LESSON 2
Basic Pharmacokinetics

OBJECTIVES

After completing Lesson 2, you should be able to:

1. Define the concept of apparent volume of distribution and use an appropriate mathematical equation to calculate this parameter.
2. Identify the components of body fluids that make up extracellular and intracellular fluids and know the percentage of each component.
3. Describe the difference between whole blood, plasma, and serum.
4. Define drug clearance.
5. Describe the difference between first- and zero-order elimination and how each appears graphically.

To examine the concept of volume of distribution further, let's return to our example of the body as a tank described in Lesson 1. We assumed that no drug was being removed from the tank while we were determining volume. In reality, drug concentration in the body is constantly changing, primarily due to elimination. This flux makes it more difficult to calculate the volume in which a drug distributes.

One way to calculate the apparent volume of drug distribution in the body is to measure the plasma concentration immediately after intravenous administration before elimination has had a significant effect. The concentration just after intravenous administration (at time zero, t_0) is abbreviated as C_0 (**Figure 2-1**). The volume of distribution can be calculated using the equation:

$$\text{volume of distribution} = \frac{\text{amount of drug administered (dose)}}{\text{initial drug concentration}} \quad or \quad V(L) = \frac{X_0(mg)}{C_0(mg/L)}$$

(See **Equation 1-1**.)

C_0 can be determined from a direct measurement or estimated by back-extrapolation from concentrations determined at any time after the dose. If two concentrations have been determined, a line containing the two values and extending through the y-axis can be drawn on semilog paper. The point where that line crosses the y-axis gives an estimate of C_0. Both the direct measurement and back-extrapolation approaches assume that the drug distributes instantaneously into a single homogeneous compartment.

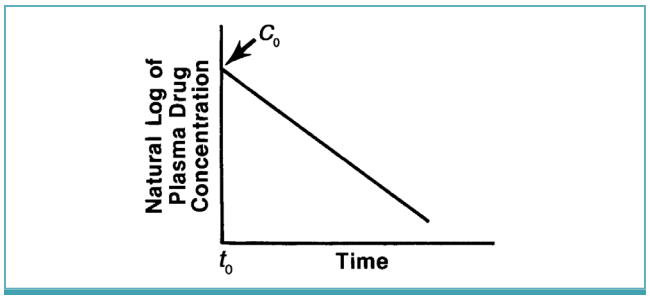

FIGURE 2-1.
Concentration resulting immediately after an intravenous injection of a drug is referred to as C_0.

The volume of distribution is an important parameter for determining proper drug dosing regimens. Often referred to as the *apparent* volume of distribution, it does not have an exact physiologic significance, but it can indicate the extent of drug distribution and aid in determination of dosage requirements. Generally, dosing is proportional to the volume of distribution. For example, the larger the volume of distribution, the larger a dose must be to achieve a desired target concentration.

To understand how distribution occurs, you must have a basic understanding of body fluids and tissues (**Figure 2-2**). The fluid portion (water) in an adult makes up approximately 60% of total body weight and is composed of intracellular fluid (35%) and extracellular fluid (25%). Extracellular fluid is made up of plasma (4%) and interstitial fluid (21%). Interstitial fluid surrounds cells outside the vascular system. These percentages vary somewhat in a child.

If a drug has a volume of distribution of approximately 15–18 L in a 70-kg person, we might assume that its distribution is limited to extracellular fluid, as that is the approximate volume of extracellular fluid in the body. If a drug has a volume of distribution of about 40 L, the drug may be distributing into all body water because a 70-kg person has approximately 40 L of body water (70 kg × 60%). If the volume of distribution is much greater than 40–50 L, the drug probably is being concentrated in tissue outside the plasma and interstitial fluid.

If a drug distributes extensively into tissues, the volume of distribution calculated from plasma concentrations could be much higher than the actual physiologic volume in which it distributes. For example, by measuring plasma concentrations, it appears that digoxin distributes in approximately 440 L in an adult. Because digoxin binds extensively to muscle tissue, plasma levels are fairly low relative to concentrations in muscle tissue. For other drugs, tissue concentrations may not be as high as the plasma concentration, so it may appear that these drugs distribute into a relatively small volume.

It is also important to distinguish among blood, plasma, and serum. *Blood* refers to the fluid portion in combination with formed elements (white cells, red cells, and platelets). *Plasma* refers only to the fluid portion of blood (including soluble proteins but not formed elements). When the soluble protein fibrinogen is removed from plasma, the remaining product is *serum* (**Figure 2-3**).

These differences in biologic fluids must be recognized when considering reported drug concentrations. The plasma concentration of a drug may be much less than the whole blood concentration if the drug is preferentially sequestered by red blood cells.

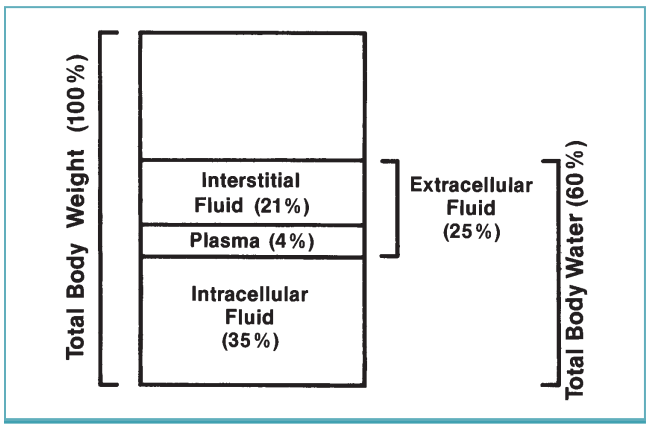

FIGURE 2-2.
Fluid distribution in an adult.

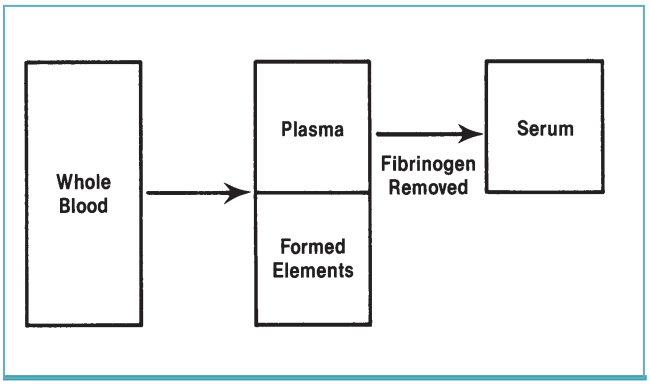

FIGURE 2-3.
Relationship of whole blood, plasma, and serum.

Clinical Correlate

Most drug concentrations are measured using plasma or serum that usually generate similar values. It is more relevant to use plasma or serum than whole blood measurements to estimate drug concentrations at the site of effect. However, some drugs, such as antimalarials, are extensively taken up by red blood cells. In these situations, whole blood concentrations would be more relevant, although they are not commonly used in clinical practice.

Clearance

Another important parameter in pharmacokinetics is clearance. *Clearance* is a measure of the removal of drug from the body. Plasma drug concentrations are affected by the rate at which drug is administered, the volume in which it distributes, and its clearance. A drug's clearance and the volume of distribution determine its half-life. The concept of half-life and its relevant equations are discussed in Lesson 3.

Clearance (expressed as volume/time) describes the removal of drug from a volume of plasma in a given unit of time (drug loss from the body). Clearance does not indicate the amount of drug being removed. It indicates the volume of plasma (or blood) from which the drug is completely removed, or cleared, in a given time period. **Figures 2-4** and **2-5** represent two ways of thinking about drug clearance. In Figure 2-4, the amount of drug (the number of dots) decreases but fills the same volume, resulting in a lower concentration. Another way of viewing the same decrease would be to calculate the volume that would be drug-free if the concentration were held constant.

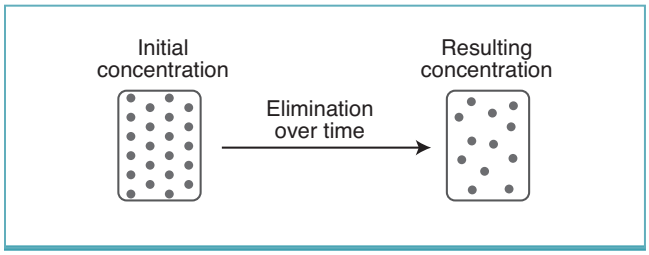

FIGURE 2-4.
Decrease in drug concentration due to drug clearance.

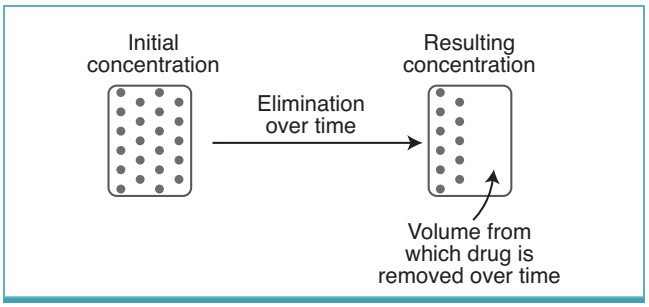

FIGURE 2-5.
Clearance may be viewed as the volume of plasma from which drug is totally removed over a specified period.

Drugs can be cleared from the body by many different mechanisms, pathways, or organs, including hepatic biotransformation and renal and biliary excretion. *Total body clearance* of a drug is the sum of all the clearances by various mechanisms.

2-1
$$Cl_t = Cl_r + Cl_m + Cl_b + Cl_{other}$$

where

Cl_t = total body clearance (from all mechanisms, where t refers to total);

Cl_r = renal clearance (through renal excretion);

Cl_m = clearance by liver metabolism or biotransformation;

Cl_b = biliary clearance (through biliary excretion); and

Cl_{other} = clearance by all other routes (gastrointestinal tract, pulmonary, etc.).

For an agent removed primarily by the kidneys, renal clearance (Cl_r) makes up most of the total body clearance. For a drug primarily metabolized by the liver, hepatic clearance (Cl_m) is most important.

A good way to understand clearance is to consider a single well-perfused organ that eliminates drug. Blood flow through the organ is referred to as Q (mL/minute) as seen in **Figure 2-6**, where C_{in} is the drug concentration in the blood entering the organ and C_{out} is the drug concentration in the exiting blood. If the organ eliminates some of the drug, C_{in} is greater than C_{out}.

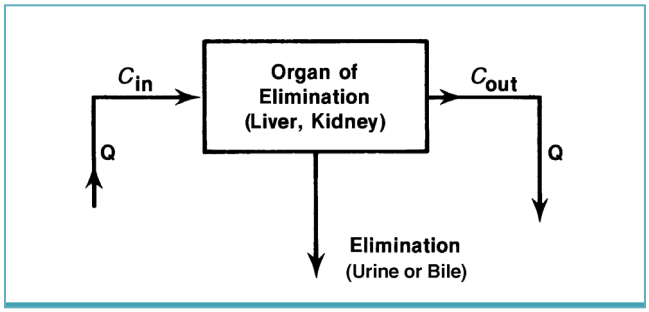

FIGURE 2-6.
Model for organ clearance of a drug.

We can measure an organ's ability to remove a drug by relating C_{in} and C_{out}. This extraction ratio (E) is:

$$E = \frac{C_{in} - C_{out}}{C_{in}}$$

This ratio must be a fraction between zero and one. Organs that are very efficient at eliminating a drug will have an extraction ratio approaching one (i.e., 100% extraction). **Table 2-1** is used as a general guide.

The drug clearance of any organ is determined by blood flow and the extraction ratio:

organ clearance = blood flow × extraction ratio

or:

2-2 $$\mathrm{Cl}_{organ} = Q \times \frac{C_{in} - C_{out}}{C_{in}} \text{ or } \mathrm{Cl}_{organ} = QE$$

If an organ is very efficient in removing drug (i.e., extraction ratio near one) but blood flow is low, clearance will also be low. Also, if an organ is inefficient in removing drug (i.e., extraction ratio close to zero) even if blood flow is high, clearance would again be low. See **Table 2-2**.

The equations noted previously are not used routinely in clinical drug monitoring, but they describe the concept of drug clearance. Examination of a single well-perfused organ to understand clearance is a noncompartmental approach; no assumptions about the number of compartments have to be made. Therefore, *clearance* is said to be a model-independent parameter. Clearance also can be related to the model-dependent parameters volume of distribution and elimination rate (discussed in Lesson 3).

TABLE 2-1. Rating of Extraction Ratios

Extraction Ratio (E)	Rating
> 0.7	High
0.3–0.7	Intermediate
< 0.3	Low

Clearance may also be a useful parameter for constructing dosage recommendations in clinical situations. It is an index of the capacity for drug removal by the body's organs.

Clinical Correlate

Blood flow and the extraction ratio will determine a drug's clearance. Propranolol is a drug that is eliminated exclusively by hepatic metabolism. The extraction ratio for propranolol is greater than 0.9, so most of the drug presented to the liver is removed by one pass through the liver. Therefore, clearance is approximately equal to liver blood flow (Cl = $Q \times E$: when $E \sim 1.0$, Cl ~ Q). One indication of the high extraction ratio is the relatively high oral dose of propranolol compared with the intravenous dose; an oral dose is 10–20 times the equivalent intravenous dose. The difference reflects the amount of drug removed by first-pass metabolism after absorption from the gastrointestinal tract and before entry into the general circulation.

The average clearances of some commonly used drugs are shown in **Table 2-3**. These values can vary considerably between individuals and may be altered by disease.

TABLE 2-2. Effect on Clearance

Extraction Ratio (E)	Blood Flow (Q) (L/hour)	Clearance (Cl) (L/hour)
High (0.7–1.0)	Low	Low
Low (< 0.3)	High	Low
High (0.7–1.0)	High	High
Low (< 0.3)	Low	Low

TABLE 2-3. Average Clearances of Common Drugs

Amlodipine	5.9 ± 1.5 mL/min/kg
Ganciclovir	3.4 ± 0.5 mL/min/kg
Ketorolac	0.50 ± 0.15 mL/min/kg
Lansoprazole	6.23 ± 1.60 mL/min/kg
Montelukast	0.70 ± 0.17 mL/min/kg
Sildenafil	6.0 ± 1.1 mL/min/kg
Valsartan	0.49 ± 0.09 mL/min/kg

Source: Brunton LL, Lazo JS, Parker KL (editors), *The Pharmacologic Basis of Therapeutics*, 11th edition. New York: McGraw-Hill; 2006. pp. 1798, 1829, 1839, 1840, 1851, 1872, 1883.

First-Order and Zero-Order Elimination

The simplest example of drug elimination in a one-compartment model is a single intravenous bolus dose of a drug. It is first assumed that:

1. Distribution and equilibration to all tissues and fluids occurs instantaneously so a one-compartment model applies.
2. Elimination is first order.

Most drugs are eliminated by a first-order process, and the concept of first-order elimination must be understood. With *first-order elimination*, the amount of drug eliminated in a set amount of time is directly proportional to the amount of drug in the body. The amount of drug eliminated over a certain time period increases as the amount of drug in the body increases; likewise, the amount of drug eliminated per unit of time decreases as the amount of drug in the body decreases.

With the first-order elimination process, although the amount of drug eliminated may change with the amount of drug in the body, the fraction of a drug in the body eliminated over a given time remains constant. In practical terms, the fraction or percentage of drug being removed is the same with either high or low drug concentrations. For example, if 1000 mg of a drug is administered and the drug follows first-order elimination, we might observe the patterns in **Table 2-4**.

TABLE 2-4. First-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated over Preceding Hour (mg)	Fraction of Drug Eliminated over Preceding Hour
0	1000	—	—
1	880	120	0.12
2	774	106	0.12
3	681	93	0.12
4	599	82	0.12
5	527	72	0.12
6	464	63	0.12
7	408	56	0.12

The actual amount of drug eliminated is different for each fixed time period depending on the initial amount in the body, but the fraction removed is the same, so this elimination is first order. Because the elimination of this drug (like most drugs) occurs by a first-order process, the amount of drug eliminated decreases as the concentration in plasma decreases. The actual fraction of drug eliminated over any given time (in this case 12%) depends on the drug itself and the individual patient's capacity to eliminate the drug.

On the other hand, with *zero-order elimination*, the amount of drug eliminated does not change with the amount or concentration of drug in the body, but the fraction removed varies (**Figure 2-7**). For example, if 1000 mg of a drug is administered and the drug follows zero-order elimination, we might observe the patterns in **Table 2-5**.

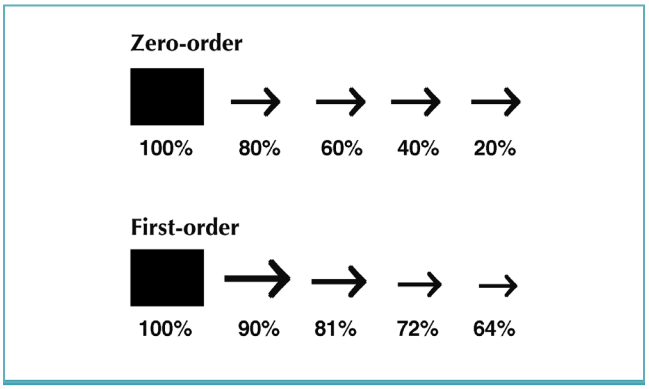

FIGURE 2-7.
Zero- versus first-order elimination. The size of the arrow represents the amount of drug eliminated over a unit of time. Percentages are the fraction of the initial drug amount remaining in the body.

TABLE 2-5. Zero-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated over Preceding Hour (mg)	Fraction of Drug Eliminated over Preceding Hour
0	1000	—	—
1	850	150	0.15
2	700	150	0.18
3	550	150	0.21
4	400	150	0.27
5	250	150	0.38

Now that we have examined zero- and first-order elimination, let's return to our simple one-compartment, intravenous bolus situation. If the plasma drug concentration is continuously measured and plotted against time after administration of an intravenous dose of a drug with first-order elimination, the plasma concentration curve shown in **Figure 2-8** would result. To predict concentrations at times when we did not collect samples, we must linearize the plot by using semilog paper (**Figure 2-9**).

Clinical Correlate

Most antimicrobial agents (e.g., aminoglycosides, cephalosporins, and vancomycin) display first-order elimination when administered in usual doses. The pharmacokinetic parameters for these drugs are not affected by the size of the dose given. As the dose and drug concentrations increase, the amount of drug eliminated per hour increases while the fraction of drug removed remains the same.

Some drugs (e.g., phenytoin), when given in high doses, display zero-order elimination. Zero-order elimination occurs when the body's ability to eliminate a drug has reached its maximum capability (i.e., all transporters are being used). As the dose and drug concentrations increase, the amount of drug eliminated per hour does not increase, and the fraction of drug removed declines.

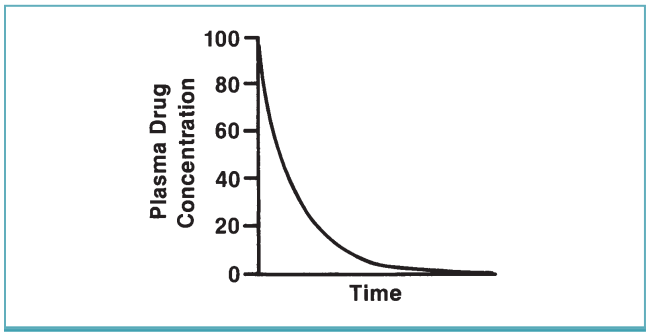

FIGURE 2-8.
Plasma drug concentration versus time after an intravenous (bolus) drug dose, assuming a one-compartment model with first-order elimination (linear *y*-scale).

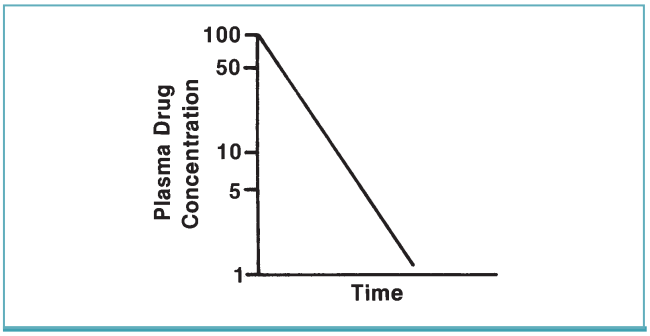

FIGURE 2-9.
As in Figure 2-8, but with a log scale *y*-axis.

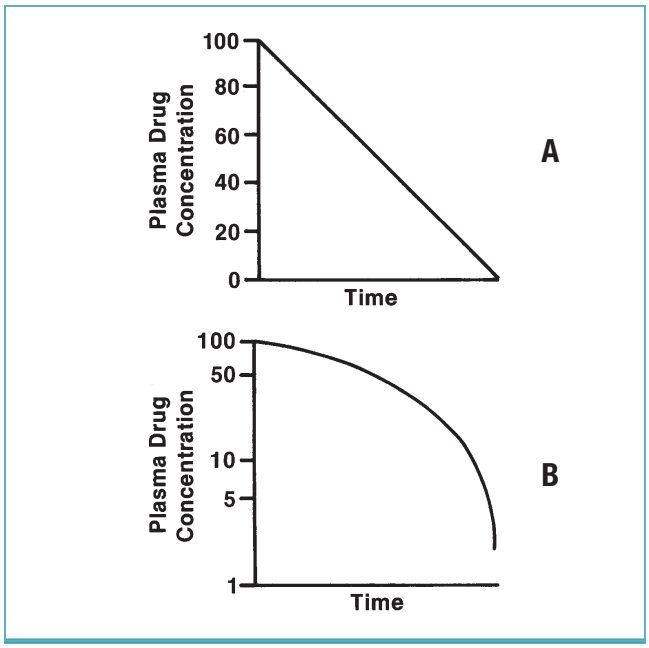

FIGURE 2-10.
Plasma drug concentrations versus time after an intravenous (bolus) drug dose, assuming a one-compartment model with zero-order elimination (**A**, linear plot; **B**, log plot).

For a drug with first-order elimination, the natural log of plasma concentration versus time plot is a straight line. Conversely, plots with zero-order elimination would be as shown in **Figure 2-10**. Note that for a drug with zero-order elimination, the plot of the plasma concentration versus time is linear (plot A in Figure 2-10), whereas on semilog paper (representing the natural log of plasma concentration versus time) it is a curve (bottom plot in Figure 2-10). If the natural log of a plasma drug concentration versus time plot is linear, it generally can be assumed that the drug follows first-order elimination.

REVIEW QUESTIONS

2-1. The volume of distribution equals _____ divided by initial drug concentration:

A. clearance

B. initial drug concentration

C. half-life

D. dose

2-2. A dose of 1000 mg of a drug is administered to a patient, and the following concentrations result at the indicated times below. Assume a one-compartment model.

Plasma Concentration (mg/L)	Time after Dose (hours)
100	2
67	4
45	6

An estimate of the volume of distribution would be:

A. 10 L.

B. 22.2 L.

C. 6.7 L.

D. 5 L.

2-3. If a drug is poorly distributed to tissues, its apparent volume of distribution is probably:

A. large.

B. small.

2-4. For the body fluid compartments below, rank them from the lowest volume to the highest, in a typical 70-kg person.

A. Plasma < extracellular fluid < intracellular fluid < total body water

B. Extracellular fluid < intracellular fluid < plasma < total body water

C. Intracellular fluid < extracellular fluid < plasma < total body water

D. Total body water < plasma < intracellular fluid < extracellular fluid

2-5. *Plasma* refers only to the fluid portion of blood, including soluble proteins but not formed elements.

A. True

B. False

2-6. The units for clearance are:

A. concentration/half-life.

B. dose/volume.

C. half-life/dose.

D. volume/time.

2-7. Total body clearance is the sum of clearance by the kidneys, liver, and other routes of elimination.

A. True

B. False

2-8. To determine drug clearance, we must first determine whether a drug best fits a one- or two-compartment model.

A. True

B. False

2-9. With a drug that follows first-order elimination, the amount of drug eliminated per unit time:

A. remains constant while the fraction of drug eliminated decreases.

B. decreases while the fraction of drug eliminated remains constant.

ANSWERS

2-1. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. You can determine the correct answer from the units in the numerator and denominator. They should cancel to yield a volume unit. *Grams* divided by *grams per liter* would leave you with *liter* as the unit. The

volume is therefore determined from the dose, or amount of drug given, and the resulting initial concentration.

2-2. A. *Incorrect answer*. You may have used 100 mg/L as the initial concentration.

B. *Incorrect answer*. You may have used an incorrect initial concentration.

C. CORRECT ANSWER. To find the initial concentration, plot the given plasma concentration and time values on semilog paper, connect the points, and read the value of the *y*-axis (concentration) when *x* (time) = 0. This should be 150 mg/L. You can then determine the volume of distribution using the equation volume of distribution = dose/initial concentration.

D. *Incorrect answer*. You may have used an incorrect initial concentration, or you may have used linear graph paper instead of semilog paper.

2-3. A. *Incorrect answer*. Drug concentrations are generally measured in plasma. When drug distributes poorly into tissues, the plasma level will be increased. Examining the equation volume of distribution = dose/initial concentration, as the initial concentration increases, the volume will decrease.

B. CORRECT ANSWER

2-4. A. CORRECT ANSWER. See Figure 2-2. Plasma would be 2.8 L, extracellular fluid would be 18 L, intracellular fluid would be 25 L, and total body water would be 42 L.

B, C, D. *Incorrect answers*

2-5. A. CORRECT ANSWER
B. *Incorrect answer*

2-6. A, B, C. *Incorrect answers*. The units for clearance are volume/time.

D. CORRECT ANSWER

2-7. A. CORRECT ANSWER. Total body clearance can be determined as the sum of individual clearances from all organs or routes of elimination.
B. *Incorrect answer*

2-8. A. *Incorrect answer*

B. CORRECT ANSWER. It is not necessary to specify a model to determine drug clearance.

2-9. A. *Incorrect answer*
B. CORRECT ANSWER. With first-order elimination, the amount of drug eliminated in any time period is determined by the amount of drug present at the start. Although the amount of drug eliminated in successive time periods may decrease, the fraction of the initial drug that is eliminated remains constant.

Discussion Points

D1. Drug Y is given by an intravenous injection and plasma concentrations are then determined as follows:

Time after Injection (hours)	Concentration (mg/L)
0	12
1	9.8
2	7.9
3	6.4
4	5.2
5	4.2
6	3.4
7	2.8
8	2.2

Is this drug eliminated by a first- or zero-order process? Defend your answer.

D2. Which of the following patient scenarios is associated with a smaller volume of distribution?

A. Dose = 500 mg and initial serum concentration is 40 mg/L

B. Dose = 20 mg and initial serum concentration is 1.5 mg/L

D3. Explain how a person who weighs 70 kg can have a volume of distribution for a drug of 700 L.

D4. For drug X, individual organ clearances have been determined as follows:

Renal clearance	180 mL/minute
Hepatic clearance	22 mL/minute
Pulmonary clearance	5.2 mL/minute

How would you describe the clearance of drug X?