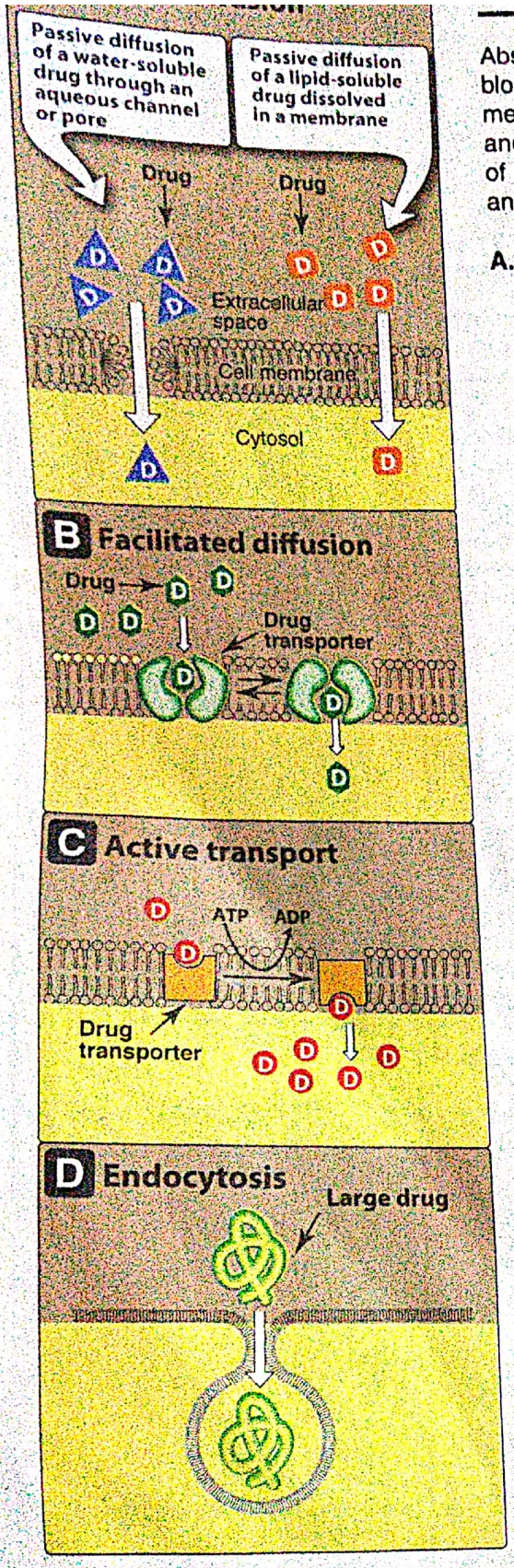

Figure 1.6
Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

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). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis (Figure 1.6).

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers.

2. **Facilitated diffusion:** Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

3. **Active transport:** This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using specific carrier proteins. Energy-dependent active transport is driven by the hydrolysis of adenosine triphosphate. It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

4. **Endocytosis and exocytosis:** This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Vitamin B_{12} is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.

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B. 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:

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

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):

$$BH^+ \leftrightharpoons B + H^+$$

A drug passes through membranes more readily if it is uncharged (Figure 1.7). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH^+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. 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 ionization constant, pK_a (Figure 1.8). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

2. **Blood flow to the absorption site:** The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption from SC administration.]

3. **Total surface area available for absorption:** With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

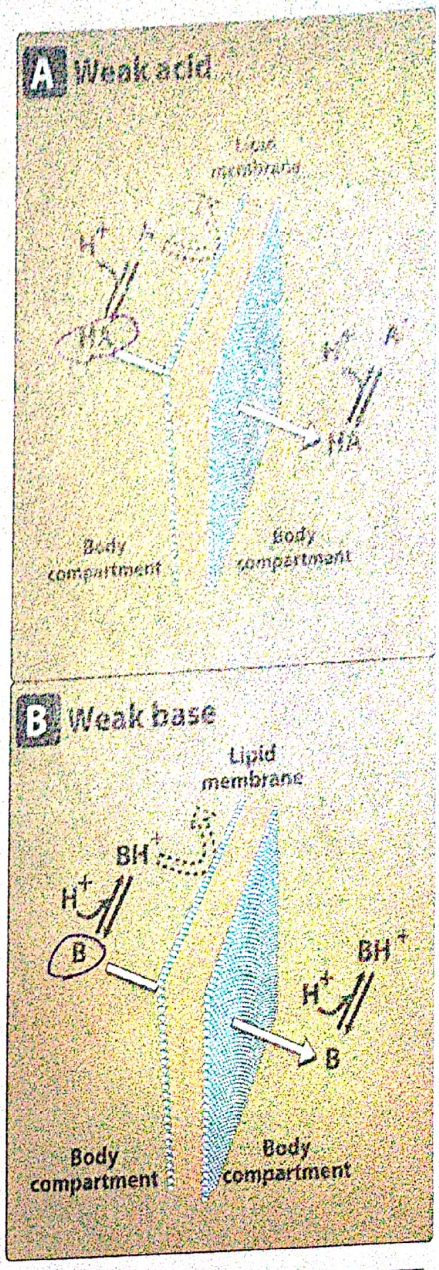

Figure 1.7
A. Diffusion of the nonionized form of a weak acid through a lipid membrane. **B.** Diffusion of the nonionized form of a weak base through a lipid membrane.

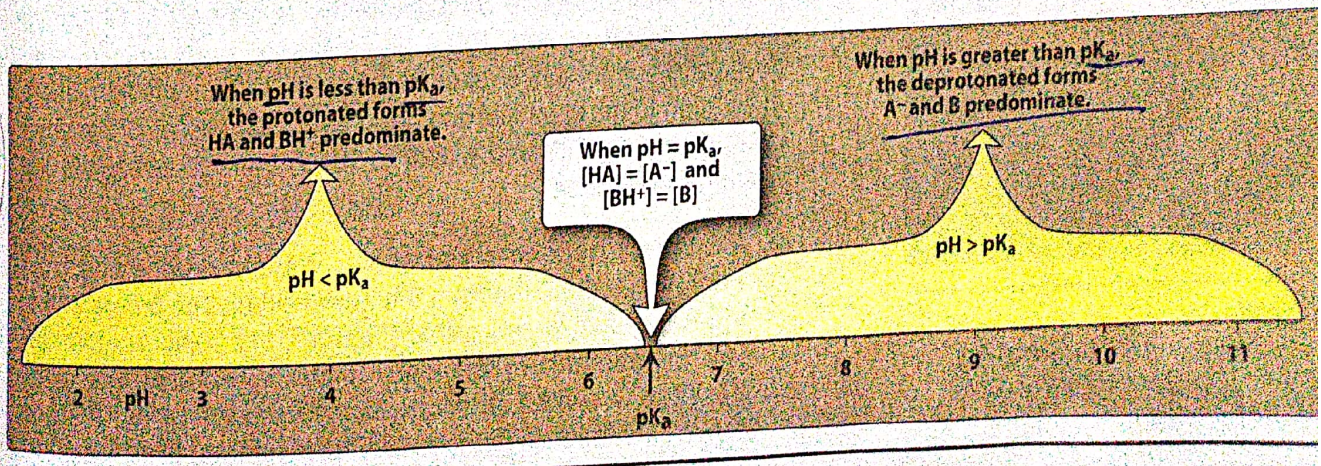

Figure 1.8

depends on the ambient pH and pK, of the drug. For

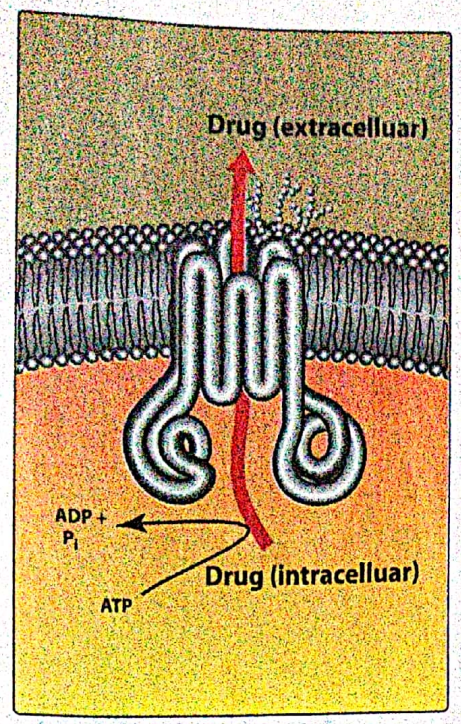

Figure 1.9
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

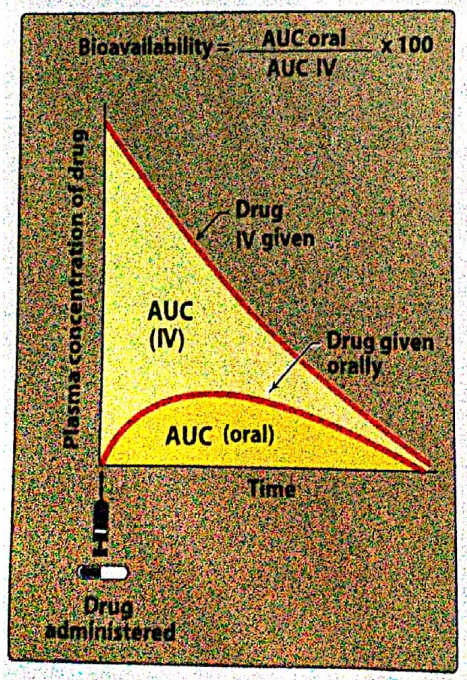

Figure 1.10
Determination of the bioavailability of a drug. AUC = area under curve; IV = intravenous

4. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

5. **Expression of P-glycoprotein:** P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it "pumps" drugs out of the cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

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.

1. **Determination of bioavailability:** Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. The total AUC reflects the extent of absorption of the drug. Bioavailability of a drug given orally is the ratio of the AUC following oral administration to the AUC following IV administration (assuming IV and oral doses are equivalent; Figure 1.10).

2. **Factors that influence bioavailability:** In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to the chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

   a. **First-pass hepatic metabolism:** When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation (Figure 1.11). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass

metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual or transdermal route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

b. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

c. **Chemical instability:** Some drugs, such as *penicillin G*, are unstable in the pH of the gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

d. **Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

D. Bioequivalence

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

E. Therapeutic equivalence

Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient, and use the same route of administration) with similar clinical and safety profiles. [Note: Clinical effectiveness often depends on both the maximum serum drug concentration and the time required (after administration) to reach peak concentration. Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.]

IV. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues. For drugs administered IV, absorption is not a factor, and the initial phase (from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which the drug