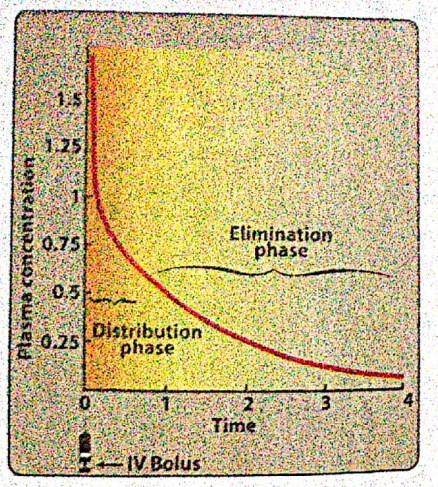

Figure 1.12
Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

rapidly leaves the circulation and enters the tissues (Figure 1.12). The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to the "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of *propofol* (see Chapter 13). High blood flow, together with high lipophilicity of *propofol*, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

B. Capillary permeability

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

C. Binding of drugs to plasma proteins and tissues

1. **Binding to plasma proteins:** Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment. Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein). This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. **Binding to tissue proteins:** Many drugs accumulate in tissues, leading to higher concentrations in tissues than in the extracellular fluid and blood. Drugs may accumulate as a result of binding

to lipids, proteins, or nucleic acids. Drugs may also be actively transported into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of cyclophosphamide, can cause hemorrhagic cystitis because it accumulates in the bladder.)

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. In contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

The apparent volume of distribution, V_d, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

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

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

   a. **Plasma compartment:** If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume or about 4 L in a 70-kg individual. *Heparin* (see Chapter 22) shows this type of distribution.

   b. **Extracellular fluid:** If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14 L in a 70-kg individual).

c. **Total body water:** If a drug has a low molecular weight and is lipophilic, it can move into the interstitium through the slit junctions and also pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent V_d.

2. **Apparent volume of distribution:** A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular components, such as lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and cells), and nucleic acids (abundant in cell nuclei). Therefore, the volume into which drugs distribute is called the apparent volume of distribution (V_d). V_d is a useful pharmacokinetic parameter for calculating the loading dose of a drug.

3. **Determination of V_d:** The fact that drug clearance is usually a first-order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time (Figure 1.14). The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of V_d as

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L (from the graph in Figure 1.14B), then V_d = 10 mg/1 mg/L = 10 L.

4. **Effect of V_d on drug half-life:** V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow but also on the fraction of the drug in the plasma. If a drug has a large V_d, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases V_d can increase the half-life and extend the duration of action of the drug. [Note: An exceptionally large V_d indicates considerable sequestration of the drug in some tissues or compartments.]

V. DRUG CLEARANCE THROUGH METABOLISM

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination and urinary elimination. Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug present is eliminated in a given unit of time (Figure 1.14A). Mo