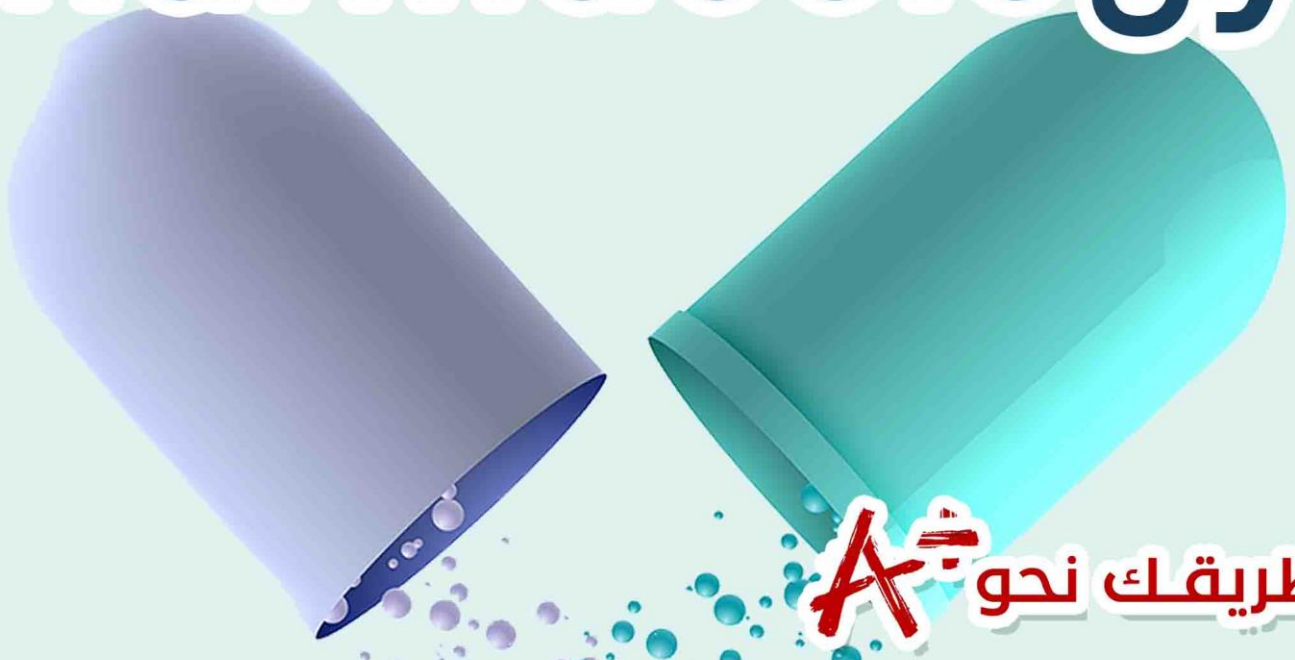
Pharmacology



طريقك نحو A

Pharma one (I)

For Pharmacy & Pharma.D students

Done by:

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Calma Study

Chapter: #1

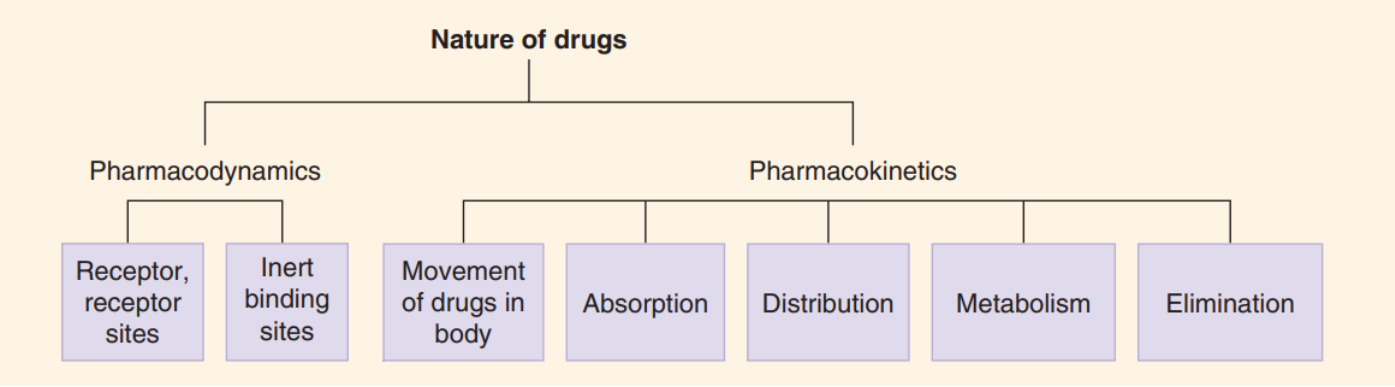
للاستفسارات والتسجيل في الشروحات

واتساب: ٠٧٧٩٢٠٩٠٤٧.

Introduction to Pharmacology:

- Branches of Pharmacology
  - Medical pharmacology:
    - ➔ The use of chemicals in the prevention, diagnosis, & treatment of diseases in humans.
  - Toxicology
    - ➔ Deals with the undesirable effects of chemicals on living systems.
      - Drug with small dose = No effect.
      - Drug with optimum dose = The desirable effect.
      - Drug with large dose = Undesirable effect (Related & Non-related).
        - ✓ Ototoxicity, Tendon rupture, Allergy.
  - Pharmacodynamics
    - ➔ The actions of drug on the body.
    - ➔ Focuses on biochemical & physiological drug effects & how they produce such effects.
  - Pharmacokinetics
    - ➔ The effects of the body on drugs.
    - ➔ Deals with drug absorption, distribution, metabolism, and elimination (ADME).
  - Pharmacotherapeutics
    - ➔ Rational use of drugs in the management of diseases.
  - Pharmacogenomics (Pharmacogenetics):
    - ➔ The relation of individual's genetic makeup to the response to specific drugs.
- Drug:
  - It is any substance that changes its biologic function through its chemical actions.
  - May be **endogenous** or **exogenous**.
  - **Poisons** are drugs that have exclusively harmful effects.

The Nature of Drugs

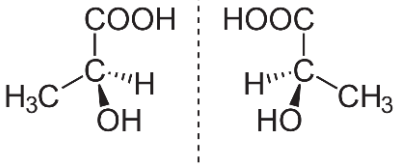


- Drug Size
  - Most drugs have molecular weights between 100 and 1000 (for specificity of action).
  - In most cases be at least 100 MW (small sized drug) thus more selective.
  - Drugs larger than 1000 MW hard to diffuse between body compartments.

- **Drug-Receptor Bonds**
  - Drugs interact with receptors by chemical bonds (covalent, electrostatic, and hydrophobic).
  - Covalent bonds:
    - ➔ The strongest (irreversible),
    - ➔ Example: the bond between Aspirin & cyclooxygenase.
  - Electrostatic bonding: More common and weaker.
  - Hydrophobic bonds: the weakest type.
    - ➔ Examples: Hydrogen, Van der Waals, and hydrophobic bonds

☒ **Notes:**

- The drugs that use weak bonds are more selective than that bind by strong bonds.
- Thus, if we wished to design a highly selective short-acting drug:
  - ➔ We would avoid molecules that form covalent bonds.
  - ➔ We would choose a molecule that forms weaker bonds.



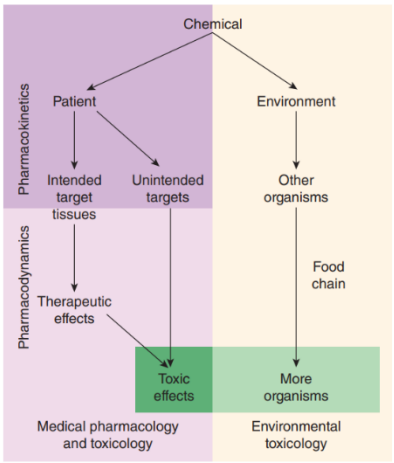
- **Drug Shape**
  - Chirality (stereoisomerism):
    - ➔ More than half drugs are chiral molecules (enantiomeric pairs).
    - ➔ One enantiomer more potent than the other enantiomer = better fit to the receptor.
  - The shape of a drug molecule must be such as to permit binding to its receptor site.
    - ➔ left-oriented receptor binds with left-oriented drug more effectively than right-oriented.
    - ➔ right-oriented receptor binds with right-oriented drug more effectively than left-oriented.

☒ **Note: the isomers are equipotent as a-receptor blockers.**

- Enzymes:
  - ➔ Are stereoselective.
  - ➔ Brack the susceptible drug for elimination.
  - ➔ The duration of action of one enantiomer may differ from other.
- The drug transporters.
  - ➔ May be stereoselective.

DRUG-BODY INTERACTIONS

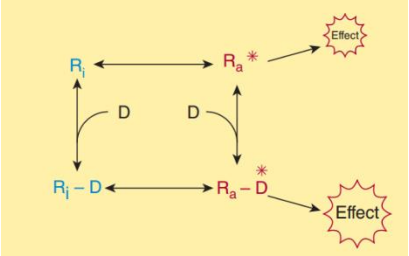
- The interactions between a drug and the body are divided into:
- **Pharmacodynamic**: The actions of the drug on the body.
- **Pharmacokinetics**: The actions of the body on the drug.
  - Absorption, Distribution, Metabolism and Excretion of drugs
  - Play a significant role in the choice and administration of a particular drug for a particular patient, (patient with impaired renal function).



Pharmacodynamic Principles

- The actions of the drug on the body to produce its effect.
  - Most drugs must bind to a receptor to bring about an effect.

- Receptors:
  - The receptor is postulated to exist in the inactive (Ri) form and in the activated form (Ra).
  - Normally each receptor must be bound to ligand to produce an effect.
  - Some receptors must exist in the Ra form and produce the same effect as agonist-induced activity even in the absence of agonist = constitutive activity.



- Effect of stimulation of the receptor forms:
  1. Ri → No Stimulates → No effect.
  2. Ra* → Effectors Stimulation → Constitutive activity.
  3. Ra + D* ⇌ Ra-D (Ra*) → Effectors Stimulation → Response.
  4. Ri + D* ⇌ Ri-D (Ri*) → No Stimulation → No response or diminished activity.

- Ligand types & Their effect on Receptors:

	Effect on Ra	Effect on Ri
Full agonist:	Ra + D* ⇌ Ra-D (Ra*) = 99% Have high affinity for Ra configuration and stabilize it,	Ri + D* ⇌ Ri-D (Ri*) = 1%
Partial agonist:	Bind to Ra configuration & stabilize it but not as fully as full agonists,	Thus, a significant fraction of receptors exists in Ri –D pool.
Antagonist:	Fixing the fractions of drug-bound Ri and Ra in the same relative amounts as in the absence of any drug	
Inverse Agonist:		Has a higher affinity for Ri than Ra. Stabilizes a large fraction in Ri–D pool.

☒ Note:
- Partial agonists Have low intrinsic efficacy which means that it is independent of affinity for the receptor.
- Partial agonists have agonist-antagonist properties.
  - ➔ Pindolol, β-adrenoceptor partial agonist, act as agonist (if no full agonist is present) or as an antagonist (if a full agonist such as epinephrine is present).
- Antagonist: leads to no change in activity, so the drug will appear to be without effect.
  - ➔ The presence of the antagonist at the receptor site will block access of agonists to the receptor and prevent the usual agonist effect.
  - ➔ This prevention is called neutral antagonism.

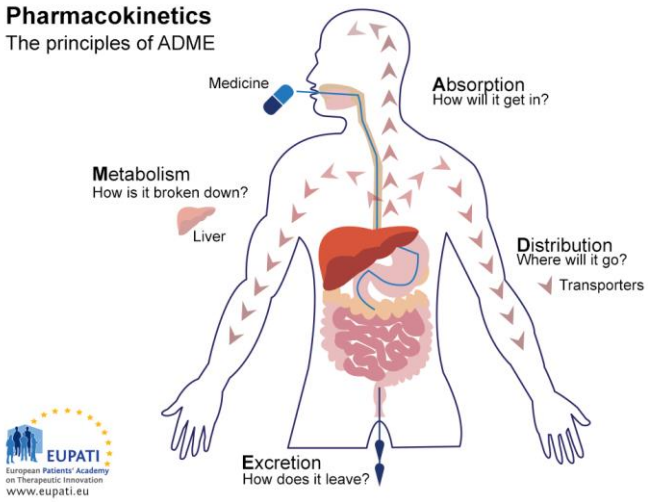
- Receptors and Inert Binding Sites:
  - Receptors Binding Sites
    - ➔ The receptors have characteristic of Specificity (Selectivity):
      - Each Receptor is specific for certain substance Depends on receptor binding site.
    - ➔ It must change its function upon binding in such a way.
  - Inert Binding Sites:
    - ➔ Nonregulatory molecules such as plasma albumin will result in no detectable change in the function of the biologic system.
    - ➔ Affects drug distribution within the body & determines the amount of free drug in circulation.

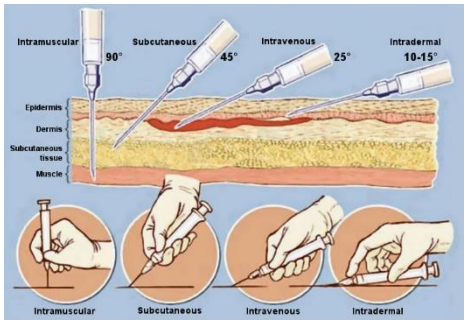
Pharmacokinetic Principles

- In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route.
  - Routes of administrations (ROA):
    - ➔ Oral (swallowed): maximal convenience, the main ROA that Subjected to the first-pass effect.
    - ➔ Rectal: as suppository not convenient for adults, partial avoidance of the first-pass effect.
    - ➔ Buccal and sublingual (Not swallowed): Direct absorption into systemic venous circulation, bypassing the hepatic portal circuit and first-pass metabolism.
    - ➔ Inhalation: Usually very rapid absorption for Respiratory.
    - ➔ Topical: application to the skin or to the mucous membrane for local effect
    - ➔ Transdermal: application to the skin for systemic effect.
    - ➔ Parenteral: all of them bypass the hepatic portal circuit and first-pass metabolism
      - Intravenous (IV):
      - Intramuscular (IM):
      - Subcutaneous (SC):

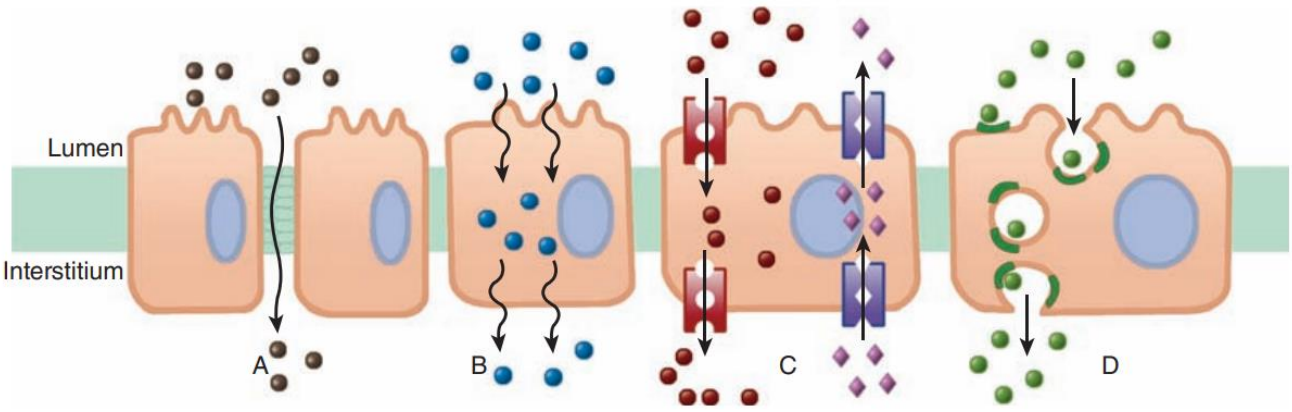
❖ The Movement of Drugs in the Body

- A drug is administered into one body compartment and then must move to its site of action in another compartment, → This requires that the drug be **absorbed** into the blood from its site of administration and **distributed** to its site of action, **permeating** through the various barriers, Finally, after bringing about its effect, a drug should be **eliminated**.
- Pharmacokinetics: The actions of the body on the drug.
  - Absorption, Distribution, Metabolism, Excretion.





- Permeation:
  - Mechanisms:
    - ➔ Passive diffusion: water soluble or fat soluble.
      - Aqueous diffusion:
        - ⇨ Across epithelial membrane tight junctions and the endothelial lining of blood vessels through aqueous pores that permit the passage of molecules.
      - Lipid diffusion:
        - ⇨ Most important limiting factor for drug permeation.
    - ➔ Special carriers:
      - For too large or too fat-insoluble substances (i.e., peptides, amino acids, and glucose).
      - By synthesizing drugs that resembles those molecules thus they permeate through.
        - ⇨ NET: Norepinephrine reuptake from synapse
        - ⇨ SERT: Serotonin reuptake from synapse
        - ⇨ VMAT: Transport of Monoamines into their vesicles
        - ⇨ MDR1: Transport of many xenobiotics out of cells
    - ➔ Endocytosis and exocytosis:
      - Large or impermeant substances that enter cells only by endocytosis.
        - ⇨ It requires the presence of specific receptors to enhance the coating.



- Fick's Law of Diffusion:
  - The magnitude of the concentration gradient. (طردية)
  - Permeability of the plasma membrane to the substance. (طردية).
  - The surface area. (طردية)
  - The molecular weight of the substance. (عكسية)
  - Thickness of the membrane. (عكسية)

$$\text{Rate} = C_1 - C_2 \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area} \qquad (1)$$

- Ionization of Weak Acids and Weak Bases; the Henderson-Hasselbalch Equation
  - Ionized (charged) molecules are water-soluble and lipid insoluble.
  - Non-ionized (uncharged) molecules are lipid-soluble and water insoluble.

$C_8H_7O_2COOH \rightleftharpoons C_8H_7O_2COO^- + H^+$

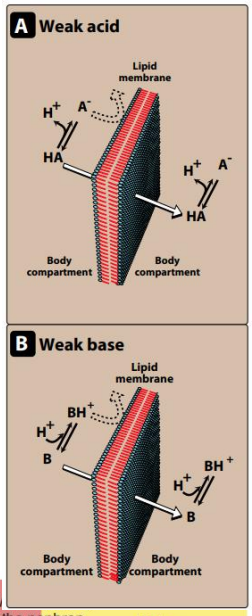
Neutral aspirin — Aspirin anion — Proton

$C_{12}H_{11}ClN_3NH_3^+ \rightleftharpoons C_{12}H_{11}ClN_3NH_2 + H^+$

Pyrimethamine cation — Neutral pyrimethamine — Proton

- Henderson-Hasselbalch Equation:

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = pK_a - pH \qquad (2)$$



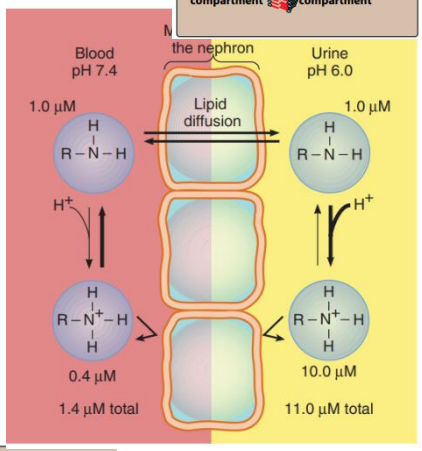
➔ This equation applies to both acidic and basic drugs.

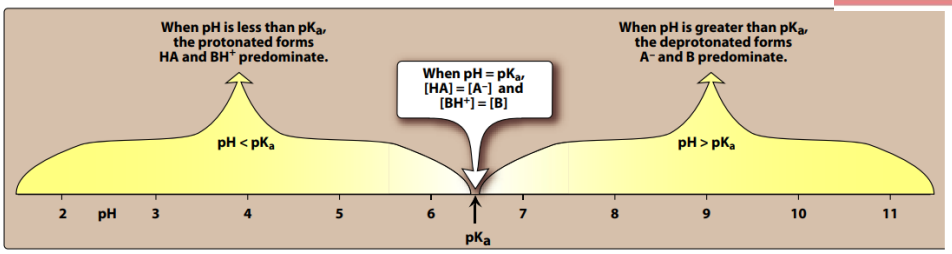
➔ The lower the pH relative to pKa, the greater the protonated form of drug.

- Uncharged form is the lipid-soluble, thus:
  - ⇨ More of a weak acid will be in the lipid-soluble form at acid pH,
    - ↳ Weak acids are best absorbed in the acidic media.
  - ⇨ More of a basic drug will be in the lipid-soluble form at alkaline pH.
    - ↳ Weak bases are best absorbed in the alkaline media.

➔ Is Henderson-Hasselbalch Equation affect the excretion?

- This principle applied on drugs excretion.
  - ⇨ Almost all drugs are filtered at the glomerulus.
  - ⇨ If a drug is in a lipid-soluble inside the renal tubule, most of it will be reabsorbed.
    - ↳ If the goal is to accelerate its excretion, it is important to prevent its reabsorption.
      - ❖ By transforming it into ionized form.
      - ❖ The drug is "trapped" in the urine.
      - ❖ Done by adjusting urine pH.





- Example: Drug X is a weak acid whose pKa is 6.2 answer the following:
  a. The predominant form in the urine is: (ionized/nonionized).
  b. The drug will be: (excreted in urine/reabsorbed back to the blood).
  c. How to induce its excretion by (acidify/alkalization) of urine.
  d. What are the answers if the drug was weak base (same/opposite) answers.

- Thus, weak acids are usually excreted faster in alkaline urine; weak bases are usually excreted faster in acidic urine; why? Due to ionization of drugs in different pH.

☒ <u>Notes:</u>

- <u>Tertiary amines are nonionized groups & quaternary amines are ionized groups.</u>
- <u>Hemodialysis:</u>
  - ➔ <u>If a drug is in a water-soluble inside the blood vessels it will stay inside.</u>
    - If the goal is to accelerate its excretion, unfortunately we can't alkaline the blood, instead we can do Hemodialysis (غسيل للدم).

➔ The percentage of ionized vs nonionized drug:

Weak acid	Weak base
pH>pKa - Unprotonated ☐ Protonated - Nonionized ☐ Ionized	pH>pKa - Unprotonated ☐ Protonated - Ionized ☐ Nonionized
pH <pKa - Protonated ☐ Unprotonated - Ionized ☐ Nonionized	pH <pKa - Protonated ☐ Unprotonated - Nonionized ☐ Ionized

- "Protonated" means associated hydrogen ion.
- The percentage is according to the equation: $\log\left(\frac{Protonated}{Unprotonated}\right) = pka - pH$

❖ Absorption of Drugs:

- Routes of Administration (ROA):
  - Routes into the blood: high bioavilability (high plasma concentration of the drug).
  - Routes into the GIT: lower bioavilability (low plasma concentration of the drug).
- Blood Flow:
  - Blood flow influences absorption from: intramuscular, subcutaneous & gastrointestinal tract.
  - High blood flow facilitates absorption (maintains a high drug-to-blood concentration gradient).
- Concentration
  - Drug concentration at the site of administration determines concentration gradient.
  - More Drug concentration at the site of administration more absorption.
  - Drug concentration in the vehicle is important in the absorption of drugs applied topically.

Table 2: Summary of factors affecting absorption

Factors Affecting Absorption	↓ Absorption	↑ Absorption
pH	Weak acid drugs in alkaline environments Or weak base drugs in acidic environments.	Weak acid drugs in acidic environments Or weak base drugs in alkaline environments.
Blood Flow	↓ perfusion to organs that absorb drugs (e.g., skin, GIT) this can occur in shock states.	↑ perfusion to organs that absorb drugs
Contact Time	↓ contact time (e.g., diarrhea)	↑ contact time (e.g., constipation)
Total Surface Area	↓ Total Surface Area, this occurs in diseases that destroy the brush border of the GIT cells.	↑ Total Surface Area
P-Glycoprotein	If P-Glycoproteins are found in apical surface of GIT cells.	No P-Glycoproteins

❖ Distribution of Drugs

- Apparent Volume of Distribution (Vd) and Physical Volumes
  - Vd relates the drug amount in the body to plasma concentration.
  - The physical volumes of body compartments:
    - ➔ Less important in pharmacokinetics.
    - ➔ However, obesity alters the ratios of total body water to body weight and fat to total body weight, and this may be important when using of highly lipid-soluble drugs.

TABLE 1–2 Average values for some physical volumes within the adult human body.

Compartment	Volume (L/kg body weight)
Plasma	0.04
Blood	0.08
Extracellular water	0.2
Total body water	0.6
Fat	0.2–0.35

- Determinants of Distribution
  - Size of the organ **(طرديا)**
    - ➔ The larger the organ, more concentration gradient between it & blood, faster disterbution.
  - Blood flow **(طرديا)**
    - ➔ It is related to rate of uptake from the organ not the amount of drug in tissue at equilibrium.
    - ➔ Well-perfused tissues (eg, brain, heart, kidneys, and splanchnic organs) usually have faster tissue distribution than poorly perfused tissues (eg, fat, bone).
  - Lipid Solubility **(طرديا)**
    - ➔ If the drug is lipid-soluble, the concentration in the perivascular extracellular space will be lower and diffusion from the vessel into the extravascular tissue space will be facilitated.
    - ➔ Drug is lipid-soluble faster tissue distribution.
  - Binding **(حسب موقع الارتباط)**
    - ➔ Binding of a drug to macromolecules in the blood or a tissue compartment tends to increase the drug's concentration in that compartment & prevent its movement into other one.
    - ➔ Example:
      - o Warfarin is strongly bound to plasma albumin,
        - ⇨ Which restricts warfarin's diffusion out of the vascular compartment.
        - ⇨ Lower tissue distribution.
      - o Chloroquine is strongly bound to extravascular tissue proteins.
        - ⇨ Which results in a marked reduction in the plasma concentration of chloroquine.
        - ⇨ Higher tissue distribution.

❖ Metabolism of Drugs

- Drug Metabolism as a Mechanism of Activation or Termination of Drug Action
  - Metabolism of a drug sometimes terminates its action to become inactive.
    - ➔ The action of many drugs (eg, sympathomimetics, phenothiazines) is terminated before they are excreted because they are metabolized to biologically inactive derivatives.
    - ➔ Conversion to an inactive metabolite is a form of elimination.
  - Metabolism of some other drugs to become active.
    - ➔ Called prodrugs (eg, levodopa, minoxidil) are inactive as administered and must be metabolized in the body to become active.

- Drug disposition: distribution as well as metabolism and elimination.

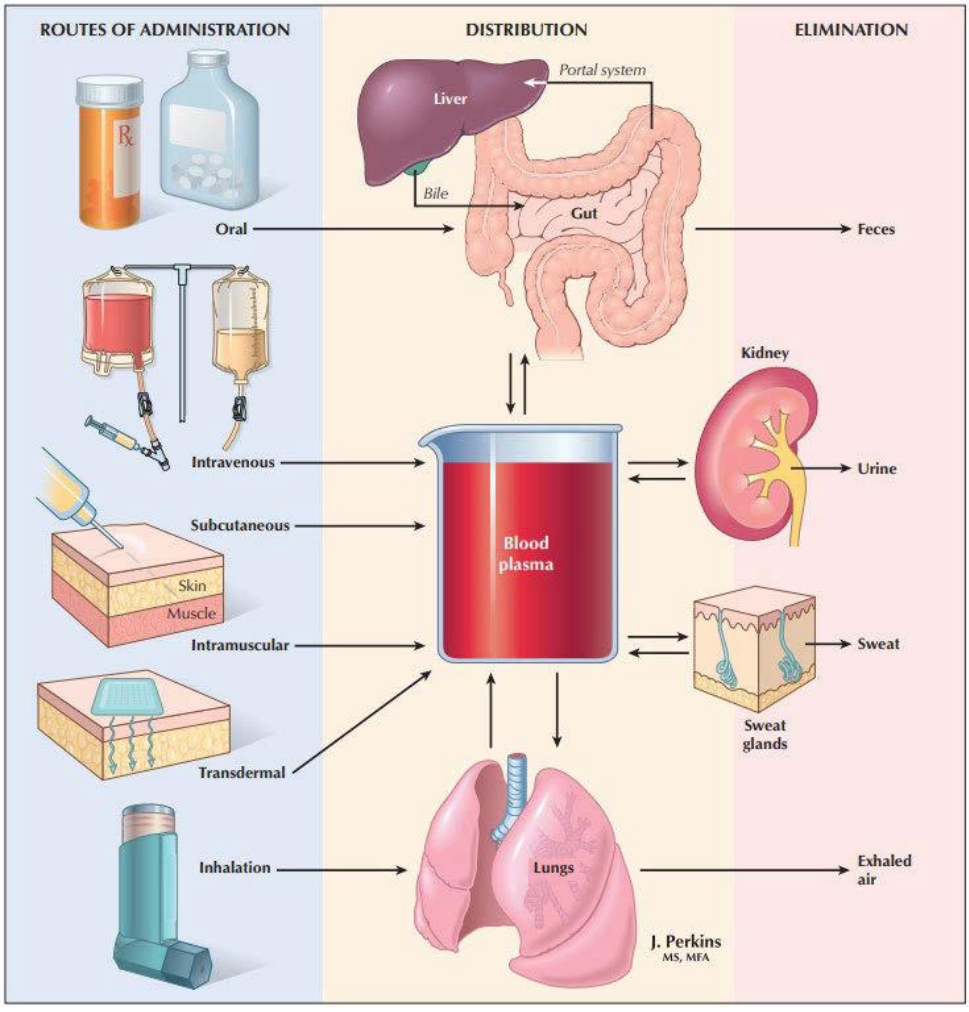
❖ Elimination of Drugs

- The rate of elimination following the last dose determines the duration of action for many drugs.
  - Therefore, knowledge of the time course of concentration in plasma is important in predicting the intensity and duration of effect for most drugs.

- Routes Of Excretion:
  - Kidney (For most drugs and their metabolites).
  - Lungs (Volatile anesthetic gases).
  - Liver (a major route too).
  - Others: Milk, Sweat, Tears…

☒ Note: Drug elimination is not the same as drug excretion: A drug may be eliminated by metabolism (be inactive) long before the modified molecules are excreted from the body.

- For drugs with active metabolites (eg, diazepam), elimination of the parent molecule by metabolism is not synonymous with termination of action.
- For drugs that are not metabolized, excretion is the mode of elimination.
- Drugs combine irreversibly with their receptors disappearance from the bloodstream is not equivalent to cessation of drug action:
  ➔ very prolonged action
  ➔ elimination depends on turnover of the receptors.



Questions:

1. A 3-year-old is brought to the emergency department having just ingested a large overdose of tolbutamide, an oral antidiabetic drug. Tolbutamide is a weak acid with a pKa of 5.3. It is capable of entering most tissues, including the brain. On physical examination, the heart rate is 100/min, blood pressure 90/50 mm Hg, and respiratory rate 20/min. Which of the following statements about this case of tolbutamide overdose is most correct?
   (A) Urinary excretion would be accelerated by administration of NH4Cl, an acidifying agent
   (B) Urinary excretion would be accelerated by giving NaHCO3, an alkalinizing agent
   (C) Less of the drug would be ionized at blood pH than at stomach pH
   (D) Absorption of the drug would be slower from the stomach than from the small intestine
   (E) Hemodialysis is the only effective therapy

   Answer: B
2. Botulinum toxin is a large protein molecule. Its action on cholinergic transmission depends on an intracellular action within nerve endings. Which one of the following processes is best suited for permeation of very large protein molecules into cells?
   (A) Aqueous diffusion
   (B) Endocytosis
   (C) First-pass effect
   (D) Lipid diffusion
   (E) Special carrier transport

   Answer: B

3. A 12-year-old child has bacterial pharyngitis and is to receive an oral antibiotic. She complains of a sore throat and pain on swallowing. The tympanic membranes are slightly reddened bilaterally, but she does not complain of earache. Blood pressure is 105/70 mm Hg, heart rate 100/mm, temperature 37.8 °C (100.1 °F). Ampicillin is a weak organic acid with a pKa of 2.5. What percentage of a given dose will be in the lipid-soluble form in the duodenum at a pH of 4.5?
   (A) About 1%
   (B) About 10%
   (C) About 50%
   (D) About 90%
   (E) About 99%

   Answer: A

THE END OF CHAPTER 1