السلام عليكم ورحمة الله وبركاته

Al-Mustaqbal University College

Pharmacology I 3rd stage

Introduction & Pharmacokinetics

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INTRODUCTION TO PHARMACOLOGY

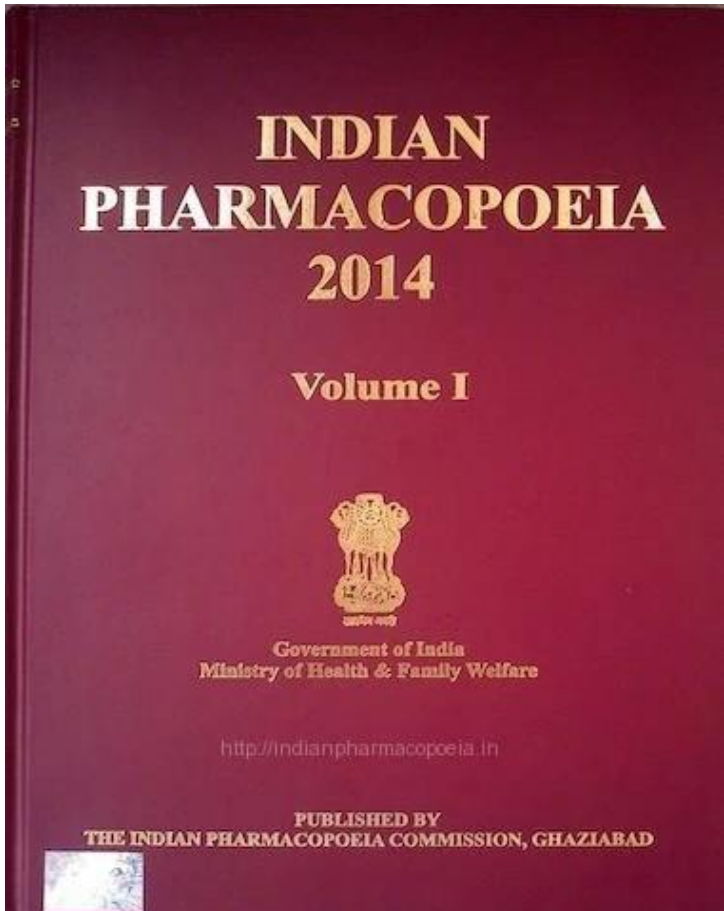
- **Pharmacology:** It is the science of drugs derived from two Greek words: Pharmakon (Greek word for drugs) and logos (the Greek word for science). It is the study of the actions of drugs on living system.

Drug

- Any chemical that affects the processes of a living organism

Pharmacopeia: is a book which contains a list of established and officially approved drug with description of their physical and chemical characteristics and tests for their identification, purity, methods of storage etc.
some of the pharmacopeia's are:

- Indian Pharmacopeia.(I.P.)
- British Pharmacopeia (B.P.)
- European Pharmacopeia.(E.P)
- United states Pharmacopeia.(U.S.P).



Basics of Drug Action

- **Desired action** – the expected response of a medication.
- **Side effects** –known and frequently experienced, expected reaction to drug.
- **Adverse reaction** –unexpected, unpredictable reactions that are not related to usual effects of a normal dose of the drug.

Drug Interaction

• Takes place when one drug alters the action of another drug.

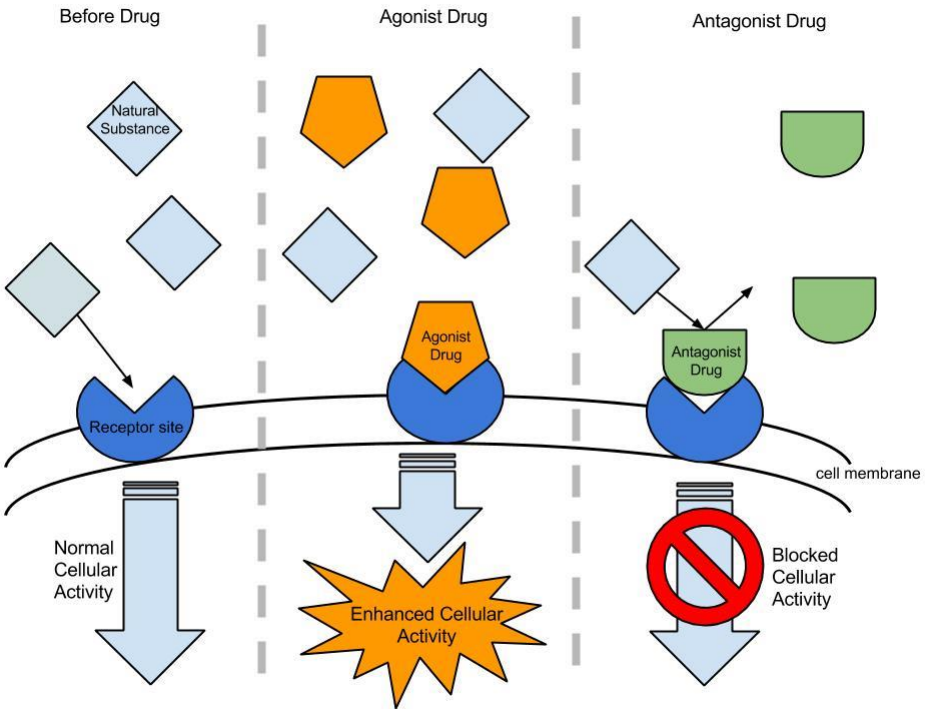
• Some are helpful but often produce adverse effects.

Additive effect- takes place when 2 drugs are given together & double the effect is produced.

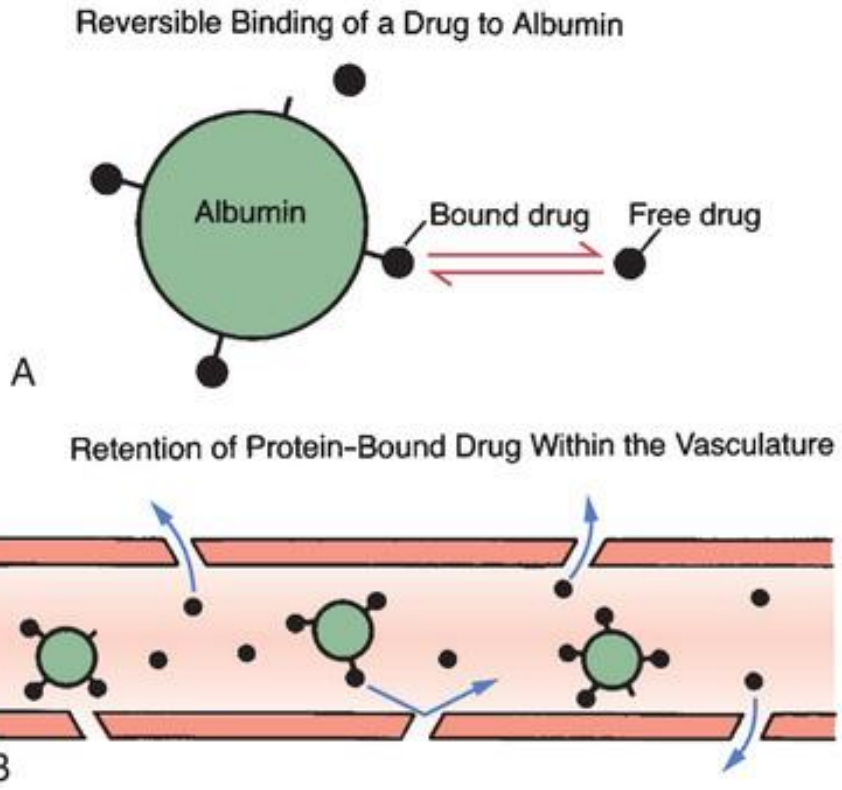
Alcohol + aspirin= Pain relief

- **Antagonist-** a chemical blocks another chemical from getting to a receptor

- **Antagonistic effect-** takes place when 1 drug interferes with the action of another drug.
- Eg. Protamine sulpha to counteract heparin toxicity

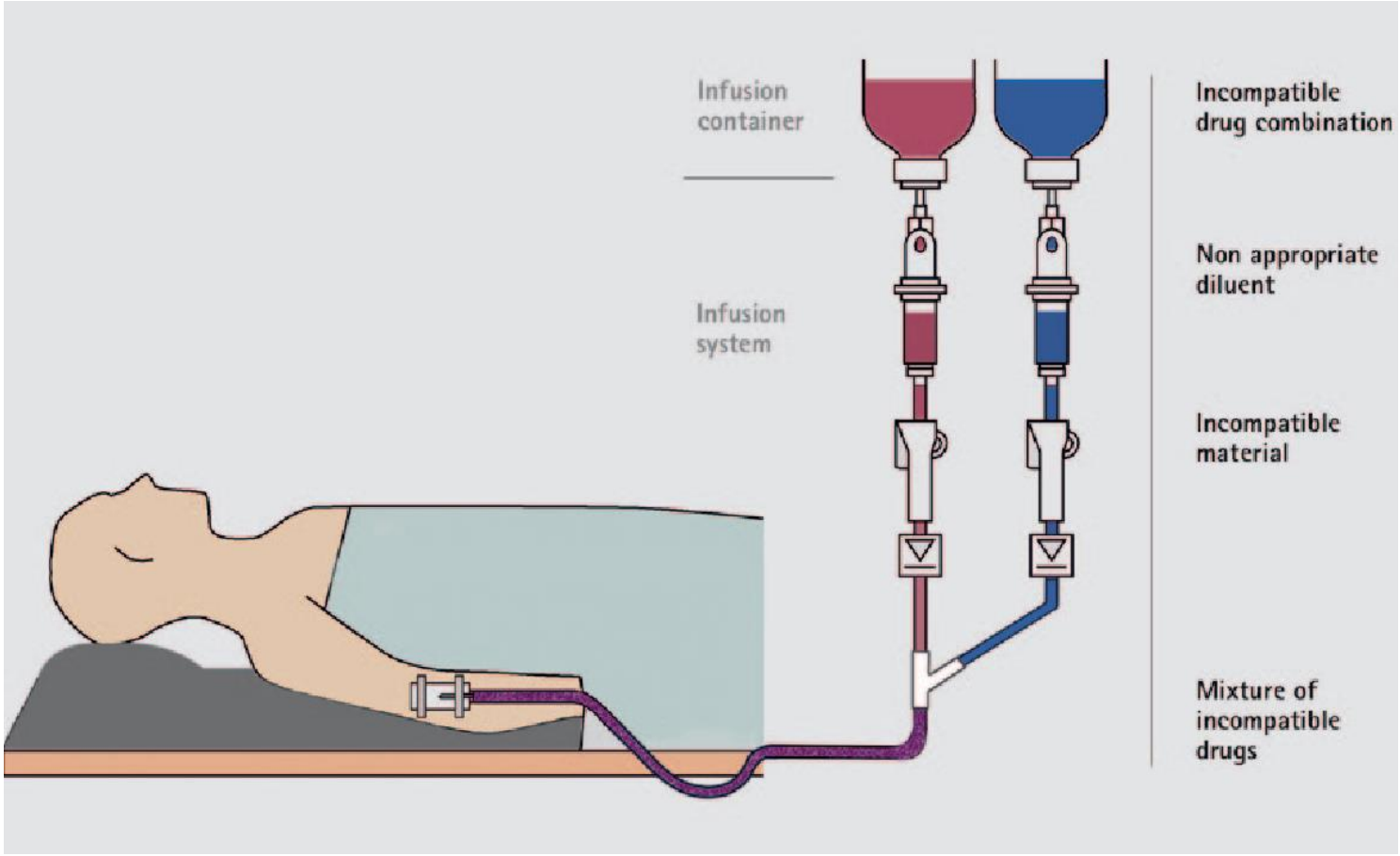


Displacement effect - takes place when 1 drug replaces another at the drug binding site, increasing the effect of the 1st drug.



- **Incompatibility** –occurs when 2 drugs mixed together in a syringe produce a chemical reaction so they cannot be given.

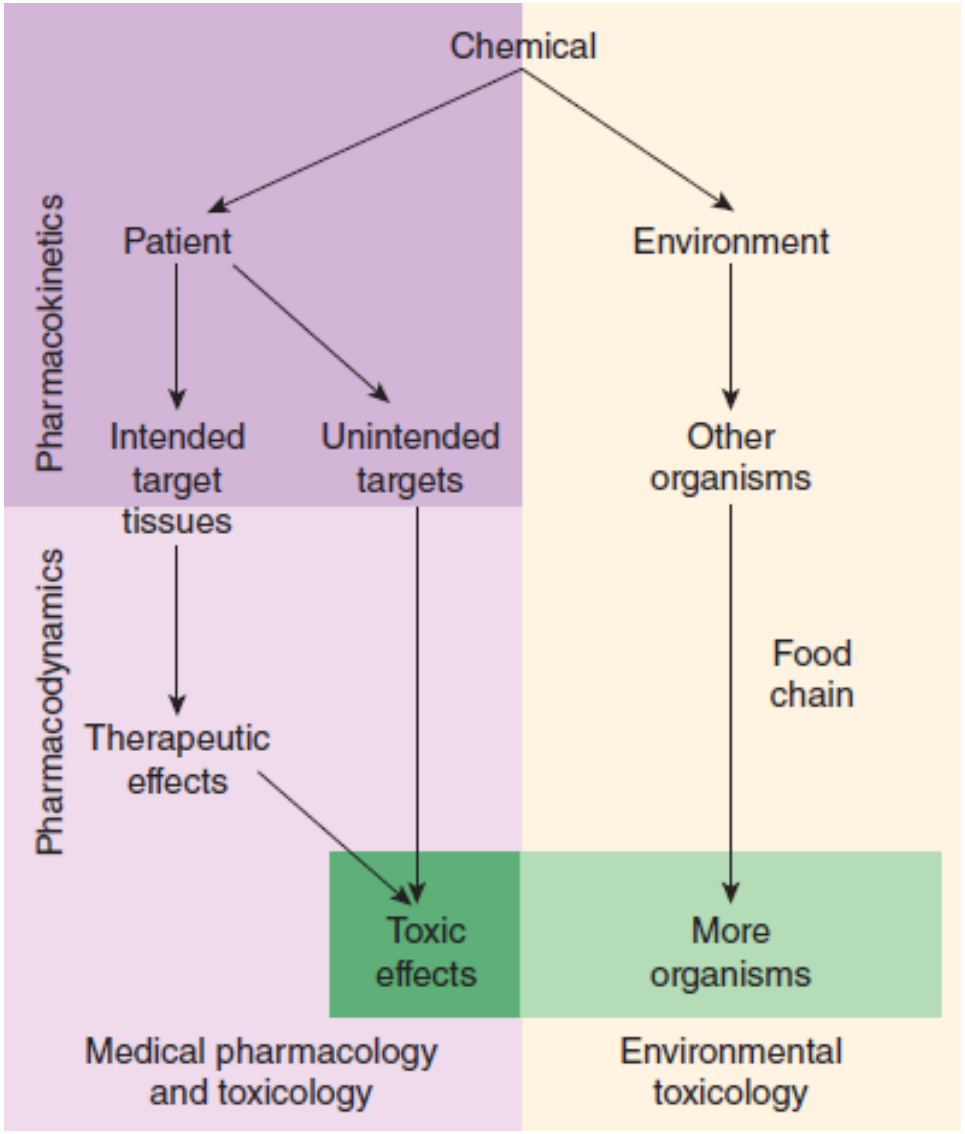
e.g. Protamine sulfate & vitamin K



Interference- occurs when 1 drug promotes the rapid excretion of another, thus reducing the activity of the 1st.

• **Synergistic effect** takes place when the effect of 2 drugs taken at the same time is greater than the sum of each drug given alone.

E.g. combining diuretics & adrenergic blockers to lower the BP

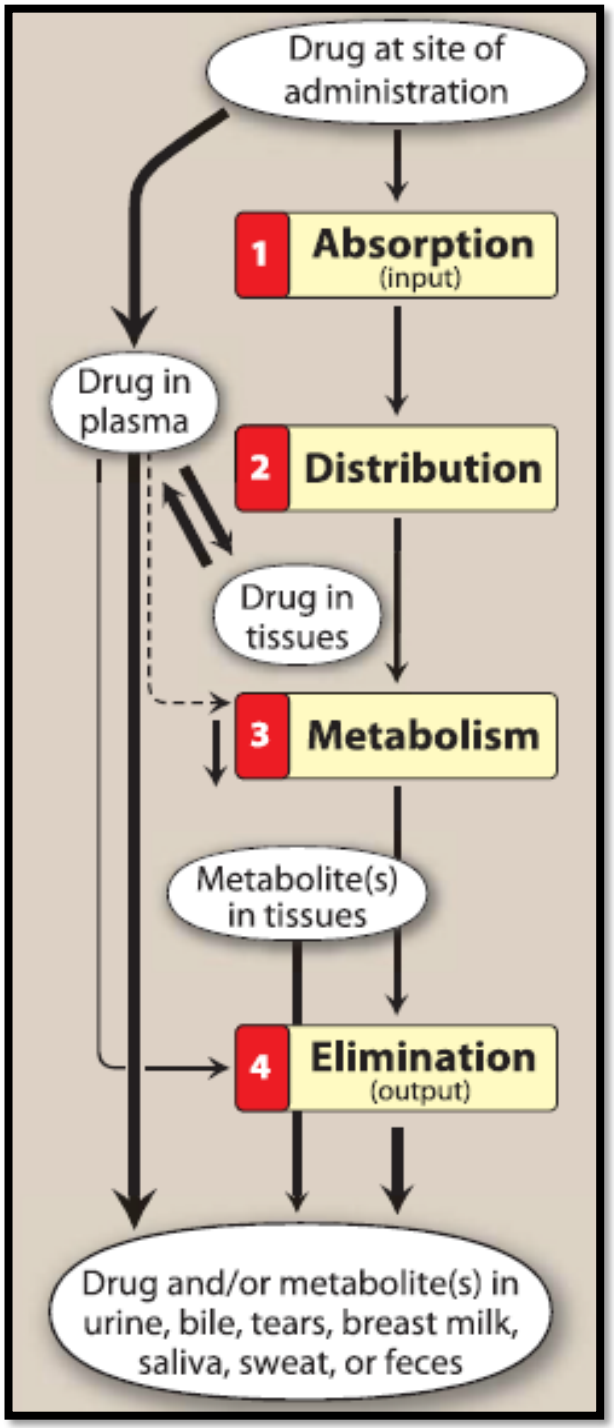

Chemical
Patient
Environment
Pharmacokinetics
Intended target tissues
Unintended targets
Other organisms
Pharmacodynamics
Food chain
Therapeutic effects
Toxic effects
More organisms
Medical pharmacology and toxicology
Environmental toxicology

Pharmacokinetics:

Pharmacokinetics:

refers to what the body does to a drug.

Four pharmacokinetic properties determine the onset, intensity, and duration of drug action



Absorption: First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

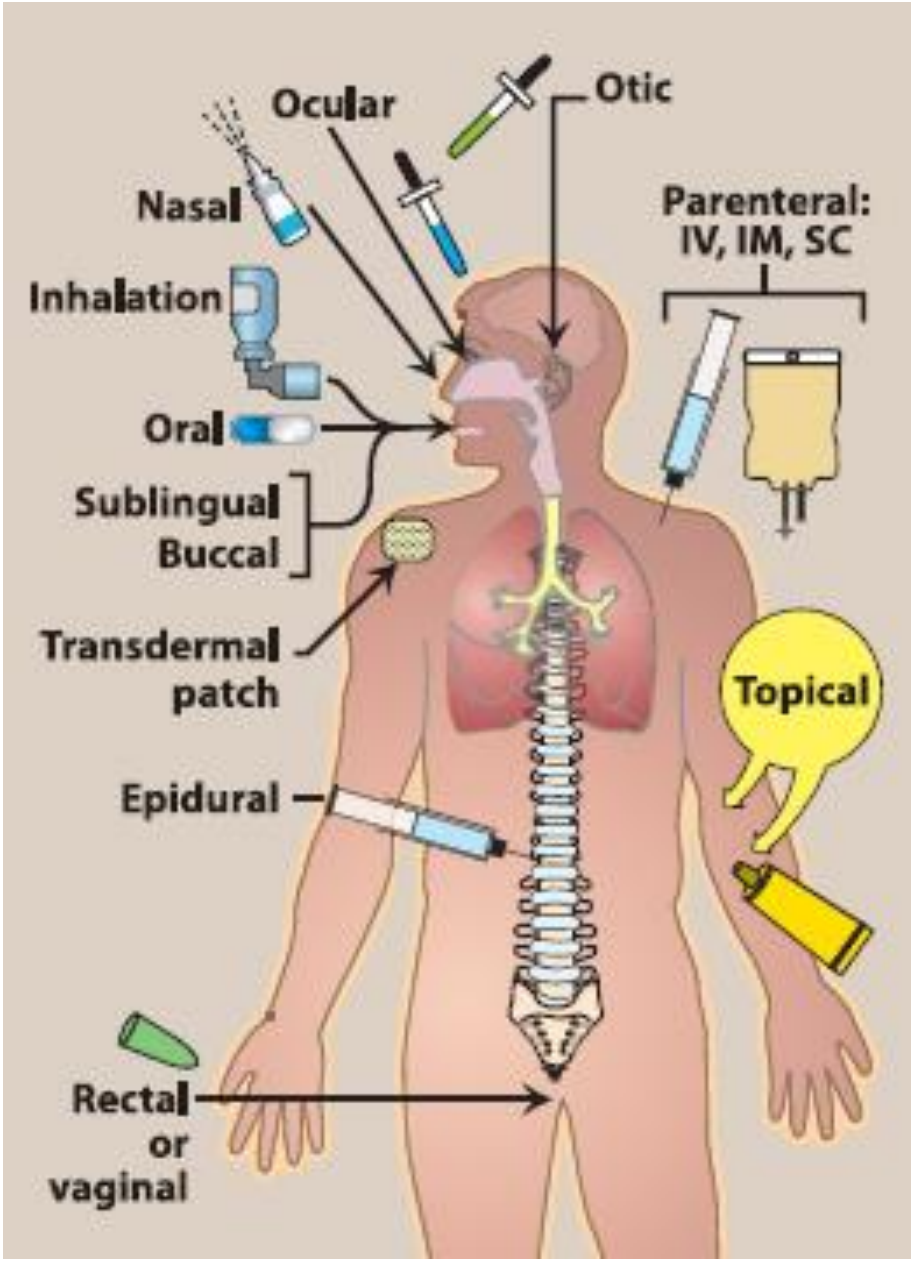
• Distribution: Second, the drug may reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

• Metabolism: Third, the drug may be biotransformed through metabolism by the liver or other tissues.

• Elimination: Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

ROUTES OF DRUG ADMINISTRATION

The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical



1- Enteral

Enteral administration (administering a drug by mouth) is the most common, convenient, and economical method of drug administration.

The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual) or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

2-Parenteral

The parenteral route introduces drugs directly into the systemic circulation.

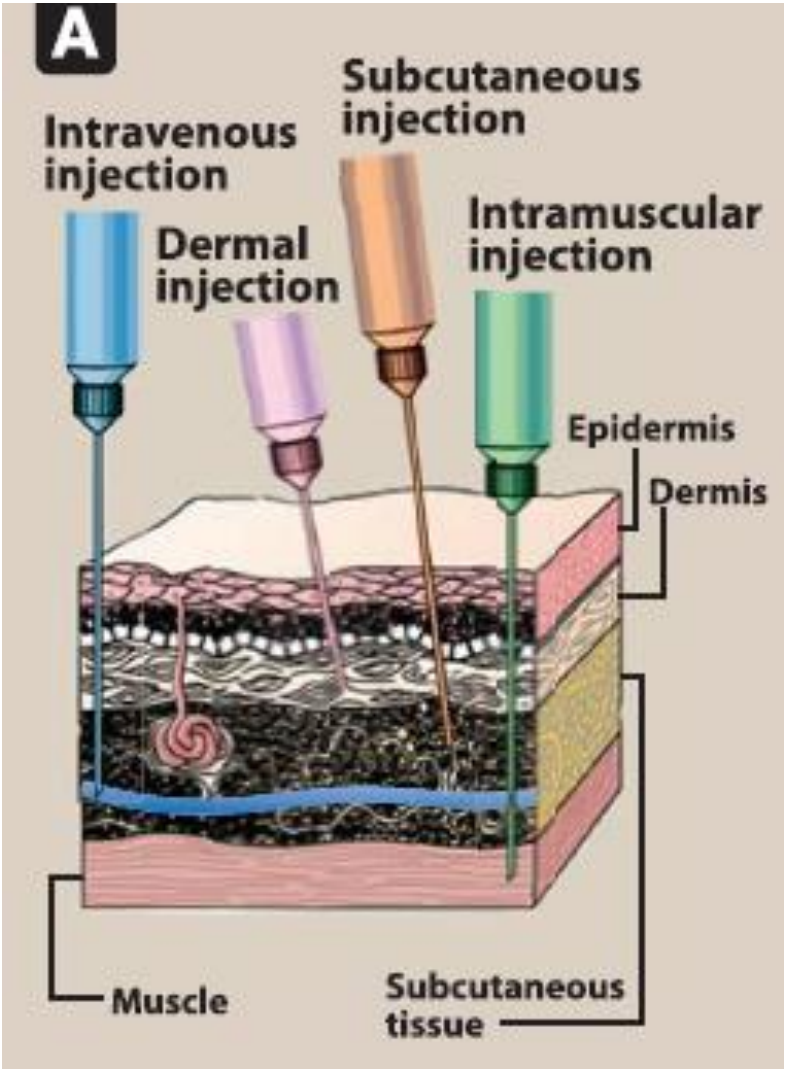
Parenteral administration is used for

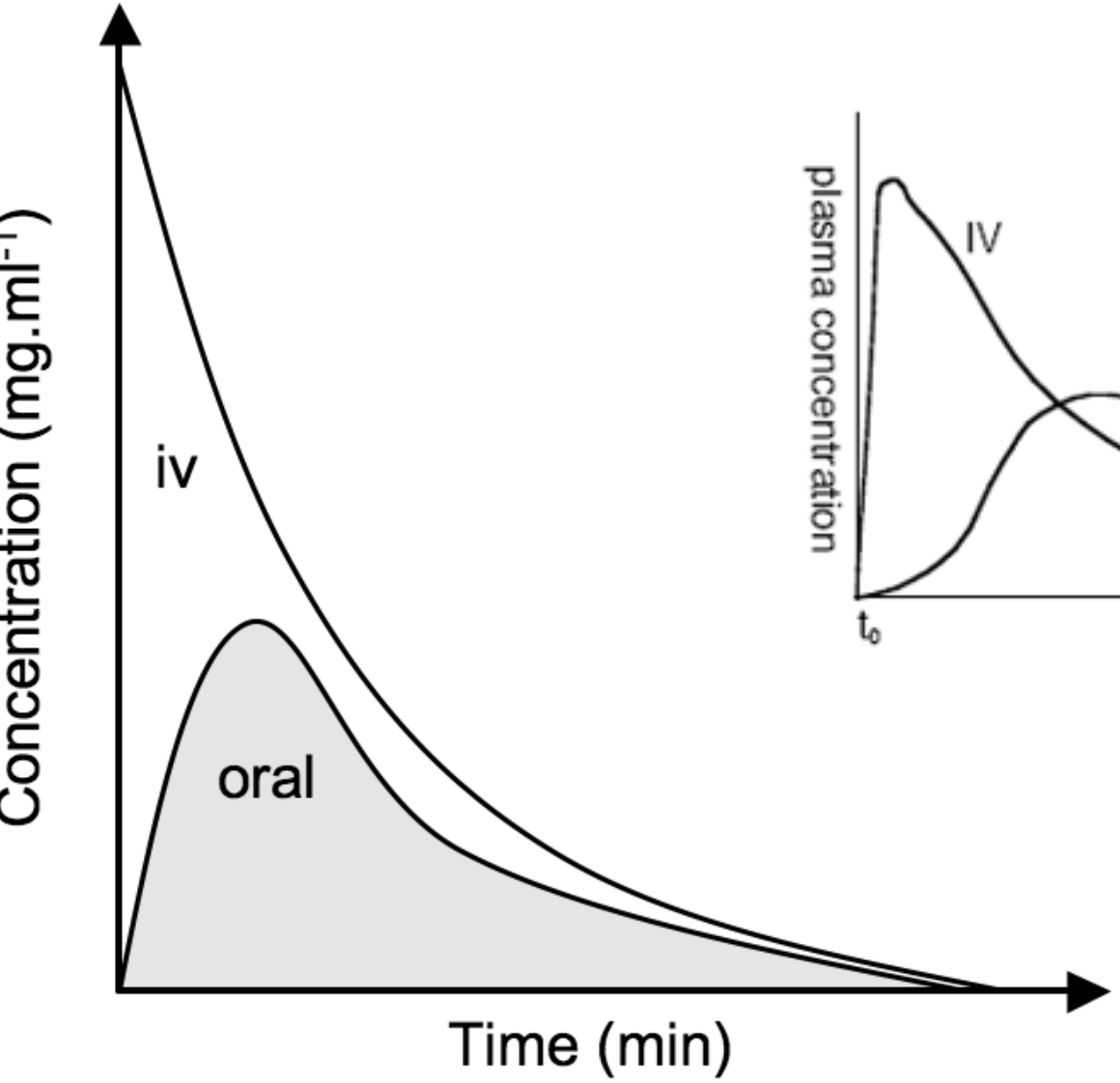
- drugs that are poorly absorbed from the Gl tract (for example, heparin) .
- or unstable in the Gl tract (for example, insulin).
- also used for patients unable to take oral medications (unconscious patients)
- and in circumstances that require a rapid onset of action.

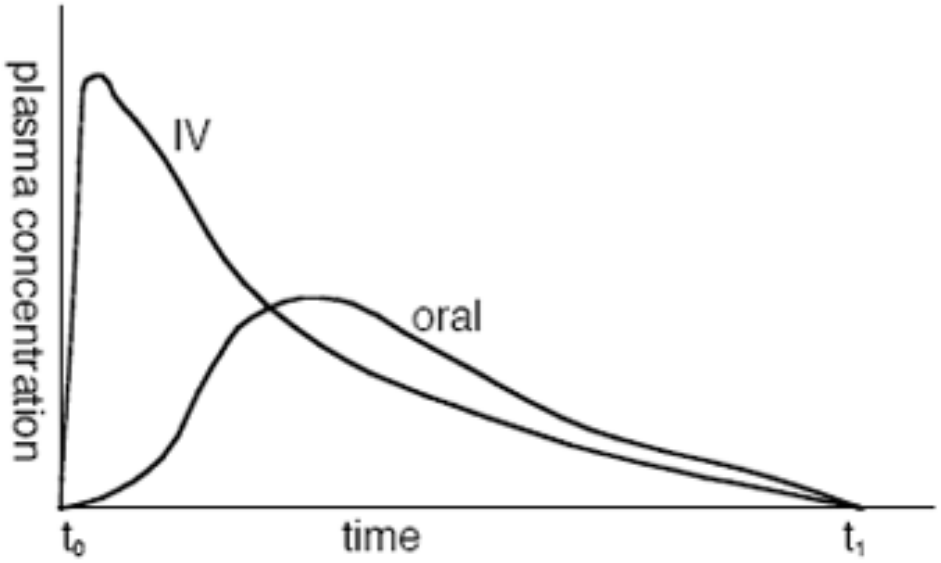
Intravenous (IV): delivered straight to bloodstream.

IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered.

Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly.







Plasma Concentration-Time Curve

Subcutaneous (SC): Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route.

Intradermal: The intradermal (I D) route involves injection into the dermis, the more vascular layer of skin under the epidermis.

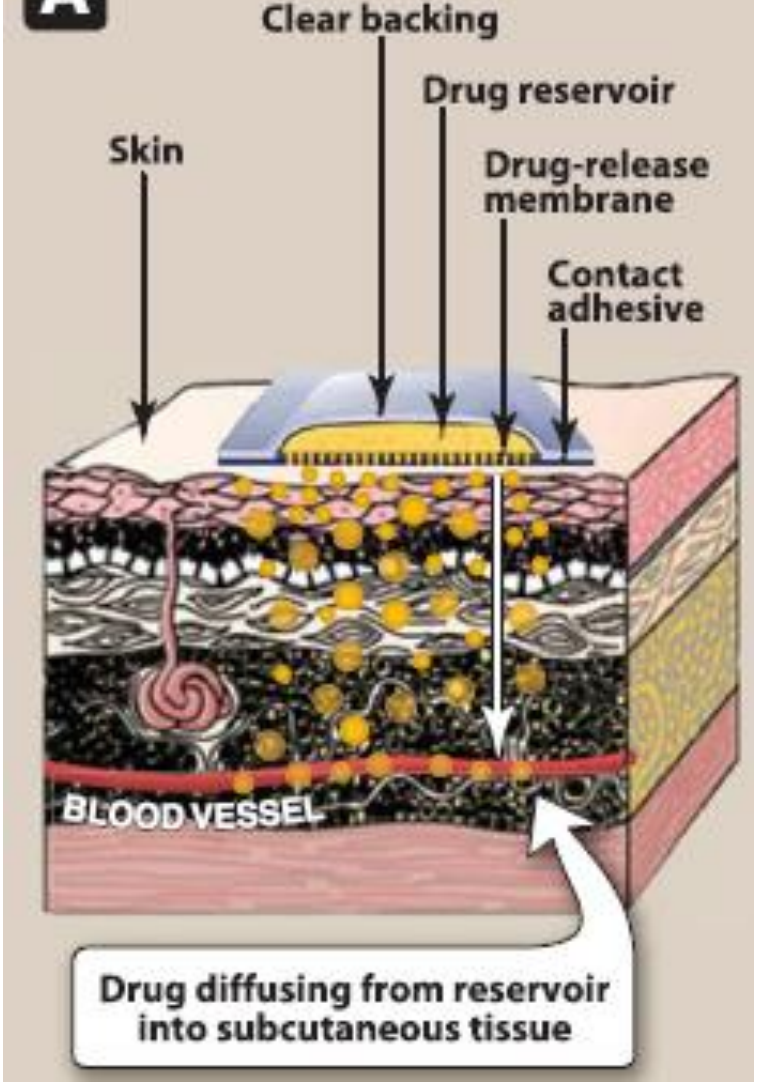
Other

1. Oral inhalation and nasal preparations: Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium.

2. Intrathecal/intraventricular: When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.

3. Topical: Topical application is used when a local effect of the drug is desired.

4. Transdermal: This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch.



5-Rectal: Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration

Absorption of Drugs

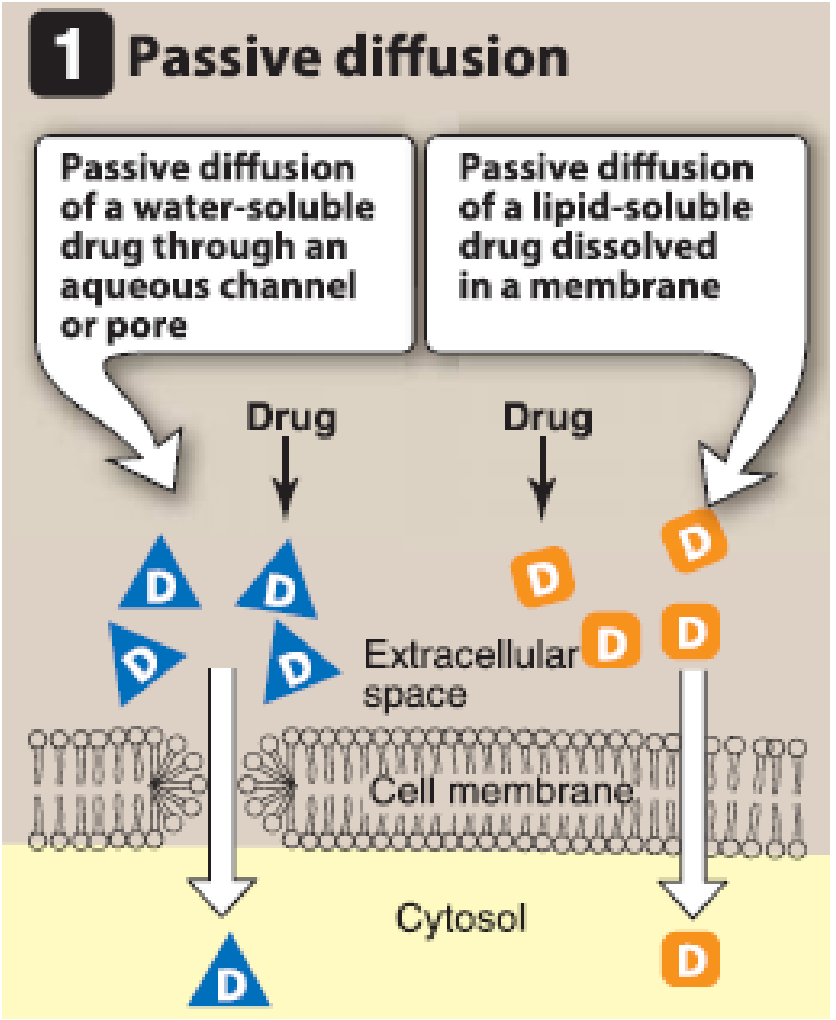
Absorption is the transfer of a drug from the site of administration to the bloodstream.

The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug,
and the route of administration (which influences bioavailability).

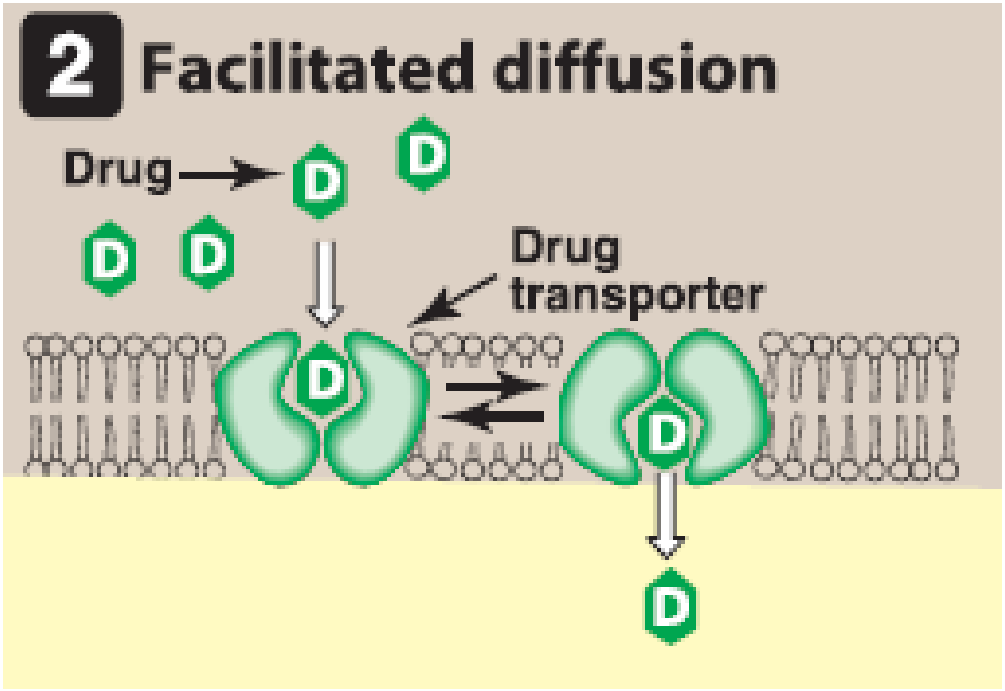
Mechanisms of absorption of drugs from the GI tract

1- Passive diffusion: the drug moves from an area of high concentration to one of lower concentration.

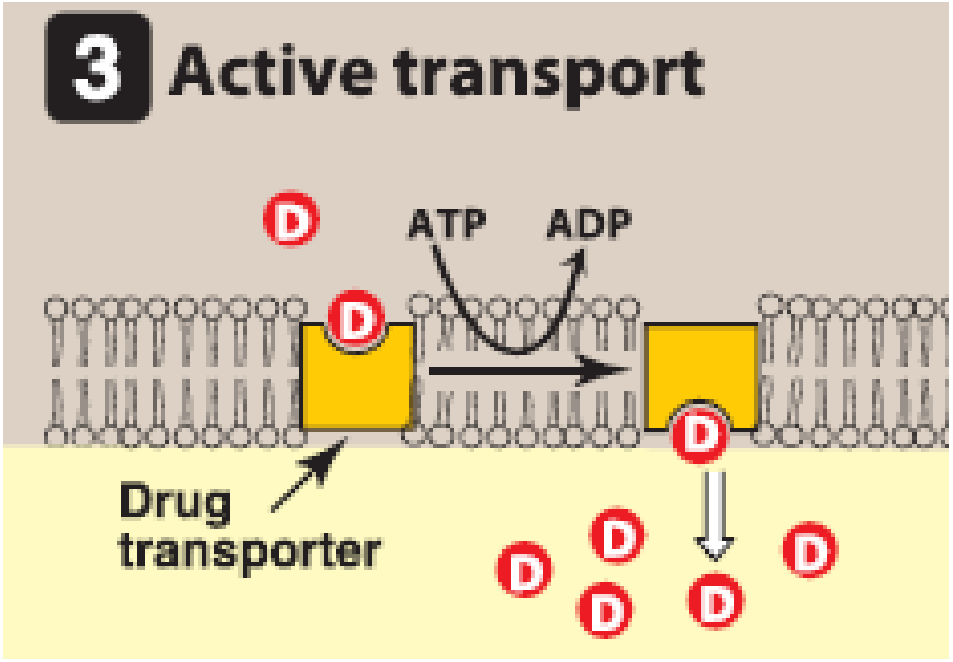
Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity.



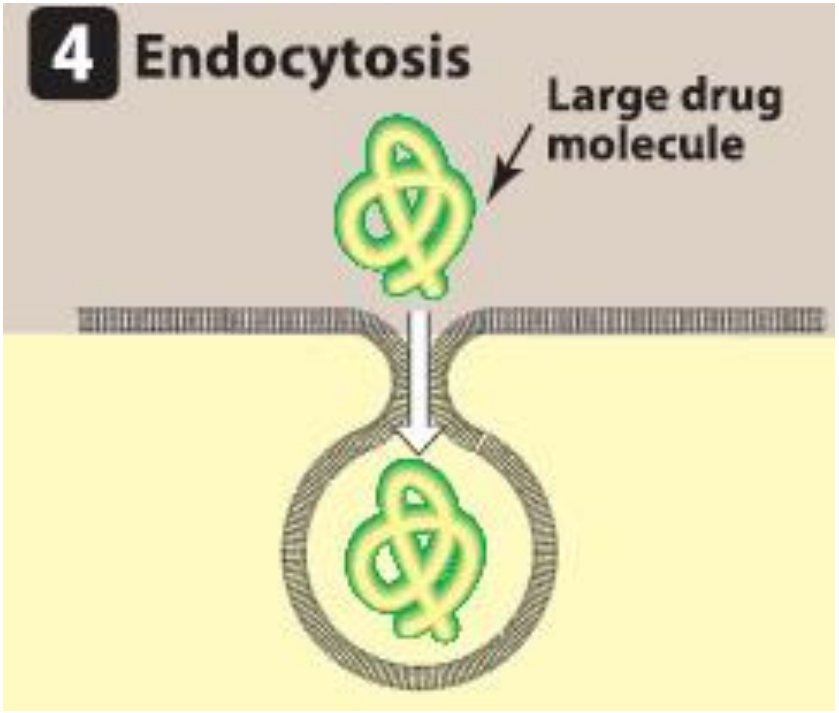
2. Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins (undergo conformational Changes) that facilitate the passage of large molecules. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.



3. Active transport: Energy and carriers are required to move non-fat soluble substances across the cell membrane e.g against concentration gradient.



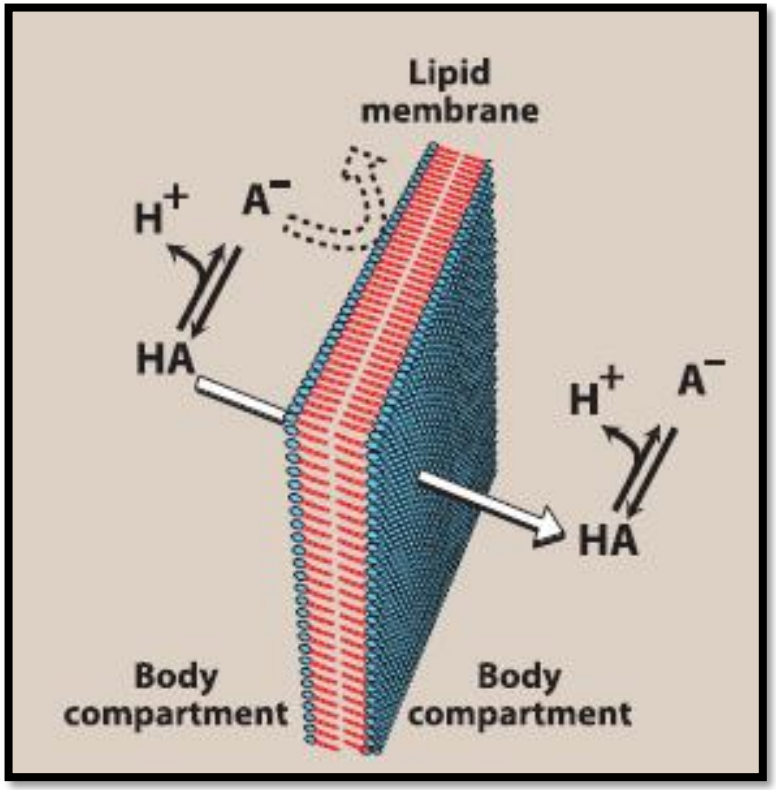
4. Endocytosis and exocytosis: Endocytosis involves engulfment of a drug (large size) by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis.



Factors influencing absorption

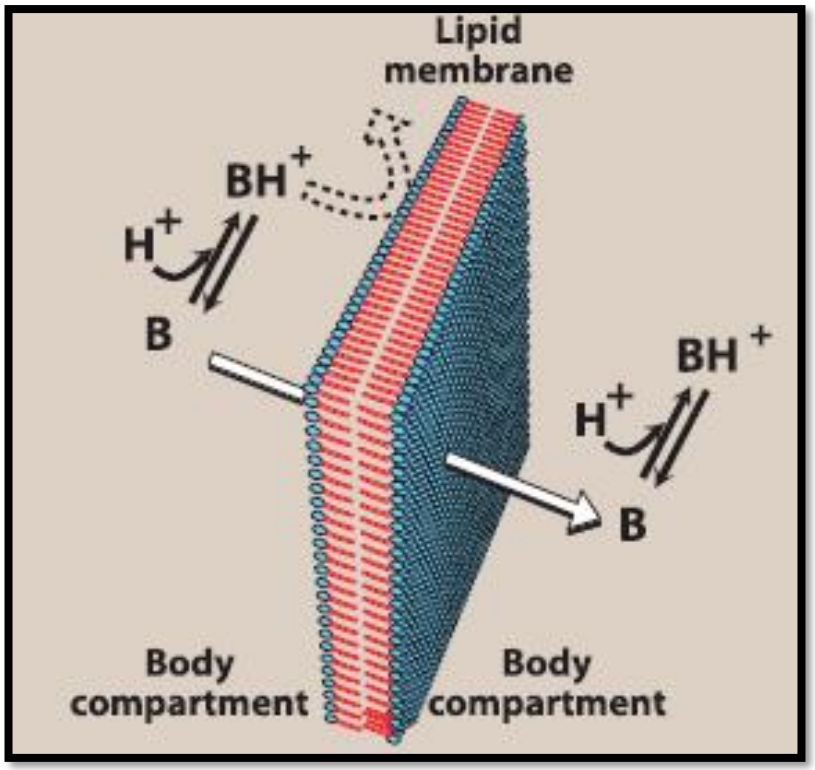
1. Effect of pH on drug absorption: Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H+), causing a charged anion (A-) to form:

$$HA \rightleftharpoons H^+ + A^-$$



Weak bases (BH^+) can also release an H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftharpoons B + H^+$$



2. Blood flow to the absorption site.
3. Total surface area available for absorption.
4. Contact time at the absorption surface.
5. Expression of P-glycoprotein.

C. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous routes of administration.

Factors that influence bioavailability:

a. First-pass hepatic metabolism.
b. Solubility of the drug.
c. Chemical instability.
d. Nature of the drug formulation.

D. Bioequivalence and other types of equivalence

Two drug formulations are bioequivalent if they show comparable biavailability and similar times to achieve peak blood concentrations.

DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues.

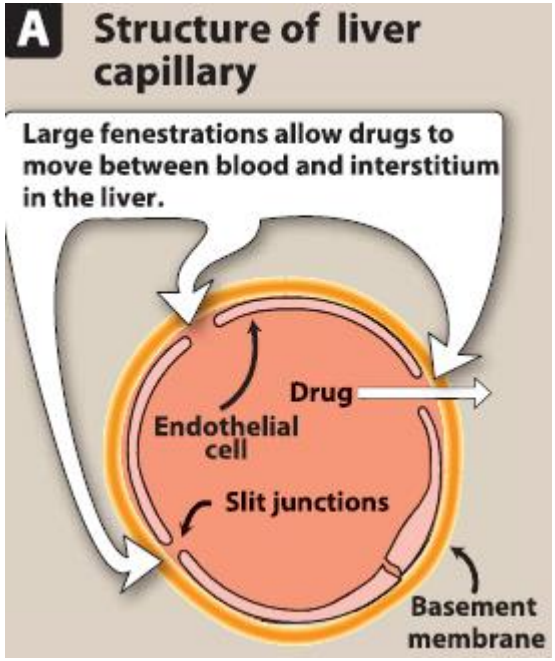
A-Blood flow

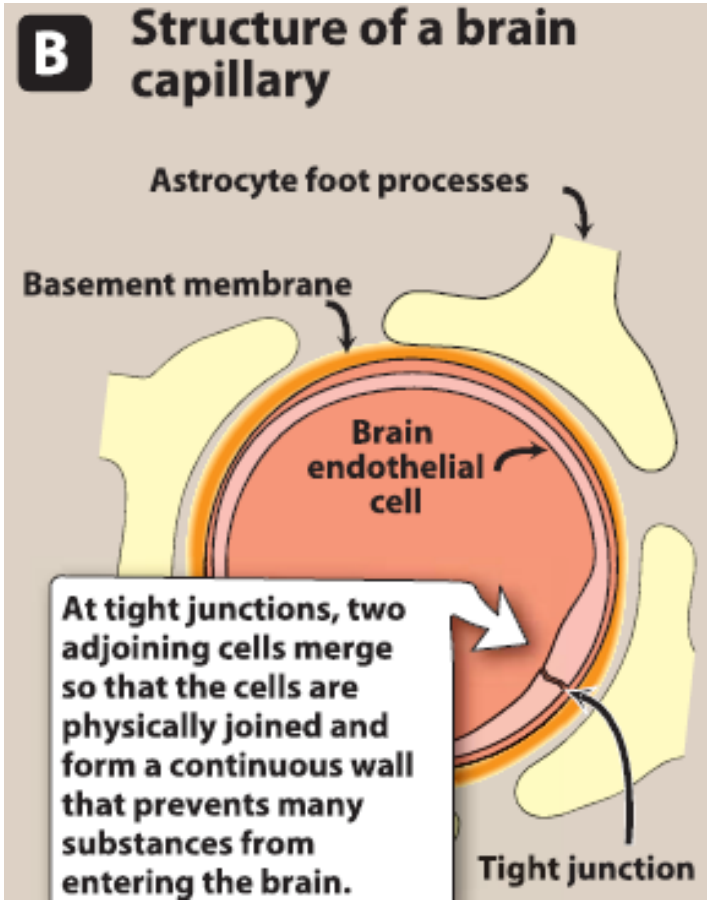
The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles.

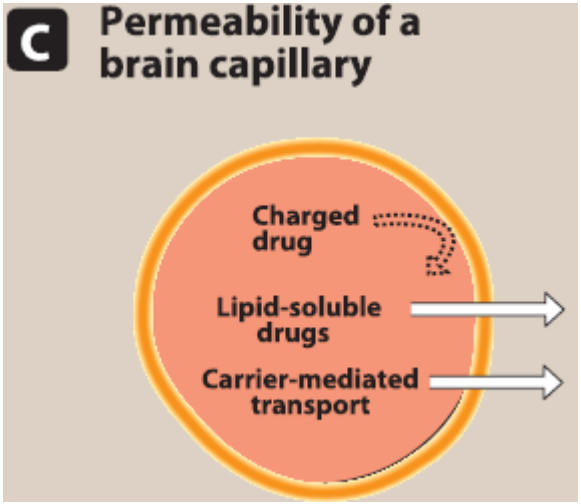
Adipose tissue, skin, and viscera have still lower rates of blood flow.
High blood flow, together with high lipophilicity of propofol, permits rapid distribution into the CNS and produces anesthesia.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.







C. Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows transfer out of the vascular compartment. Albumin is the major drug binding protein, and it may act as a drug reservoir.

2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood.

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes.

Lipophilic drugs readily move across most biologic membranes.
These drugs dissolve in the lipid membranes and penetrate the entire cell surface.

The major factor influencing the distribution of lipophilic drugs is blood flow to the area.

By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

The apparent volume of distribution, Vd, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma.

It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

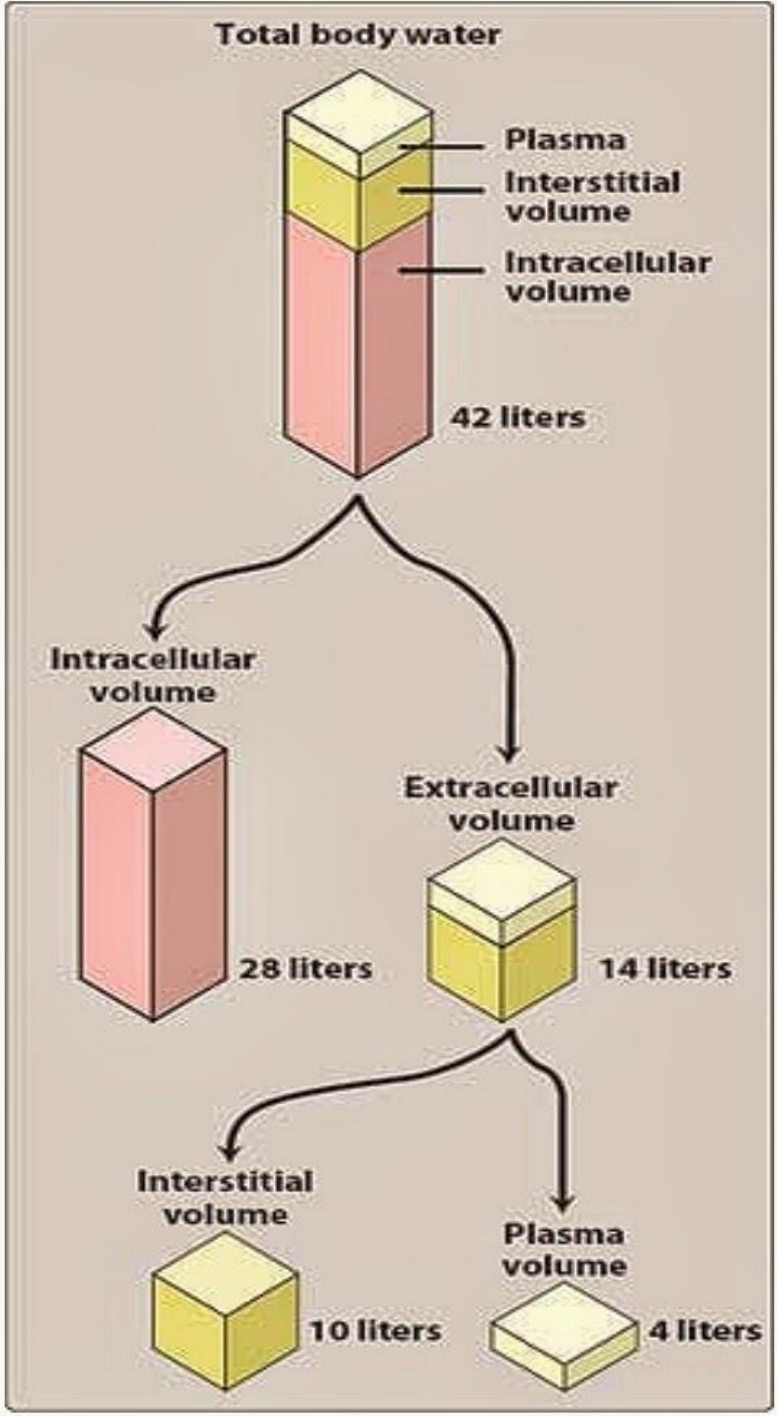
1. Distribution into the water compartments in the body:

a. Plasma compartment: If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma {vascular) compartment.

As a result, it has a low Vd that approximates the plasma volume, or about 4 L in a 70-kg individual. Heparin shows this type of distribution.

b. Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid.

These drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14 Lin a 70-kg individual). Aminoglycoside antibiotics show this type of distribution.



c. Total body water: If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid.

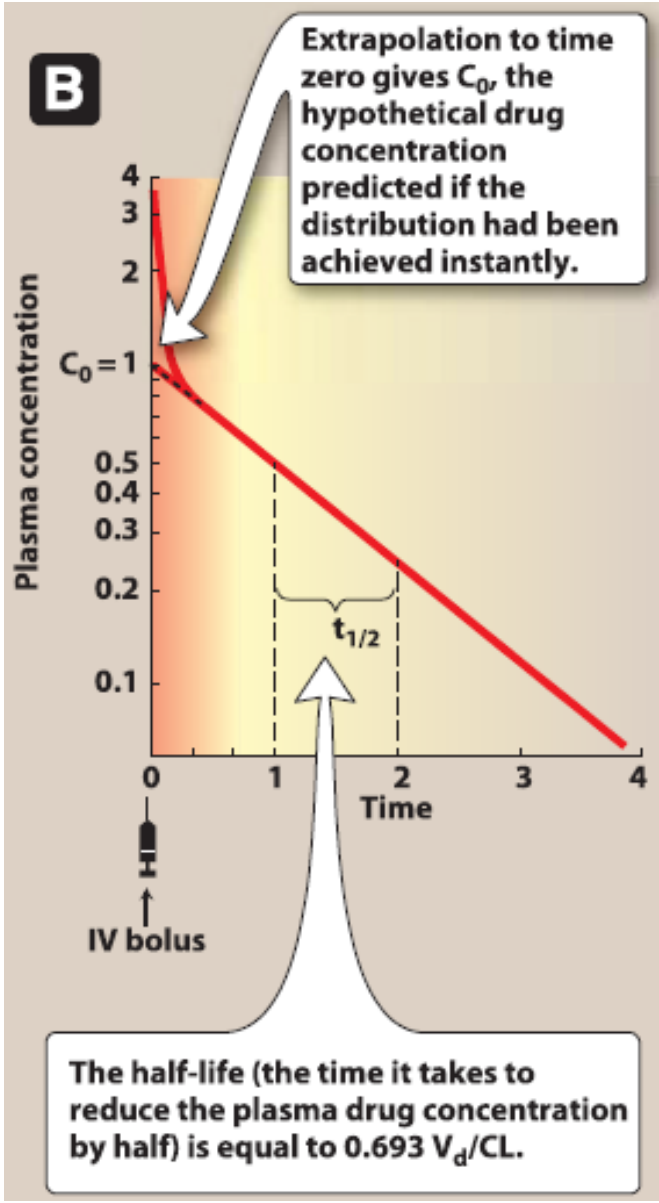
These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual.

Ethanol exhibits this apparent Vd. [Note: In general, a larger Vd indicates greater distribution into tissues; a smallerVd suggests confinement to plasma or extracellular fluid.]

2. Determination of V d:

The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of Vd as

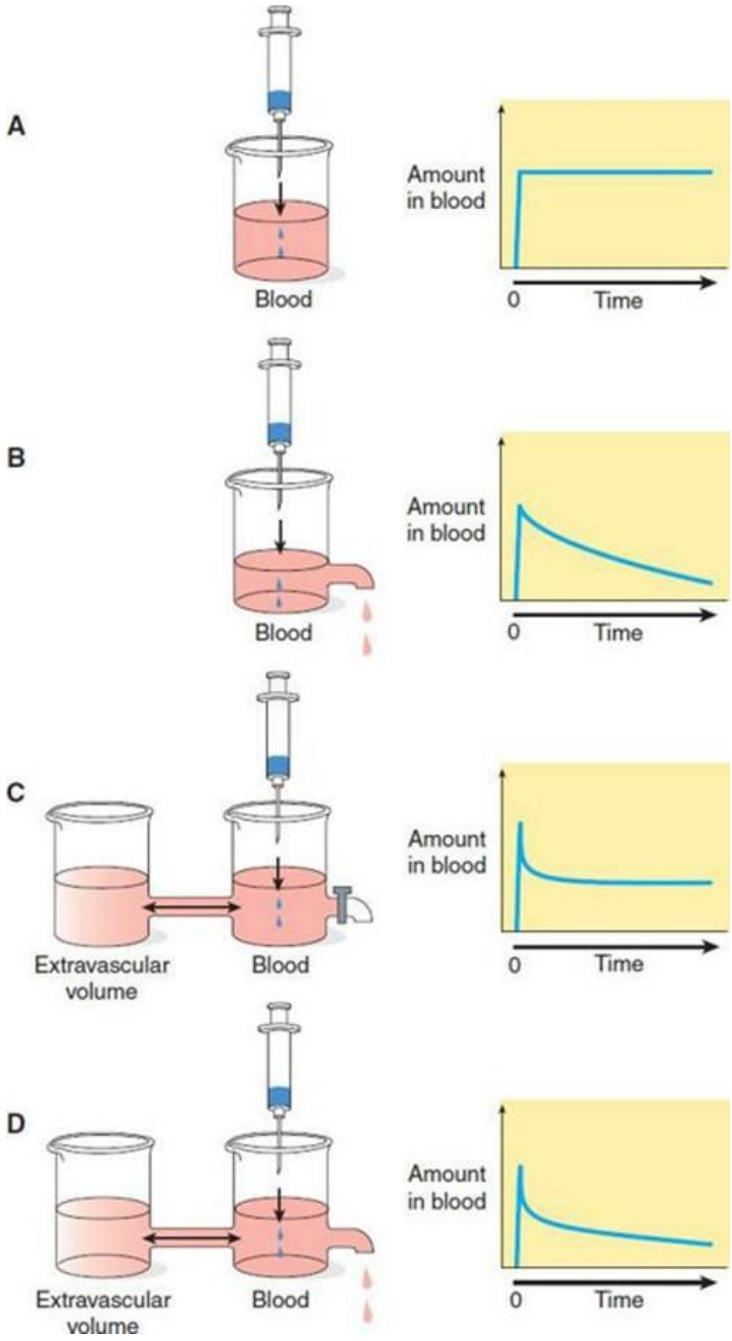
$$V_d = \frac{\text{Dose}}{C_0}$$



3- Effect of Vd on drug half-life:

If a drug has a large Vd, most of the drug is in the extraplasmic space and is unavailable to the excretory organs.

Therefore, any factor that increases Vd can increase the half-life and extend the duration of action of the drug.

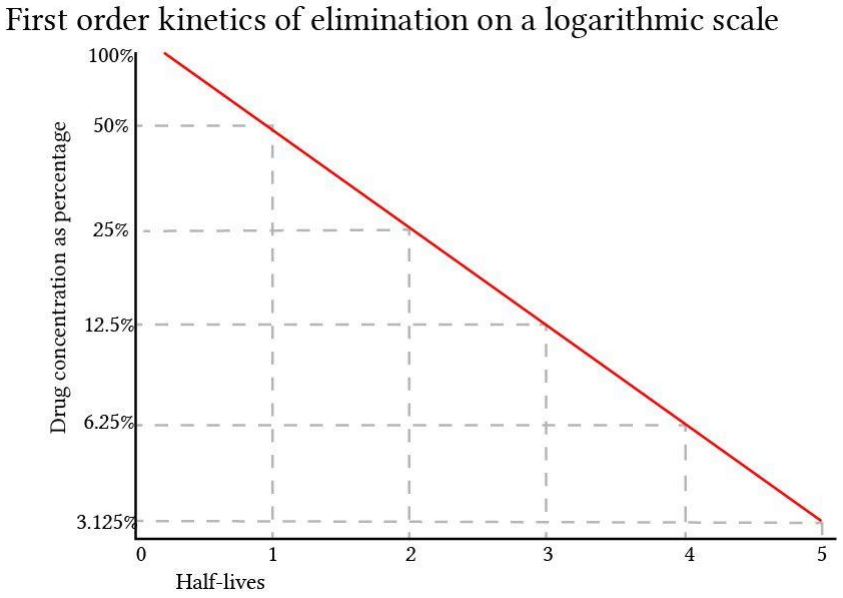


V. Drug Clearance Through Metabolism

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from
the body.]

A. Kinetics of metabolism

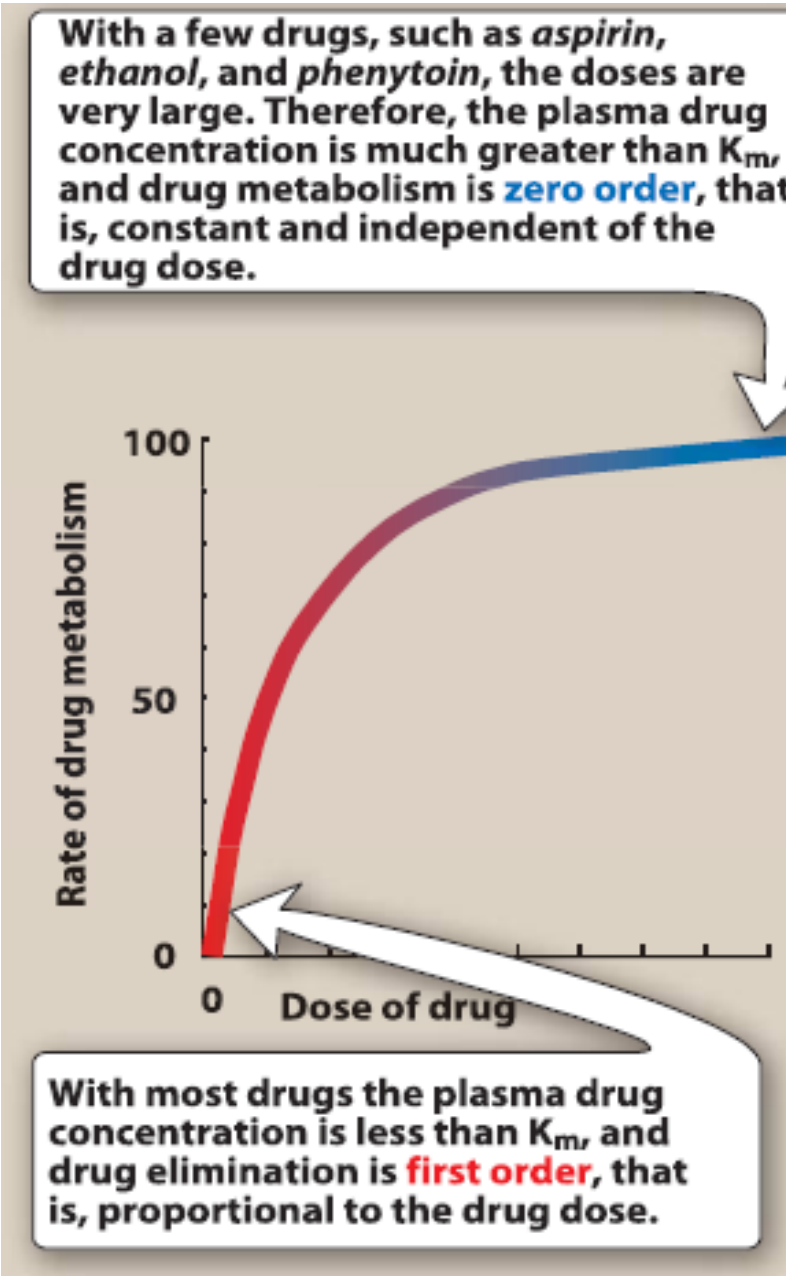
1. First-order kinetics: that a constant fraction of drug is metabolized per unit of time (that is, with each half-life, the concentration decreases by 50%). First-order kinetics is also referred to as linear kinetics.



2. Zero-order kinetics: With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. The enzyme is saturated by a high free drug concentration, and the rate of metabolism remains constant over time.

This is also called nonlinear kinetics.

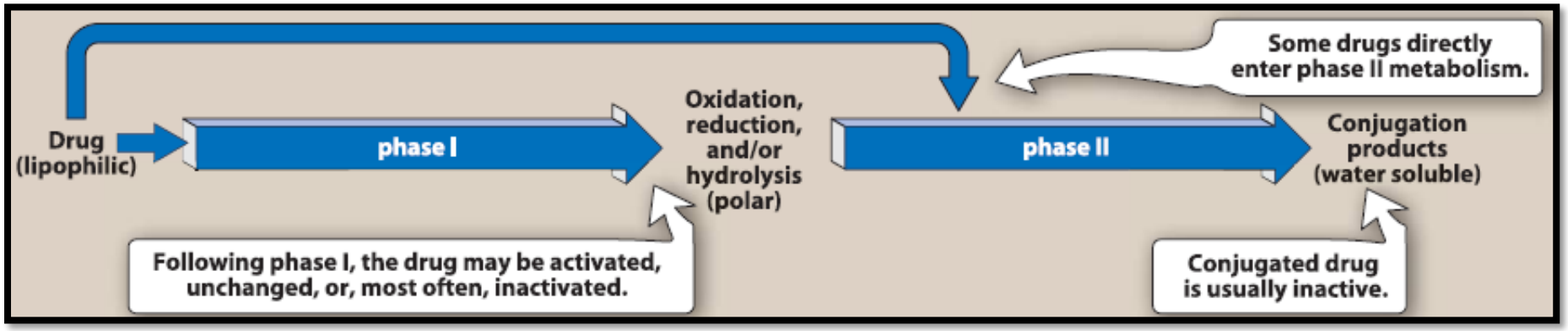
A constant amount of drug is metabolized per unit of time. The rate of elimination is constant and does not depend on the drug concentration.



Reactions of drug metabolism

The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules.

Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II



1. Phase 1: Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as -OH or -NH_2•

Phase I reactions usually involve:
Reduction,
Oxidation, or
Hydrolysis.

Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

a. Phase I reactions utilizing the cytochrome P450 (CYP) system:
CYP is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and Gl tract.

The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A. A second number indicates the specific isozyme, as in CYP3A4.

Genetic variability: P450 enzymes exhibit considerable genetic variability among individuals and racial groups.

CYP Inducers: The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions. Certain drugs (for example, phenobarbital, rifampin, and carbamazepine) are capable of inducing CYP isozymes.

CYP inhibitors: Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity.

The more important CYP inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes.

Phase I reactions not involving the P450 system:

These include amine oxidation (for example, oxidation of catecholamines or histamine),

Alcohol dehydrogenation (for example, ethanol oxidation),

Esterases (for example, metabolism of aspirin in the liver),

and hydrolysis (for example, of procaine).

2. Phase II: This phase consists of conjugation reactions.

If the metabolite from phase I is sufficiently polar, it can be excreted by the kidneys.

However, many phase I metabolites are still too lipophilic to be excreted.

A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are often therapeutically inactive.

A notable exception is morphine-6-glucuronide, which is more potent than morphine.

Glucuronidation is the most common and the most important conjugation reaction. [Note: Drugs already possessing an -OH, -NH2 , or -COOH group may enter phase II
directly and become conjugated without prior phase I metabolism. The highly polar drug conjugates are then excreted by the kidney or in bile.

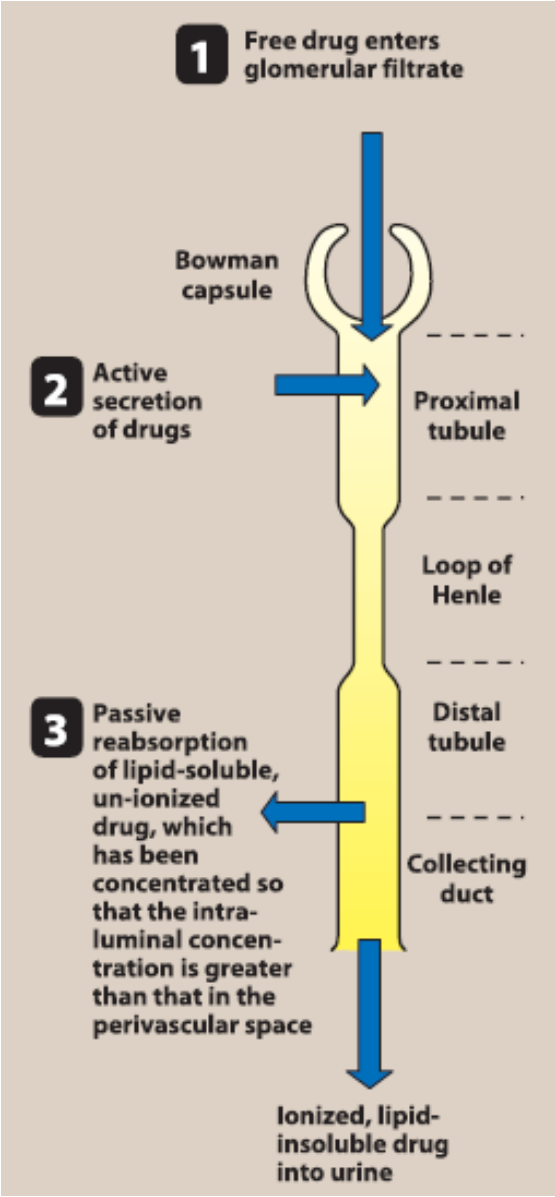
Drug Clearance By the Kidney

Drugs must be sufficiently polar to be eliminated from the body.

Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine.

Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

1. Glomerular filtration: Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin} flows through the capillary slits into the Bowman space as part of the glomerular filtrate. The glomerular filtration rate (GFR) is normally about 120 ml/min/1.73m^2 but may diminish significantly in renal disease.



2. Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases).

3. Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space.

The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation.

Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug.

Generally, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine.

This process is called "ion trapping: For example, a patient presenting with phenobarbital (weak acid) overdose can be given bicarbonate, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

Plasma concentration of a drug following continuous IV infusion:

Following initiation of a continuous IV infusion, the plasma concentration of a drug rises until a steady state (rate of drug elimination equals rate of drug administration) is reached, at which point the plasma concentration of the drug remains constant.

How many half lives is required to reach steady state?

a drug reaches steady state in about 4 to 5 half-lives.

2. Loading dose: Sometimes rapid obtainment of desired plasma levels is needed (for example, in serious infections or arrhythmias).

Therefore, a "loading dose" of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state.

Disadvantages of loading doses include increased risk of drug toxicity and a longer time for the plasma concentration to fall if excess levels occur.


Thank You