magnitude greater than that of muscle (Table 10–1), entry of thiopental into the brain is the more rapid process.

Penicillin, a relatively large polar compound, does not readily pass through membranes. The faster rate of entry of penicillin into muscle than into brain arises from the greater porosity of muscle capillaries. Recall from Chap. 9 (p. 126) for many tissues, e.g., muscle, capillary membranes appear to be very porous and have little influence on the entry of drugs of usual molecular weight (100 to 400 g/mole) into the interstitial fluids, regardless of the drug's physicochemical properties. There may be a permeability limitation at the tissue cell membrane, but in terms of measurement of drug in the *whole* tissue, there would appear to be only a partial impedance to the entry of either ionized or polar compounds, or both. Other tissues, for example, much of the central nervous system, anatomically have a permeability limitation at the capillary level that impedes movement of drug into the tissue as a whole, as observed with penicillin. This observation, especially with a number of polar organic dyes, led to the concept of *blood-to-brain* and *blood-to-cerebrospinal fluid* barriers.

The effect of a high equilibrium distribution ratio (K_P) on the time to achieve distribution equilibrium, discussed previously for a perfusion-rate limitation, applies equally well to a permeability-rate limitation. A permeability-rate limitation simply decreases the rate of entry and hence increases the time to reach distribution equilibrium over that of perfusion. Where the equilibrium lies is independent, however, of which process is rate-limiting.

If the arterial concentration is maintained long enough, the unbound concentration in tissue becomes the same as that in plasma. Sometimes, however, this equality is not observed. Reasons for lack of equality include maintenance of sink conditions by metabolism, active transport, bulk flow of interstitial fluids through both lymphatic channels and ducts, and pH gradients across cell membranes. Inequality in unbound concentration is frequently observed in the cerebrospinal fluid relative to plasma for large polar molecules, e.g., many antibiotics. The most likely explanation here is that the rate of fluid formation is sufficiently fast and the rate of diffusion sufficiently slow so that the resulting concentration, even at steady state, remains below that of the diffusible unbound drug in plasma. Another example is that of the distribution of albumin in the body (Table 10–3). Albumin slowly diffuses across the endothelial linings of the capillaries. The bulk flow of water in the interstitial fluids and lymphatic vessels provides a means of removing albumin from the tissues. The resulting tissue concentration is much below that of plasma. Albumin also diffuses into the cerebrospinal fluid, but the rate is so slow compared to the rate of production of the fluid that the concentration is virtually immeasurable. When there is a breakdown in the blood–cerebrospinal fluid barrier, as occurs for example in meningitis, albumin is found in the fluid as a result of an increased rate of entry.

Table 10–3. Distribution of Albumin in the Body[a]

ORGAN	AMOUNT (g/70-kg subject)	CONCENTRATION (g/kg organ)
Intravascular		
Plasma	140	43
Extravascular		
Muscle	50	2.3
Skin	40	7.7
Liver	2	1.4
Gut	8	5
Other tissues	110	3
Total:	210	
Total body	350	

[a]Adapted from compilation of data of Peters, T.: Serum albumin. *In* The Plasma Proteins. 2nd Ed., Vol. 1. Edited by F.W. Putnam. New York, Academic Press, 1975, p. 162.

EXTENT OF DISTRIBUTION

Multiple equilibria occur within plasma where drug can bind to various proteins, examples of which are listed in Table 10–4. Acidic drugs commonly bind to albumin, the most abundant plasma protein. Basic drugs often bind to α_1-acid glycoprotein and to lipoproteins. Proteins, such as γ-globulin, transcortin, fibrinogen, and thyroid-binding globulin, bind specific compounds. Distribution within each tissue also involves multiple equilibria. Tissue distribution can involve both binding to a wide variety of substances and partitioning into fat.

Apparent Volume of Distribution

The concentration in plasma achieved after distribution is complete is a result of the dose administered and the extent of tissue distribution. Recall from Chap. 3 that, at equilibrium, the extent of distribution is defined by an apparent volume of distribution (V):

$$V = \frac{\text{Amount in body at equilibrium}}{\text{Plasma drug concentration}} = \frac{A}{C} \qquad 7$$

This parameter is useful in relating amount in body to plasma concentration, and the converse. Recall, also, that volumes of distribution vary widely, with illustrative values ranging from 3 L/70 kg body weight to 40,000 L/70 kg body weight, a value far in excess of total body size.

Knowing plasma volume, V_P, and volume of distribution, V, the fraction of drug in body in and outside plasma can be estimated. The amount in plasma is $V_P \cdot C$; the amount in the body is $V \cdot C$. Therefore,

$$\text{Fraction of drug in body in plasma} = \frac{V_P}{V} \qquad 8$$

It is evident that the larger the volume of distribution, the smaller is the fraction in plasma. For example, for a drug with a volume of distribution of 100 L, only 3% resides in plasma.

The remaining fraction, given by

$$\text{Fraction of drug in body outside plasma} = \frac{(V - V_P)}{V} \qquad 9$$

includes drug in the blood cells. For the example considered above, 97% is outside plasma. Although this fraction can be readily determined, the actual distribution of drug outside plasma cannot.

The reason why the volume of distribution is an apparent volume and why its value differs among drugs may be appreciated by considering the simple model shown in Fig. 10–4.

Table 10–4. Representative Proteins to Which Drugs Bind in Plasma

PROTEIN	MOLECULAR WEIGHT (g/mole)	NORMAL CONCENTRATIONS g/L	NORMAL CONCENTRATIONS µM
Albumin	67,000	35–50	500–700
α_1-Acid glycoprotein	42,000	0.4–1.0	9–23
Lipoproteins	200,000–2,400,000	Variable	
Cortisol binding globulin (transcortin)	53,000	0.03–0.07	0.6–1.4

In this model, drug in the body is entirely accounted for in plasma, of volume V_P, and one tissue compartment, of volume V_T. At distribution equilibrium, the amount of drug in each location can be expressed in terms of plasma concentration, C, volumes of plasma and tissue and distribution ratio, as follows:

$$A = \underset{\text{Amount in plasma}}{V_P \cdot C} + \underset{\text{Amount in tissue}}{V_T \cdot K_P \cdot C} \qquad 10$$

And since $A = V \cdot C$ (Eq. 7), it follows, on dividing the equation above by C, that

$$V = V_P + V_T \cdot K_P \qquad 11$$

The product $V_T \cdot K_P$ is the apparent volume of a tissue viewed from measurement of drug in plasma. Thus, by expanding the model to embrace all tissues of the body, it is seen that the volume of distribution of a drug is the volume of plasma plus the sum of the apparent volumes of distribution of each tissue. For some tissues the value of K_P is large, which explains why the volume of distribution of some drugs can be much greater than total body size. Fat, for example, occupies approximately 20% of body volume. If the K_P value in fat is 5, then this tissue alone has an apparent volume of distribution equal to that of body volume. Remember, however, even when a perfusion rate limitation applies, it takes approximately 7 hrs for distribution equilibrium to occur in fat (Fig. 10–2B).

The volume of distribution of a specific drug can vary widely among patients. The reasons for such differences are now explored. Before doing so, however, a general point is considered.

Binding Within Blood. Within blood, drug can bind to many components including blood cells and plasma proteins. As a consequence of binding, the concentration of drug in whole blood (C_b), in plasma (C) and unbound in plasma water (Cu) can differ greatly. For ease of chemical analysis, plasma is the most common fluid analyzed. In many respects this choice is unfortunate. One of the primary goals of measuring concentration is to relate the measurement to pharmacologic response and toxicity. However, only unbound drug can pass through most cell membranes, the protein-bound form being too large. Accordingly, the unbound drug concentration is undoubtedly more closely related to the activity of the drug than is the total plasma concentration. Yet unbound concentration is only occasionally measured, primarily because the methods for doing so are often tedious, lack

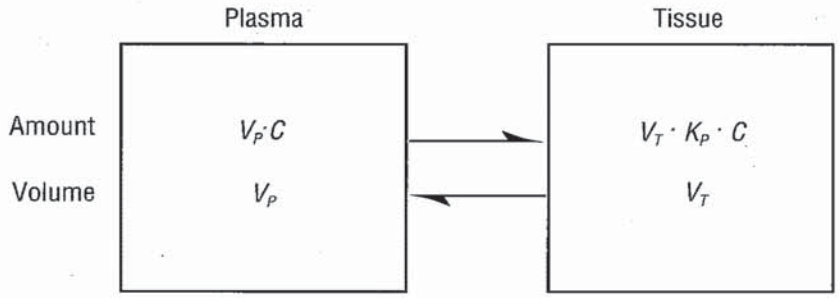

Fig. 10–4. The effect of tissue binding on drug distribution is illustrated by a drug that distributes between plasma and a tissue. The physiologic volumes are V_P and V_T, respectively. At equilibrium the amount of drug in each location depends on the equilibrium distribution (partition) ratio, K_P, the plasma and the tissue volumes, and the plasma concentration.

accuracy and precision, and are costly. Nonetheless, it is helpful to define an unbound volume of distribution, Vu,

$$Vu = \frac{\text{Amount in body at equilibrium}}{\text{Unbound plasma concentration}} = \frac{A}{Cu} \qquad 12$$

which permits the amount of drug in the body to be related to the unbound drug concentration.

Sometimes whole blood concentration is measured. Once again an appropriate volume term, V_b, can be defined. Namely,

$$V_b = \frac{\text{Amount in body at equilibrium}}{\text{Concentration in whole blood}} = \frac{A}{C_b} \qquad 13$$

As the amount of drug in body is independent of the site of measurement, it follows from Eqs. 7, 12, and 13 that

$$V \cdot C = Vu \cdot Cu = V_b \cdot C_b \qquad 14$$

The values of these volume terms can differ markedly for a given drug. The term most often quoted in the literature is based on measurement of drug in plasma (i.e., V). Examples of drugs with differing values of V are given in Fig. 3–2 (p. 22).

Plasma Protein Binding. The principal concern with plasma protein binding is related to its variability within and among patients in various therapeutic settings. The degree of binding is frequently expressed as the bound-to-total concentration ratio. This ratio has limiting values of 0 and 1.0. Drugs with values greater than 0.9 are said to be highly bound.

As stated previously, unbound, rather than bound, concentration is frequently more important in therapeutics. Therefore, the fraction of drug in plasma unbound, fu,

$$fu = Cu/C \qquad 15$$

is of greater utility than fraction bound. Obviously, only if fu is constant is total plasma concentration a good measure of changes in unbound drug concentration. Approximate values of fu usually associated with therapy for representative drugs are shown in Fig. 10–5.

Binding is a function of the affinity of the protein for the drug. The affinity is characterized by an association constant, K_a. Because the number of binding sites on a protein is limited, binding also depends on the molar concentrations of both drug and protein. For a single binding site on the protein, the association is simply summarized by the following reaction:

$$\text{Drug} + \text{Protein} \rightleftharpoons \text{Drug-protein complex} \qquad 16$$

Equilibrium may lie either to the right or to the left. High affinity, of course, implies that equilibrium lies far to the right. This is a relative statement, however, as the greater the protein concentration for a given drug concentration, the greater the bound drug concentration and the converse. From mass law considerations, the equilibrium is expressed in terms of the concentrations of unbound-drug, Cu, unoccupied protein, P, and bound drug, Cbd, thus

$$K_a = \frac{Cbd}{Cu \cdot P} \qquad 17$$

The unoccupied protein concentration depends on the total protein concentration, P_t. These two concentrations are related by $fu_p = P/P_t$, where fu_p is the fraction of the total number of binding sites unoccupied. Furthermore, the unbound concentration is $fu \cdot C$ and the bound concentration is $(1 - fu) \cdot C$. Appropriately substituting into Eq. 17, it therefore follows upon rearrangement that

$$fu = \frac{1}{1 + K_a \cdot fu_p \cdot P_t} \qquad 18$$

From this relationship the value of fu is seen to depend on the total protein concentration, as illustrated in Fig. 10–6 for the binding of propranolol to α_1-acid glycoprotein. When fu is small (<0.1), Eq. 18 is approximately $1/(K_a \cdot fu_p \cdot P_t)$. By taking the ratio of this equation for normal and altered conditions, the value of fu (fu') when the concentration of binding protein is altered (P_t') is,

$$fu' = \frac{P_t}{P_t'} \cdot fu \qquad 19$$

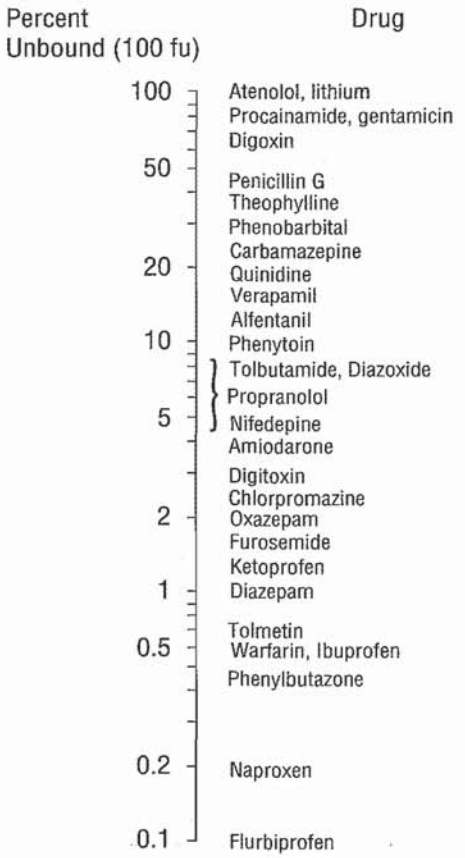

Fig. 10–5. The fraction of drug in plasma not bound to protein varies widely among drugs.

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