I. DOSE–RESPONSE RELATIONSHIPS

A. Drug effects are produced by altering the normal functions of cells and tissues in the body via one of four general mechanisms:

1. Interaction with receptors, naturally occurring target macromolecules that mediate the effects of endogenous physiologic substances such as neurotransmitters and hormones.

a. Figure 1-1 illustrates the four major classes of drug–receptor interactions, using specific examples of endogenous ligands.

(1) Ligand-activated ion channels. Figure 1-1A illustrates acetylcholine interacting with a nicotinic receptor that is a nonspecific Na+/K+ transmembrane ion channel. Interaction of a molecule of acetylcholine with each subunit of the channel produces a conformational change that permits the passage of Na+ and K+.

Other channels that are targets for various drugs include specific Ca2+ and K+ channels.

(2) G-protein–coupled receptors (Fig. 1-1B–D). G-protein–coupled receptors compose the largest class of receptors. The receptors all have seven transmembrane segments, three intracellular loops, and an intracellular carboxy-terminal tail. The biologic activity of the receptors is mediated via interaction with a number of G (GTP binding)-proteins.

(a) Gαs-coupled receptors. Figure 1-1B illustrates a β-adrenoceptor, which when activated by ligand binding (e.g., epinephrine) exchanges GDP for GTP. This facilitates the migration of Gαs (Gαstimulatory) and its interaction with adenylyl cyclase (AC). Gαs-bound AC catalyzes the production of cyclic AMP (cAMP) from adenosine triphosphate (ATP); cAMP activates protein kinase A, which subsequently acts to phosphorylate and activate a number of effectors. The βγ dimer may also activate some effectors. Hydrolysis of the guanosine triphosphate (GTP) bound to the Gα to guanosine diphosphate (GDP) terminates the signal.

(b) Gαi (Gains)-coupled receptors (Fig. 1-1C). Ligand binding (e.g., somatostatin) to Gαi (Gainsinhibitory)-coupled receptors similarly exchanges GTP for GDP, but Gαi inhibits adenylyl cyclase, leading to reduced cAMP production.

(c) Gq (and G11)-coupled receptors (Fig. 1-1D). Gq (and G11) interact with ligand (e.g., serotonin)-activated receptors and increase the activity of phospholipase C (PLC). PLC cleaves the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). DAG activates protein kinase C, which can subsequently phosphorylate and activate a number of cellular proteins; IP3 causes the release of Ca2+ from the endoplasmic reticulum into the cytoplasm, where it can activate many cellular processes.

(3) Receptor-activated tyrosine kinases (Fig. 1-1E). Many growth-related signals (e.g., insulin) are mediated via membrane receptors that possess intrinsic tyrosine kinase activity as illustrated for the insulin receptor. Ligand binding causes conformational changes in the receptor; some receptor tyrosine kinases are monomers that dimerize upon ligand binding. The liganded receptors then autophosphorylate tyrosine residues, which recruits cytoplasmic proteins to the plasma membrane where they are also tyrosine phosphorylated and activated.
(4) **Intracellular nuclear receptors** (Fig. 1-1F). Ligands (e.g., cortisol) for nuclear receptors are lipophilic and can diffuse rapidly through the plasma membrane. In the absence of ligand, nuclear receptors are inactive because of their interaction with chaperone proteins such as heat-shock proteins like HSP-90. Binding of ligand promotes structural changes in the receptor that facilitate dissociation of chaperones, entry of receptors into the nucleus, hetero- or homodimerization of receptors, and high-affinity interaction with the DNA of target genes. DNA-bound nuclear receptors are able to recruit a diverse number of proteins called coactivators, which subsequently act to increase transcription of the target gene.

2. **Alteration of the activity of enzymes** by activation or inhibition of the enzyme’s catalytic activity

3. **Antimetabolite action** in which the drug, acting as a nonfunctional analogue of a naturally occurring metabolite, interferes with normal metabolism.
4. **Nonspecific chemical or physical interactions** such as those caused by antacids, osmotic agents, and chelators

B. **The graded dose–response curve** expresses an individual’s response to increasing doses of a given drug. The magnitude of a pharmacologic response is proportional to the number of receptors with which a drug effectively interacts (Fig. 1-2). The graded dose–response curve includes the following parameters:

1. **Magnitude of response** is graded; that is, it continuously increases with the dose up to the maximal capacity of the system, and it is often depicted as a function of the logarithm of the dose administered (to see the relationship over a wide range of doses).
2. \( ED_{50} \) is the dose that produces the half-maximal response; the threshold dose is that which produces the first noticeable effect.

3. **Intrinsic activity** is the ability of a drug once bound to activate the receptor.
   
a. **Agonists** are drugs capable of binding to, and activating, a receptor.
   
   (1) **Full agonists** occupy receptors to cause maximal activation; intrinsic activity = 1.
   
   (2) **Partial agonists** can occupy receptors but cannot elicit a maximal response. Such drugs have an intrinsic activity of less than 1 (Fig. 1-3; drug C).

b. **Antagonists** bind to the receptor but do not initiate a response; that is, they block the action of an agonist or endogenous substance that works through the receptor.

   (1) **Competitive antagonists** combine with the same site on the receptor as the agonist but have little or no efficacy and an intrinsic activity of 0. Competitive antagonists may be reversible or irreversible. Reversible, or equilibrium, competitive antagonists are not

---

**FIGURE 1-1.** (continued).

**FIGURE 1-2.** Graded dose–response curve.
covalently bound, shift the dose–response curve for the agonist to the right, and increase the ED$_{50}$; that is, more agonist is required to elicit a response in the presence of the antagonist (Fig. 1-4). Because higher doses of agonist can overcome the inhibition, the maximal response can still be obtained.

2. **Noncompetitive antagonists** bind to the receptor at a site other than the agonist-binding site (Fig. 1-5) and either prevent the agonist from binding correctly or prevent it from activating the receptor. Consequently, the effective amount of receptor is reduced. Receptors unoccupied by antagonist retain the same affinity for agonist, and the ED$_{50}$ is unchanged.

4. **Potency of a drug** is the relative measure of the amount of a drug required to produce a specified level of response (e.g., 50%) compared to other drugs that produce the same effect via the same receptor mechanism. The potency of a drug is determined by the affinity of a drug for its receptor and the amount of administered drug that reaches the receptor site. The relative potency of a drug can be demonstrated by comparing the ED$_{50}$ values of two full agonists; the drug with the lower ED$_{50}$ is more potent. (For example, in Fig. 1-3, drug A is more potent than drug B.)

5. **The efficacy of a drug** is the ability of a drug to elicit the pharmacologic response. Efficacy may be affected by such factors as the number of drug–receptor complexes formed, the ability of the drug to activate the receptor once it is bound, and the status of the target organ or cell.

6. **Slope** is measured at the midportion of the dose–response curve. The slope varies for different drugs and different responses. Steep dose–response curves indicate that a small change in dose produces a large change in response.

7. **Variability** reflects the differences between individuals in response to a given drug.
8. **Therapeutic index (TI)** relates the desired therapeutic effect to undesired toxicity; it is determined using data provided by the quantal dose–response curve. The therapeutic index is defined as TD\textsubscript{50}/ED\textsubscript{50} (i.e., the ratio of the dose that produces a toxic effect in half of the population to the dose that produces the desired effect in half of the population). Note that the therapeutic index should be used with caution in instances when the quantal dose–response curves for the desired and toxic effects are not parallel.

C. **The quantal dose–response curve** (Figs. 1-6A and B) relates the dosage of a drug to the frequency with which a designated response will occur within a population. The response may be an “all-or-none” phenomenon (e.g., individuals either do or do not fall asleep after receiving a sedative) or some predetermined intensity of effect. The quantal dose–response curve is obtained via transformation of the data used for a frequency distribution plot to reflect the cumulative frequency of a response. In the context of the quantal dose–response curve, ED\textsubscript{50} indicates the dose of drug that produces the response in half of the population. (Note that this differs from the meaning of ED\textsubscript{50} in a graded dose–response curve.)

II. **DRUG ABSORPTION**

Drug absorption is the movement of a drug from its site of administration into the bloodstream. In many cases, a drug must be transported across one or more biologic membranes to reach the bloodstream.

A. **Drug transport across membranes**
   1. **Diffusion of un-ionized drugs** is the most common and most important mode of traversing biologic membranes; drugs diffuse passively down their concentration gradient. Diffusion can be influenced significantly by the lipid–water partition coefficient of the drug, which is the ratio of solubility in an organic solvent to solubility in an aqueous solution. In general, absorption increases as lipid solubility (partition coefficient) increases. Other factors that also can influence diffusion include the concentration gradient of the drug across the cell membrane, and the surface area of the cell membrane.

   2. **Diffusion of drugs that are weak electrolytes**
      a. Only the un-ionized form of drug can diffuse across biologic membranes.
      b. The degree of ionization of a weak acid or base is determined by the pK of the drug and pH of its environment according to the Henderson-Hasselbalch equation.

         (1) For a weak acid, A,
         \[ \text{HA} \rightleftharpoons H^+ + A^- \]
         \[ \text{pH} = \text{pK} + \log[A^-] / [HA] \text{, and} \]
         \[ \log [A^-] / [HA] = \text{pH} - \text{pK} \]
where HA is the concentration of the protonated, or un-ionized, form of the acid and A\(^{-}\) is the concentration of the ionized, or unprotonated, form.

(2) For a weak base, B,

\[ \text{pH} = \text{pK} + \log[B]/[BH^{+}], \]

and

\[ \log[B]/[BH^{+}] = \text{pH} - \text{pK} \]

where BH\(^{+}\) is the concentration of the protonated form of the base, and B is the concentration of the unprotonated form.

c. When the pK of a drug equals the pH of the surroundings, 50% ionization occurs; that is, equal numbers of ionized and un-ionized species are present. A lower pK reflects a stronger acid; a higher pK corresponds to a stronger base.

d. Drugs with different pK values will diffuse across membranes at different rates.

e. The pH of the biologic fluid in which the drug is dissolved affects the degree of ionization and, therefore, the rate of drug transport.

3. **Active transport** is an energy-dependent process that can move drugs against a concentration gradient, as in protein-mediated transport systems. Active transport occurs in only one
direction and is saturable. It is usually the mode of transport for drugs that resemble actively transported endogenous substances such as sugars, amino acids, and nucleosides.

4. **Filtration** is the bulk flow of solvent and solute through channels (pores) in the membrane. Filtration is seen with small molecules (usually with a molecular weight less than 100) that can pass through pores. Some substances of greater molecular weight, such as certain proteins, can be filtered through intercellular channels. Concentration gradients affect the rate of filtration.

5. **Facilitated diffusion** is movement of a substance down a concentration gradient. Facilitated diffusion is carrier mediated, specific, and saturable; it does not require energy.

B. Routes of administration

1. **Oral administration** is the most convenient, economical, and common route of administration; it is generally safe for most drugs.
   a. Sites of absorption
      (1) **Stomach**
         (a) Lipid-soluble drugs and weak acids, which are normally un-ionized at the low pH (1 to 2) of gastric contents, may be absorbed directly from the stomach.
         (b) Weak bases and strong acids ($pK_a = 2$ to 3) are not normally absorbed from this site since they tend to exist as ions that carry either a positive or negative charge, respectively.
      (2) **Small intestine**
         (a) The small intestine is the primary site of absorption of most drugs because of the very large surface area across which drugs, including partially ionized weak acids and bases, may diffuse.
         (b) Acids are normally absorbed more extensively from the small intestine than from the stomach, even though the intestine has a higher pH (approximately 5).
   b. The **bioavailability of a drug** is the fraction of drug (administered by any route) that reaches the bloodstream unaltered (bioavailability $= 1$ for intravenous administration). Bioequivalence refers to the condition in which the plasma concentration versus time profiles of two drug formulations are identical.
      (1) The first-pass effect influences drug absorption by metabolism in the liver or by biliary secretion. After absorption from the stomach or small intestine, a drug must pass through the liver before reaching the general circulation and its target site. If the capacity of liver metabolic enzymes to inactivate the drug is great, only limited amounts of active drug will escape the process. Some drugs are metabolized so extensively as a result of hepatic metabolism during the first pass that it precludes their use.
      (2) Other factors that may alter absorption from the stomach or small intestine include the following:
         (a) Gastric emptying time and passage of drug to the intestine may be influenced by gastric contents and intestinal motility. A decreased emptying time generally decreases the rate of absorption because the intestine is the major absorptive site for most orally administered drugs.
         (b) Gastrointestinal (GI) blood flow plays an important role in drug absorption by continuously maintaining the concentration gradient across epithelial membranes. The absorption of small, very lipid-soluble molecules is "blood flow limited;" whereas highly polar molecules are "blood flow independent."
         (c) Stomach acid and inactivating enzymes may destroy certain drugs. Enteric coating prevents breakdown of tablets by the acid pH of the stomach.
         (d) Interactions with food, other drugs, and other constituents of the gastric milieu may influence absorption.
         (e) Inert ingredients in oral preparations or the special formulation of those preparations may alter absorption.
   2. **Parenteral administration** includes three major routes: intravenous (IV), intramuscular (IM), and subcutaneous (SC). Parenteral administration generally results in more predictable bioavailability than oral administration.
a. With IV administration, the drug is injected directly into the bloodstream (100% bioavailable). It represents the most rapid means of introducing drugs into the body and is particularly useful in the treatment of emergencies when absolute control of drug administration is essential.

b. After IM and SC administration, many drugs can enter the capillaries directly through “pores” between endothelial cells. Depot preparations for sustained release may be administered by IM or SC routes, but some preparations may cause irritation and pain.

3. Other routes of administration
   a. Inhalation results in rapid absorption because of the large surface area and rich blood supply of the alveoli. Inhalation is frequently used for gaseous anesthetics, but it is generally not practical. Inhalation may be useful for drugs that act on the airways, such as epinephrine and glucocorticoids, which are used to treat bronchial asthma.
   b. Sublingual administration is useful for drugs with high first-pass metabolism, such as nitroglycerin, since hepatic metabolism is bypassed.
   c. Intrathecal administration is useful for drugs that do not readily cross the blood–brain barrier.
   d. Rectal administration minimizes first-pass metabolism and may be used to circumvent the nausea and vomiting that sometimes result from oral administration. Use of rectal administration may be limited by inconvenience or patient noncompliance.
   e. Topical administration is used widely when a local effect is desired or to minimize systemic effects, especially in dermatology and ophthalmology. Preparations must be nonirritating. Note that drugs administered topically may sometimes produce systemic effects.

III. DRUG DISTRIBUTION

Drug distribution is the movement of a drug from the bloodstream to the various tissues of the body.

A. Distribution of drugs is the process by which a drug leaves the bloodstream and enters the extracellular fluids and tissues. A drug must diffuse across cellular membranes if its site of action is intracellular. In this case, lipid solubility is important for effective distribution.

1. Importance of blood flow
   a. In most tissues, drugs can leave the circulation readily by diffusion across or between capillary endothelial cells. Thus, the initial rate of distribution of a drug depends heavily on blood flow to various organs (brain, liver, kidney > muscle, skin > fat, bone).
   b. At equilibrium, or steady state, the amount of drug in an organ is related to the mass of the organ and its properties, as well as to the properties of the specific drug.

2. Volume of distribution (V_d) is the volume of total body fluid into which a drug “appears” to distribute after it reaches equilibrium in the body. Volume of distribution is determined by administering a known dose of drug (expressed in units of mass) intravenously and measuring the initial plasma concentration (expressed in units of mass/volume):

\[ V_d = \frac{\text{amount of drug administered (m/g)}}{\text{initial plasma concentration (mg/L)}} \]

Volume of distribution is expressed in units of volume. In most cases, the “initial” plasma concentration, C_0, is determined by extrapolation from the elimination phase (see VII).

a. Standard values of volumes of fluid compartments in an average 70-kg adult are as follows: plasma = 3 liters; extracellular fluid = 12 liters; and total body water = 41 liters.

b. Features of volume of distribution:
   (1) V_d values for most drugs do not represent their actual distribution in bodily fluids. The use of V_d values is primarily conceptual; that is, drugs that distribute extensively have relatively large V_d values and vice versa.
   (2) A very low V_d value may indicate extensive plasma protein binding of the drug. A very high value may indicate that the drug is extensively bound to tissue sites.
   (3) Among other variables, V_d may be influenced by age, sex, weight, and disease processes (e.g., edema, ascites).
3. **Drug redistribution** describes when the relative distribution of a drug in the body changes with time. This is usually seen with highly lipophilic drugs such as thiopental that initially enter tissues with high blood flow (e.g., the brain) and then quickly redistribute to tissues with lower blood flow (e.g., skeletal muscle and adipose tissue).

4. **Barriers to drug distribution**
   a. Blood–brain barrier
      1. Because of the nature of the blood–brain barrier, ionized or polar drugs distribute poorly to the CNS, including certain chemotherapeutic agents and toxic compounds, because they must pass through, rather than between, endothelial cells.
      2. Inflammation, such as that resulting from meningitis, may increase the ability of ionized, poorly soluble drugs to cross the blood–brain barrier.
      3. The blood–brain barrier may not be fully developed at the time of birth.
   b. Placental barrier
      1. Lipid-soluble drugs cross the placental barrier more easily than polar drugs; drugs with a molecular weight of less than 600 pass the placental barrier better than larger molecules.
      2. The possibility that drugs administered to the mother may cross the placenta and reach the fetus is always an important consideration in therapy.
      3. Drug transporters (e.g., the P-glycoprotein transporter) transfer drugs out of the fetus.

B. **Binding of drugs by plasma proteins.** Drugs in the plasma may exist in the free form or may be bound to plasma proteins or other blood components, such as red blood cells.

1. **General features of plasma protein binding**
   a. The extent of plasma protein binding is highly variable and ranges from virtually 0% to more than 99% bound, depending on the specific drug. Binding is generally reversible.
   b. Only the free drug is small enough to pass through the spaces between the endothelial cells that form the capillaries; extensive binding retards the rate at which the drug reaches its site of action and may prolong duration of action.
   c. Some plasma proteins bind many different drugs, whereas other proteins bind only one or a limited number. For example, serum albumin tends to bind many acidic drugs, whereas α₁-acid glycoprotein tends to bind many basic drugs.
   d. There are few, if any, documented changes in a drug’s effect due to changes in plasma protein binding.

IV. DRUG ELIMINATION AND TERMINATION OF ACTION

A. **Mechanisms of drug elimination and termination of action**
   1. In most cases, the action of a drug is terminated by enzyme-catalyzed conversion to an inactive (or less active) compound and/or elimination from the body via the kidney or other routes.
   2. Redistribution of drugs from the site of action may terminate the action of a drug, although this occurs infrequently. For example, the action of the anesthetic thiopental is terminated largely by its redistribution from the brain (where it initially accumulates as a result of its high lipid solubility and the high blood flow to that organ) to the more poorly perfused adipose tissue.

B. **Rate of drug elimination from the body**
   1. **First-order elimination.** The elimination of most drugs at therapeutic doses is “first-order,” where a constant fraction of drug is eliminated per unit time; that is, the rate of elimination depends on the concentration of drug in the plasma, and is equal to the plasma concentration of the drug multiplied by a proportionality constant:

   \[
   \text{Rate of elimination from body (mass/time)} = \text{Constant} \times [\text{Drug}]_{\text{plasma}} \text{(mass/vol)}
   \]

   Because the rate of elimination is given in units of mass/time and concentration is in units of mass/volume, the units of the constant are volume/time. This constant is referred to as the “clearance” of the drug (see IV C).
2. Zero-order kinetics. Infrequently, the rate of elimination of a drug is “zero-order,” where a constant amount of drug is eliminated per unit time. In this case, the mechanism by which the body eliminates the drug (e.g., metabolism by hepatic enzymes, active secretion in the kidney) is saturated. The rate of drug elimination from the body is thus constant and does not depend on plasma concentration.

C. Clearance (CL). Conceptually, clearance is a measure of the capacity of the body to remove a drug. Mathematically, clearance is the proportionality constant that relates the rate of drug elimination to the plasma concentration of the drug. Thus, drugs with “high” clearance are rapidly removed from the body, and drugs with “low” clearance are removed slowly. As noted in IV B, the units of clearance are volume/time.

1. Specific organ clearance is the capacity of an individual organ to eliminate a drug. Specific organ clearance may be due to metabolism (e.g., “hepatic clearance” by the liver) or excretion (e.g., “renal clearance” by elimination in the urine).

   \[
   \text{Rate of elimination by organ} = \text{CL}_{\text{organ}} \times [\text{Drug}]_{\text{plasma perfusing organ}}
   \]

   or

   \[
   \text{CL}_{\text{organ}} = \frac{\text{Rate of elimination by organ}}{[\text{Drug}]_{\text{plasma perfusing organ}}}
   \]

2. Whole body clearance is the capacity of the body to eliminate the drug by all mechanisms. Therefore, whole body clearance is equal to the sum of all of the specific organ clearance mechanisms by which the active drug is eliminated from the body:

   \[
   \text{CL}_{\text{whole body}} = \text{CL}_{\text{organ 1}} + \text{CL}_{\text{organ 2}} + \cdots + \text{CL}_{\text{organ N}}
   \]

   The term “clearance” generally refers to whole body clearance unless otherwise specified. In this case,

   \[
   \text{Rate of elimination from body} = \text{CL}_{\text{whole body}} \times [\text{Drug}]_{\text{plasma}}
   \]

   and

   \[
   \text{CL}_{\text{whole body}} = \frac{\text{Rate of elimination from body}}{[\text{Drug}]_{\text{plasma}}}
   \]

3. Plasma clearance is numerically the same as whole body clearance, but this terminology is sometimes used because clearance may be viewed as the volume of plasma that contains the amount of drug removed per unit time (recall that the units of clearance are volume/time). If not specified, this term refers to the volume of plasma “cleared” of drug by all bodily mechanisms (i.e., whole body clearance). The term may also be applied to clearance by specific organs; for example, renal plasma clearance is the volume of plasma containing the amount of drug eliminated in the urine per unit time.

V. BIOTRANSFORMATION (METABOLISM) OF DRUGS

A. General properties

1. Biotransformation is a major mechanism for drug elimination; most drugs undergo biotransformation, or metabolism, after they enter the body. Biotransformation, which almost always produces metabolites that are more polar than the parent drug, usually terminates the pharmacologic action of the parent drug and, via excretion, increases removal of the drug from the body. However, other consequences are possible, notably after phase I reactions, including similar or different pharmacologic activity, or toxicologic activity.

2. Many drugs undergo several sequential biotransformation reactions. Biotransformation is catalyzed by specific enzyme systems, which may also catalyze the metabolism of endogenous substances such as steroid hormones.
3. The liver is the major site of biotransformation, although specific drugs may undergo biotransformation primarily or extensively in other tissues.

4. Biotransformation of drugs is variable and can be affected by many parameters, including prior administration of the drug in question or of other drugs; diet; hormonal status; genetics; disease (e.g., decreased in cardiac and pulmonary disease); age and developmental status (the very elderly and very young may be more sensitive to drugs, in part, because of decreased or undeveloped levels of drug-metabolizing enzymes); and liver function (in cases of severe liver damage, dosage adjustments may be required for drugs eliminated largely via this route).

5. Possible consequences of biotransformation include the production of inactive metabolites (most common), metabolites with increased or decreased potencies, metabolites with qualitatively different pharmacologic actions, toxic metabolites, or active metabolites from inactive prodrugs.

6. Metabolites carry ionizable groups, and are often more charged and more polar than the parent compounds. This increased charge may lead to a more rapid rate of clearance because of possible secretion by acid or base carriers in the kidney; it may also lead to decreased tubular reabsorption.

B. Classification of biotransformation reactions

1. Phase I (nonsynthetic) reactions involve enzyme-catalyzed biotransformation of the drug without any conjugations. Phase I reactions include oxidations, reductions, and hydrolysis reactions; they frequently introduce a functional group (e.g., –OH) that serves as the active center for sequential conjugation in a phase II reaction.

2. Phase II (synthetic) reactions include conjugation reactions, which involve the enzyme-catalyzed combination of a drug (or drug metabolite) with an endogenous substance. Phase II reactions require a functional group—an active center—as the site of conjugation with the endogenous substance. Phase II reactions require energy indirectly for the synthesis of “activated carriers,” the form of the endogenous substance used in the conjugation reaction (e.g., uridine diphosphate [UDP]-glucuronate).

C. Enzymes catalyzing phase I biotransformation reactions include cytochrome P-450, aldehyde and alcohol dehydrogenase, deaminases, esterases, amidases, and epoxide hydratases. Enzymes catalyzing phase II biotransformation reactions include glucuronyl transferase (glucuronide conjugation), sulfotransferase (sulfate conjugation), transacylases (amino acid conjugation), acetylases, ethylases, methylases, and glutathione transferase. These enzymes are present in numerous tissues; some are present in plasma. Subcellular locations include cytosol, mitochondria, and endoplasmic reticulum. Only those enzymes located in the endoplasmic reticulum are inducible by drugs.

1. Cytochrome P-450 monooxygenase (mixed function oxidase)

a. General features (Table 1-1)

   (1) Cytochrome P-450 monooxygenase plays a central role in drug biotransformation. A large number of families (at least 18 in mammals) of cytochrome P-450 (abbreviated “CYP”) enzymes exists, each member of which catalyzes the biotransformation of a unique spectrum of drugs, with some overlap in the substrate specificities. This enzyme system is the one most frequently involved in phase I reactions.

   (2) The cytochrome P-450 families are referred to using an arabic numeral (e.g., CYP1, CYP2, etc.). Each family has a number of subfamilies denoted by an upper case letter (e.g., CYP2A, CYP2B, etc.). The individual enzymes within each subfamily are denoted by another arabic numeral (e.g., CYP3A1, CYP3A2, etc.).

   (3) Cytochrome P-450 catalyzes numerous reactions, including aromatic and aliphatic hydroxylations; dealkylations at nitrogen, sulfur, and oxygen atoms; heteroatom oxidations at nitrogen and sulfur atoms; reductions at nitrogen atoms; and ester and amide hydrolysis.

   (4) The CYP3A subfamily is responsible for up to half of the total cytochrome P-450 in the liver and accounts for approximately 50% of the metabolism of clinically important drugs. CYP3A4 is a particularly abundant enzyme.
b. **Localization.** The primary location of cytochrome P-450 is the liver, which has the greatest specific enzymatic activity and the highest total activity; but it is also found in many other tissues, including the adrenals, ovaries and testis, and tissues involved in steroidogenesis and steroid metabolism. The enzyme’s subcellular location is the endoplasmic reticulum. Lipid membrane location facilitates the metabolism of lipid-soluble drugs.

c. **Mechanism of reaction**

(1) In the overall reaction, the drug is oxidized and oxygen is reduced to water. Reducing equivalents are provided by nicotinamide adenine dinucleotide phosphate (NADPH), and generation of this cofactor is coupled to cytochrome P-450 reductase.

(2) The overall reaction for aromatic hydroxylation can be described as

\[
\text{Drug} + \text{O}_2 + \text{NADPH} + \text{H}^+ \rightarrow \text{Drug} - \text{OH} + \text{NADP}^+ + \text{H}_2\text{O}
\]

d. **Genetic polymorphism** of several clinically important cytochrome P-450s, particularly CYP2C and CYP2D, is a source of variable metabolism in humans, including differences among racial and ethnic groups. These enzymes have substantially different properties (V_max or K_m).

e. **Induction** (Table 1-1)

(1) Induction is brought about by drugs and endogenous substances, such as hormones. Any given drug preferentially induces one form of cytochrome P-450 or a particular set of P-450s.

(2) When caused by drugs, induction is pharmacologically important as a major source of drug interactions. A drug may induce its own metabolism (metabolic tolerance) and that of other drugs catalyzed by the induced P-450.

### Table 1-1

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Drug Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Clozapine, imipramine, mexiletine, naproxen, tacrine, sertraline</td>
<td>Cimetidine, fluvoxamine, ticlopidine</td>
<td>Omeprazole, tobacco</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Diclofenac, glipizide, ibuprofen, losartan, naproxen, phenytion, piroxicam, tamoxifen, tolbutamide, warfarin</td>
<td>Amiodarone, fluconazole, isoniazid</td>
<td>Rifampin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Amitriptyline, clomipramine, cyclophosphamide, diazepam, omeprazole, phenytion, progesterone</td>
<td>Fluoxetine, fluvoxamine, ketoconazole, omeprazole, ticlopidine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>β-blockers: Metoprolol, propranolol, timolol</td>
<td>Amiodarone, bupropion, chlorpheniramine, cimetidine, clomipramine, fluoxetine, haloperidol, methadone, paroxetine, quinidine, ritonavir</td>
<td></td>
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<tr>
<td></td>
<td>Antiarrhythmic agents: Mexiletine</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>CNS agents: Amitriptyline, clomipramine, codeine, desipramine, imipramine, dextromethorphan haloperidol, paroxetine, risperidone, thioridazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4,5,7</td>
<td>Calcium channel blockers: Diltiazem, felodipine, nifedipine, verapamil</td>
<td>Amiodarone, cimetidine, clarithromycin, clindamycin, erythromycin, fluvoxamine, grapefruit juice, indinavir, imatinib, isoniazid,itraconazole, nefazodone, nelfinavir, ritonavir, verapamil</td>
<td>Carbamazepine, phenobarbital, phenytoin, rifampin, St. John’s wort, troglitazone</td>
</tr>
<tr>
<td></td>
<td>HMG-CoA reductase inhibitors: Atorvastatin, lovastatin, simvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CNS agents: Alprazolam, buspirone, diazepam, methadone, midazolam, triazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macrolide antibiotics: Clarithromycin, erythromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticancer agents: Cyclophosphamide, tamoxifen, vinblastine, vincristine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV protease inhibitors: Indinavir, ritonavir, saquinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: Chlorpheniramine, cyclosporine, quinidine, tacrolimus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Induction can be caused by a wide variety of clinically useful drugs (drug–drug interactions), such as omeprazole, rifampin, carbamazepine, and St. John’s wort.

Some of the same drugs that induce CYP3A4 can induce the drug efflux transporter P-glycoprotein (e.g., rifampin, St. John’s wort).

**Inhibition** (Table 1-1)

1. Competitive or noncompetitive (clinically more likely) inhibition of P-450 enzyme activity can result in the reduced metabolism of other drugs or endogenous substrates such as testosterone.

2. Inhibition can be caused by a number of commonly used drugs, including cimetidine, fluconazole, fluoxetine, and erythromycin, and is another major source of drug–drug interactions.

3. Some of the same drugs that inhibit CYP3A4 can inhibit the drug efflux transporter P-glycoprotein (e.g., amiodarone, clarithromycin, erythromycin, ketoconazole).

### 2. Glucuronyl transferase

**a. General features**

1. Glucuronyl transferase is a set of enzymes with unique but overlapping specificities that are involved in phase II reactions.

2. It catalyzes the conjugation of glucuronic acid to a variety of active centers, including –OH, –COOH, –SH, and –NH₂.

**b. Mechanism of reaction**

1. UDP-glucuronic acid, the active glucuronide donor, is formed from uridine triphosphate (UTP) and glucose 1-phosphate.

2. Glucuronyl transferase then catalyzes the conjugation to the active center of the drug.

**c. Location and induction**

1. Glucuronyl transferase is located in the endoplasmic reticulum.

2. It is the only phase II reaction that is inducible by drugs and is a possible site of drug interactions.

### D. Hepatic extraction of drugs

General extraction by the liver occurs because of the liver’s large size (1500 g) and high blood flow (1 mL/g/min).

1. **The extraction ratio** is the amount of drug removed in the liver divided by the amount of drug entering the organ; a drug completely extracted by the liver would have an extraction ratio of 1. Highly extracted drugs can have a hepatic clearance approaching 1500 mL/min.

2. **First-pass effect.** Drugs taken orally pass across membranes of the GI tract into the portal vein and through the liver before entering the general circulation.

   a. **Bioavailability** of orally administered drugs is decreased by the fraction of drug removed by the first pass through the liver. For example, a drug with a hepatic extraction ratio of 1 would have 0% bioavailability; a drug such as lidocaine, with an extraction ratio of 0.7, would have 30% bioavailability.

   b. In the presence of hepatic disease, drugs with a high first-pass extraction may reach the systemic circulation in higher than normal amounts, and dose adjustment may be required.

## VI. EXCRETION OF DRUGS

### A. Routes of excretion

May include urine, feces (e.g., unabsorbed drugs and drugs secreted in bile), saliva, sweat, tears, milk (with possible transfer to neonates), and lungs (e.g., alcohols and anesthetics). Any route may be important for a given drug, but the kidney is the major site of excretion for most drugs.

1. Some drugs are secreted by liver cells into the bile, pass into the intestine, and are eliminated in the feces (e.g., rifampin, indomethacin, estradiol).

2. Drugs may also be reabsorbed from the intestine (i.e., undergo enterohepatic circulation). In this manner, the persistence of a drug in the body may be prolonged.
B. Net renal excretion of drugs

1. Net renal excretion of drugs is the result of three separate processes: the amount of drug filtered at the glomerulus, plus the amount of drug secreted by active transport mechanisms in the kidney, less the amount of drug passively reabsorbed throughout the tubule.

   a. Filtration
   (1) Most drugs have low molecular weights and are thus freely filtered from the plasma at the glomerulus.
   (2) Serum protein binding reduces filtration because plasma proteins are too large to be filtered.
   (3) The glomerular filtration rate is 30%–40% lower during newborns’ first year of life than in adults.

   b. Secretion
   (1) The kidney proximal tubule contains two transport systems that may secrete drugs into the ultrafiltrate, one for organic acids and a second for organic bases. These systems require energy for active transport against a concentration gradient; they are a site for potential drug–drug interactions because drugs may compete with each other for binding to the transporters.
   (2) Plasma protein binding does not normally have a large effect on secretion because the affinity of the transport systems for most drugs is greater than the affinity of plasma binding proteins.

   c. Reabsorption
   (1) Reabsorption may occur throughout the tubule; some compounds, including endogenous compounds such as glucose, are actively reabsorbed.
   (2) Reabsorption of the un-ionized form of drugs that are weak acids and bases can occur by simple passive diffusion, the rate of which depends on the lipid solubility and pK of the drug and also on the concentration gradient of the drug between the urine and the plasma.
   (3) Reabsorption may be affected by alterations of urinary pH, which also affect elimination of weak acids or bases by affecting the degree of ionization. For example, acidification of the urine will result in a higher proportion of the un-ionized form of an acidic drug and will facilitate reabsorption.

2. Renal clearance of drugs

   a. Renal clearance measures the volume of plasma that is cleared of drug per unit time:

   \[ \text{CL (mL/min)} = \frac{U \times V}{P} \]

   where \( U \) = concentration of drug per milliliter of urine, \( V \) = volume of urine excreted per minute, and \( P \) = concentration of drug per milliliter of plasma.
   (1) A drug excreted by filtration alone (e.g., insulin) will have a clearance equal to the glomerular filtration rate (GFR; 125–130 mL/min).
   (2) A drug excreted by filtration and complete secretion (e.g., para-aminobiphenyl) will have a clearance equal to renal plasma clearance (650 mL/min).
   (3) Clearance values between 130 and 650 mL/min suggest that a drug is filtered, secreted, and partially reabsorbed.

   b. A variety of factors influence renal clearance, including age (some mechanisms of excretion may not be fully developed at the time of birth), other drugs, and disease.

   c. In the presence of renal failure, the clearance of a drug may be reduced significantly, resulting in higher plasma levels. For those drugs with a narrow therapeutic index, dose adjustment may be required.

VII. PHARMACOKINETICS

Pharmacokinetics describes changes in plasma drug concentration over time. Although it is ideal to determine the amount of drug that reaches its site of action as a function of time after administration, it is usually impractical or not feasible. Therefore, the plasma drug concentration is measured. This
provides useful information, because the amount of drug in the tissues is generally related to plasma concentration.

A. Distribution and elimination

1. One-compartment model (Fig. 1-7)
   a. The drug appears to distribute instantaneously after IV administration of a single dose. If the mechanisms for drug elimination, such as biotransformation by hepatic enzymes and renal secretion, are not saturated following the therapeutic dose, a semilog plot of plasma concentration versus time will be linear.
   b. Drug elimination is first order; that is, a constant fraction of drug is eliminated per unit time. For example, one-half of the drug is eliminated every 8 hours. Elimination of most drugs is a first-order process.
   c. The slope of the semilog plot is \(-k\), where \(k\) is the rate constant of elimination and has units of time\(^{-1}\), and the intercept on the \(y\) axis is \(C_0\) (Note: \(C_0\) is used to calculate \(V_d\) for drugs that obey a one-compartment model.)
   d. The plasma drug concentration \(C_t\) at any time \(t\) after administration is given by
      \[
      \ln C_t = \ln C_0 - kt
      \]
      (or \(\log C_t = \log C_0 - kt/2.303\), if logs to the base 10 are used rather than natural logs), and the relationship of the plasma concentrations at any two points in time is given by
      \[
      \ln C_2 = \ln C_1 - k(t_2 - t_1)
      \]
      or
      \[
      \log C_2 = \log C_1 - k/2.303(t_2 - t_1)
      \]
   e. The rate constant of elimination \((k)\), the \(V_d\), and the whole body clearance \((CL)\) are related by the expression
      \[
      CL = k \times V_d
      \]

2. Two-compartment model (Fig. 1-8)
   a. The two-compartment model is a more common model for distribution and elimination of drugs. Initial rapid changes in the plasma concentration of a drug are observed because of a distribution phase, the time required for the drug to reach an equilibrium distribution
between a central compartment, such as the plasma space, and a second compartment, such as the aggregate tissues and fluids to which the drug distributes.

b. After distribution, a linear decrease in the log drug concentration is observed if the elimination phase is first order.

c. For drugs that obey a two-compartment model, the value of \( C_0 \) obtained by extrapolation of the elimination phase is used to calculate \( V_d \), and the elimination rate constant, \( k \), is obtained from the slope of the elimination phase.

d. The expressions for \( \ln C_t \) and CL shown above for a one-compartment model also apply during the elimination phase for drugs that obey a two-compartment model.

3. First-order elimination

a. First-order elimination accounts for elimination of most drugs. It refers to the elimination of a constant fraction of drug per unit time; that is, the rate of elimination is a linear function of the plasma drug concentration.

b. First-order elimination occurs when elimination systems are not saturated by the drug.

4. Zero-order elimination

a. In this model, the plot of the log of the plasma concentration versus time will be concave upward, and a constant amount of drug will be eliminated per unit time (e.g., 10 mg of drug will be eliminated every 8 hours). This is referred to as zero-order elimination, or zero-order kinetics. (Note that after an interval of time sufficient to reduce the drug level below the saturation point, first-order elimination occurs.)

b. Zero-order elimination may occur when therapeutic doses of drugs exceed the capacity of elimination mechanisms.

B. Half-life (\( t_{1/2} \))

1. Half-life is the time it takes for the plasma drug concentration to be reduced by 50%. This concept applies only to drugs eliminated by first-order kinetics.

2. Half-life is determined from the log plasma drug concentration versus time profile for drugs fitting a one-compartment model or from the elimination phase for drugs fitting the two-compartment model. As long as the dose administered does not exceed the capacity of the elimination systems (i.e., the dose does not saturate those systems), the half-life will remain constant.

3. The half-life is related to the elimination rate constant (\( k \)) by the equation \( t_{1/2} = 0.693/k \) and to the volume of distribution (\( V_d \)) and clearance (CL) by the equation \( t_{1/2} = 0.693 V_d/CL \).

4. For all doses in which first-order elimination occurs, >95% of the drug will be eliminated in a time interval equal to five half-lives. This applies for therapeutic doses of most drugs.
C. Multidose kinetics

1. Repeat administration
   a. If a drug that is eliminated by first-order kinetics is administered repeatedly (e.g., one tablet every 8 hours), the average plasma concentration of the drug will increase until a mean steady-state level is reached. (This will not occur for drugs that exhibit zero-order elimination.)
   b. The interval of time required to reach steady state is equal to five half-lives.

2. Steady state
   a. Some fluctuation in plasma concentration will occur even at steady state.
   b. Levels will be at the high point of the steady state range shortly after a dose is administered; levels will be at the low point immediately before administration of the next dose. Hence, steady state designates an average plasma concentration and the range of fluctuations above and below that level.
   c. The magnitude of fluctuations can be controlled by the dosing interval. A shorter dosing interval decreases fluctuations, and a longer dosing interval increases them. On cessation of multidose administration, >95% of the drug will be eliminated in a time interval equal to five half-lives if first-order kinetics applies.

3. Maintenance dose rate
   a. Maintenance dose rate is the dose of a drug required per unit time to maintain a desired steady-state level in the plasma to sustain a specific therapeutic effect.
   b. To determine the dose rate required to maintain an average steady-state plasma concentration of drug, multiply the desired plasma concentration by the CL:

   \[
   \text{Maintenance dose rate} = \text{Desired [drug]_{plasma}} \times \text{Clearance (CL)}
   \]

   (amount / time) = (amount / volume) \times (volume / time)

   This yields dose rate in units of amount per time (e.g., mg/hour). One may understand this fundamental relationship in the following way: To remain at steady state, the dose rate must equal the elimination rate; that is, the rate at which the drug is added to the body must equal the rate at which it is eliminated. Recall that the elimination rate = CL \times [Drug]_{plasma}. Therefore, because the dose rate must equal the elimination rate to be at steady state, dose rate also equals CL \times Desired [drug]_{plasma}.
   c. If one administers a drug at the maintenance dose rate, a steady state plasma concentration of drug will be reached in four to five half-lives. (Note: This is four to five half-lives, not four to five doses!)

4. Loading dose
   a. A large loading dose may be needed initially when the therapeutic concentration of a drug in the plasma must be achieved rapidly (e.g., a life-threatening situation in which one cannot wait for 5 half-lives for the drug to reach the desired steady-state level). In this situation one may administer a loading dose.
   b. To calculate the loading dose, select the desired plasma concentration of drug and multiply by the \( V_d \):

   \[
   \text{Loading dose} = \text{Desired [drug]_{plasma}} \times V_d
   \]

   (amount or mass) = (mass / volume) \times (volume)

   c. After administration of the loading dose (which rapidly achieves the desired plasma concentration of drug), one administers the drug at the maintenance dose rate to maintain the drug concentration at the desired steady-state level.
Review Test for Chapter 1

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Somatostatin interacts with
   (A) G_i-protein–coupled receptor
   (B) G_q-protein–coupled receptor
   (C) Ligand-activated ion channel
   (D) Receptor-activated tyrosine kinase
   (E) Intracellular nuclear receptor

2. Cortisol is capable of targeting intranuclear receptors secondary to its ability to
   (A) Recruit intracellular kinases
   (B) Undergo autophosphorylation
   (C) Diffuse through lipid membranes
   (D) Interact with G-proteins
   (E) Interact with adenylyl cyclase

3. Which of the following parameters is used to indicate the ability of a drug to produce the desired therapeutic effect relative to a toxic effect?
   (A) Potency
   (B) Intrinsic activity
   (C) Therapeutic index
   (D) Efficacy
   (E) Bioavailability

4. A 64-year-old woman with a history of multiple abdominal surgeries due to Crohn’s disease presents to the emergency room with obstipation and feculent emesis. A diagnosis of small bowel obstruction is made, and she is taken to the operating room for lysis of adhesions and resection of stenosed region of small bowel. Postoperatively, the patient is noted to have elevated blood pressure, and oral metoprolol is administered; however, no improvement of hypertension is observed. This is likely due to
   (A) The first-pass effect
   (B) Decreased passage of drug through intestine
   (C) Decreased GI blood flow
   (D) Destruction of drug by stomach acid
   (E) Increased protein binding of the drug

5. An important feature of congestive heart failure (CHF) regarding drug action is
   (A) Impaired blood flow to the intestine
   (B) Increased protein binding of various drugs
   (C) Increased volume of distribution
   (D) Increased drug elimination
   (E) Altered drug kinetics

6. Which of the following is the term used to describe the elimination rate via metabolism catalyzed by alcohol dehydrogenase when the enzyme is saturated?
   (A) Zero-order kinetics
   (B) First-order elimination
   (C) Clearance
   (D) Biotransformation
   (E) Redistribution

7. A 69-year-old woman is being treated in the intensive care unit for presumed staphylococcal sepsis. To avoid problems with possible resistance, she is empirically given IV vancomycin while waiting for the culture results to come back. Vancomycin is a renally excreted drug. The patient’s routine laboratory work-up reveals a creatinine value of 3.2, indicating acute renal failure. What specific considerations will have to be made with regard to adjustments of the prescribed medication?
   (A) She will have to be switched to an oral (per nasogastric tube) vancomycin preparation
   (B) The patient will need to be water restricted to decrease the volume of distribution
   (C) No changes to the current regimen will be made because the condition of the patient is life-threatening and the drug needs to be administered regardless
   (D) The dose of vancomycin will need to be reduced because of increased accumulation
   (E) Dosage adjustments will have to be made because the patient is currently ventilated
8. Glucuronidation reactions
   (A) Are considered phase I reactions
   (B) Require an active center as the site of conjugation
   (C) Include the enzymatic activity of alcohol dehydrogenase
   (D) Located in mitochondria are inducible by drugs
   (E) Require nicotinamide adenine dinucleotide phosphate (NADPH) for the enzymatic reaction

9. A 38-year-old woman presents to her psychiatrist with a request to try a different antidepressant medication, since she doesn’t feel her current medication is helping. She even felt so depressed that she started drinking heavily in the past couple of months. The doctor wants to try imipramine; however, since this drug is known to undergo an extensive first-pass effect, he orders a hepatic function panel before prescribing it, given the patient’s recent history of alcohol use. What is the rationale for the doctor’s decision?
   (A) In the presence of hepatic dysfunction, drugs with a high first-pass metabolism reach high systemic concentrations
   (B) The results of the hepatic function panel may reveal a particular susceptibility to the drug
   (C) Bioavailability of imipramine is increased by the fraction of drug removed by the first pass
   (D) The drug is more rapidly metabolized by the liver when hepatic aminotransferase levels are elevated
   (E) Solubility of the drug is affected in the face of hepatic damage

10. A 43-year-old man who was recently fired from a well-paying job decides to commit suicide and ingests a jarful of his antiseizure medication, phenobarbital. His wife finds him at home sleeping, but notices that he has diminished breathing, low body temperature, and skin reddening. She brings him to the ER, where he is appropriately diagnosed with barbiturate overdose. The patient is given bicarbonate to alkalinize his urine. How does alkalinization of urine with bicarbonate help to overcome the toxic effects of phenobarbital in this situation?
   (A) It increases glomerular filtration
   (B) It decreases proximal tubular secretion
   (C) It decreases distal tubular reabsorption
   (D) It enhances drug metabolism
   (E) It decreases untoward side effects

11. Erythromycin is prescribed “qid,” or four times daily, because of its short half-life. The rationale for such a frequent dosing schedule is
   (A) To achieve the steady-state plasma concentration of the drug
   (B) To avoid the toxicity of the drug because of its low therapeutic index
   (C) To aid more complete distribution of the drug
   (D) To inhibit the first-pass metabolism of the drug
   (E) To ensure that the drug concentration remains constant over time

12. A 13-year-old boy suffers two tonic-clonic seizures within 1 week. He is diagnosed with epilepsy, and phenytoin therapy is started. To achieve proper drug concentrations in plasma, the patient is first given a loading dose, followed by maintenance doses. The blood level of phenytoin is frequently monitored to adjust the maintenance dose as needed. What is the rationale behind such a regimen?
   (A) If drug is administered at a maintenance dose rate, steady-state concentration will be reached after two half-lives
   (B) A loading dose is administered to achieve the desired plasma concentration rapidly
   (C) The maintenance dose rate usually does not equal the elimination rate, which is why the loading dose is required
   (D) Loading dose of the drug does not depend on the volume of distribution, whereas the maintenance dose does
   (E) The maintenance dose rate does not depend on clearance of the drug, whereas the loading dose does

13. A 78-year-old woman is started on digoxin for her congestive heart failure (CHF). Her initial dose is 0.25 mg. The \( C_0 \), obtained by extrapolation of the elimination phase, is determined to be 0.05 mg/L. What is the patient’s apparent volume of distribution?
   (A) 0.5 L
   (B) 0.2 L
   (C) 0.0125 L
   (D) 1 L
   (E) 5 L

14. A drug has a volume of distribution of 50 L and undergoes zero-order elimination at a rate of 2 mg/hour at plasma concentrations greater
than 2 mg/L. If a patient is brought to the ER with a plasma concentration of 4 mg/L of the drug, how long will it take (in hours) for the plasma concentration to decrease 50%?

(A) 1  
(B) 2  
(C) 10  
(D) 25  
(E) 50

15. You administer a 100 mg tablet of drug X to a patient every 24 hours and achieve an average steady-state plasma concentration of the drug of 10 mg/L. If you change the dose regimen to one 50 mg tablet every 12 hours, what will be the resulting average plasma concentration (in mg/L) of the drug after five half-lives?

(A) 2.5  
(B) 5  
(C) 10  
(D) 20  
(E) 40

16. Following IV administration, the initial rates of drug distribution to different tissues depend primarily on which of the following parameters?

(A) Blood flow to the tissues  
(B) Fat content of the tissues  
(C) Degree of ionization of the drug in the tissues  
(D) Active transport of the drug out of different cell types  
(E) Specific organ clearances

17. A drug is administered in the form of an inactive pro-drug. The pro-drug increases the expression of a cytochrome P-450 that converts the pro-drug to its active form. With chronic, long-term administration of the pro-drug, which of the following will be observed?

(A) The potency will decrease  
(B) The potency will increase  
(C) The efficacy will decrease  
(D) The efficacy will increase

18. Which subfamily of cytochrome P-450s is responsible for the highest fraction of clinically important drug interactions resulting from metabolism?

(A) CYP1A  
(B) CYP2A  
(C) CYP3A  
(D) CYP4A  
(E) CYP5A

19. In most patients, an antibiotic is eliminated 25% by hepatic metabolism, 50% by renal filtration, and 25% by biliary excretion. If the normal maintenance dose rate = 10 mg/hour, what dose rate will you administer to a patient 12 normal with a creatinine clearance that is (assume that hepatic and biliary clearances are normal)?

(A) 2.5 mg/hour  
(B) 5.0 mg/hour  
(C) 6.0 mg/hour  
(D) 7.5 mg/hour  
(E) 20 mg/hour

20. If the oral dosing rate of a drug is held constant, what will be the effect of increasing the bioavailability of the preparation?

(A) Increase the half-life for first-order elimination  
(B) Decrease the first-order elimination rate constant  
(C) Increase the steady-state plasma concentration  
(D) Decrease the total body clearance  
(E) Increase the volume of distribution

21. You administer to a patient an oral maintenance dose of drug calculated to achieve a steady-state plasma concentration of 5 mcg/L. After dosing the patient for a time sufficient to reach steady state, the average plasma concentration of drug is 10 mcg/L. A decrease in which of the following parameters explains this higher than anticipated plasma drug concentration?

(A) Bioavailability  
(B) Volume of distribution  
(C) Clearance  
(D) Half-life

22. Administration of an IV loading dose to a patient of drug X yields an initial plasma concentration of 100 mcg/L. The table below illustrates the plasma concentration of X as a function of time after the initial loading dose.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma Conc. (mcg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>12.5</td>
</tr>
</tbody>
</table>

What is the half-life (in hours) of drug X?

(A) 1  
(B) 2  
(C) 4  
(D) 5  
(E) 9
23. Which of the following factors will determine the number of drug-receptor complexes formed?
   (A) Efficacy of the drug
   (B) Receptor affinity for the drug
   (C) Therapeutic index of the drug
   (D) Half-life of the drug
   (E) Rate of renal secretion

24. Which of the following is an action of a non-competitive antagonist?
   (A) Alters the mechanism of action of an agonist
   (B) Alters the potency of an agonist
   (C) Shifts the dose-response curve of an agonist to the right
   (D) Decreases the maximum response to an agonist
   (E) Binds to the same site on the receptor as the agonist

25. The renal clearance of a drug is 10 mL/min. The drug has a molecular weight of 350 and is 20% bound to plasma proteins. It is most likely that renal excretion of this drug involves
   (A) Glomerular filtration
   (B) Active tubular secretion
   (C) Passive tubular reabsorption
   (D) Both glomerular filtration and active tubular secretion
   (E) Both glomerular filtration and passive tubular reabsorption
1. The answer is A. Somatostatin binds to $G_i$-coupled protein receptor, initiating exchange of GTP for GDP, which inhibits adenylyl cyclase and leads to reduced cAMP production. $G_q$-protein-coupled receptor is an example of the phospholipase C pathway, in which interaction with the ligand leads to increased phospholipase C activity and eventual activation of protein kinase C via PIP$_2$ and IP$_3$ pathway. This is exemplified by interaction of epinephrine with its receptor. Ligand-activated ion channel is an example of interaction of specific ligand with an ion channel, which permits passage of ions through the channel. Acetylcholine is an example of such interaction. Receptor-activated tyrosine kinase is exemplified by insulin, where binding of ligand activates specific tyrosine kinase, leading to a cascade of reactions within the cell. Finally, intracellular nuclear receptor is exemplified by cortisol, which binds to it and exerts its effects on DNA replication.

2. The answer is C. The ability to target intracellular receptors depends on the ligand’s ability to cross lipid barriers, such as the nuclear envelope. Recruitment of intracellular kinases is characterized by some receptor-activated tyrosine kinases. Autophosphorylation is a feature of many different kinases. Interaction with G-proteins and adenylyl cyclase are characteristics of membrane receptors.

3. The answer is C. Lithium is an example of drug with a very low therapeutic index, which requires frequent monitoring of the plasma level to achieve the balance between the desired effect and untoward toxicity. Potency of the drug is the amount of drug needed to produce a given response. Intrinsic activity of the drug is the ability to elicit a response. Efficacy of the drug is the maximal drug effect that can be achieved in a patient under a given set of conditions. Bioavailability of the drug is the fraction of the drug that reaches the bloodstream unaltered.

4. The answer is B. Adequate passage of drug through the small intestine is required to observe the effects of the drug, because most of the absorption takes place in the small intestine. After extensive abdominal surgery, especially that involving a resection of a portion of small bowel, the passage may be slowed, or even stopped, for a period of time. Abdominal surgery rarely results in reduced blood flow to the intestine, nor does such an operation influence protein binding, or the first-pass effect. Destruction of drug by stomach acid does not depend on intra-abdominal surgery.

5. The answer is C. Because of the patient’s edema and ascites, the apparent volume of distribution will be increased, which may require small adjustments in his usual medication doses. Edematous states do not influence GI blood flow, nor do they affect drug–protein interactions. Drug elimination may be slowed with congestive heart failure (CHF) exacerbation, not increased. Drug kinetics are generally not changed by edematous states.

6. The answer is A. Alcohol is one of the drugs that follow zero-order kinetics (i.e., higher drug concentrations are not metabolized because the enzyme that is involved in the process is saturable). In first-order elimination, the rate of elimination actually depends on the concentration of the drug, multiplied by proportionality constant. Clearance is a measure of the capacity of the body to remove the drug. Biotransformation simply refers to the general mechanism of a particular drug’s elimination. Redistribution is one of the possible fates of a drug, which usually terminates drug action.

7. The answer is D. Since vancomycin is cleared by the kidneys, renal functional status needs to be considered when prescribing such a drug, because it may accumulate and produce undesirable toxic side effects. Switching from the vancomycin to an oral preparation will reduce its bioavailability. There is no indication that the patient is in the state of increased volume of distribution (such as edema), and water restriction will not have a noticeable effect on apparent volume of
distribution. Changes to the current regimen are necessary because of the patient’s acute renal failure, and this has to be done regardless of the urgency of the situation. The fact that the patient is being ventilated may indicate that she needs extra hydration because of increased insensible losses, but this has nothing to do with her vancomycin dose directly.

8. The answer is B. Glucuronidation reactions, which are considered phase II reactions, require an active center (a functional group) as the site of conjugation. Phase I reactions are biotransformation reactions, not conjugation reactions. Alcohol dehydrogenase is an example of a phase I reaction. Phase II reactions’ enzymes are located in the endoplasmic reticulum, not mitochondria. Nicotinamide adenine dinucleotide phosphate (NADPH) is required for aromatic hydroxylation, an example of a phase I reaction.

9. The answer is A. First-pass metabolism simply means passage through the portal circulation before reaching the systemic circulation. In the face of liver dysfunction, drug levels may reach higher concentrations. A hepatic function panel is generally not used to deduce a patient’s susceptibility to the drug. Bioavailability of drugs is decreased, not increased by the fraction removed after the first pass through the liver. Drugs are usually less rapidly metabolized when hepatic enzymes are elevated (which indicates hepatic dysfunction). Solubility of drugs has nothing to do with hepatic damage.

10. The answer is C. Alterations of urinary pH affect renal distal tubular reabsorption of drugs by changing the degree of ionization. Glomerular filtration depends mainly on the size of the drug as well as protein binding. Proximal tubular secretion will not be affected by alkalinization of urine. This process depends on the availability of transporters. Drug metabolism is not affected at the levels of the kidney, where most elimination takes place. Alkalinization of urine is unlikely to affect undesirable side effects of the drug.

11. The answer is A. Dosing schedules of drugs are adjusted according to their half-lives to achieve steady-state plasma concentration. Attempting to avoid the toxicity of the drug because of its low therapeutic index represents an unlikely scenario, since to reduce toxicity of a drug with a low therapeutic index, one would reduce the dosing schedule, not increase it. Distribution of drug is generally not affected by dosing schedule. Nor is dose scheduling affected by first-pass metabolism. Some fluctuation in plasma concentration occurs even at steady state; it is the average concentration over time that is the goal of steady state.

12. The answer is B. The rationale for the loading dose is to give a patient a sufficient dose of a medication to achieve the desired effect quickly, which is necessary in some situation (such as prevention of further seizures). When drug is administered at maintenance rate, steady state is achieved after about five half-lives. The maintenance dose is usually equal to the elimination rate. The loading dose depends on the volume of distribution, whereas the maintenance dose depends on the clearance of the drug.

13. The answer is E. To calculate the volume of distribution, use the formula in which the dose of the drug is divided by the plasma concentration. In this case, 0.25 mg is divided by 0.05 mg/L, giving the result of 5 L for volume of distribution.

14. The answer is E. For the plasma concentration of drug to decrease by 50%, half the drug present in the body initially must be eliminated. The amount of drug in the body initially is the volume of distribution $\times$ the plasma concentration (50 liters $\times$ 4 mg/liter = 200 mg). When the plasma concentration falls to 2 mg/liter, the body will contain 100 mg of drug (50 L $\times$ 2 mg/L = 100 mg). Since the body eliminates the drug at a rate of 2 mg/hour, it will require 50 hours for 100 mg of the drug to be eliminated.

15. The answer is C. A 100 mg tablet every 24 hours is a dose rate of 4.17 mg/hour (100/24 = 4.17), which is the same dose rate as one 50 mg tablet every 12 hours (50/12 = 4.17). Thus, the average plasma concentration will remain the same, but decreasing both the dose and the dose interval will decrease the peak to trough variation of plasma concentration.

16. The answer is A. The initial rate of distribution of a drug to a tissue depends primarily on the rate of blood flow to that tissue. At longer times, however, a drug may undergo redistribution
among various tissues, e.g., a very lipophilic drug may become concentrated in adipose tissue with time.

17. **The answer is B.** The induction of the cytochrome P-450 following chronic administration will increase the conversion of the inactive pro-drug to the active form. This will shift the dose–response curve of the pro-drug to the left (i.e., increase its potency) without changing its efficacy.

18. **The answer is C.** The CYP3A subfamily is responsible for roughly 50% of the total cytochrome P450 activity present in the liver and is estimated to be responsible for approximately 12 of all clinically important untoward drug interactions resulting from metabolism.

19. **The answer is D.** Maintenance dose rate = (clearance) × (desired plasma concentration), and the whole body clearance is the sum of all the individual organ clearances. In most patients the hepatic metabolism, renal filtration, and biliary excretion account for 25%, 50%, and 25% of the whole body clearance, respectively. Since the creatinine clearance in this patient indicates that the renal filtration is only half normal, the renal clearance of the drug will be decreased by 12. This means that the whole body clearance will be 75% of that of normal (25% hepatic, 25% renal, and 25% biliary). Therefore, the dose should also be 75% of the standard dose.

20. **The answer is C.** If the oral dosing rate is constant but bioavailability increases, the fraction of the administered dose that reaches the general circulation unaltered increases. This, in turn, will increase the steady-state plasma concentration.

21. **The answer is C.** Steady-state plasma concentration of drug = (dose rate)/(clearance). Thus, a decrease in clearance will increase the plasma drug concentration, whereas an increase in any of the other three parameters will decrease the steady state plasma concentration.

22. **The answer is C.** Inspection of the plasma concentration values indicates that the half-life of drug does not become constant until 1–9 hours after administration. The drug concentration decreases by 12 (from 50 to 25 mcg/L) between 1 and 5 hours (a 4-hour interval) and again decreases by 12 (from 25 to 12.5 mcg/L) between 5 and 9 hours (again, a 4-hour interval). This indicates the half-life of the drug is 4 hours. The rapid decrease in plasma concentration between 0 and 1 hour, followed by a slower decrease thereafter (and the constant half-life thereafter) indicates that this drug obeys a two-compartment model with an initial distribution phase followed by an elimination phase. The half-life is always determined from the elimination phase data.

23. **The answer is B.** Receptor affinity for the drug will determine the number of drug–receptor complexes formed. Efficacy is the ability of the drug to activate the receptor after binding has occurred. Therapeutic index (TI) is related to safety of the drug. Half-life and secretion are properties of elimination and do not influence formation of drug–receptor complexes.

24. **The answer is D.** A noncompetitive antagonist decreases the magnitude of the response to an agonist but does not alter the agonist’s potency (i.e., the ED_{50} remains unchanged). A competitive antagonist interacts at the agonist binding site.

25. **The answer is E.** This drug will undergo filtration and passive reabsorption. Because the molecular weight of the drug is small, free drug will be filtered. Because 20% of the drug is bound to plasma proteins, 80% of it is free and available for filtration, which would be at a rate of 100 mL/min (i.e., 0.8 × 125 mL/min; 125 mL/min is the normal glomerular filtration rate [GFR]). A clearance of 10 mL/min must indicate that most of the filtered drug is reabsorbed.