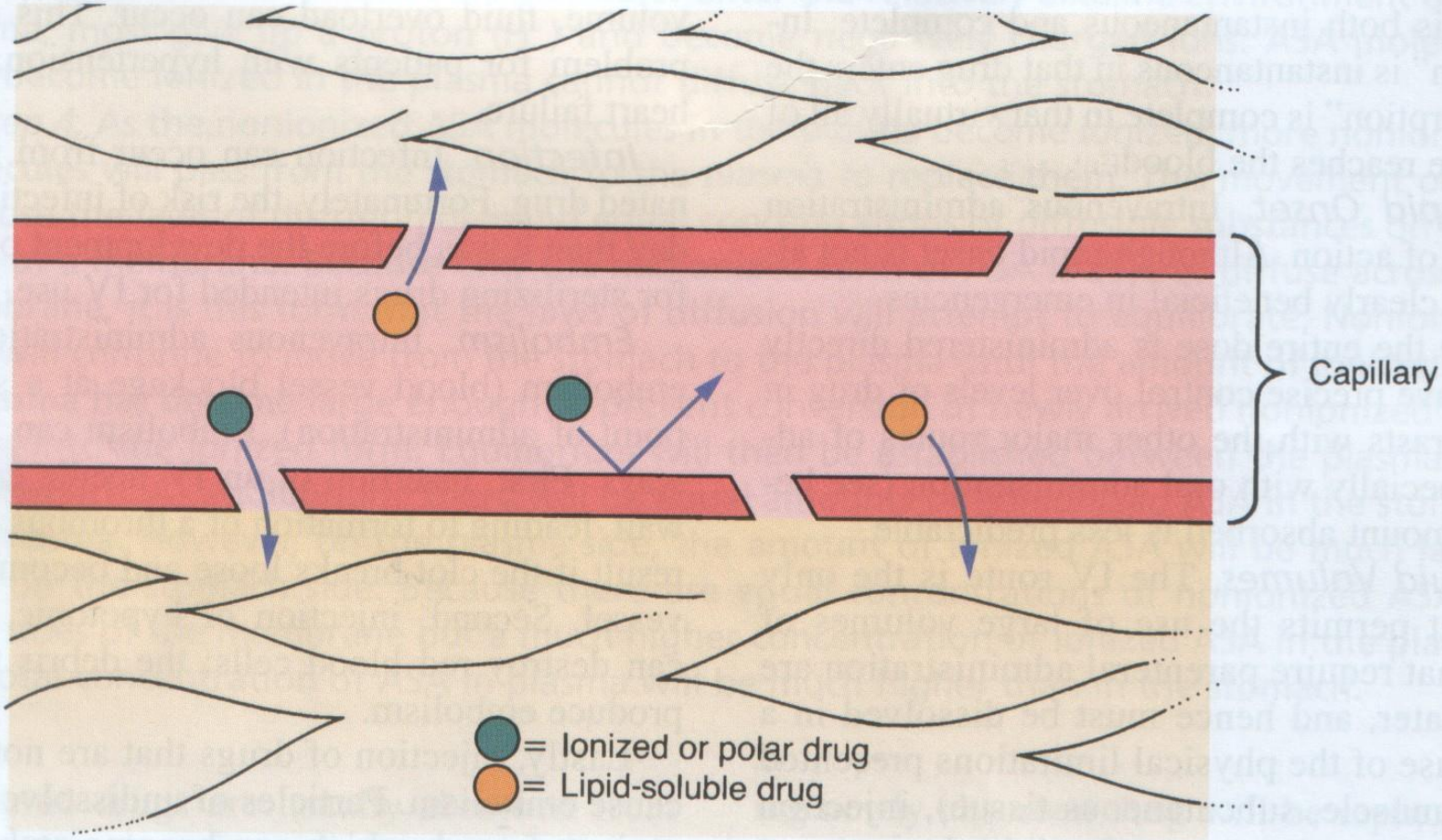
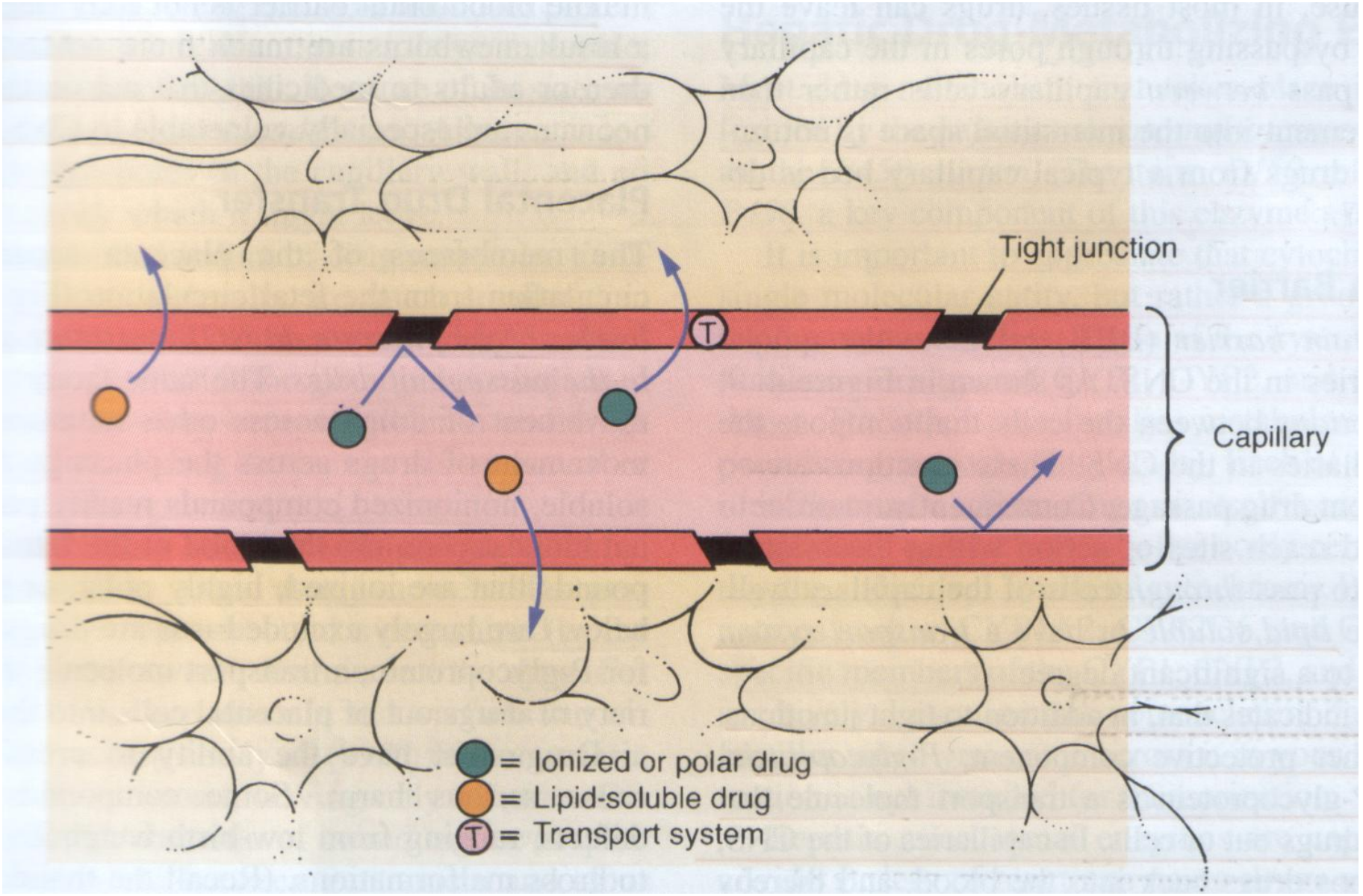
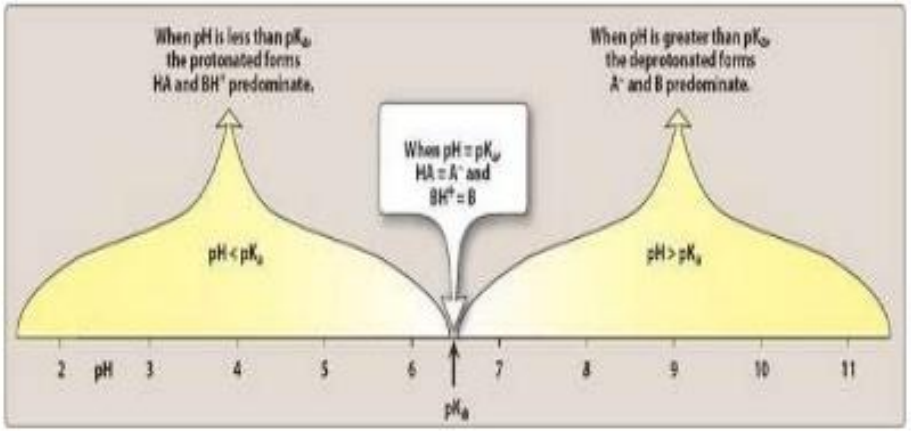


Figure 4–7 ■ Drug movement at typical capillary beds.
In most capillary beds, "large" gaps exist between the cells that compose the capillary wall. Drugs and other molecules can pass freely into and out of the bloodstream through these gaps. As illustrated, lipid-soluble compounds can also pass directly through the cells of the capillary wall.


Tight junction
T
Capillary
= Ionized or polar drug
= Lipid-soluble drug
T = Transport system

The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the pK_a.



The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

Bioavailability:

The Bioavailable Fraction is the percentile fraction of the total dose that enters the systemic circulation. With the IV route of administration 100% of the drug enters the systemic circulation and bioavailability is equal to 1. With the oral route, only a fraction of the total dose enters the systemic circulation, and the Bioavailable Fraction is equal to that fraction.

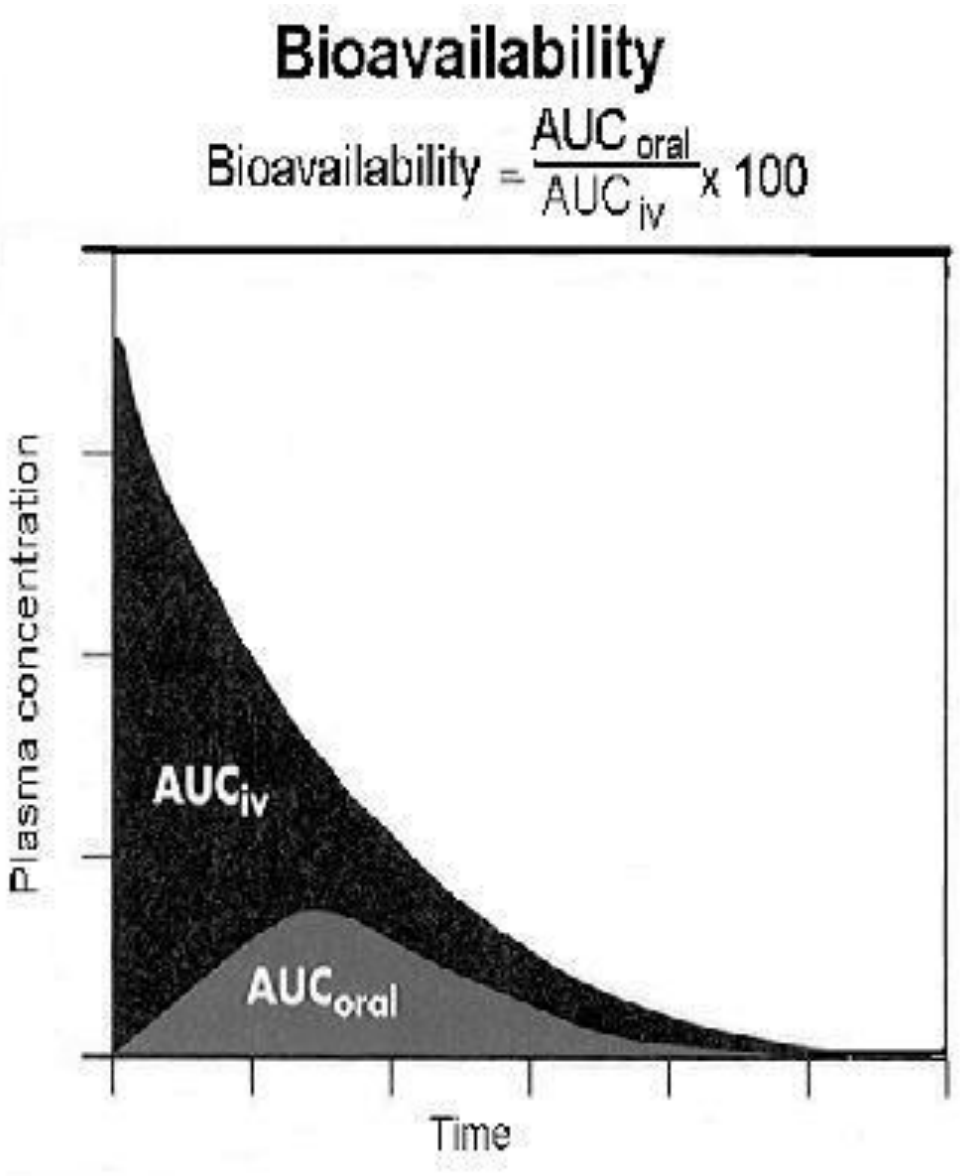
Why do we care about bioavailability?

Answer: the true dose is not the drug swallowed, but is the drug available to exert its effect

One can compare the Bioavailable Fractions of two preparations, or of a single preparation under different conditions, by comparing the **areas under the curve of** plots of plasma drug concentration versus time.

Bioavailability fraction is not the only important parameter of bioavailability; maximal plasma levels or concentrations **(Cmax) can also vary for different pharmaceutical preparations. Cmax** predicts the degree of pharmacological (or toxicological) effect.

Two separate pharmaceutical preparations may contain the same amount of the same compound, but they may not exhibit identical bioavailability and may not yield identical plasma drug concentrations in the same patient.



Bioequivalence:

- “Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same.
- Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards."

Therapeutic bioequivalence:

- When a generic drug is claimed bioequiavalent to a reference drug, it is assumed that they are therapeutically equivalent

Factors affecting bioavailability:

Factors that can affect bioavailability include:

- the size and type of the pill/capsule

Liquids>solids

Solution>suspension>capsule>tablet>coated tablet

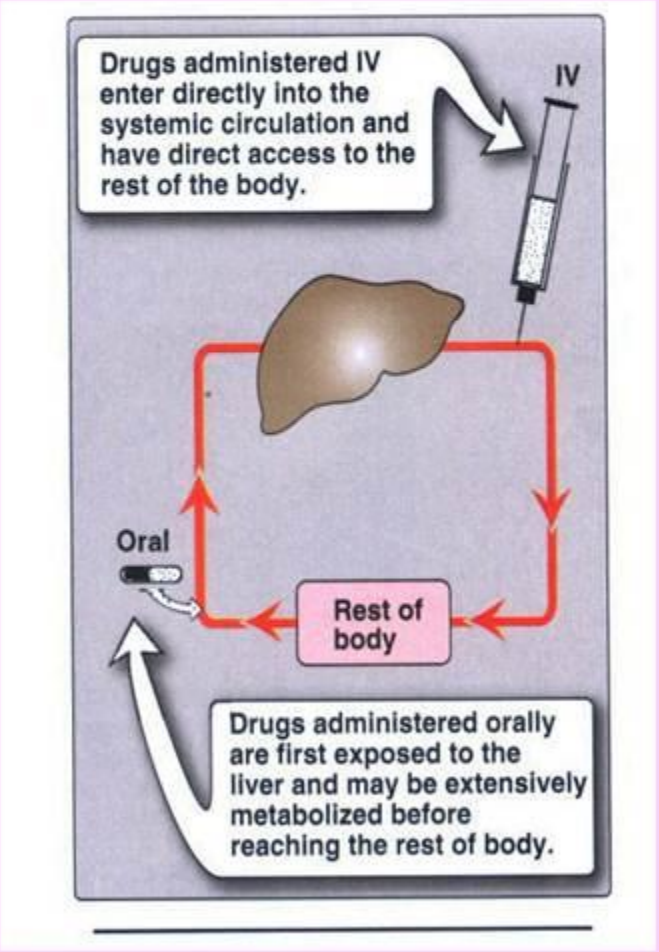
Cyrstalloids>colloids

- the type of inert ingredients included in the preparation
- the crystalline properties
- rates of dissolution of the drug itself
- *first-pass effect*

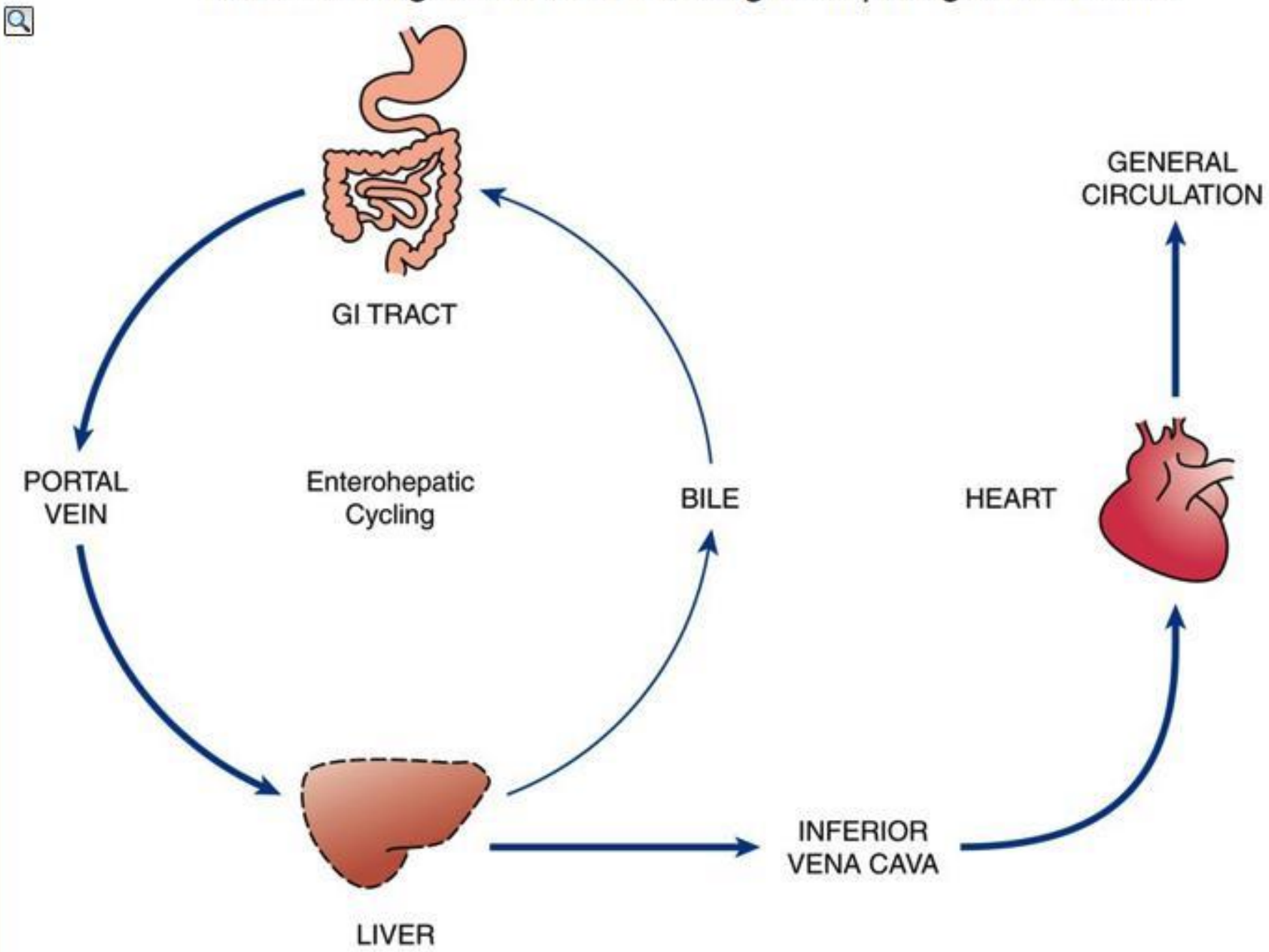
FIRST PASS METABOLISM/ FIRSTPASS EFFECTS/ PRESYSTEMIC METABOLISM

It is the phenomenon of drug metabolism. Where the concentration of a drug is greatly reduced before it reaches the systemic circulation

First Pass Effect may be defined as the loss of drug as it passes through the gastrointestinal membranes and the liver, for the first time, during the absorption process after oral administration. This is also known Pre-Systemic elimination.



limited to drugs that have first undergone hepatic glucuronidation.



- Alternative administration routes like suppository, IV, IM, inhalational aerosol and sublingual avoid the first pass effect because they allow drugs to be adsorbed directly into the systemic circulation

The most common drugs affected by first pass effect:

- Nitroglycerin: 90% of nitroglycerin is cleared during a single passage through the liver, which is the primar reason why this agent is not administered orally.
- Opioids
- Beta blockers
- Nitrates

Why do we care about first-pass effect?

Answer: Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target organ.

Low	Intermediate	High-not given orally	High oral dose
Phenobarbitone	Aspirin	Isoprenaline	Propranolol
Phenylbutazone	Quinidine	Lignocaine	Alprenolol
Tolbutamide	Desipramine	Hydrocortisone	Verapamil
Pindolol	Nortriptyline	Testosterone	Salbutamol

- Usually more lipophilic drugs
- There is huge difference between oral and parenteral dosage
- First pass efect differs between patients so that it is difficult to manage the oral dosage
- While chronical usage, plasma concentration of the drug may be increase
- Combine theraphy of two drugs which are metabolised by the same enzyme system may increase plasma concentration of the drug
- Enterohepatic circulation may increase the time of drug effect

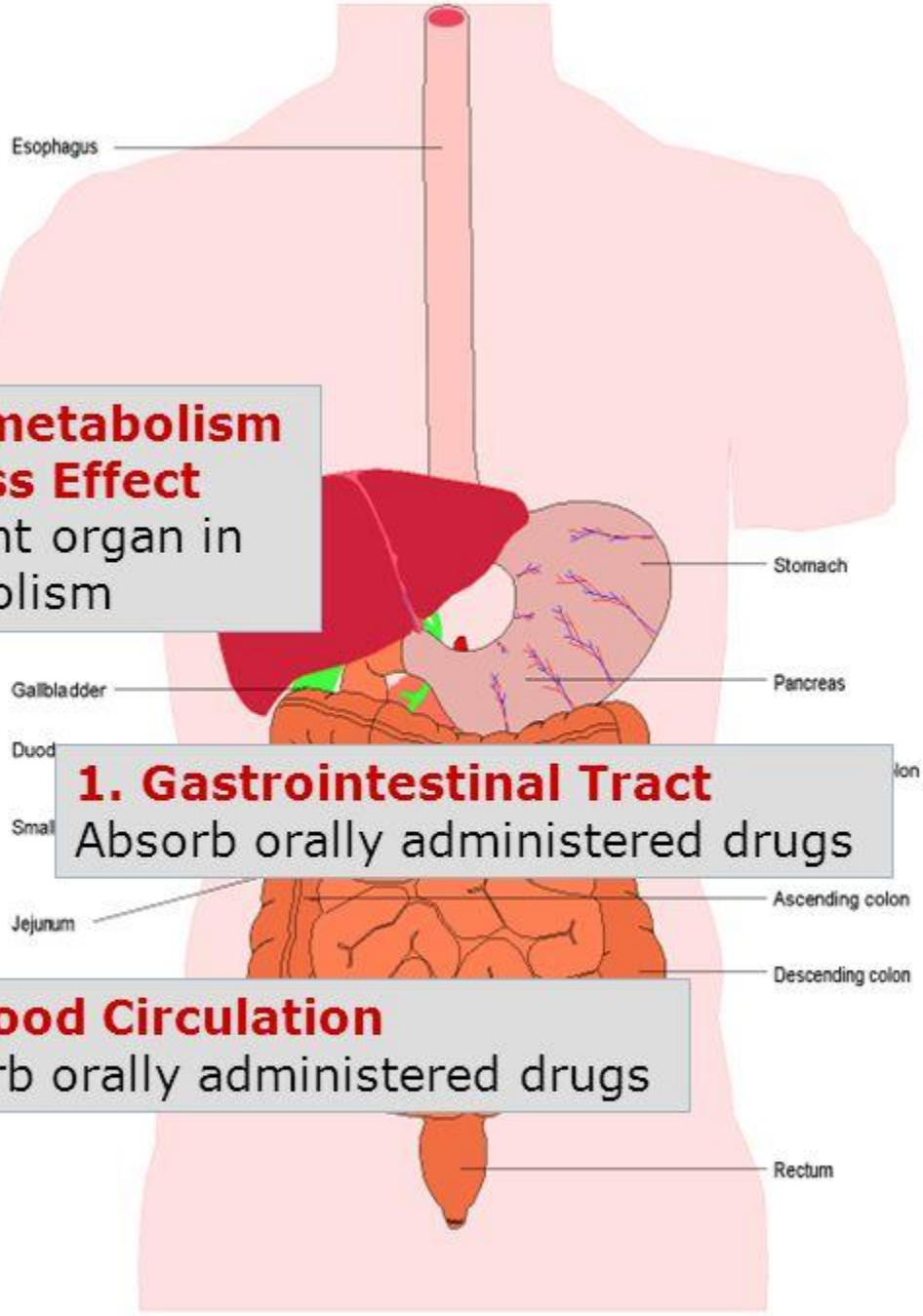
Sites of Drug Biotransformation

2. Liver (hepatic metabolism or First Pass Effect
The most important organ in drug metabolism

Some drugs may decrease Oral bioavailability
Lidocaine (ineffective)
Isoproterenol
Meperidine
Morphine
Nitroglycerin
Pentazocaine
Propoxyphene
Propranolol
salicylamide

1. Gastrointestinal Tract
Absorb orally administered drugs

3. Blood Circulation
Absorb orally administered drugs



DIGESTIVE SYSTEM

DISTRIBUTION

Definition:

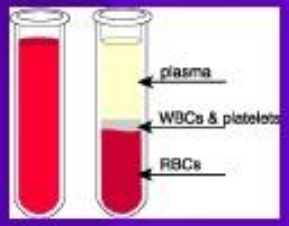
the passage of drugs from blood to tissues

(İlacın geriye dönüşümlü olarak kan dolaşımından hücreler arası alana (hücredışı sıvı) veya hücre içi sıvıya geçmesidir.)

What is blood made of?

Blood is made of four different parts. They are:

PLASMA

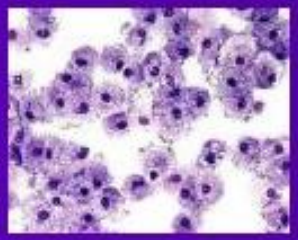


Yellow liquid made of water. It is like a river for the blood cells to float.

RED BLOOD CELLS

Carry oxygen from the air you breathe to all parts of the body.

WHITE BLOOD CELLS

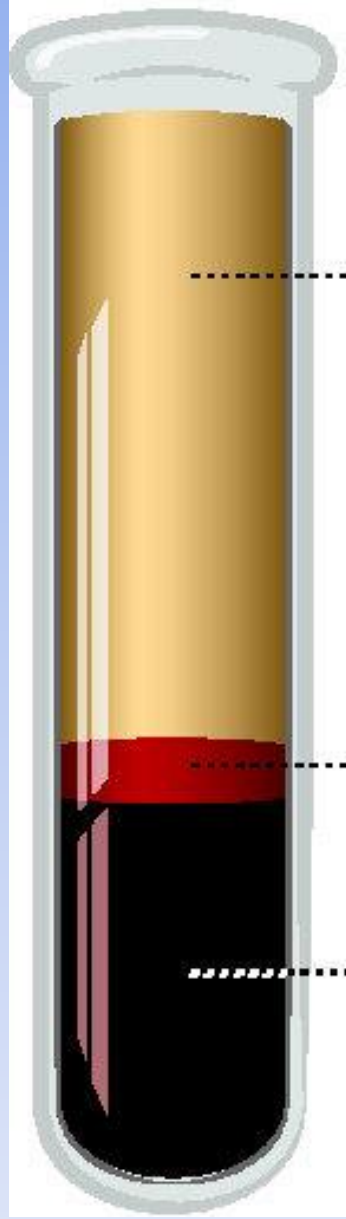


They are the body´s soldiers against disease, they attack germs to protects us.

PLATELETS

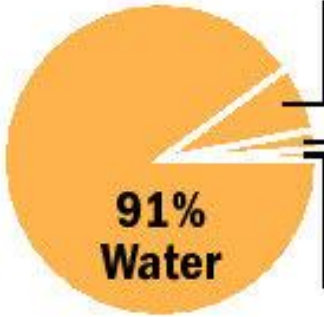
They allow your blood to clot around a cut.

Orthopedic therapy



In platelet-rich plasma therapy, blood is spun in a centrifuge to separate plasma and red blood cells from the white blood cells and platelets that aid in clotting and healing.

PLASMA: 55%



7% blood proteins
Globulin, fibrinogen, albumin

2% nutrients
Amino acids, lipids, sugars

1% hormones, electrolytes

CELLULAR COMPONENTS: 45%

- **White blood cells** defend against infection
- **Platelets** aid in blood-clotting, growth factors
- **Red blood cells** Transport oxygen

Source: National Space Biomedical Research Institute

THE COLUMBUS DISPATCH

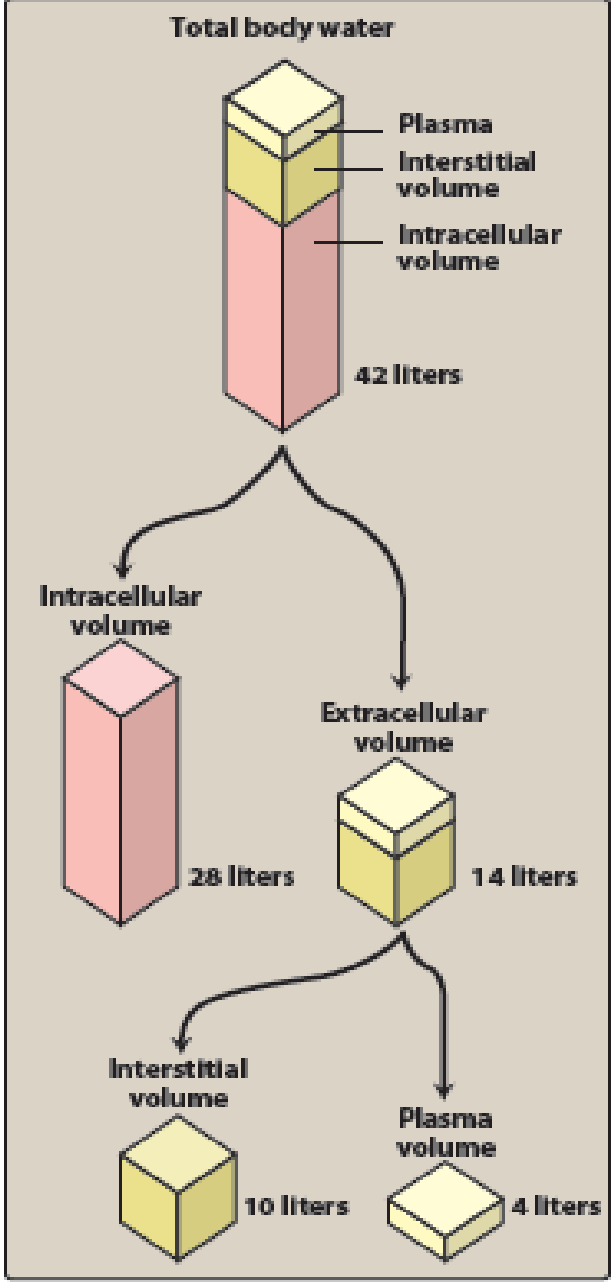


Figure 1.14
Relative size of various distribution volumes within a 70-kg individual.

Factors That Affect the Rate of Drug Distribution:

1. Blood flow

Rapidly perfused tissues respond quickly

- Brain , Liver , Kidney

Less rapidly perfused tissues respond to drug more slowly

- Muscle , Skin

Poorly perfused tissues respond very slowly to drug

- Fat

2. Capillary permeability (differences in capillary structure)

3. Tissue perfussion rate

4. Afinity of the drug to the related tissue (ex.digoxin has greater affinity for protein of cardiac or skeletal muscle than plasma proteins)

5. *Binding to plasma proteins*

Capillary permeability

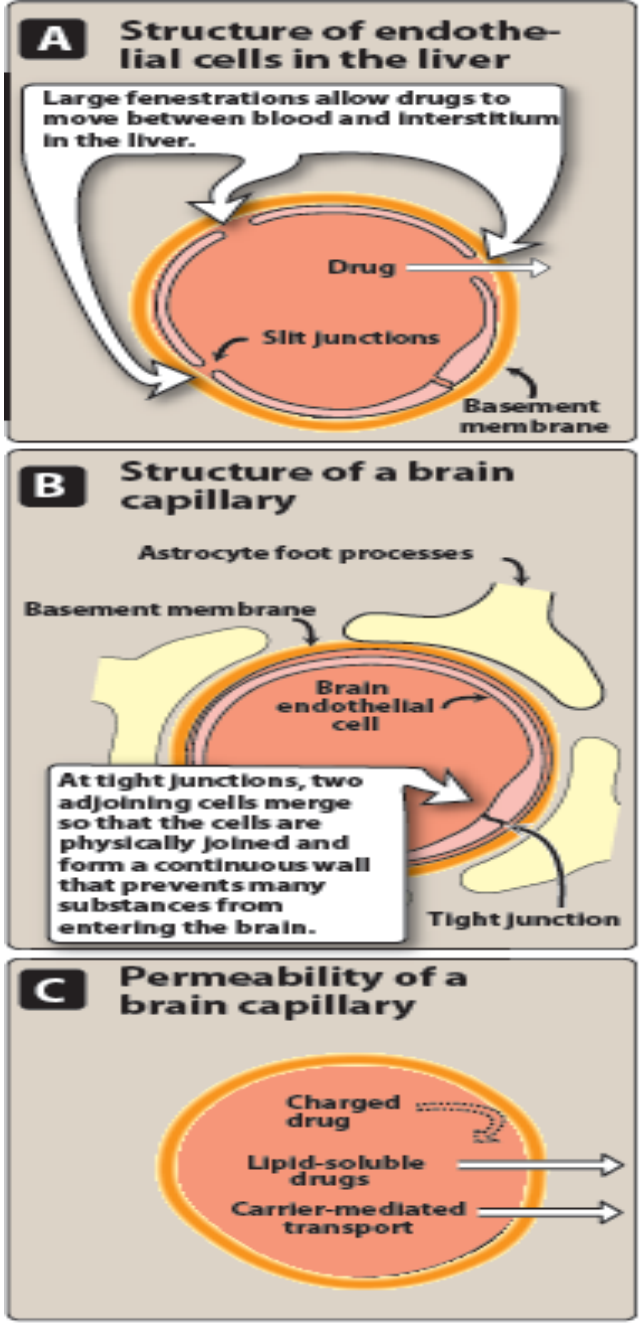


Figure 1.13
Cross section of liver and brain capillaries.

Diffusion speed: If the drug is suitable for passive transport → lipophilic, non-ionized or less ionized and with small molecular weight, it's speed of distribution from blood to tissues is higher.

Physiological components that drugs distribute in:

- Plasma (approximately half of the total blood volume)
- Interstitial fluid (between cells) *(BOS ve diğer vücut boşluklarındaki sıvılar)*
- Intracelular fluid (inside the cell)

**But, the drug molecules may not distribute homogenously because of protein binding potential.

**Few of them distribute in only plasma compartment as drugs that have high molecular weight=polisaccharides (dextran and heparin)

**In the other hand, as alcohol and urea, small non-ionized drugs distribute without binding plasma proteins easily and homogenously.

Plasma protein binding 1:

- Many drugs interact with plasma or tissue proteins or with other macromolecules to form a drug-macromolecule complex. The formation of drug protein complex is named drug-protein binding
- The concentration of drug at target organ should be measured through plasma concentration. So the effect of the drug may be estimated at target organ.
- Binding is a very important effect on drug dynamics since only free (unbound) drug interacts with receptors

Plasma protein binding 2:

The proteins commonly involved in binding with drugs are;

- **Albumin** – acidic and neutral compounds tend to bind

- Lipoproteins
- Alpha-1 glycoprotein-basic compounds tend to bind

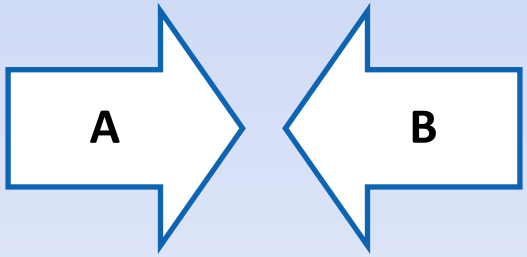
- ❖ The bound drug is kept in the blood stream while unbound component may be metabolised or excreted, making it active part.
- ❖ So, if a drug is 95% bound to a binding protein and 5% is free, that means 5% is active in the system and causing pharmacological effects

Plasma protein binding 3:

- Drug protein binding may be reversible or irreversible
- Irreversible drug-protein binding is usually a result of chemical activation of the drug which then attaches strongly to the protein or macromolecule by covalent chemical bounding
- Irreversible drug binding accounts for certain types of drug toxicity that may occur over a long term period. For ex., hepatotoxicity of high doses of acetaminophen is due to the formation of reactive metabolite intermediates that interact with liver proteins.
- Reversible drug-protein binding implies that the drug binds the protein with weaker chemial bonds, such as hydrogen bonds or vander Waals forces.

If two drugs together ?

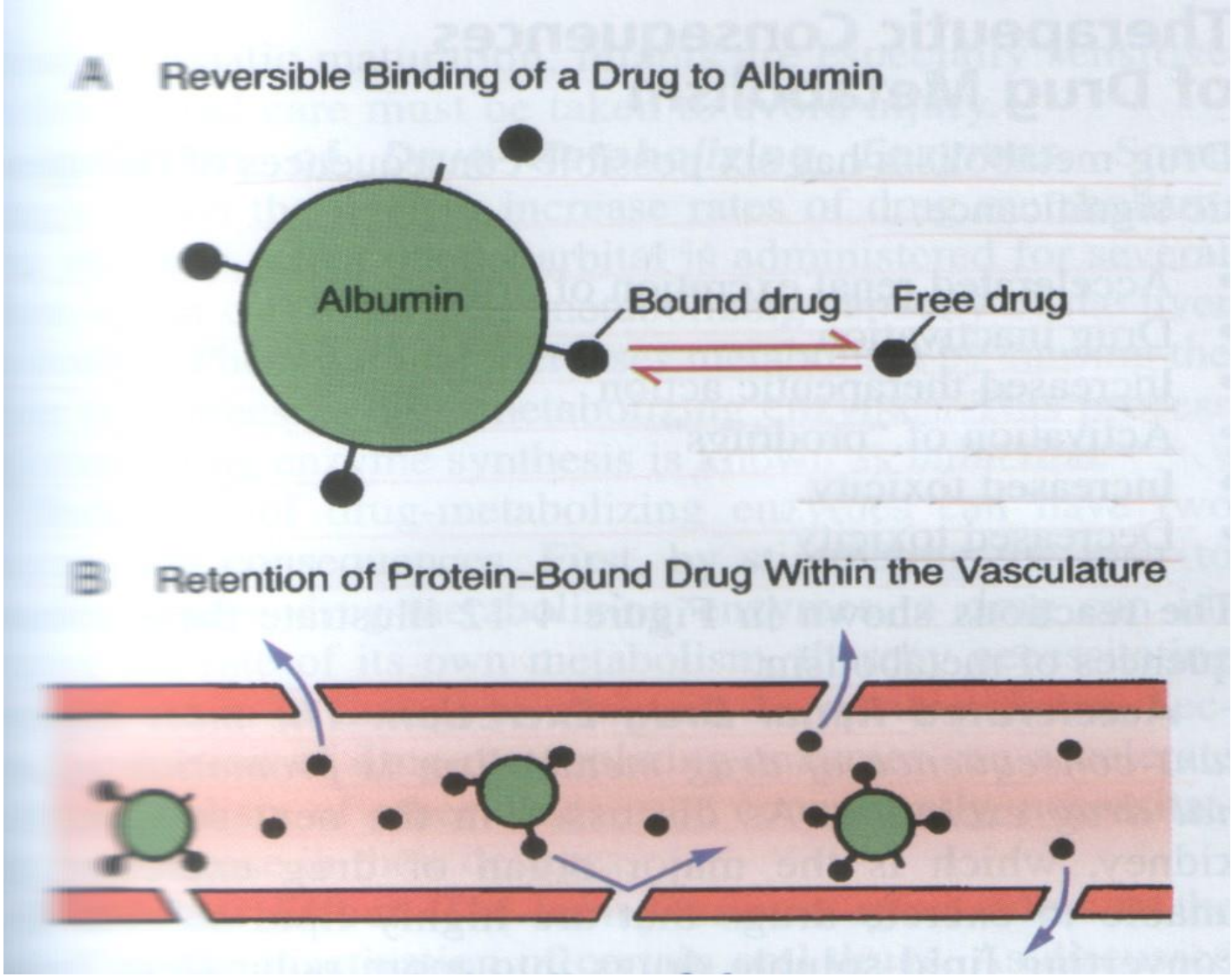
- Using two drugs at the same time may effect eash other's fraction bound
- For ex., drug A and drug B are both protein bound drugs. If A is given, it will bind to plasma proteins in the blood
- If B is also given, it can displace A from protein, thereby increasing A's fraction unbound. This may increase the effects of A since only the unbound fraction may exhibit activity.



Relationship between protein concentration and drug concentration

- If the protein binding is reversible there is a chemical equilibrum existing between bound and unbound states:

- At low drug concentrations, most of the drug may be bound to the protein
- Whereas at high concentrations, the protein-binding sites may become saturated, with a consequent rapid increase in the free drug concentrations



When the free drug concentration decreases, the bound drugs become free and maintains the equilibrum. Bound drugs remain as reservoir of drugs. It affects the drug action time.

Common drugs which bind to proteins

To albumin

- Dicoumarol
- Warfarin
- Fenilbutazone
- Sulphonamides
- Tolbutamide
- Furosemide
- Digitoxin
- Diazepam
- Phenitoin
- Aspirin
- Salicylates

To alpha-1 glycoprotein

- Dipiridamol
- Quinidine
- Imipramine
- Propranolol
- Lidocaine

In disease states:

Albumin

- **<u>Hipoalbuminemia:</u>** In chronical liver disease (cirrhrosis), chronical renal failure and severe malabsorption, hipoalbuminemia occurs or the albumin binding system may be damaged. So, in acute therapy, drug dosage should be reduced. But, during chronical drug therapy, when hipoalbuminemia occurs slowly that the elimination phase of the drug differs so that it may not be neccecary to change the dosage.

Alpha-1 glycoprotein

- The amount of this protein increases in Infection, severe inflamation (romatoid arthritis, ulcerative colitis, crhon's disease), burn, myocardial infarction, cancer, trauma and organ transplantation.

If not;

- If the drugs did not bind to plasma proteins, time of their existence in the body, so the time of their existence at target organ and time of their effect would be so short. For continuing their effects, they had to be given more often.

Tissue binding

- Certain drugs may also be stored in the body tissues. This is called sequestration. It maintains the drugs distribute into the tissues not equally.
- The tissue storage may have a role as reservoir, so that therapeutical and adverse effects may be prolonged.

Tissue storage

Drugs may also accumulate in specific organs or get bound to specific tissue constituents, e.g.:

- **Heart and skeletal muscles** – digoxin (to muscle proteins)
- **Liver** – chloroquine, tetracyclines, digoxin
- **Kidney** – digoxin, chloroquine
- **Thyroid gland** – iodine
- **Brain** – chlorpromazine, isoniazid, acetazolamide
- **Retina** – chloroquine (to nucleoproteins)
- **Iris** – ephedrine, atropine (to melanin)
- **Bones and teeth** – tetracyclines, heavy metals (to mucopolysaccharide of connective tissue)
- **Adipose tissues** – thiopental, ether, minocycline, DDT

Redistribution

- Highly lipid soluble drugs when given by iv or by inhalation initially get distributed to organs with high blood flow, ex. Brain, liver, heart, kidney etc.
- If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of the drug action
- Later,less vascular but more bulky tissues (fat, muscle) take up the drug and plasma concentration falls and drug is withdrawn from these sites
- Greater lipid solubility of the drug, faster is its redistribution.

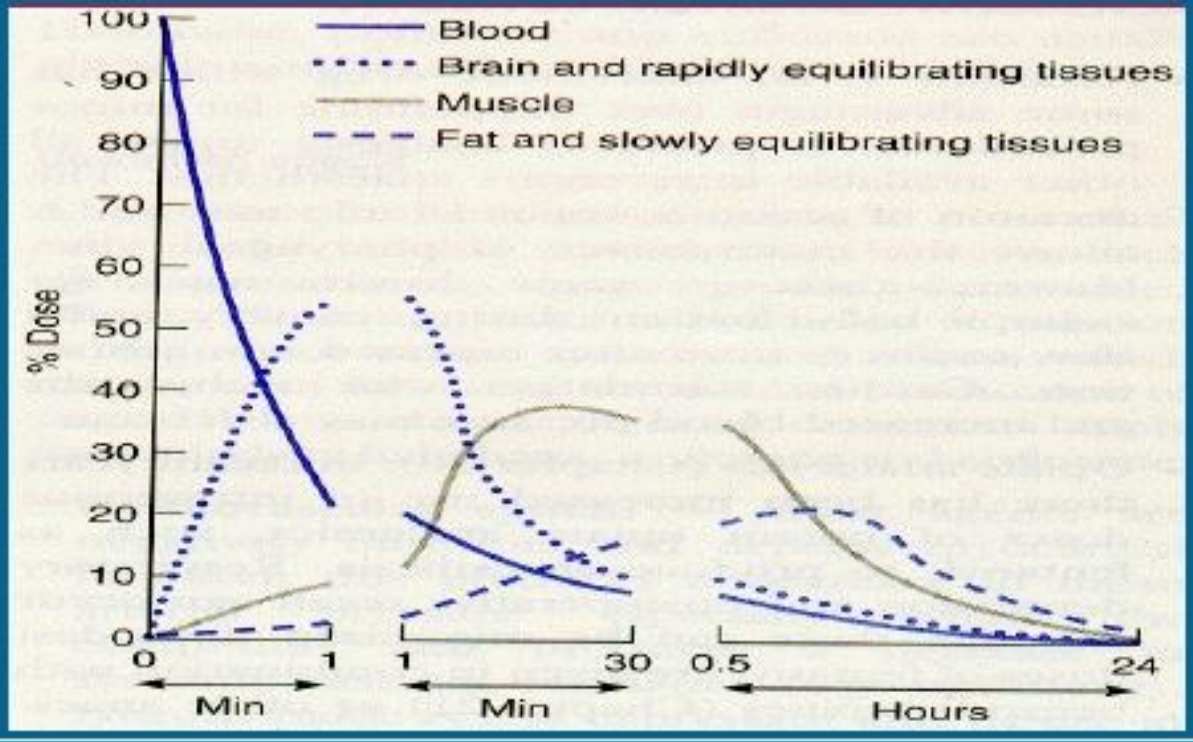
  Ex. Thiopental sodium, general anesthetics, gases

When thiopental is given by iv, in the first several minutes it distributes in brain which is rich with lipophilic parts. After 3 hours, approximately 70% of drug in the body has been transfered to fat tissue, this drug can be also transfered into skeletal muscle

- So; redistribution maintances the drugs to get far from the target place in a short period of time and finishes the effect of the drug quickly. Redistribution is one of the mechanisms that ends the drug effect as metabolism or excretion.

Redistribution

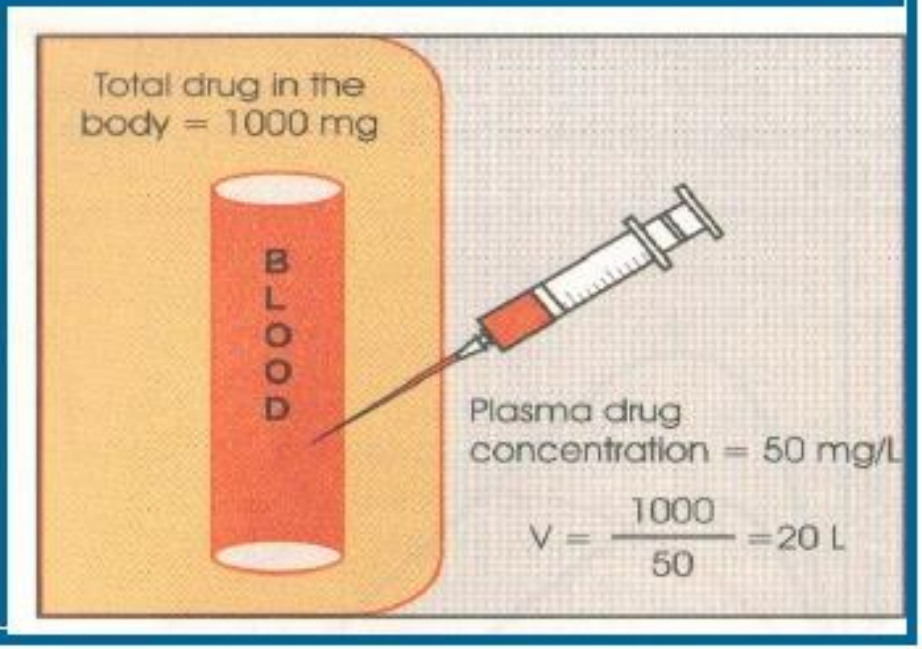
- Highly lipid soluble drugs – distribute to brain, heart and kidney etc. immediately followed by muscle and Fats



Volume of Distribution (V)

- Definition: Apparent Volume of distribution is defined as the volume that would accommodate all the drugs in the body, if the concentration was the same as in plasma
- Expressed as: in Liters

$$V = \frac{\text{Dose administered IV}}{\text{Plasma concentration}}$$



Volume of Distribution (Liter):

Expressed as liters of body water in a 70 (154 lb) Kg man.

Vd = amount of drug in body (g)
unbound plasma drug concentration (g/liter)

Calculate Vd when 1 g is administered iv and the plasma drug level is 0.024 g/L.
Vd = 1 g/.024 g/L = 42 L **(Total Body Water)**

(Sanal dağılım hacmi
V_d=Vücuttaki ilaç miktarı/C
Sanal dağılım hacmi ilacın ne oranda dokulara dağıldığının bir göstergesidir.
Sanal dağılım hacmi i.v ilaç uygulamasından sonra plazma konsantrasyonunu tayin etmek için kullanılabilir.
C=i.v dose/V_d

Tersine plazmada istenen konsantrasyon biliniyorsa verilecek doz tayin edilebilinir.)

The benefits of Vd

1) To measure the drug amount at time of plasma concentration or vice versa, if the amount is known, to measure plasma concentration
2) To be sure about the concentration of drug must be given to get a recommended plasma concentration
3) According to total clearence, to measure the elimination rate *(clearance will be explained in further studies)*

***When Vd is very high, it usually means (not always) that big part of the body has been effected by the drug or selective part of the body has been effected by the drug. The high Vd also shows a long duration of drug action.**

Why is Vd important?

- The apparent Vd reflects a balance between binding to tissues which decreases plasma concentration and makes the apparent volume lager, and binding to plasma proteins which increases plasma concentration and makes the apparent volume smaller. Changes in either tissue or plasma binding can change the apparent Vd determined from plasma concentration measurements. Older people have a relative decrease in skeletal muscle mass and tend to have a smaller apparent Vd of digoxin (which binds to muscle proteins). Vd may be overestimated in obese patients if based on body weight and the drug does not enter fatty tissues well, is the case with digoxin. In contrast; theophyline has a Vd similar to that of total body water. Adipose tissue has almost as much water in it as other tissues, so that the apparent total Vd of thephyline is proportional to body weight even in obese patients.

- Abnormal accumulation of fluid-edema,ascites,pleural effusion-can markedly increase the Vd of drugs such as gentamicin that are hydrophylic and have small Vd.

Vd of heparin 4 L means?

- It means heparin distributes about 4 liters of the body fluid
- So it remains just in blood

Because;

Heparin has very large molecular weight

Extensive plasma protein binding

Vd of aminoglycosides 14 liter means?

- It has a low molecular weight but is hydrophylic
- So it can move through the endothelial gap junctions of the capillaries into the interstitial fluid
- It distributes into (plasma water+instertitial fluid)=extracellular fluid (14 liters)

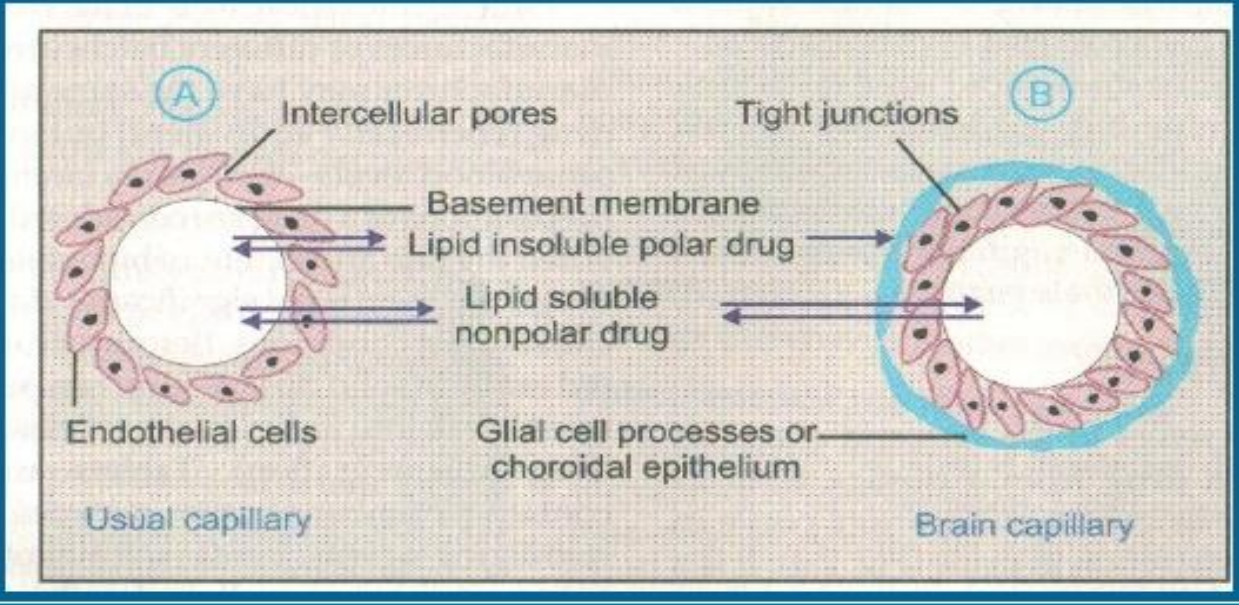
Why ethanol has high Vd=60% total body water 42 L?

- Ethanol is a drug has a low molecular weight and is hydrophobic, so it can move into the plasma+insterstitial fluid+cell

Brain and cerebrospinal fluid penetration:

Brain and CSF Penetration

Blood brain barrier (BBB): includes the capillary endothelial cells (which have tight junctions and lack large intracellular pores) and an investment of glial tissue, over the capillaries. A similar barrier is loctated in the choroid plexus



Brain and CSF Penetration – contd.

- BBB is lipoidal and limits the entry of non-lipid soluble drugs (amikacin, gentamicin, neostigmine etc.).

(Only lipid soluble unionized drugs penetrate and have action on the CNS)

- Efflux carriers like P-gp (glycoprotein) present in brain capillary endothelial cell (also in intestinal mucosal, renal tubular, hepatic canicular, placental and testicular cells) extrude drugs that enter brain by other processes.

(Inflammation of meanings of brain increases permeability of BBB)

- Dopamine (DA) does not enter brain, but its precursor levodopa does. This is used latter in parkinsonism.

Transfer from placenta to fetus:

- Placenta is the membrane seperating fetal blood from the maternal blood
- Passive diffusion is mostly used by lipophilic and non-ionized drugs to enter into fetus easily. Barbiturates, anesthetics and morphine can pass through placenta easily.
- Teratogenicity is important.

Placental Transfer

- Only lipid soluble Drugs can penetrate – limitation of hydrophillic drugs
- Placental P-gp serves as limiting factor
- But, REMEMBER, its an **incomplete barrier** – some influx transporters operate
- Thalidomide

KEEP
CALM
AND
HAVE A
NICE DAY