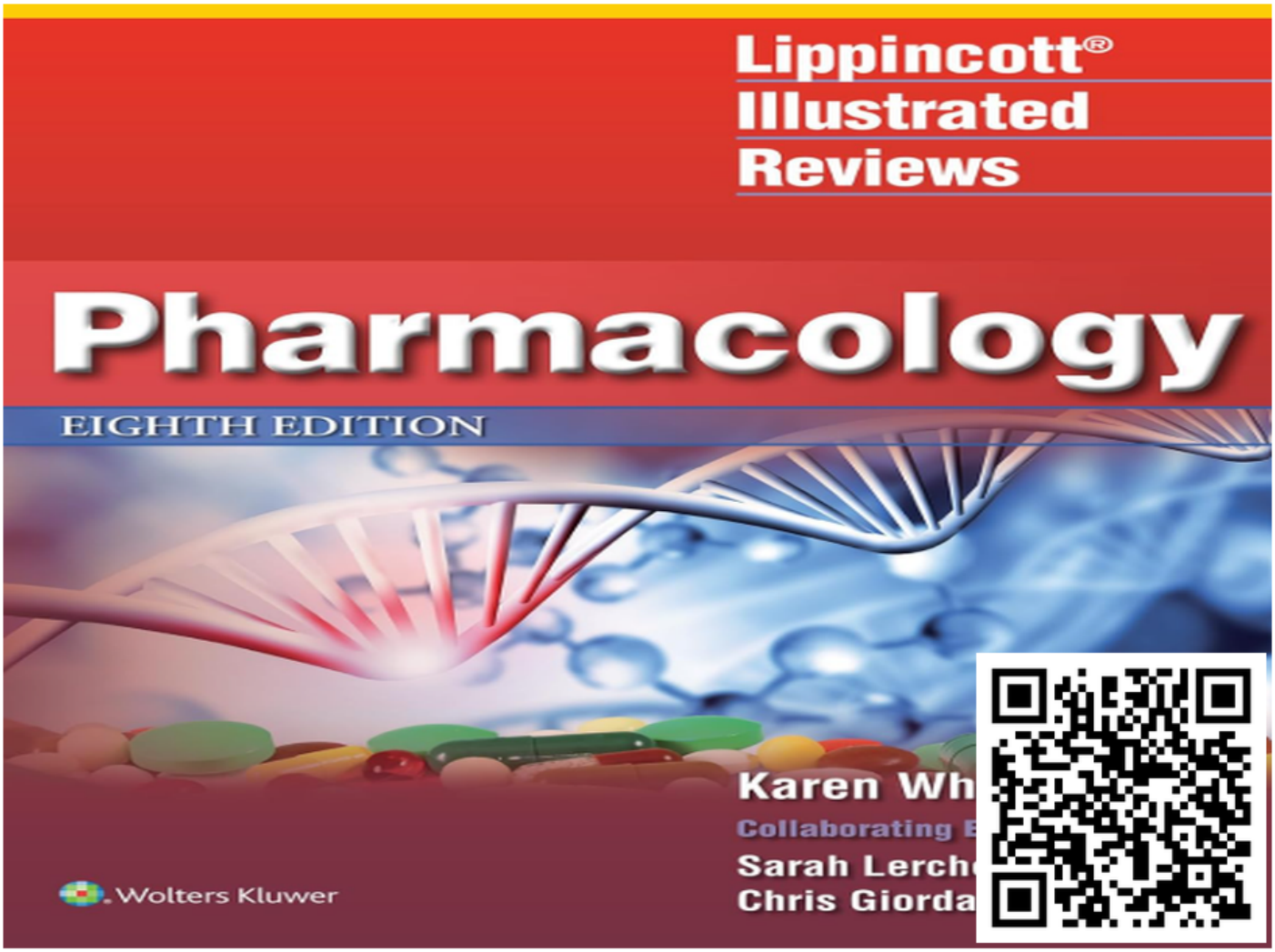

Lippincott® Illustrated Reviews

Pharmacology

EIGHTH EDITION

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Lippincott® Illustrated Reviews: Pharmacology

Eighth Edition

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Richard A. Harvey, PhD

1936–2017

Co-creator and series editor of the *Lippincott Illustrated Reviews* series, in collaboration with Pamela C. Champe, PhD (1945–2008).

Illustrator and co-author of the first books in the series: *Biochemistry, Pharmacology, and Microbiology and Immunology*.

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Table of Contents

Unit VII: Special Topics in Pharmacology

UNIT I:
Principles of Drug Therapy

1

Pharmacokinetics

Venkata Kashyap Yellepeddi

I. OVERVIEW

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Four pharmacokinetic properties determine the onset, intensity, and duration of drug action (Figure 1.1):

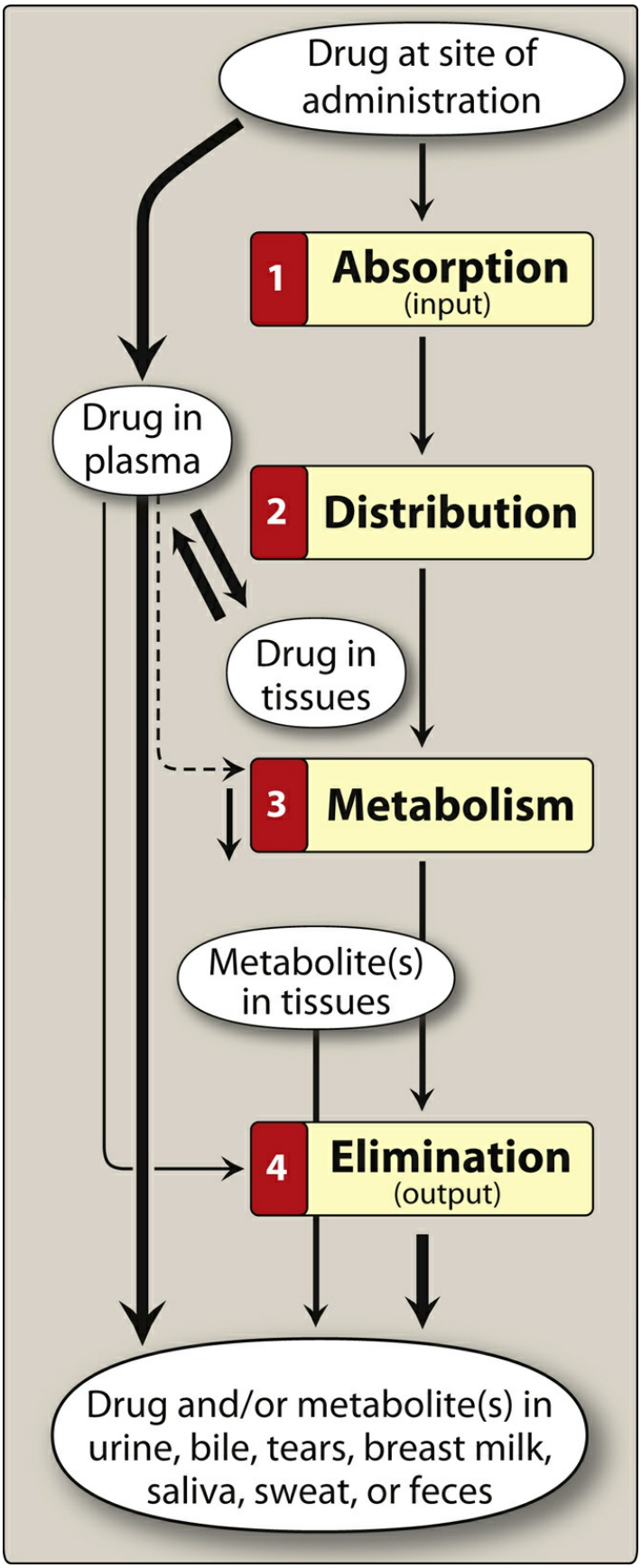

Drug at site of administration
1 Absorption (input)
Drug in plasma
2 Distribution
Drug in tissues
3 Metabolism
Metabolite(s) in tissues
4 Elimination (output)
Drug and/or metabolite(s) in urine, bile, tears, breast milk, saliva, sweat, or feces

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

- **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.

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, dose, frequency, and duration of treatment.

II. 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, among others (Figure 1.2).

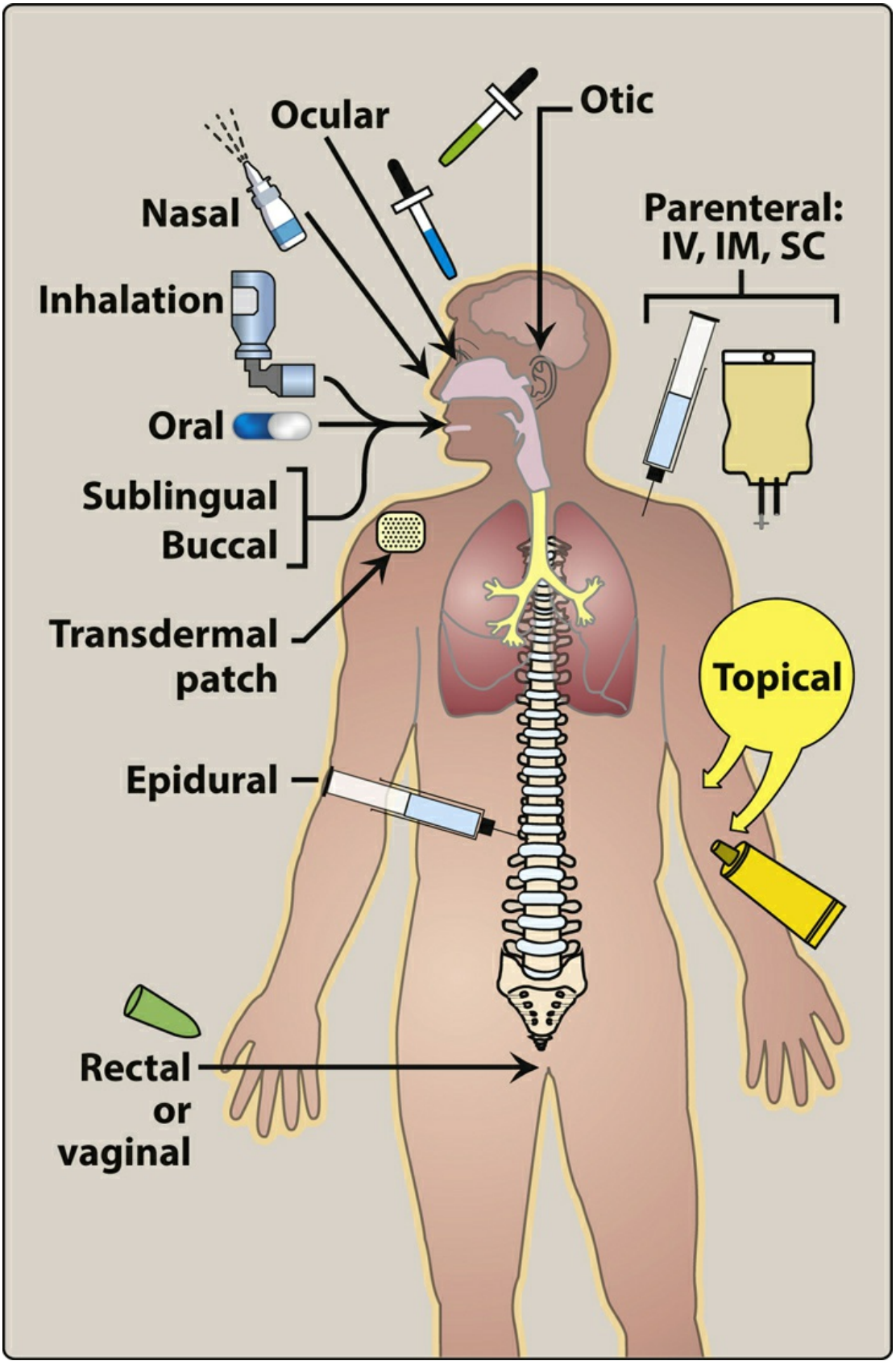

Ocular
Otic
Nasal
Parenteral:
IV, IM, SC
Inhalation
Oral
Sublingual
Buccal
Transdermal
patch
Topical
Epidural
Rectal
or
vaginal

Figure 1.2 Commonly used routes of drug administration.IV = intravenous; IM = intramuscular; SC = subcutaneous.

A. 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.

1. Oral: Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

    a. Enteric-coated preparations: An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, *omeprazole*) that are acid labile, and for drugs that are irritating to the stomach, such as *aspirin*.

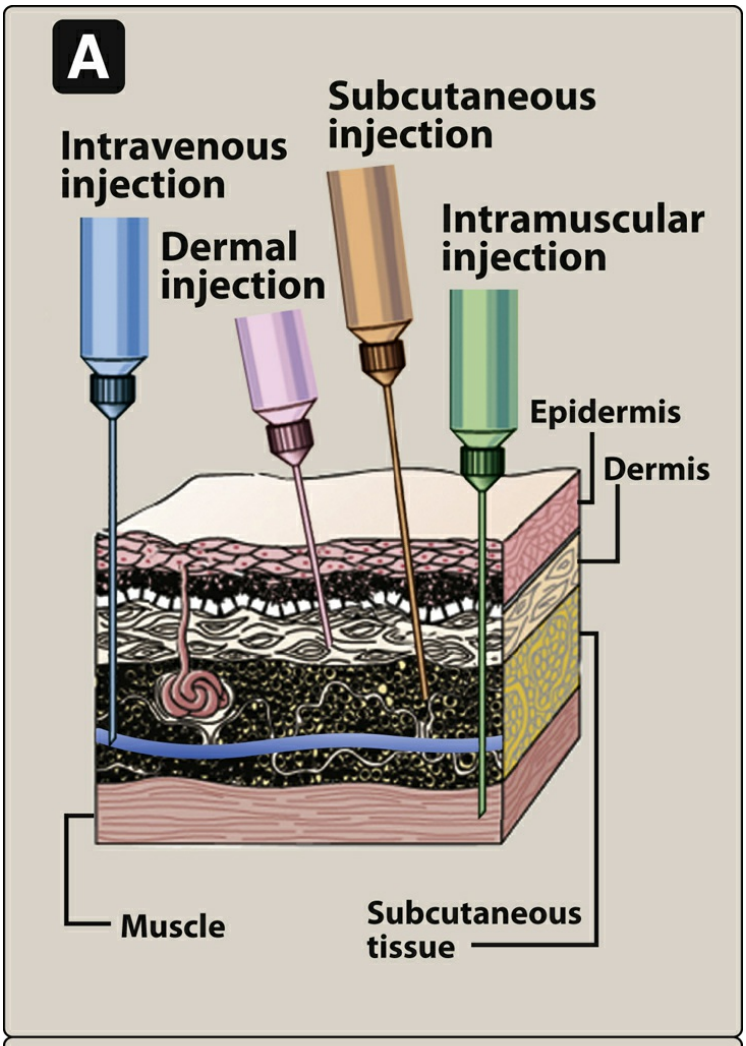
    b. Extended-release preparations: Extended-release (abbreviated ER, XR, XL, SR, CR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral *morphine* is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

2. **Sublingual/Buccal:** The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of

administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (see discussion of first-pass metabolism below).

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fear, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, subcutaneous, and intradermal (Figure 1.3).


A
Intravenous injection
Subcutaneous injection
Dermal injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

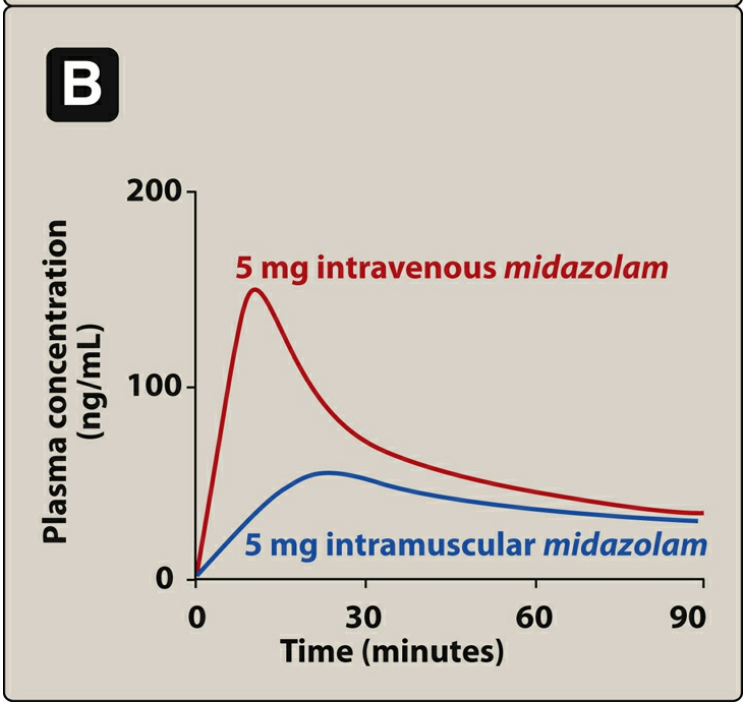

B
200
100
0
Plasma concentration (ng/mL)
5 mg intravenous midazolam
5 mg intramuscular midazolam
0
30
60
90
Time (minutes)

Figure 1.3 **A.** Schematic representation of subcutaneous and intramuscular injection. **B.** Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

1. Intravenous: Intravenous (IV) injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker *rocuronium.* IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

2. Intramuscular: Drugs administered intramuscular (IM) can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol or oil. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

3. Subcutaneous: Like IM injection, subcutaneous (SC) injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

4. Intradermal: The intradermal route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route.

C. 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/or pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an

aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. **Intrathecal/Intraventricular:** The blood–brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). 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 (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.

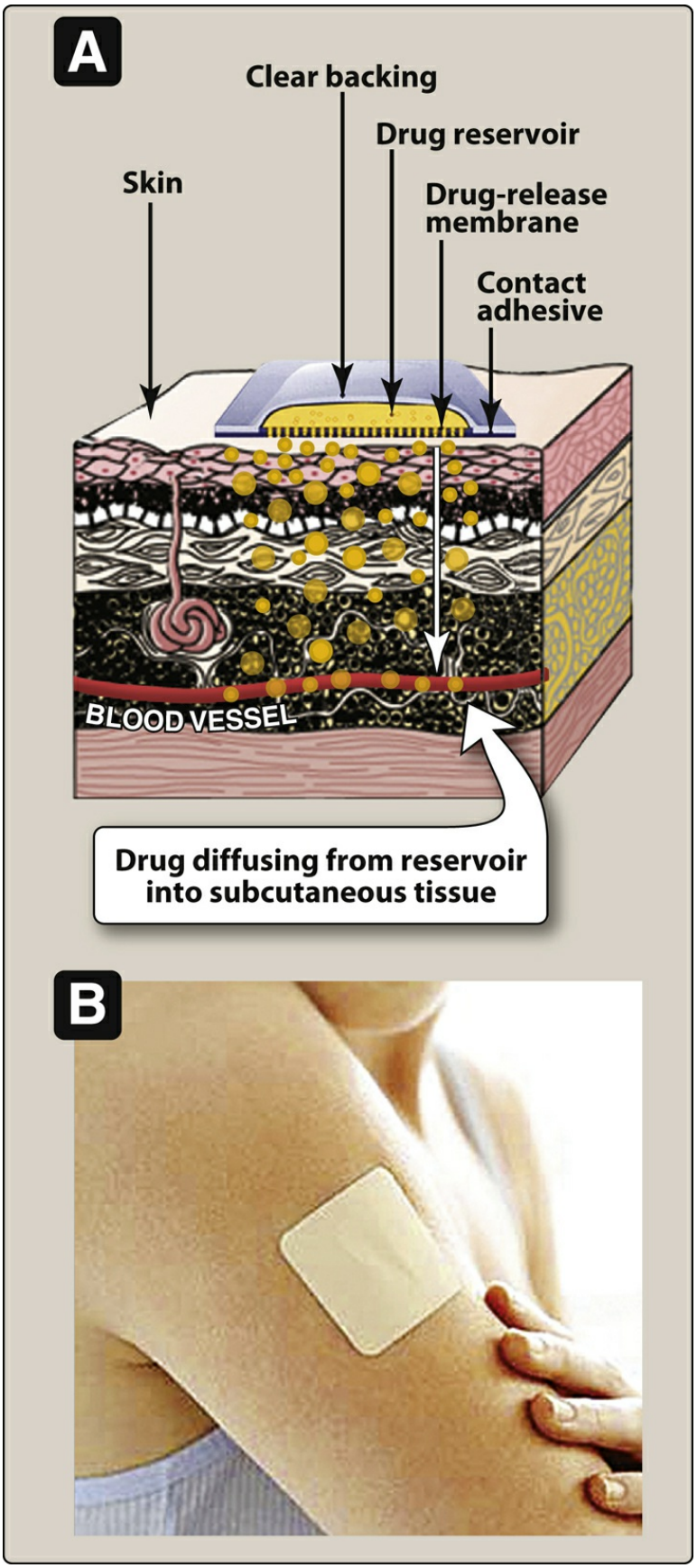

A
Clear backing
Drug reservoir
Skin
Drug-release membrane
Contact adhesive
BLOOD VESSEL
Drug diffusing from reservoir into subcutaneous tissue
B

Figure 1.4 **A.** Schematic representation of a transdermal patch. **B.** Transdermal nicotine patch applied to the arm.

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. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes characteristics of the common routes of administration, along with example drugs.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* • *Amoxicillin*
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intra-vaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream
Transdermal (patch)	• Slow and sustained	• Bypasses first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

Figure 1.5 The absorption pattern, advantages, and disadvantages of the most common routes of administration.

III. 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). 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).

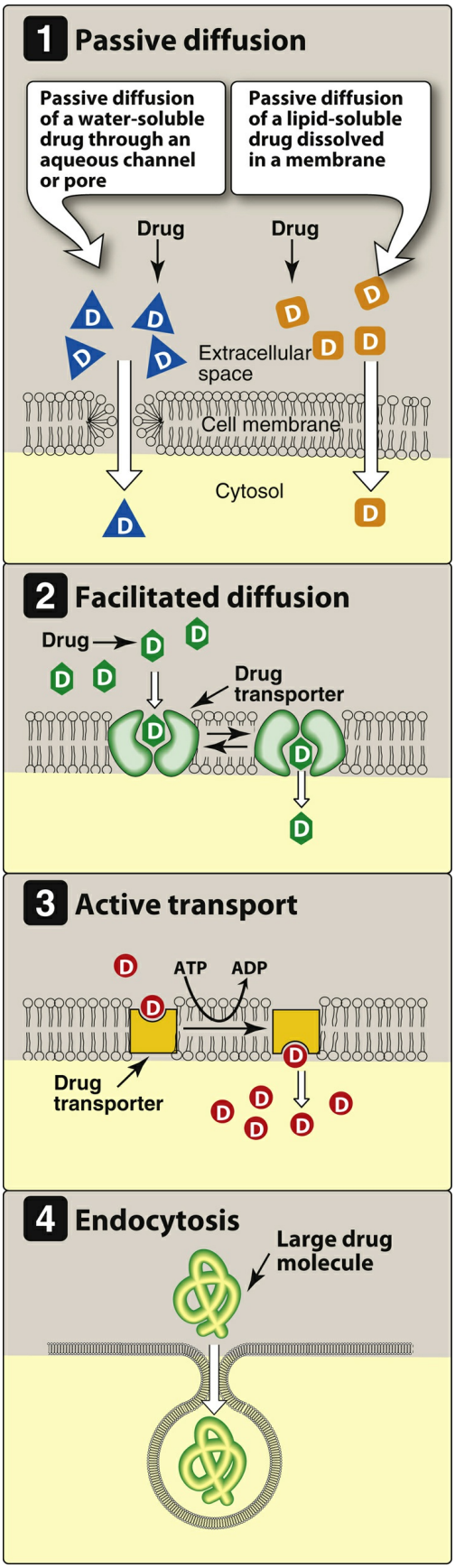

1 Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
Extracellular space
Cell membrane
Cytosol
2 Facilitated diffusion
Drug
Drug transporter
3 Active transport
ATP
ADP
Drug transporter
4 Endocytosis
Large drug molecule

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

1. **Passive diffusion:** The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, 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. 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 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. 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. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.
4. **Endocytosis:** 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. For example, Vitamin B_{12} is transported across the gut wall by endocytosis. [Note: Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the

nerve terminal and released by exocytosis.]

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:

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

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):

$$BH^+ \rightleftarrows B + H^+$$

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.

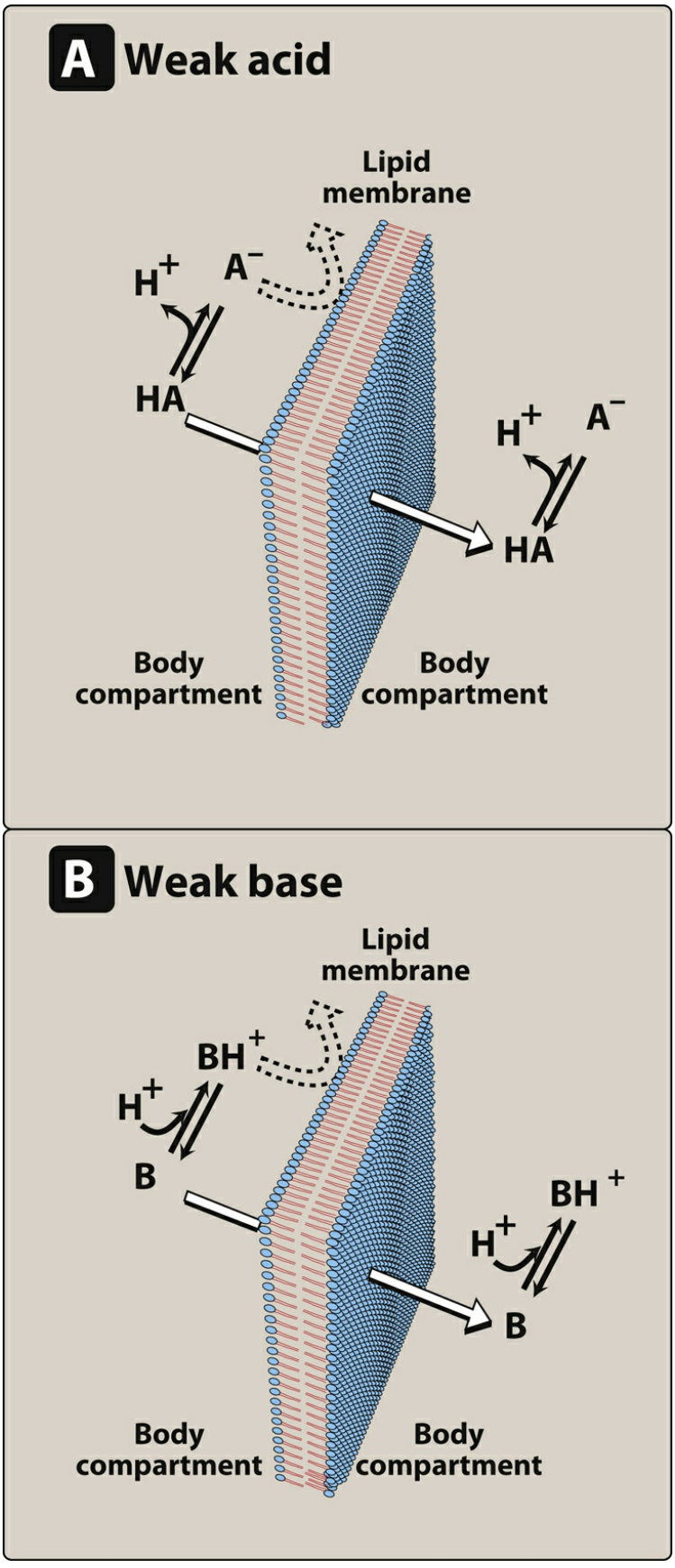

A
Weak acid
Lipid membrane
H+
A−
HA
H+
A−
HA
Body compartment
Body compartment
B
Weak base
Lipid membrane
BH+
H+
B
BH+
H+
B
Body compartment
Body compartment

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.

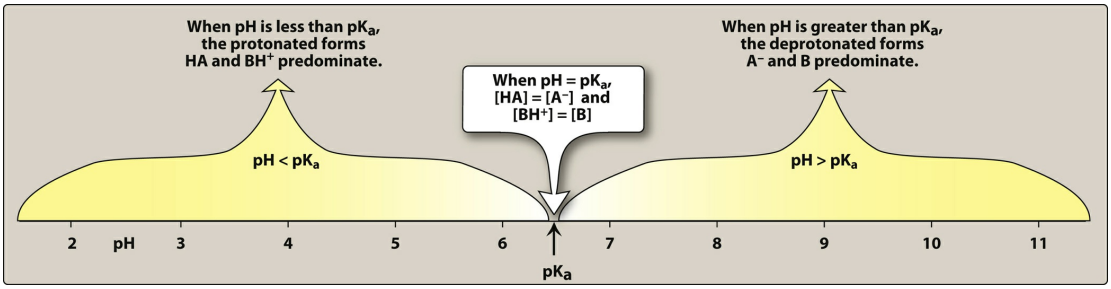


Figure 1.8 The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug.For illustrative purposes, the drug has been assigned a pK_a of 6.5.

2. **Blood flow to the absorption site:** The intestines receive much more blood flow than does 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.
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. [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 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.

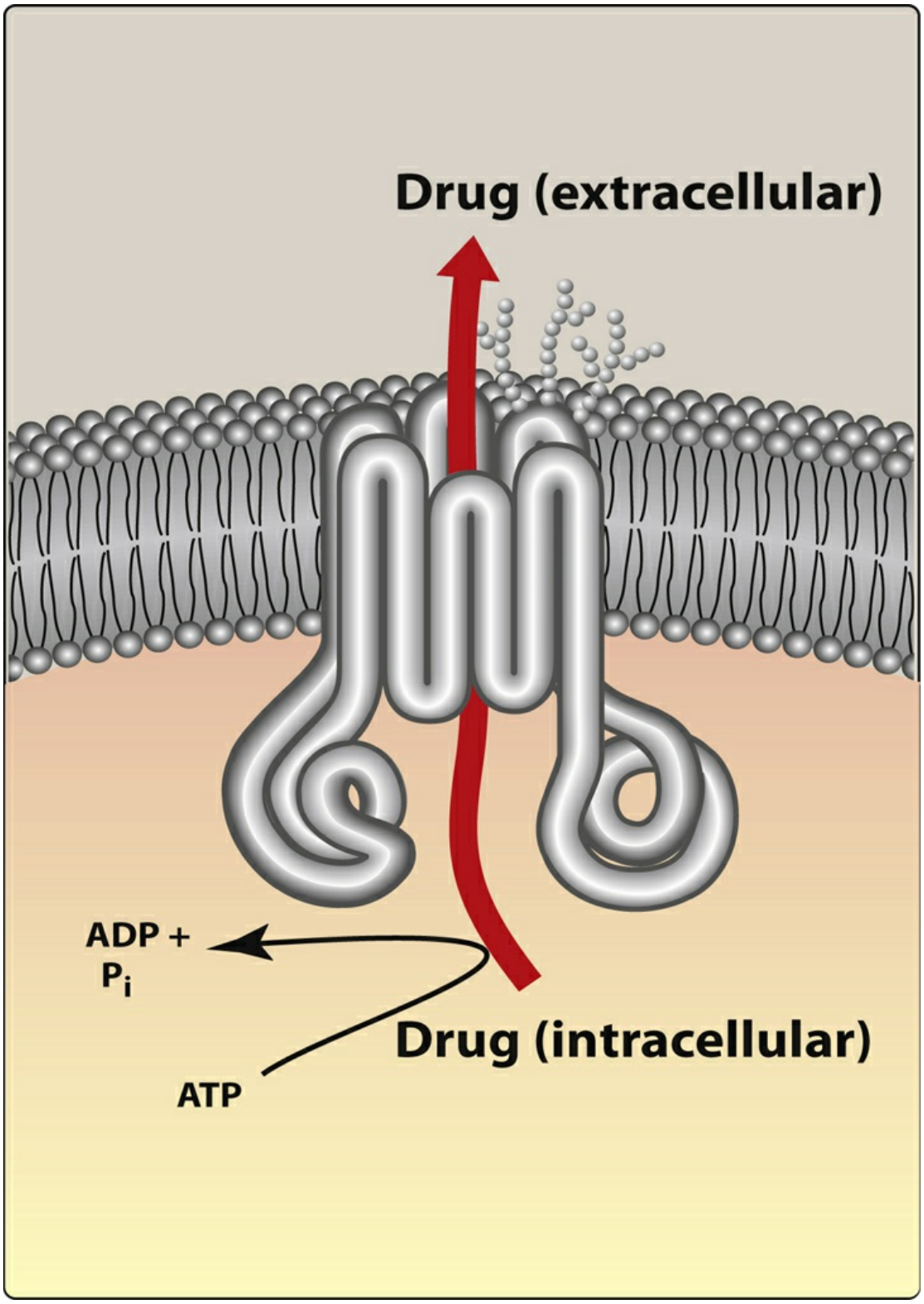


Figure 1.9 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

Clinical Application 1.1: P-glycoprotein and Multidrug Resistance in Cancer

Multidrug resistance (MDR) is a significant obstacle to achieving positive treatment outcomes with chemotherapy in cancer treatment. MDR is caused by overexpression of P-glycoprotein efflux pumps in cancer cells. P-glycoprotein pumps reduce the intracellular accumulation of anticancer drugs such as *paclitaxel*, vinca alkaloids, and anthracyclines (*doxorubicin, daunorubicin*) by effectively pumping drugs out of the cell. The reduced accumulation of chemotherapeutic drugs in cancer cells leads to resistance and ultimately results in poor prognoses in various cancers. P-glycoprotein-mediated MDR in cancer can be overcome by co-administering P-glycoprotein pump inhibitors with chemotherapeutic agents. Unfortunately, there are no approved P-glycoprotein inhibitors for clinical use in cancer chemotherapy to reverse MDR. However, several clinical trials are currently investigating the usefulness of co-administering P-glycoprotein pump inhibitors with anticancer drugs such as *paclitaxel, docetaxel, doxorubicin, and vinorelbine* to reverse MDR in various cancers.

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. A schematic depiction of determination of bioavailability is provided in Figure 1.10.

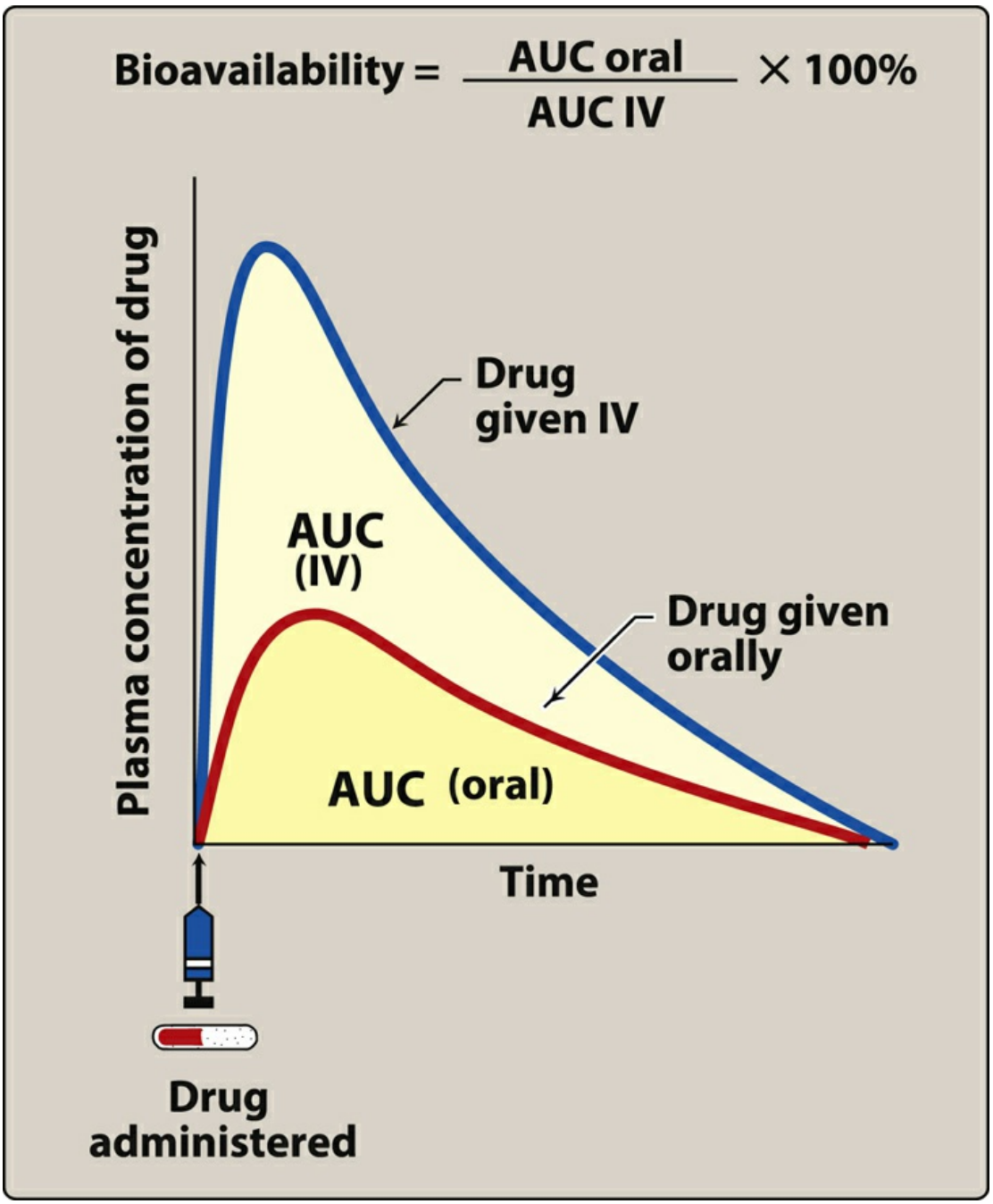


Figure 1.10 Determination of the bioavailability of a drug.AUC = area under curve; IV = intravenous.

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 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 absorbe 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, transdermal, or intravenous 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.

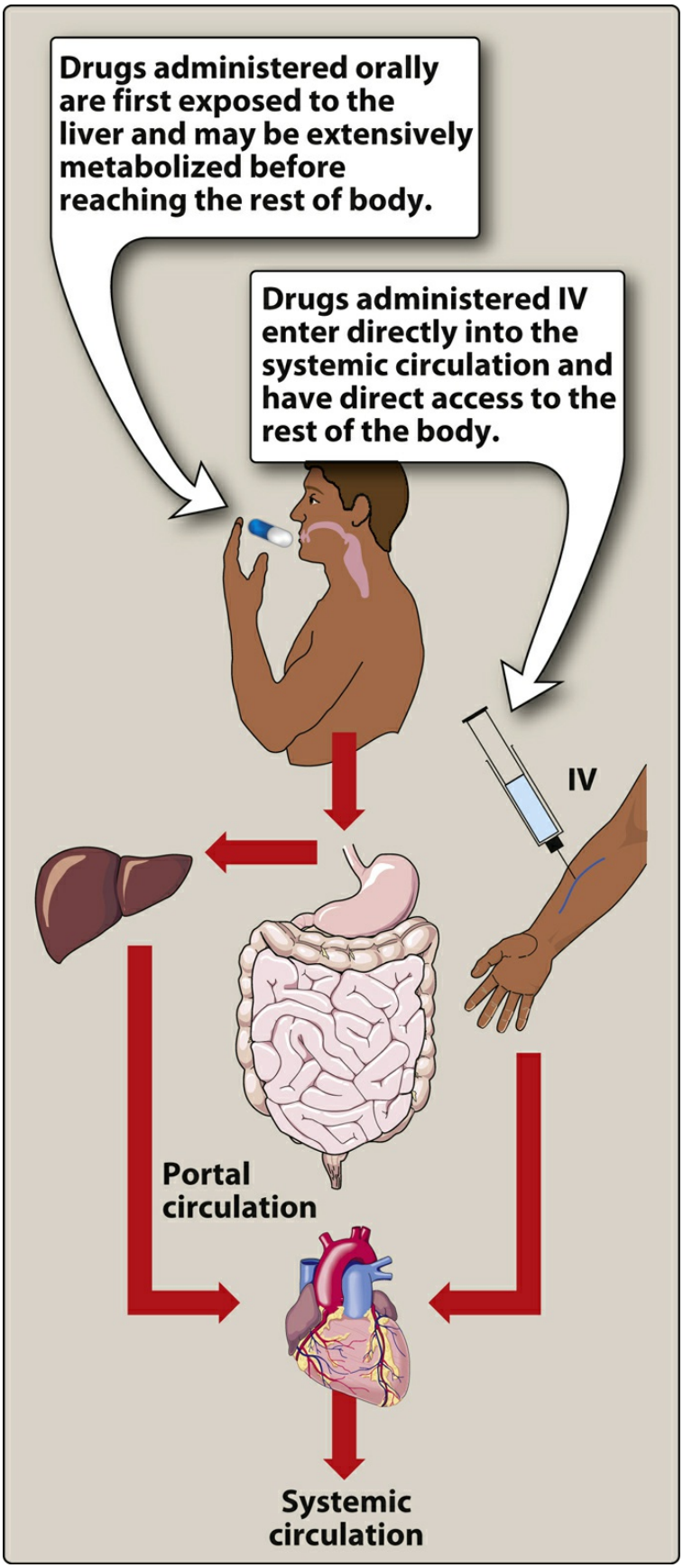

Drugs administered orally are first exposed to the liver and may be extensively metabolized before reaching the rest of body.
Drugs administered IV enter directly into the systemic circulation and have direct access to the rest of the body.
IV
Portal circulation
Systemic circulation

Figure 1.11 First-pass metabolism can occur with orally administered drugs.IV = intravenous.

b. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are 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 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 and other types of equivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence requires that drug products are bioequivalent and pharmaceutically equivalent.

IV. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues. For drugs administered IV, absorption is not a factor, and the initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues (Figure 1.12). The distribution of a drug from the plasma to the interstitium depends on cardiac

output and local blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.

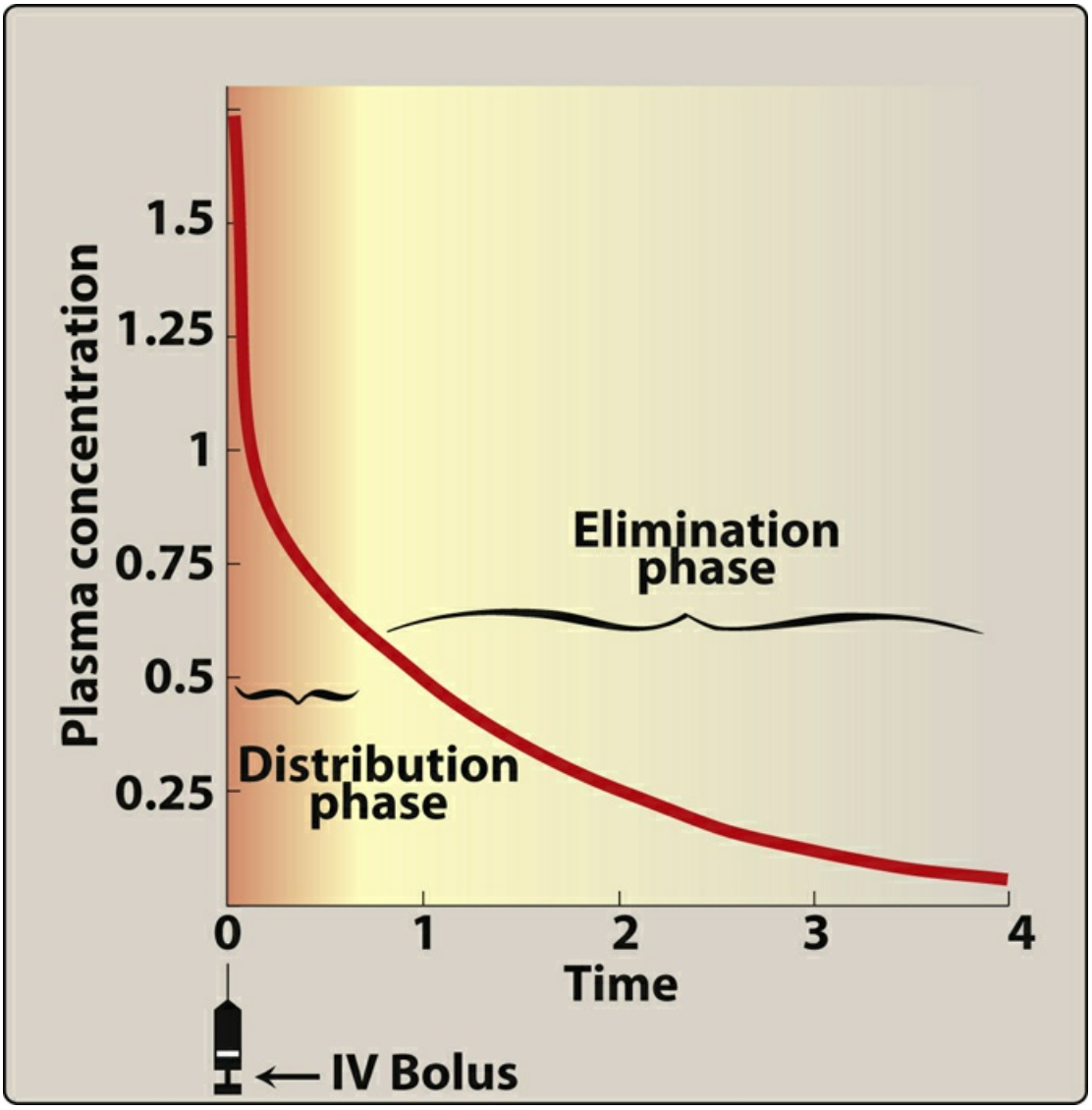


Figure 1.12 Drug concentrations in serum after a single injection of drug.Assume that the drug distributes and is subsequently eliminated.

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. Variation in blood flow partly

explains the short duration of hypnosis produced by an IV bolus of *propofol* (see Chapter 20). High blood flow, together with high lipophilicity of *propofol*, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.13A). In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.13B). To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries *levodopa* into the brain. Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions (Figure 1.13C). These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.

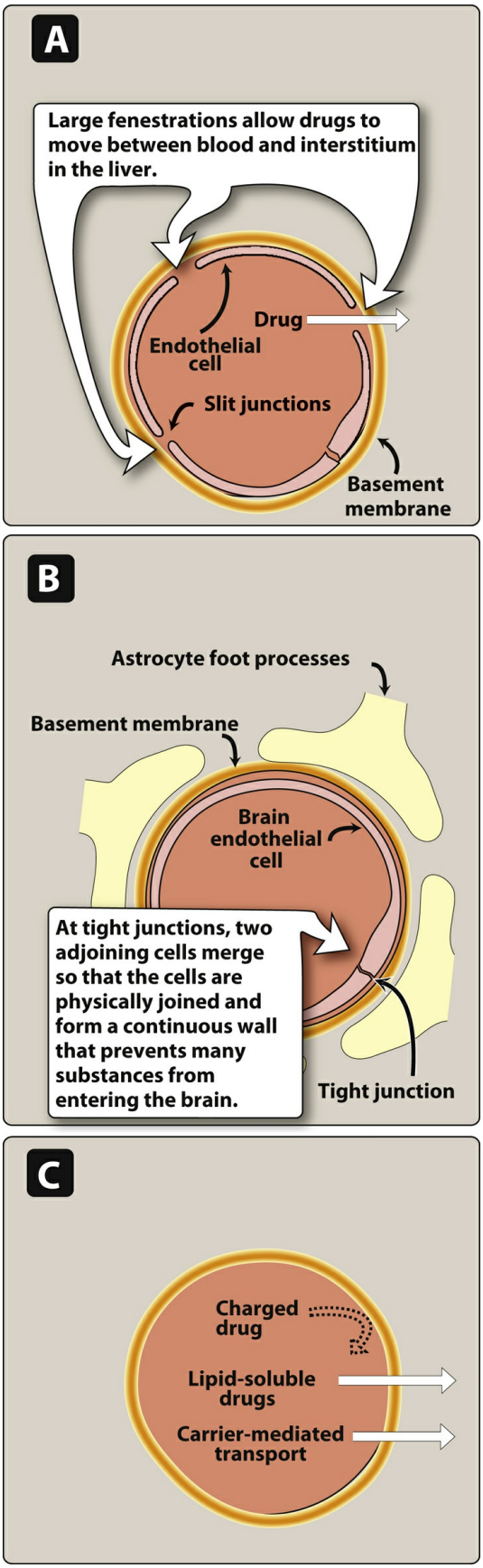

A
Large fenestrations allow drugs to move between blood and interstitium in the liver.
Drug
Endothelial cell
Slit junctions
Basement membrane
B
Astrocyte foot processes
Basement membrane
Brain endothelial cell
At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.
Tight junction
C
Charged drug
Lipid-soluble drugs
Carrier-mediated transport

Figure 1.13 Cross section of liver and brain capillaries.**A.** Structure of liver capillary. **B.** Structure of a brain capillary. **C**. Permeability of a brain capillary.

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. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide*, can cause hemorrhagic cystitis because it accumulates in the bladder.)

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, V_d, 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).

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

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. **Distribution into the water compartments in the body:** Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

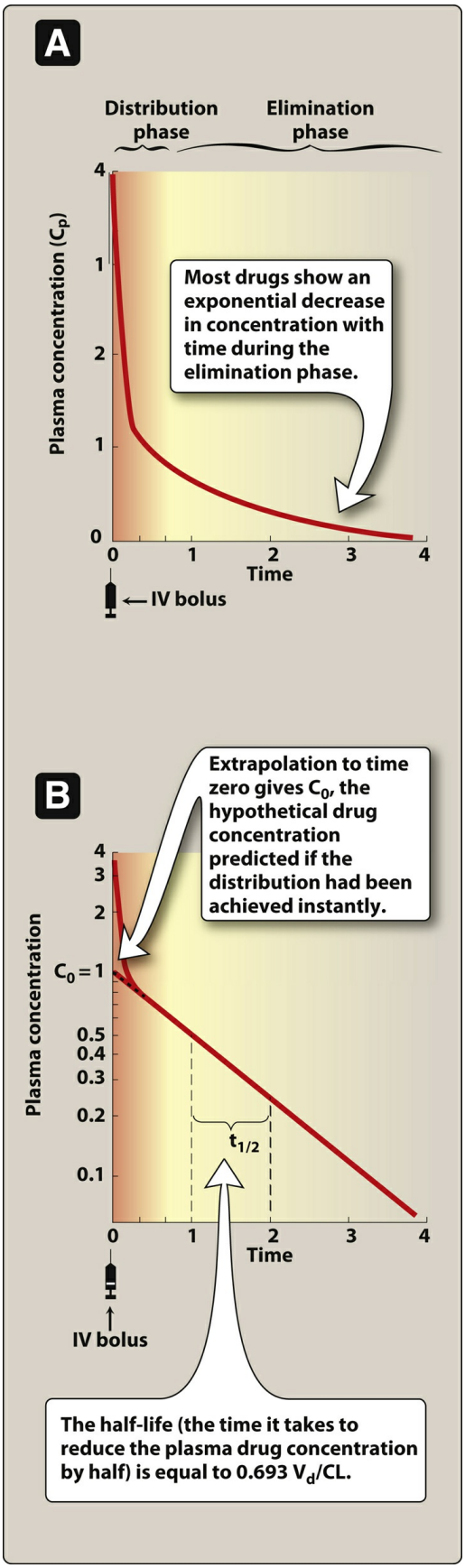
   a. **Plasma compartment:** If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. *Heparin* (see Chapter 13) 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. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, 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 L in a 70-kg individual). Aminoglycoside antibiotics (see Chapter 30) 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 V_d. [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

2. **Determination of V_d:** The fact that drug clearance is usually a first-order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time (Figure 1.14). 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 V_d as:

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


A
Distribution phase
Elimination phase
Plasma concentration (C_p)
4
1
2
1
0
0
1
2
3
4
Time
Most drugs show an exponential decrease in concentration with time during the elimination phase.
IV bolus
B
Extrapolation to time zero gives C_0, the hypothetical drug concentration predicted if the distribution had been achieved instantly.
Plasma concentration
4
3
2
$C_0 = 1$
0.5
0.4
0.3
0.2
0.1
$t_{1/2}$
0
1
2
3
4
Time
IV bolus
The half-life (the time it takes to reduce the plasma drug concentration by half) is equal to 0.693 V_d/CL.