Chapter 3

Pharmacokinetics: The Absorption, Distribution, and Excretion of Drugs

OBJECTIVES

After studying this chapter, the reader should be able to:

• Explain the meaning of the terms absorption, distribution, metabolism, and excretion.

• List two physiologic factors that can alter each of the processes of absorption, distribution, and excretion.

• Explain how bioavailability can impact drug response and product selection.

• Compare the roles of passive diffusion and carrier-mediated transport in drug absorption.

• Describe two types of drug interaction and explain how they might affect drug response and safety.

KEY TERMS
- achlorhydra
- adipose
- albumin
- aqueous
- bioavailability
- bioequivalent
- biotransformation
- blood-brain barrier
- capillary permeability
- cardiac decompensation
- carrier-mediated transport
- catalyze
- concentration gradient
- dissolution
- distribution
- epithelium
- equilibrium
- excretion
Safe and effective drug treatment is not only a function of the physical and chemical properties of drugs, but also a function of how the human body responds to the administration of medication. The study of the bodily processes that affect the movement of a drug in the body is referred to as pharmacokinetics. To understand the pharmacology of drugs, the pharmacy technician must also understand the four fundamental pathways of drug movement and modification in the body (Fig. 3.1). First, drug absorption from the site of administration permits entry of the compound into the bloodstream. Once absorbed, the drug may then leave the bloodstream and disperse into the tissues and intracellular fluids where it can reversibly bind to receptors. This dispersal is called distribution. While some drug molecules are binding to receptors, others may be released from the receptors and be picked up again by the bloodstream. Drug particles in the bloodstream are available to undergo biochemical changes, referred to as metabolism, in the liver or other tissues. Finally, the drug and its metabolites are excreted from the body in urine or feces. Metabolism and excretion are both pathways of drug elimination from the body.

Absorption, distribution, metabolism, and excretion are sometimes referred to collectively as ADME processes. These processes determine when the drug appears in the bloodstream and for how long it remains there. In order for a drug to cause a therapeutic response, it must reach adequate concentrations in the blood so that it can reach and interact with drug receptors in adequate numbers to trigger a noticeable action. The course of drug action is, therefore, directly correlated with the concentration of the drug in the bloodstream, and is dependent upon the ADME processes.
Knowledge of these processes and the ways that they can vary between individuals is an important part of understanding how and why a drug is selected for a patient. To investigate the pharmacokinetic characteristics of a study drug (drug X), researchers will give a group of healthy adults a standard dose of drug X intravenously (IV) or orally at the start of the study. Blood is drawn from the study subjects repeatedly, at predetermined times, and analyzed for the amount of drug per volume of blood at each point in time. The value obtained is the serum or plasma concentration of the drug at the time the blood was drawn. When serum drug concentrations are graphed versus time, the result is the serum concentration versus time curve illustrated in Figure 3.2.

Urine is also collected from the study subjects to monitor for the appearance of drug X or related metabolites. Immediately after intravenous administration and at a later time after oral or other routes of administration, the amount of drug in the blood will reach a peak (peak serum concentration) and then begin to fall off, eventually disappearing from the blood completely. The time it takes for the serum concentration to fall by one half is called the $t_{1/2}$, or half-life, of elimination.

At some point after the drug is no longer detectable in the blood, the last of the drug and its metabolites, which have been filtered out by the kidneys, will also disappear from the urine. Plasma concentration data collected from this type of study is plotted against time and analyzed in order to understand the behavior of a specific drug in the body. This type of pharmacokinetic data, collected from average adults, is the basis for determining dose, dosing intervals, and limitations on the safe use of a drug. However, it is important for the technician student to remember that individuals do not always behave the way the average adult does. It is individual differences in ADME processes that create the need to modify doses or select different drugs in order to prevent poor treatment outcomes and adverse effects.

Absorption

Absorption is the transfer of a drug from its site of administration to the bloodstream. The rate and extent of absorption depends on the route of administration, the formulation and chemical properties of the drug, and physiologic factors that can impact the site of absorp-
When a drug is administered intravenously, absorption is not required because the drug is transferred from the administration device directly into the bloodstream. In the case of intravenous administration, the entire dose of the drug is available to move to the sites of drug action. Administration by other routes may result in less availability due to incomplete absorption. When this occurs, less of the drug is delivered by the bloodstream to the site of action. When a tablet or capsule is swallowed it must dissolve before it can be absorbed. The dissolving of a tablet or capsule is referred to as dissolution. Manufacturing processes and the water solubility of the drug affect dissolution rates. Highly water-soluble medications dissolve more readily in the gastrointestinal (GI) tract, while fat-soluble drugs dissolve more slowly. Drugs with smaller particle sizes go into solution more readily. The inert ingredients added to formulations can also affect their dissolution. Manufacturers must avoid producing tablets so compacted that they pass through the GI tract without ever dissolving. Tablets that dissolve too early are also problematic, because they taste bad and are difficult to swallow. Special formulations or coatings can be used to delay dissolution, thereby protecting the drug from stomach acid or allowing the gradual release of the drug to intentionally lengthen the absorption process. These are referred to as delayed or sustained release formulations. These are referred to as delayed or sustained release formulations. Liquid preparations do not require the step of dissolution. This explains the more rapid onset of action seen with liquid formulations as compared with the same drug given in tablet or capsule form.

Once dissolution has occurred, the drug molecules must pass through the selectively permeable membranes of the cells lining the gastrointestinal tract to reach the bloodstream. Depending on their chemical and physical properties, drugs will be absorbed either by passive diffusion or carrier-mediated transport across these membranes. Passive diffusion occurs when there is a high concentration of the drug on one side of the membrane and a low concentration on the other side. This difference from one side of the membrane to the other is called a concentration gradient. It is the natural tendency of substances to move from a region of higher concentration to a region of lower concentration; in other words, substances move down the concentration gradient. Drug molecules move across membranes or move through pores between the epithelial cells (Fig. 3.3). Diffusion is most efficient with...
drugs that are small molecules. This movement is solely driven by the kinetic energy within molecules, and continues until concentrations reach equilibrium. When equilibrium exists, the concentration of the substance is approximately equal on both sides of the membrane.

Passive diffusion does not involve a carrier molecule and the process is not a saturable process. Saturable processes are limited to a certain rate of activity by some aspect of the process. The vast majority of drugs gain access to the blood stream by diffusion. Drugs, which are usually somewhat lipid-soluble (fat-soluble), readily move across most biological membranes. Those drugs that are highly water-soluble penetrate the cell membrane through aqueous channels.

A few drugs that closely resemble naturally occurring compounds are absorbed via carrier-mediated transport. This process requires carrier proteins that attach to and actively carry the drug molecules across the membrane, utilizing a natural “pump” mechanism. This method of absorption is limited by the availability of the carrier protein and is therefore, saturable. Carrier-mediated transport requires energy and can move molecules against the concentration gradient. For an illustration of passive diffusion and carrier-mediated transport see Figure 3.4.

**Bioavailability**

The relationship between the drug dose and the amount ultimately delivered to the bloodstream is defined as bioavailability and is generally expressed as a percentage. If a 1 gram dose of a drug is administered by mouth, and half of that reaches the systemic circulation, the drug is 50% bioavailable. Bioavailability is calculated, not measured directly. Previously, the half-life of elimination and how it is determined was discussed. The same graph of serum concentrations against time also provides the data necessary to derive bioavailability. The area under the plasma concentration versus time curve represents the total amount of the drug reaching the circulatory system (see Fig. 3.2).

This curve will have a different shape depending on the route of drug administration. The curve obtained from plotting values after intravenous administration of a drug serves as a reference for complete bioavailability. To determine bioavailability for nonintravenous formulations, the area under the curve obtained after drug administration is compared with the area achieved when the same dose is given intravenously. The ratio of the two is the bioavailability of the formulation tested.

The acid environment or presence of food in the stomach, the solubility and other chemical properties of the drug, and the effect of the initial exposure to metabolic processes in the liver may all reduce the amount of drug that reaches the systemic circulation after oral administration, thereby reducing the bioavailability of the drug. When a drug is absorbed through the GI tract, it must travel through the liver before entering the systemic cir-
calculation (see Fig. 3.5). If the drug is subject to metabolism by the liver, the amount of drug that reaches the systemic circulation is decreased. Some drugs, such as propranolol or enalapril, undergo significant metabolism during a single passage through the liver. This is called the **first-pass effect**. When drugs are highly susceptible to the first-pass effect, the oral dose needed to cause a response will be significantly higher than the intravenous dose used to cause the same response.

Bioavailability becomes important in drug product selection. While two generic products may contain the same active ingredients, they may not have the same dissolution or absorption characteristics and therefore cannot be considered **bioequivalent**. In the case of extended-release products, the change in dissolution characteristics is intentional. In some cases, however, products are simply poorly manufactured and should be avoided. Generic equivalent products approved by the Food and Drug Administration (FDA) must meet a standard of less than 20% variation from the comparison product, an amount that does not significantly affect therapeutic efficacy or safety in most cases. In practice, however, most generic products typically vary from the original by less than 5%. Bioequivalency data is published by the FDA’s Center for Drug Evaluation and Research in the “Approved Drug Products with Therapeutic Equivalence Evaluations” publication, universally referred to as the “Orange Book” and available on the web.

**Factors Affecting Absorption**

A number of patient-specific factors can affect absorption. Absorption from any site of administration requires blood flow. A patient who is in shock or cardiopulmonary arrest will need to have medications administered intravenously to achieve the desired response because of the reduced blood circulation in these situations. Most absorption after oral administration occurs in the small intestine because of its larger surface area and therefore greater blood flow. Significant impairment of absorption can result when sections of the small intestine are removed for medical reasons.

Contact time with the epithelial lining of the GI tract is also an important factor in drug absorption. In people with a very rapid transit time through the GI tract, due to severe diarrhea for example, medication cannot be effectively absorbed. Conversely, anything that delays stomach emptying (for instance, a large meal) will also delay and potentially reduce absorption.

**Figure 3.5** Orally administered drugs are exposed to metabolic processes in the liver before they reach the systemic circulation, which may significantly reduce bioavailability. (Adapted with permission from Harvey RA, Champe PC, Howland RD, et al. *Lippincott’s Illustrated Reviews: Pharmacology*, 3rd ed. Baltimore: Lippincott Williams & Wilkins, 2006.)
Some medications exhibit drug-food or drug-drug interactions with other compounds present in the GI tract. Specific foods or other drugs may bind a drug and prevent absorption. The interaction between tetracycline and dairy products or antacids is a good example of this effect.

Although excess exposure to stomach acid may negatively impact some drugs, patients with very low levels of stomach acid (achlorhydria) may experience inadequate tablet dissolution and therefore poor drug absorption. Achlorhydria is most common in the elderly population.

**Distribution**

Once a drug is absorbed into the bloodstream it can be carried throughout the body. This process is called distribution, and is a reversible process; while some molecules may be interacting with receptors on cell membranes or inside of cells, other molecules may move back into the bloodstream. The delivery of a drug from the bloodstream to the site of drug action primarily depends on blood flow, capillary permeability, the degree of binding (attachment) of the drug to blood and tissue proteins, and the relative lipid-solubility of the drug molecule.

Blood flow to different organs of the body is not equal. The most vitally important organs of the body receive the greatest supply of blood. These organs include the brain, liver, and kidneys. Skeletal muscle and bone receive less blood, and adipose tissue (fat) receives the least. If blood flow were the only factor affecting distribution, it would be reasonable to expect that high concentrations of administered medications would always appear in the brain and liver. In reality, few drugs exhibit good penetration of the central nervous system. The anatomical structure of the capillary network in the brain creates a significant barrier to the passage of many drugs and is commonly referred to as the blood-brain barrier. This barrier is an adaptation that for the most part protects brain tissue from invasion by foreign substances. To readily penetrate into the brain, drugs must be fairly small and lipid-soluble or must be picked up by the carrier-mediated transport mechanism in the central nervous system. This explains why the small and highly fat-soluble anesthetic gases quickly and easily penetrate the brain to cause anesthesia, while other larger and water soluble molecules like penicillin antibiotics penetrate the central nervous system to a much lesser degree.

Compare the fairly impermeable capillaries of the brain to the highly permeable capillary walls in the liver and spleen (Fig. 3.6). These capillaries have gaps between their cells that allow large proteins to pass through to the capillary basement membrane. Capillary structure here is well adapted to the function of the liver, the key protein producer in the body and a center for chemical change of other compounds. In order to function, the liver must have access to amino acids, sugars, and other large molecules from the bloodstream. These molecules undergo chemical processing in the liver, and then must be moved out of the hepatic cells and back to the bloodstream.

**Factors Affecting Distribution**

The blood is composed of a number of elements, including plasma, red and white blood cells, and plasma proteins. Most drugs reversibly bind to plasma proteins in varying degrees. Albumin is the plasma protein with the greatest capacity for binding drugs. Binding to plasma proteins affects drug distribution into tissues, because only drug that is not bound is available to penetrate tissues, bind to receptors, and exert activity. As free drug leaves the bloodstream, more bound drug is released from binding sites. In this way, drugs maintain a balance between free and bound drug that is unique to each compound, based

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- **achlorhydria** The absence of hydrochloric acid from the gastric juices.
- **capillary permeability** Property of capillary walls that allows for exchange of specific, fat-soluble molecules.
- **adipose** Fat, or tissue containing fat cells.
- **blood-brain barrier** An anatomical barrier that prevents many substance from entering the brain, created as a result of the relative impermeability of capillaries in the brain.
- **albumin** Any of a number of water-soluble proteins that occur in blood plasma or serum, and other animal substances.
cardiac decompensation
Failure of the heart to maintain adequate blood circulation; symptoms include shortness of breath and edema.

volume of distribution
The theoretical volume required if the amount of drug in the body was distributed throughout the body at the same concentration measured in the blood.

Figure 3.6 Diagram demonstrating the difference in the anatomy of brain and liver capillaries. The tight junctions in brain capillaries prevent passage of most drugs into the brain. (Adapted with permission from Harvey RA, Champe PC, Howland RD, et al. Lippincott’s Illustrated Reviews: Pharmacology, 3rd ed. Baltimore: Lippincott Williams & Wilkins, 2006.)

on its affinity for plasma proteins. Albumin, then, acts as a reservoir of an administered drug.

Some drugs have a high affinity for binding to serum proteins and may be 95% to 98% protein bound. With highly protein bound drugs, low albumin levels (as in protein-calorie malnutrition, or chronic illness) may lead to toxicity because there are fewer than the normal sites for the drug to bind. The amount of free drug is significantly increased in that case. The physician or pharmacist must consider the patient’s serum albumin level when the dose of a highly protein bound medication is selected.

Competition for binding sites is one important way that drugs might interact. If a patient is using two highly protein bound drugs at the same time, there will be competition for binding sites on the albumin. The drug with the greatest affinity for the albumin will bind, and is thought to disrupt the normal ratio of free to bound drug for the second medication. As a result, the second medication will be more available to distribute to the site of action and potentially cause side effects.

Other patient variables that can affect distribution include body composition, cardiac decompensation (heart failure), and age of the patient. These factors all affect the apparent volume of distribution ($V_d$) of a drug and ultimately play a role in determining the appropriate dose of a drug. Volume of distribution is the theoretical volume needed to account for all of the drug in the body based on the serum concentration in a blood sample. For example, assume that a 1-gram dose of drug X is given by IV injection to a patient. Thirty
minutes later the serum concentration \( (C_p) \) is 25mcg/ml. If the drug were evenly distributed through the body, the apparent volume of distribution would have to be 40 liters (L) to account for the entire dose of the drug.

\[ C_p = \frac{\text{Dose (amount in the body)}}{V_d} \]

The adult human body is about 60% water. Therefore, the body of an average adult who weighs 70 kg (about 150 lbs) contains 42 L, or 10 gallons, of water. Total body water can be conceptually divided into three spaces or compartments. The fluid contained in the bloodstream makes up about 5 L, or about 9% of the volume of an average sized adult. The total water outside of the cells (extracellular fluid) includes the plasma volume plus the fluid in the interstitial space and is about 14 L. Intracellular fluid makes up the remaining 28 L. Drugs with high molecular weights or drugs that are extremely hydrophilic (with a strong affinity for water) tend to stay within the circulatory system and organs with a rich blood supply, and have a smaller apparent volume of distribution. Small, highly lipophilic drugs have a large apparent volume of distribution.

### Case 3.1

John Q. Brewer was a frequent flyer in the emergency room. John had an alcohol addiction problem, and one night he came to the emergency room with seizures. John’s wife said that he had been sober for 2 days. This afternoon she said he began to see things, and then the seizures began. The ER physician controlled the seizures with the benzodiazepine lorazepam, and wanted to follow that with a large oral dose of the anticonvulsant phenytoin and a prescription for ongoing phenytoin to be used for 6 months. The ER pharmacist suggested that because John was an alcoholic his albumin levels were probably low, and therefore he needed a reduced dose of albumin. The two conferred and decided to give John half the usual dose and check his albumin level.

Volume of distribution often becomes important when dosing calculations are made based on weight. A short, obese woman who weighs 250 lbs cannot handle the same dose of an aminoglycoside antibiotic that a tall, muscular man of the same weight would require. This is because a greater portion of the woman’s body is made up of fat. Aminoglycoside drugs are water-soluble and stay mainly in extracellular fluid, therefore dosing must be based on adjusted body weight, which will more correctly reflect the true volume of extracellular fluid in the body.

Dosing of medications in infants and children requires special consideration. It is the often-repeated wisdom of pediatric health care specialists that “children are not simply small adults.” This means that dosing cannot simply be adjusted based on the lower weight of children. The body composition of children is very different from adults. Their bodies contain a much higher percentage of water and a lower percentage of muscle and fat. Albumin levels may also be lower, especially in neonates. These variations result in different values for volume of distribution and significantly affect drug dosing.

### Metabolism

Drugs are eliminated from the body either unchanged through the kidneys and bile, or they may undergo chemical changes that allow them to be more easily excreted. The process of undergoing chemical changes is called biotransformation, or metabolism. As previously noted, anything absorbed through the GI tract goes directly into the portal circula-
tion that feeds into the liver. The liver is adapted to clear toxins from the body and is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues.

The kidneys cannot efficiently excrete highly fat-soluble drugs that readily cross cell membranes because they are reabsorbed in the last stages of filtration. These compounds must first be metabolized in the liver to more water-soluble compounds and then removed. There are two types of metabolic processes drugs undergo in the liver. Most undergo one or both types of reactions.

In the first type of reaction drugs are made more polar through oxidation-reduction reactions or hydrolysis. These reactions use metabolic enzymes, most often those of the cytochrome P450 enzyme system, to catalyze the biotransformation. In enzyme-catalyzed reactions, the rate of the reaction is accelerated by the presence of enzymes. A limited amount of enzyme is present at any given time in the liver. Since the rate of enzyme-catalyzed drug metabolism is limited by the quantity of available enzyme, metabolism in these cases is considered a saturable process. This means that the rate of conversion will only continue at the normal pace until the available supply of enzyme is used. At that point, metabolism is slowed until enzyme becomes available again. For the usual doses of most drugs, these reactions never reach saturation. There are a few drugs where doses may reach the saturation point of the enzymes. Once enzymes become saturated, blood levels increase exponentially toward toxicity. Examples include metabolism of alcohol and phenytoin.

The second type of metabolism involves conjugation reactions. In this type of reaction the drug undergoing change is joined with another substance, such as glucuronic acid, sulfurous acid, acetic acid, or an amino acid. Glucuronidation is the most common conjugation reaction. The result of conjugation is a more water-soluble compound that is easier for the kidneys to excrete. These metabolites are most often therapeutically inactive.

Some agents are initially administered as an inactive compound (prodrug) in order to improve availability or reduce side effects. Metabolism converts the prodrug to the active form. Fosphenytoin, for example, is a prodrug of phenytoin, a drug used for seizure disorders. Fosphenytoin is more completely and quickly absorbed when given by IM injection than phenytoin and can be used in critical situations with greater ease because it does not require insertion of an intravenous catheter.

Factors Affecting Metabolism

Metabolism of drugs can vary widely between population groups. Deficiency of some drug metabolizing enzymes is genetic and will result in poor tolerance of certain drugs. For example, many Asians and Native Americans have difficulty metabolizing drugs that require acetylation, such as ethanol. These individuals will exhibit a low tolerance of such drugs, and can suffer adverse drug reactions at a much higher rate than the average population. Age is another important variable that has a bearing on metabolism. Organ function gradually declines with age and the elderly may poorly tolerate drugs that require metabolism. The very young require special consideration of drug dosing because of immaturity of their organ systems. This subject matter is worthy of further study for those technicians who will be serving these special populations.

Drug interactions may occur between two drugs that are metabolized by the same enzyme systems in the liver. Because there is a limit on available enzymes for metabolism, excess drug will remain active and free to exert an effect elsewhere in the body. Usually, of two drugs that are metabolized by the same enzyme system, one has a higher affinity for the enzyme, and levels of the second drug build up. In some cases, the drug being metabolized will induce the production of more of the enzymes. Enzyme induction sets the stage for another type of drug interaction, because the increased production of metabolizing enzymes may result in higher rates of removal and the need for an increased dose of the second drug. A good example of a drug that stimulates production of metabolizing enzymes is phenobarbital, a drug used to treat some forms of epilepsy.
Excretion

When a drug is taken into and distributed throughout the body, it must be subsequently removed, or concentrations of the drug would continue to rise with each successive dose. The complete removal of the drug from the body is referred to as elimination. Elimination of the drug encompasses both the metabolism of the drug, and excretion of the drug through the kidneys, and to a much lesser degree into the bile. Excretion into the urine is one of the most important mechanisms of drug removal.

The kidneys act as a filter for the blood and create urine as a vehicle for removal of waste. Blood enters the kidney through renal arteries and then is filtered by the glomerulus (see Chapter 21). The glomerular filtrate becomes concentrated and substances are removed as it passes through the renal tubule and eventually becomes urine. Drug molecules in the bloodstream that are not bound to albumin are also filtered out into the glomerular filtrate. When drugs have not been converted to water soluble compounds in the liver, they are likely to be reabsorbed back into the bloodstream at the end of the filtration process, and will cycle through the body again. If they are water soluble, they will end up in the urine and be excreted.

When a medication is given repeatedly, as most are in real patients, the total amount of drug in the body will increase up to a point and then stabilize. At this point, the amount being taken in by the patient is equal to the amount being removed by the liver and kidneys (Fig. 3.7). This state of equilibrium is called steady state, and drug levels will remain fairly constant unless there is a dose change, an interruption in treatment, or failure of the organs of elimination. The therapeutic effects of many drugs are closely correlated to a specific range of steady state serum drug levels, and physicians or clinical pharmacists will monitor these levels and adjust doses when necessary so that patients obtain the appropriate drug response.

Factors Affecting Excretion

The complete elimination of a drug from the body is dependent on normal liver and kidney function. The kidney is the major organ of excretion; however, the liver also contributes to elimination through metabolism and excretion into the feces via the bile. When a patient has reduced kidney function or another problem that lengthens the half-life of a drug, dosage adjustment is required. If the dosage is not adjusted, the drug will accumulate in the body.
Kidney or liver failure, or conditions where blood flow to these organs is reduced, complicate drug and dose selection. Drugs that are dependent upon excretion through the kidneys are not the best choice for patients with renal failure. Patients with liver disease will better tolerate drugs that can be cleared exclusively through the kidneys. Age must be considered in a discussion of drug excretion. The very young and very old will have lower rates of excretion; the old because of deterioration in organ function and the very young, because the kidneys have not reached full maturity. Doses often require reduction in these patients. Drug interactions, such as when multiple drugs compete for metabolic processes, can also reduce drug removal.

Clearly, the interactions between a drug and the human body are incredibly complex. This makes choosing the most appropriate medication and dose complicated, and that choice becomes more obscure when a patient is taking many other medications. This complexity makes it all the more essential that prescriptions be filled carefully and accurately at all times.

Review Questions

Multiple Choice

Choose the best answer to the following questions:

1. Which of the following is not one of the four fundamental pathways of drug movement and modification in the body?
   a. distribution
   b. metabolism
   c. absorption
   d. dissolution
   e. elimination

2. Which is correct regarding the process of passive diffusion?
   a. It requires a carrier protein molecule.
   b. It occurs when a concentration gradient exists from one side of a membrane to the other.
   c. It is a saturable process.
   d. The only drugs that can enter cells via passive diffusion are antibiotics.
   e. None of the above are correct.

3. Which of the following factors has the potential to affect absorption of an orally administered drug?
   a. Reduction in blood flow to the intestines
   b. Increased GI transit time
   c. Extremely low levels of stomach acid
   d. Eating a large meal just prior to taking an oral medication
   e. All of the above

4. Choose the incorrect statement.
   a. Most drugs reversibly bind to plasma proteins.
   b. Albumin is the most important drug binding plasma protein.
   c. Low albumin levels can lead to drug toxicity in the case of drugs that are highly protein bound.
   d. Only a drug that is protein bound can penetrate tissues.
   e. None of the above is incorrect.
5. Elimination of drugs from the body is dependent on which of the following?
   a. Biotransformation in the liver
   b. Filtration or secretion in the kidney
   c. Sufficient blood flow to the liver and kidneys
   d. Only a and b
   e. a, b, and c

**True/False**

6. Enzymes facilitate chemical transformation reactions in drug metabolism.
   a. True
   b. False

7. After oral administration, drugs pass through the liver before they ever reach the circulation, with the potential for significantly reducing the amount of drug to reach the site of action.
   a. True
   b. False

8. Body weight is more important than age when determining the appropriate dose of a drug because a 6-month-old is just a smaller version of a 16-year-old child.
   a. True
   b. False

9. Before a tablet can be absorbed through the GI tract it must dissolve.
   a. True
   b. False

10. Half-life is defined as the time it takes for the serum concentration of a drug to drop to 0.
    a. True
    b. False

**Matching**

Match each numbered phrase to the best corresponding answer listed below.

11. Oral absorption
    a. Albumin
    b. Carrier-mediated transport
    c. Blood flow
    d. Small intestine
    e. Kidneys
    f. Cytochrome p450
    g. Serum concentration

12. Distribution
13. Protein binding
14. Enzyme catalyzed metabolism
15. Excretion

**Short Answer**

16. Compare the two mechanisms of drug transfer across cell membranes, passive diffusion, and carrier-mediated transport.
17. How might the physiology of brain capillaries affect the choice of antibiotics for treatment of meningitis, an infection of the lining of the brain and spinal cord?

18. Briefly describe the process of metabolism and explain how individual patient differences can affect metabolism and, therefore, drug selection.

19. Drug P is an experimental drug that is known to be 98% eliminated as the active, unmetabolized drug in the urine. How would a significant loss of renal function likely affect the elimination, $t_{1/2}$, and dose of this drug?

20. Describe two mechanisms for drug interactions.

FOR FURTHER INQUIRY

Consider what you have learned about the ADME processes, and use additional references if necessary, to answer one of the following questions:

1. How do the absorption characteristics and rate of elimination ($t_{1/2}$) of a drug affect patient acceptability and compliance with the physician’s instructions for use of that drug?

2. Do you think it is important for pharmacists to have access to specific patient information when reviewing prescriptions for appropriateness of the drug and dose? What kind of information should the patient profile contain?