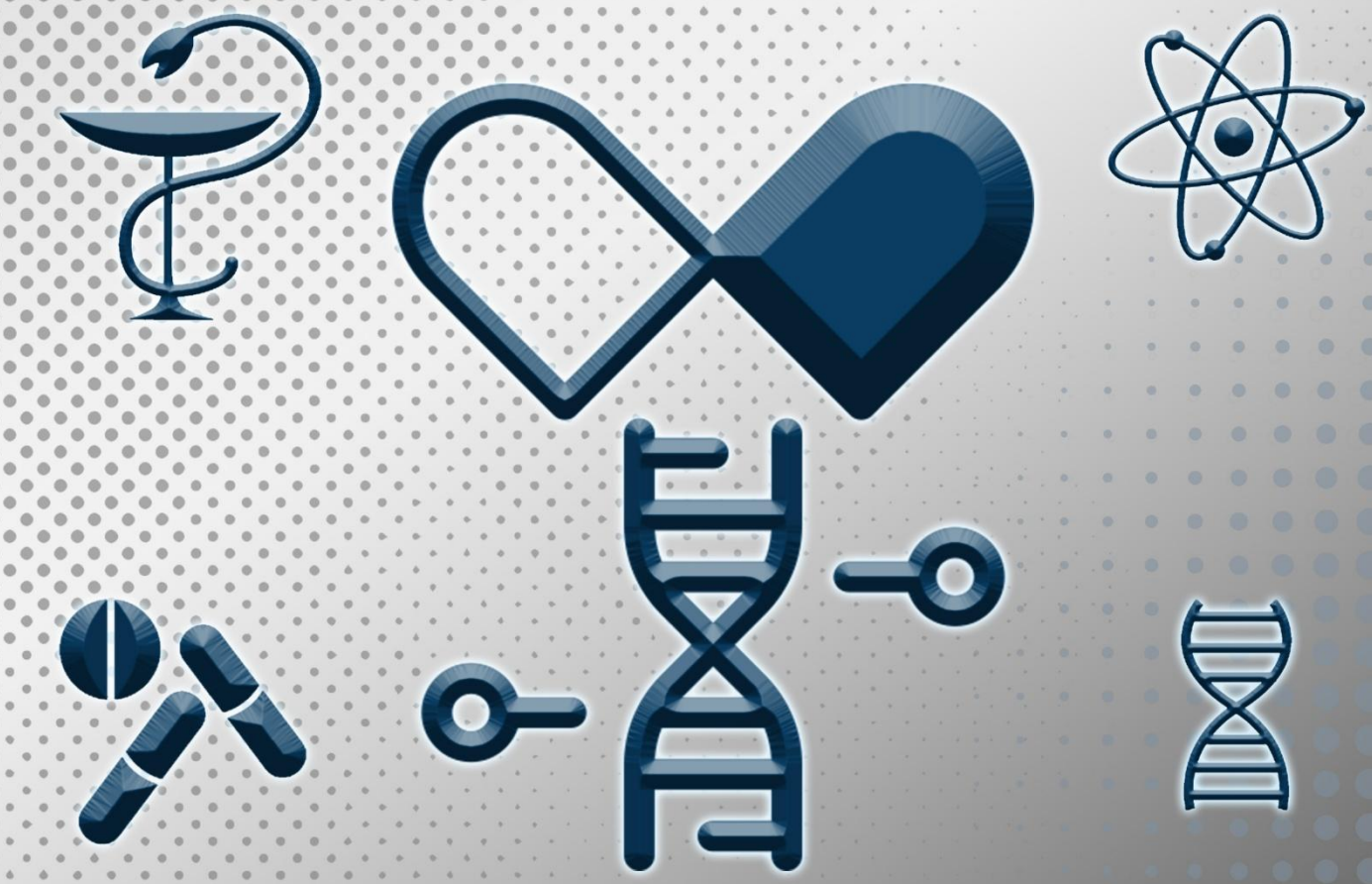
Pharmacology



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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.
- 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: The relation of individual's genetic makeup to the response to specific drugs.

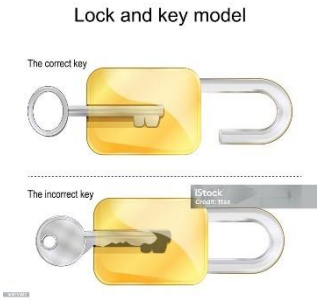
The Nature of Drugs

- Drug: It is any substance that changes the biologic function through its chemical actions.

- **Drug Size**
  - Most drugs have molecular weights between 100 and 1000.
    - ➔ 100 MW: In most cases be at least 100 MW.
      - ⇨ Determine the specificity of binding.

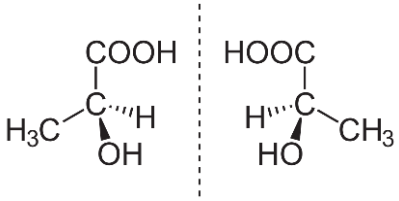
    - ➔ 1000 MW: maximum value.
      - ⇨ Determine the drug movement in the body.
      - ⇨ Drugs larger than 1000 MW hard to diffuse between body compartments.
        - ↳ Thus, administrated directly to the compartment of choice.
        - ↳ Example: Alteplase (clot-dissolving drug) administered directly to plasma.

- **Drug Shape**
  - According to **key-lock theory.**
    - ➔ The drug's shape is complementary to receptor.
  - Many receptors are stereoisomers.
  - Many drugs are stereoisomers.
    - ➔ Some are (right-oriented = R) & others are (left-oriented = S).
      - ⇨ Found as enantiomeric pairs.



  - 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.
      - ⇨ One enantiomer more potent than the other enantiomer = better fit to the receptor.

- Examples:
  - ➔ Carvedilol: contain 2 enantiomeric pairs (S & R).
    - ⇨ (S) is potent on Beta receptors & (R) is 100-weaker on Beta receptors.
    - ⇨ But both are equipotent as a-receptor blockers.
  - ➔ Ketamine: (found as racemic mixture)
    - ⇨ (R) is more potent & less toxic.
    - ⇨ (S) is less potent & more toxic.



- Pure active enantiomers: doesn't decrease side effects.

- Enzymes & drug transporters are stereoselective.
- One drug enantiomer is often more susceptible than the other to drug-metabolizing enzymes.
  - ➔ The duration of action of one enantiomer may differ from other.

- Drug-Receptor Bonds

- Drugs interact with receptors by chemical bonds (covalent, electrostatic, and hydrophobic).

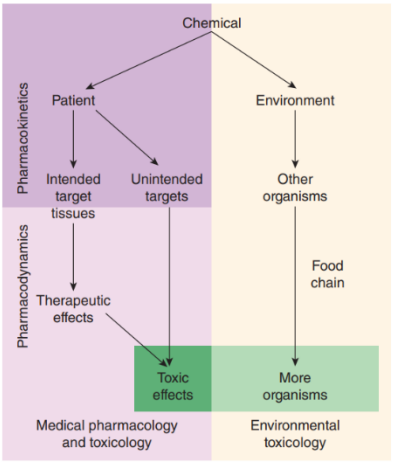
Covalent	Electrostatic	Hydrophobic
- The strongest - Irreversible - Example: o Aspirin binding to COX. o DNA-Alkylating agents. - Its effect lasts longer after the drug elimination. - Its effect reversed by synthesis of new receptor or enzyme.	- Weaker - Reversable - More common - Example: o Permanent bond between ionic molecules. o Weak hydrogen bonds. o Van der walls.	- The weakest - Reversable - Important in the interaction between highly lipid soluble drugs with lipid of the cells.

☒ Notes:

- The drugs that use weak bonds are more selective than that bind by strong bonds.
  - ➔ Because, weak bonds require very precise fit of the drug to its receptor to binds & do effect.
- 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.

Note: xenon is a completely inert gas but has a significant pharmacological effect.

DRUG-BODY INTERACTIONS

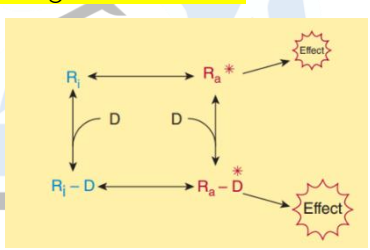


- The interactions between a drug and the body are divided into:
- **Pharmacodynamic**: The actions of the drug on the body.
- **Pharmacokinetics**: The actions of the body on the drug.
  - Absorption, Distribution, Metabolism and Excretion of drugs
  - Play a significant role in the choice and administration of drug.

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.

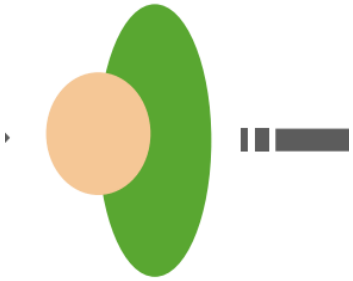
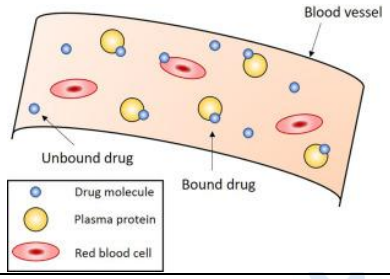
	Effect on Ra	Effect on Ri
Full agonist:	Ra + D* ⇌ Ra-D (Ra*) = 99% Have high affinity for Ra configuration and stabilize it,	Ri + D* ⇌ Ri-D (Ri*) = 1%
Partial agonist:	Bind to Ra configuration & stabilize it but not as fully as full agonists,	Thus, a significant fraction of receptors exists in Ri –D 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).
    - ⇨ Resembles the reversable antagonist.

- 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	Inert Binding Sites
- Selectivity: specific for certain substance - Change its function upon binding (regulatory.)  drug-receptor complex	- Selectivity: specific for certain substance - Can't Change its function (non-regulatory.) - Example: plasma albumin. - Affects the drug distribution & amount of free drug in the circulation. 

- Duration of action (DOA): **مدّة بقاء تأثير الدواء**
  - The drug action is terminated depending on the reversibility of drug binding.
    - ➔ **If it binds reversibly.**
      - ⇨ DOA lasts as long as the drug occupies the receptor.
      - ⇨ When it dissociates its effect is terminated.
    - ➔ **If it binds irreversibly.**
      - ⇨ DOA lasts until the drug-receptor complex is destroyed & new receptor or enzyme is synthesized (e.g., Aspirin).

The Physical Nature of drug

- Drugs **solid** at room temperature (eg, aspirin, atropine).
- Drugs **liquid** at room temperature (eg, nicotine, ethanol).
- Drugs **gaseous** at room temperature (eg, nitrous oxide).

- Oligonucleotides (small RNA segments)
  - Have entered clinical trials & are on the threshold of introduction into therapeutics.
  - siRNAs & miRNAs can interfere with protein synthesis with extreme selectivity thus may be used as therapeutic agents.
  - Also, antisense oligonucleotides (ANOs), synthesized to be complementary to natural RNA or DNA, can interfere with the readout of genes and the transcription of RNA.
  - All these included in Pharmacogenomics.

- Several drugs are inorganic elements, eg, lithium, iron, and heavy metals.

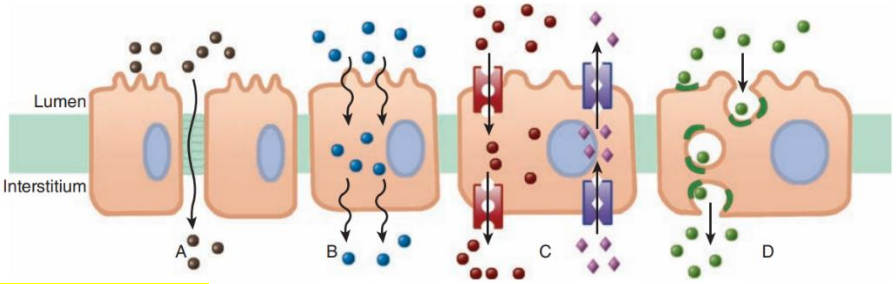
- **Chemical antagonists** may **interact directly with other drugs**,
- Whereas a few drugs (**osmotic agents**) **interact almost exclusively with water molecules**.
-

Pharmacokinetic Principles

- 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 (wall of intestine, walls of capillaries that perfuse the gut, the blood-brain barrier, the walls of the capillaries that perfuse the brain),
- Finally, after bringing about its effect, a drug should be **eliminated**, through:
  - Excretion from the body, Metabolic conversion or both.

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 – in some tissues – that permit the passage of molecules**.
        - o **aqueous pores** aren't found in the brain & testicles.
    - ➔ Lipid diffusion:
      - ⇨ Most important limiting factor for drug permeation.
        - o Due to that almost all barriers are lipid.
      - ⇨ The lipid: aqueous partition coefficient of a drug determines the drug movement.
      - ⇨ Weak acid & basis permeation depends on the pH of the media.
        - o Because they can gain or lose electrical charge according to pH.
  - 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



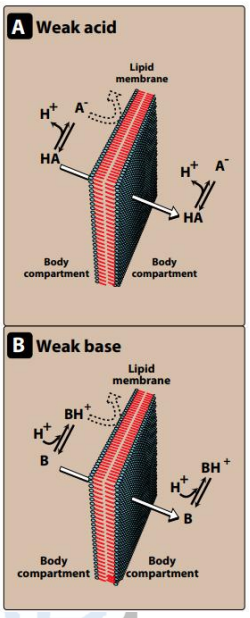
  - Endocytosis and exocytosis:
    - ➔ Large or impermeant substances that enter cells only by endocytosis.
      - ⇨ It requires the presence of specific receptors to enhance the coating.
    - ➔ Permits very large or very lipid-insoluble chemicals to enter cells.
    - ➔ For example: Proteins, Vitamin B12 and iron combine with special proteins (B12 with intrinsic factor and iron with transferrin), and the complexes.

➔ Exocytosis: Reverse process of Endocytosis.
  ⇨ Most neurotransmitters are released by exocytosis.
  ⇨

- 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)

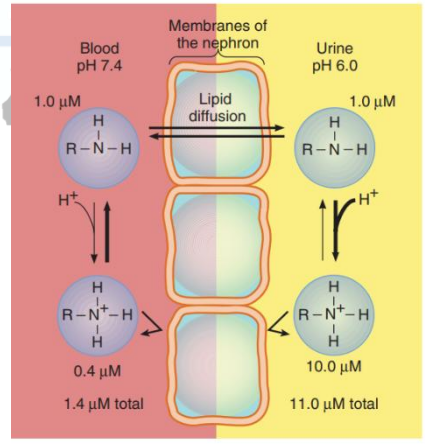
$$\text{Rate} = C_1 - C_2 \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area} \qquad (1)$$

- 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.
  - Henderson-Hasselbalch Equation:

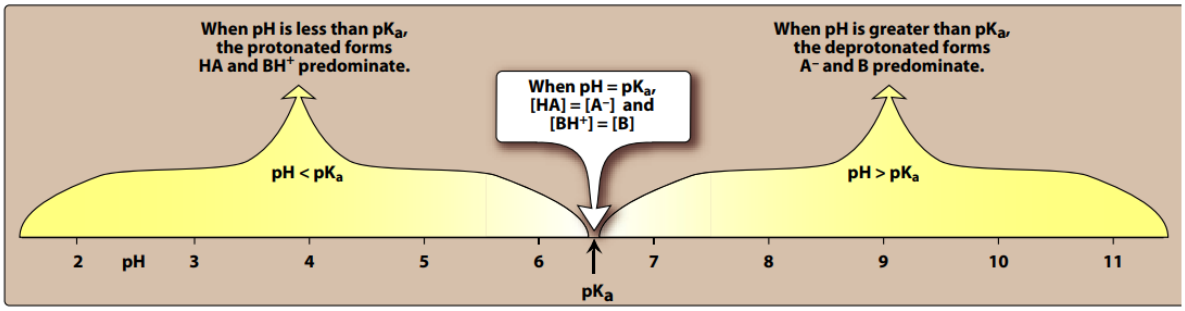


$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = pK_a - pH \qquad (2)$$

➔ This equation applies to both acidic and basic drugs.
➔ The lower the pH relative to pKa, the greater the protonated form of drug.
  o 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?
  o 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.

☒ **Notes:**

- **Tertiary amines are nonionized groups & quaternary amines are ionized groups.**
- **Hemodialysis:**
  - ➔ **If a drug is in a water-soluble inside the blood vessels it will stay inside.**
    - 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: $\log\left(\frac{Protonated}{Unprotonated}\right) = pka - pH$.

Henderson-Hasselbalch:

- Protonated weak base (charged, more water-soluble).
- Unprotonated weak base (uncharged, more lipid-soluble).
- Protonated weak acid (uncharged, more lipid-soluble)
- Unprotonated weak acid (charged, more water-soluble).

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

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

- 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).

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