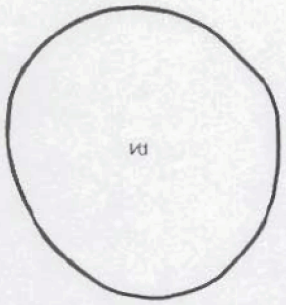
5 Volume of Distribution or Mass of a Substance in a Closed System



Volume of distribution: inject m_0, wait, take one sample.

5.1 The Experiment

In a closed system the volume of distribution Vd of a given indicator can be calculated by injecting the dose m_0, waiting until the solution is completely mixed, and then measuring the concentration $c(\infty)$ in any fluid belonging to the system.

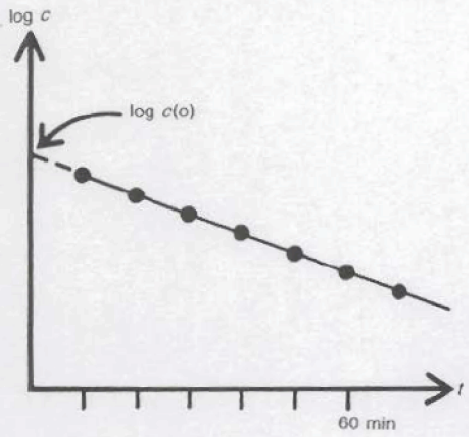
The fluid selected is the reference fluid, and the volume of distribution Vd will correspondingly be expressed in milliliters of that fluid.

Vd is defined by applying the mass balance concept: The amount of indicator in the system m_0 equals the volume of distribution Vd multiplied by the indicator concentration $c(\infty)$ within that volume. According to this definition Vd is the system's physical volume in the special case of the indicator mixing completely in one homogeneous "bag" of fluid. However, in general Vd is, as we shall discuss in more detail in Sec. 5.2, a virtual ("imaginary") volume. According to the definition

$$\text{Volume of distribution} = \text{Dose over the indicator concentration in reference fluid after complete mixing} \qquad [5.1]$$

$$Vd = \frac{m_0}{c(\infty)} \quad \text{ml}$$

The experiment may be arranged so the system will be closed, if it is not so initially. Suppose that the system is the kidney, and that we wish to measure its red cell volume. An arbitrary dose of ^{51}Cr labeled red cells could be injected intravenously and after a few minutes a blood sample taken and the kidney excised. The amount of ^{51}Cr in the total kidney is the retained dose m_0, and the amount of ^{51}Cr per ml of red cells in the blood sample is $c(\infty)$. The same Vd would have been obtained had we measured the amount m_0 of hemoglobin in the kidney and the hemoglobin concentration $c(\infty)$ in red cells.



Plasma volume

Suppose we intravenously inject an amount m_0 (mg) of a plasma indicator (i.e., an indicator that does not enter the red cells) such as high-molecular-weight dextran or ^{131}I-labeled albumin (i.e., a plasma indicator that does not rapidly leave the plasma volume). Blood samples are taken at an arbitrary site. The measured blood concentration is observed to approach some constant value $c(\infty)$ (mg/ml). Mass balance yields $Vd = m_0/c(\infty)$ (ml).

This Vd is evidently the plasma volume provided the assumptions of no loss and complete mixing hold. In practice both assumptions cannot be fulfilled simultaneously. A molecule of the size of albumin leaks out from the vascular volume at a rate of approximately 0.1% per min. Hence, waiting for complete mixing to occur (approximately 10 min in normal man) entails a 1.0% loss of indicator. We can correct for this loss by assuming that the dose of indicator remaining intravascularly after 10 min is 0.99 m_0. But the most precise result is obtained by measuring the rate of escape of the indicator, taking blood samples at 10, 20, 30, 40, 50, and 60 min, and then employing monoexponential back-extrapolation to time 0.

Red cell volume

If the same experiment is performed with ^{51}Cr-labeled red cells and $c(\infty)$ is the amount of ^{51}Cr per ml of red cells, then Eq. [5.1] yields the total volume of red cells in the intravascular space. The limitations discussed above (mixing and leaking) also apply. In fact the labeled red cells enter the interstitial space of the spleen so rapidly that the splenic extravascular red cell space is included (this also applies to the measured plasma volume that also includes other rapidly exchanging extravascular spaces, particularly in the liver).

Blood volume

By adding plasma and red cell volumes we obtain the total blood volume. Due to rapid transcapillary exchange of the indicators in special organs (spleen, liver, etc.) this blood volume is slightly larger than the anatomical blood volume (the space inside the vascular walls). The difference is in the order of a few percent. The red cell volume divided by the total blood volume is called the *whole body hematocrit*. This fractional red cell volume is approximately 10% lower than that measured in a blood sample taken from an artery or a vein, the so-called *large vessel hematocrit*. This discrepancy is due to two factors: (a) the hematocrit of the blood in the small vessels (arterioles, capillaries, and venules) is lower than that of the blood in the large vessels, and (b) the overestimation of the volume due to rapidly exchanging extravascular spaces

$$[\text{Htc}]_{\text{whole body}} = \frac{\text{Red cell volume}}{\text{Blood volume}}$$

is more pronounced in plasma than in red cell volume determination.

We have commented here on some of the problems involved in blood volume determination to show that even in the case of the most well-defined space in the body, which we can measure quite accurately, we are dealing with approximations.

5.2 Volume of Distribution ("Space") in the General Case

In most cases *Vd* must be considered an *equivalent* rather than an actual volume. Consider, for example, the case of albumin in the whole body. This plasma protein is known to be distributed so that approximately 60% of the total amount is extravascular and 40% is intravascular. For convenience assume that in a given subject equal amounts (50%) are present in the two locations. We measure a plasma volume of 3 liters using Eq. [5.1]. Is it therefore correct to say that albumin has a volume of distribution *Vd* in the total body of 6 liters? Yes, this is certainly correct as we here take plasma as our reference fluid; that is, *Vd* for albumin is 6 liters *of plasma.* But this is clearly an abstraction that to some extent is even misleading, because the extravascular albumin is known to exist in a low and variable concentration in interstitial fluid and lymph. Thus, the geometrical space in which albumin exists outside the vessels is much larger than 3 liters (perhaps approximately 6 liters).

These considerations identify the abstraction involved in defining *Vd* as the ratio $m_0/c(\infty)$. In our example *Vd* is seen to be *equivalent* since "had the plasma volume been 6 liters" and "had no albumin been located extravascularly," then this hypothetical situation would, with respect to amount of albumin, be equivalent to the actual situation. We know that plasma proteins that are larger than albumin have a relatively smaller extravascular fraction even though physically all plasma proteins are probably found in the same locations in the interstitial space. Hence *Vd* is smaller for such molecules than for albumin. This again illustrates the imaginary nature of the "space" concept in the general case.

In the experiment performed for measuring *Vd* one waits until mixing is complete before sampling from the reference fluid. This is customarily called *equilibration*—for example volume measurement of fluid or of air in a container. It should be stressed, however, that in biological space measurements the state of complete mixing in *most cases is not a state of equilibrium in the thermodynamic sense.* For example, in the case of albumin distribution, equilibrium between extra- and intravascular albumin would (thermodynamically speaking) mean that the albumin concentration was equal in these communicating spaces; that is, the active force, the continued forma-

In the swim bladder of fish active forces do influence inert gasses.

tion and convective stream of lymph which maintain the concentrations at different levels, would have to be eliminated. To take another example, consider the exchange of ^{24}Na in a sample of blood. Thermodynamic equilibrium cannot *ever* be reached, as the cells will burst before the internal and external concentrations reach their equilibrium (Donnau equilibrium) value. Only in very special cases does the state of complete mixing of an indicator in a closed system become identical to equilibrium. This is true for inert gases because active cellular forces essentially do not influence their distribution.

The tracer–mother substance case explains quite precisely the meaning of "complete mixing" in a closed system. When the specific activity has become equal at all sites, mixing is in fact the state of thermodynamic equilibrium for the "basic" system consisting solely of tracer and mother substance. Yet, for both substances (tracer and mother substance), the distribution inside the actual system (e.g., an organ or a blood sample) at complete mixing is, as mentioned in the previous section, often far from thermodynamic equilibrium.

Complete mixing in a closed system corresponds precisely to indicator steady state in an open system with convective outlets. In fact one might use the term *steady state* to denote both concepts. That stresses the fact that the volume of distribution Vd (respectively, the mass of distribution M) *is the same* whether measured after complete mixing in a closed system or in the indicator steady state in the same system. But now with the system being open. However, because *steady state* conveys the concept of ongoing (but precisely balancing) inputs and outputs we have chosen to use the term *complete mixing* for the closed system. In an operational sense this term also pertains to the actual experimental situation: inject → mix → sample.

5.3 The Mass *M*

Suppose that the substance for which we wish to measure the mass M is contained in a space of measurable size. It could for example be the intravascular mass of the protein molecule transferrin (the iron-carrying protein of M Wt. ≃ 70,000). Then a simple procedure would be the determination of the plasma volume by using labeled albumin as indicator and then by mass balance

$$\begin{aligned} \text{Mass} &= \text{Space} \times \text{Concentration} \\ [M]_{\text{transferrin}} &= V_{\text{plasma}} \times C_{\text{transferrin}} \end{aligned} \qquad [5.2]$$

However, a more direct approach for determining the mass M of a substance in a closed system consists in using a *tracer* for that substance. Suppose then that we have ^{131}I-labeled transferrin. The dose m_0 is injected into the system and one

In general
$s = c/C$
$= m/M$

waits until the indicator mixing has become complete; *that is, until the specific activity has reached the same constant value* $s(\infty)$ *throughout the entire system.* As the specific activity is the ratio of the amounts of tracer and mother substance, that is, $s(\infty) = m_0/M$, it follows that

$$\text{Mass} = \text{Dose over specific activity at indicator steady state}$$

$$M = \frac{m_0}{s(\infty)} \text{ g} \qquad [5.3]$$

Equation [5.3] is obtained directly from Eq. [5.1] if we use the type of "translation" from the hydrodynamic case to the tracer–mother substance case that was introduced in Chapter 1. Namely, Vd corresponds to M just as $c(\infty)$ corresponds to $s(\infty)$. There is one difference, however, in that we do not have to specify the reference fluid (or tissue) from which we obtain $s(\infty)$.

5.4 The Partition Coefficient λ

Consider an open system through which a carrier fluid flows. It could be an organ in the body perfused with blood. Physically speaking, the system may have several inlets. But by supplying the indicator at the same constant concentration $[c(\infty)]_{\text{blood}}$ at each the system functions as a single-inlet system. After a certain time the indicator steady state is reached with a constant amount $m(\infty) = m_0$ of the indicator retained inside the system. We define the mean concentration in the system as the amount of indicator per gram of tissue.

Then, with a tissue weight of W g,

$$\begin{aligned} \text{Dose} &= \text{Steady state residue} = \text{Weight} \times \text{mean tissue concentration at steady state} \\ m_0 &= m(\infty) = W[c'(\infty)]_{\text{tissue}} \end{aligned} \qquad [5.4]$$

But according to Eq. [5.1] this amount of indicator is also given as the product of the volume of distribution Vd (defined by using the inflow fluid as reference fluid) and the steady state inlet concentration; that is, $m_0 = Vd[c(\infty)]_{\text{blood}}$. Hence

Mass balance; two different modes of expressing it

$$\begin{aligned} \text{Residue} &= \text{Residue} = \text{Residue} \\ m(\infty) &= W[c'(\infty)]_{\text{tissue}} = Vd[c(\infty)]_{\text{blood}} \end{aligned} \qquad [5.5]$$

It should be stressed that following a widely c' used convention we express the tissue concentration in amount *per gram of tissue* and blood concentration c in amount *per milliliter of blood.* We define λ as the indicator steady-state ratio

$$\text{Partition coefficient} = \text{Tissue:blood concentration ratio at indicator steady state}$$

$$\lambda = \frac{[c'(\infty)]_{\text{tissue}}}{[c(\infty)]_{\text{blood}}} \quad \text{ml/g} \qquad [5.6]$$

With this definition Eq. [5.5] shows that

$$\lambda = \frac{[c'(\infty)]_{\text{tissue}}}{[c(\infty)]_{\text{blood}}} = \frac{Vd}{W} \quad \text{ml/g} \qquad [5.7]$$

Or, *the partition coefficient is the volume of distribution per gram of tissue weight.* λ is expressed in units of ml/g in accordance with the convention used when defining the tissue and blood concentrations. We have here followed the definition of λ used by Kety in developing the nitrous oxide method for measuring cerebral blood flow per g (or per 100 g) of brain tissue. Other investigators have used a dimensionless λ^* as the same ratio where the tissue concentration is expressed in amount per milliliter. This definition has no real conceptual advantage, as such a λ^* does, nevertheless, have a "hidden" dimension (e.g., ml of *blood* per milliliter of *tissue*). Moreover, for practical use one must always divide λ^* by the specific gravity of the tissue ρ ("rho") in order to obtain blood flow in the usual unit of ml/g instead of in ml/ml. λ^*/ρ is identical with Kety's λ as defined in Eq. [5.7].

Kety S. S. and Schmidt C. F. (1945): *Am. J. Physiol.* 143:53.

It is important to consider the tissue as including its blood. Thus $[c(\infty)]_{\text{tissue}}$ in Eq. [5.5] is (amount)/(g of tissue including its blood). This is necessary in order for Eq. [5.5] to be valid in the *in vivo* condition. It follows that Vd, W, and λ all refer to the tissue with its blood.

In general the tissue in a system is not homogeneous but may be seen as a sum of portions of a few types of tissue (e.g., fat + lean, muscle + skin, etc.). In this case it is convenient to generalize Eq. [5.5] as

$$m_0 = Vd\,[c(\infty)]_{\text{blood}} = \Sigma\, W_i[c'(\infty)]i \qquad [5.8]$$

where W_i is the weight in grams of the i^{th} tissue component in which the steady state indicator concentration is $[c'(\infty)]_i$ (amount/g), Σ denotes summation over all tissue components, and the partition coefficient for each tissue component is defined analogously to Eq. [5.4] as

$$\lambda_i = \frac{[c'(\infty)]_i}{[c(\infty)]_{\text{blood}}} \qquad [5.9]$$

Equation [5.8] may be written as

$$Vd = \frac{m_0}{[c(\infty)]_{\text{blood}}} = \Sigma\lambda_i W_i = \bar{\lambda} W \qquad [5.10]$$

Equation [5.10] defines the volume of distribution both directly, as the ratio of retained dose of indicator to a steady-

state reference concentration in a particular experiment, and indirectly, as the sum of products of partition coefficients and component tissue weights where each λ_i may be determined in a separate experiment. Thus λ_i can be obtained simply by analyzing a sample of the tissue concerned, care being taken to include the amount of naturally occurring blood in the analysis of the sample as well as in the weight used for obtaining the concentration. Determining also the substance's blood concentration yields λ_i according to Eq. [5.9].

The last equality in Eq. [5.10] defines the average partition coefficient $\bar{\lambda}$ as

$\bar{\lambda}$ is the weighted sum of λ for all tissue elements.

$$\bar{\lambda} = \frac{\Sigma \lambda_i W_i}{W}, \quad \Sigma W_i = W \qquad [5.11]$$

Thus $\bar{\lambda}$ is the weighted average of all the λ_i coefficients for the system with the weighting factor being the fractional weights W_i/W of each component.

To give an example, we can obtain the partition coefficient for the entire brain by

Brain in normal man: 60% gray matter and 40% white matter

Thus
$W_g/W = 0.60$
$W_w/W = 0.40$

$$\bar{\lambda} = \lambda_g \frac{W_g}{W} + \lambda_w \frac{W_w}{W} \qquad [5.12]$$

That is, it can be expressed as the weighted sum of the partition coefficient of gray matter λ_g and white matter λ_w with the fractional weights W_g/W and W_w/W as weighting factor.

A basic convenience of the λ parameter is that it is independent of the absolute amount of indicator. If we double the amount of indicator then both tissue and blood concentration double and λ is constant.

The λ concept plays a prominent role in all inert gas indicator methods and hence we will comment on this special type of λ. At the indicator steady state for an inert gas we have the same gas tension throughout the system. Let the tissue and blood solubility coefficient of the inert gas be defined respectively as the amount of gas in a g of tissue and in a ml of blood at a partial pressure of 1 atm.

Remember that in our usage the unit of tissue is expressed in g, and of blood in ml.

Hence, λ for an inert gas is

$$\lambda = \frac{\text{Solubility coefficient in tissue}}{\text{Solubility coefficient in blood}} \qquad [5.13]$$

This relationship is important because we know that the inert gas solubility in a tissue is independent of the functional state of that tissue. It may be living or dead but λ does not change. The inert gas solubility depends practically only on the concentration of water, protein, and lipid in the tissue. Therefore, as long as such gross physicochemical characteristics remain essentially at their normal level, the solubility coefficient in the tissue also remains constant.

For the blood, inert gas solubility in red cells is somewhat higher than in plasma. Thus the inert gas solubility in blood

is the weighted average of the constant solubility of the two components, red cells and plasma (only in severe hyperlipemia is the inert gas solubility in plasma significantly increased).

For xenon λ is almost constant in myocardium, kidney, and skeletal muscle. But for liver the variable content of neutral fat influences λ_{Xe}.

The preceding considerations led Kety to postulate that λ for an inert gas is practically a constant for the brain. This has been verified experimentally.

To illustrate how the λ concept is used a discussion will be given of the *brain: blood partition coefficient for ^{133}Xe and for ^{131}I-labeled albumin and the effect of variations in the blood volume of the brain.*

The blood in the brain may be considered as a separate tissue and hence

$$\bar{\lambda} = \lambda'_g W'_g/W + \lambda'_w W'_w/W + \lambda'_b W_b/W$$

where W'_g and W'_w are the weights of gray and white matter not including their blood and W_b is the weight of blood. The weighting factors W'_g/W, W'_w/W, and W_b/W are the corresponding fractional weights, and λ'_g, λ'_w and λ'_b are the respective partition coefficients. λ'_b is the ratio of solubilities in the blood in the brain tissue proper (excluding tissue blood) and in systemic blood. Since the hematocrit of brain tissue blood is only slightly lower than that of systemic blood, $\lambda'_b \simeq 1.00$.

The fractional weights of the three components can be calculated by

$$W'_g/W + W'_w/W + W_b/W = 1$$
$$W'_g/W'_w = 1.5$$

Let it now be assumed that the fractional blood content W_b/W varies from a low value (0.02) over a normal value (0.05) to a very high value (0.10); that is, the blood content of the brain between 2 and 10%. Table 5.1 is then obtained.

TABLE 5.1 Brain Composition (Fractional Weights) and Partition Coefficients at Different Blood Volumes

W_b/W	0.020	0.050	0.100
W'_g/W	0.588	0.570	0.540
W'_w/W	0.392	0.380	0.360
$\bar{\lambda}_{Xe}$	1.1078	1.1045	1.0990
$\bar{\lambda}_{alb}$	0.0200	0.0500	0.1000

The fractional weight of gray matter is taken to be 60% of the blood free brain; that is $W'_g/(W'_g + W'_w) = 0.6$

Constancy of $\bar{\lambda}_{\text{inert gas}}$, that is the volume of distribution per gram of tissue

For ^{133}Xe with approximative values of $\lambda'_g = 0.85$ and $\lambda'_w = 1.50$ the calculated $\bar{\lambda}$ varies less than 1% as the blood content varies fivefold. For albumin, where $\lambda'_g = \lambda'_w = 0.00$, the calculated $\bar{\lambda}$ equals the fractional blood volume and hence it varies 500%.

This example stresses a fundamental difference between indicators distributing rapidly in the entire tissue (freely diffusible indicators) and indicators that are practically confined to the vascular bed (nondiffusible indicators). The insensitivity

of $\bar{\lambda}_{\text{inert gas}}$ to local blood volume variations is of fundamental importance for the use of such indicators for indirect blood flow measurements.

5.5 Comparison of the Volume of Distribution Concept with the Clearance Concept

Both of these terms are difficult to handle. We shall in this section compare the two to show that they are closely interrelated in that they involve the same type of derivation.

The *volume of distribution* concept presupposes that there is a "relevant" reference fluid with a self-evident definition in many cases. In a hydrodynamic system where substances are exchanged across the boundaries solely by convection, the obvious reference fluid is the fluid crossing the boundary. Even then, however, the systems studied in the body are generally only approximated by so simple a scheme. Without considering the complexity of minute effects (such as metabolic production of water in the system rendering (J_{out})water slightly larger than (J_{in})water) we can just point to lymph flow or secretions. In this case we might ask: If the volume of distribution for ^{131}I-labeled albumin is expressed as ml of whole blood in a kidney ($Vd = M/C$), is the concentration C then measured in arterial blood or in renal venous blood? In other words, is the volume of distribution expressed in ml of arterial blood or in ml of venous blood? Of course the difference is slight but the example emphasizes the indirect way of obtaining Vd. In fact, a precise definition of Vd will in all instances be long and cumbersome: *The volume of distribution of a substance inside a system denotes the volume of the (arbitrary) chosen reference fluid that contains the same amount of the substance as the system does when it is in the steady state.* Thus, again with reference to ^{131}I-labeled albumin which at indicator steady state also labels extravascular albumin, the imaginary or "virtual" nature of Vd is clearly seen: It is virtual because the system functions *as if* it had contained the substance solely in Vd ml of the reference fluid.

$Vd = M/C$
(Virtual volume)

The concept of *clearance* Cl also presupposes the existence of a relevant reference fluid. Cl is the volume of reference fluid to be used in relation to the calculation of a nonconvective flux of a substance across a boundary. It is defined by $Cl = J/C$; that is, the two "primary" observations are the flux J and the concentration C. In order to calculate the clearance we must measure J and C. The flux J, since it is nonconvective, demands the use of an appropriate tracer for its measurement, and at any time the ratio of tracer flux $j(t)$ and of mother substance flux J equals the specific activity $s(t)$, which should preferably equal that of the chosen reference fluid. This is not always the case in actual experimental situations and causes difficulties in the use of the clearance concept that we discussed in Chapter 2.

$Cl = J/C$
(Virtual flow)

5.6 Summary

The principle involved in measurement of volume or mass in a closed system is the classic and simple dilution principle. It is usually explained by considering that m_0 of a dye is admixed to a bath resulting after mixing is complete in a concentration of $c(\infty)$/liter. That $Vd = m_0/c(\infty)$ is then obvious. But in practice problems are encountered as the system may not be completely closed and as complete mixing of indicator inside the system may be difficult to obtain.

In case the indicator is a tracer for a systemic mother substance, Eq. [5.2] gives

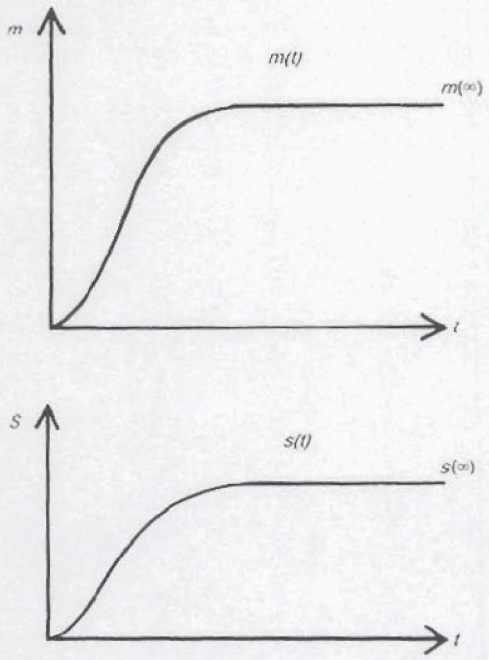
$$m_0 = Ms(\infty) \qquad [5.14]$$

where $s(\infty)$ (amount of tracer/g mother substance) is the steady state specific activity of tracer throughout the system, and M (g mother substance) is the mass of mother substance in the system. Comparison of Eqs. [5.8] and [5.14] emphasizes the fundamental difference between foreign substance indicators and tracer indicators. After mixing the foreign substance can have different concentrations in different tissue components, but a tracer has a single specific activity throughout its mother substance. This property of tracers is denoted the *tracer condition.*

$s(\infty)$ is the same in any part of the system; $c_i(\infty)$ is usually not.

Please note that we have defined Vd and M strictly as the volume and mass as calculated after complete mixing. This definition is the "Achilles heel" of the indicator dilution principle applied to a closed system because, when is mixing complete? In some cases the system's indicator concentration (measured in a suitable reference fluid i) $c_i(t)$ or the specific activity $s_i(t)$ approach the final value according to a monoexponential function that can be used for extrapolation to obtain $c_i(\infty)$ or $s_i(\infty)$. Thus we see that the basic problem is precisely the same as that encountered with the indicator methods in open systems. We cannot recommend the fairly widespread use of letting Vd or M be considered as functions of time, that is as "apparent volume or mass of distribution after X hr of distribution." Consider first the abstractness of the "virtual" volumes Vd and $\lambda = Vd/W$; to then conceive of virtual volumes $Vd(t)$ and $\lambda(t)$ that *grow with time* is truly an intellectual *tour de force.* Also, it adds almost impossible difficulties to the use of the concepts in relation to the mean transit time methods discussed in Chapters 6 and 7.

This comment is not intended to imply that one might not use the term "24 hr exchangeable mass of Na^+." This is simply an operational indication of how the experiment was made in order to almost reach equilibrium. What we object to, in terms of this example, would be to speak of an exchangeable-mass that increased from the moment of injection according to the equation $M(t) = m_0/s_{\text{plasma}}(t)$.



We may obtain the mass M in a single inlet system into which we inject a bolus of a tracer

$$M = JI = \frac{m_0}{\int_0^\infty s(t)dt} \cdot \frac{\int_0^\infty m(t)dt}{m_0} = \frac{\int_0^\infty m(t)dt}{\int_0^\infty s(t)dt} \qquad [5.15]$$

where $m(t)$ is the residue in the entire system and $s(t)$ is the specific activity at an outlet (or anywhere inside the system). The symbols will be discussed in detail in the next two chapters.

We can rewrite this as

$$M = \frac{\bar{m} \cdot T}{\bar{s} \cdot T} \text{ for } T \to \infty$$

and as $\bar{m} \to m(\infty)$ = retained dose m_0 and $\bar{s} \to s(\infty)$ for a very prolonged bolus (an infusion experiment), it follows that the closed system Eq. [5.3] is just a special case of the general Eq. [5.15] employed by Bergner.

EXERCISES

5.1 1.5 g of inulin is injected intravenously into a subject with no kidney function (maintained on hemodialysis). The equilibrium plasma inulin concentration is 100 mg/liter. Assuming no loss of the indicator give the inulin volume of distribution expressed in liters of plasma. With a hematocrit of 0.50, how large is the inulin volume of distribution, expressed in liters of blood?

Assume that the plasma volume is 3 liters and the plasma protein concentration is 7% so that we (approximating) can assume that 1 liter of plasma equals 0.93 liters of ultrafiltrate. Give the equations for and calculate the extracellular space here defined relative to inulin.

5.2 An isolated skeletal muscle weighing 40 g is perfused with an artificial plasma for 1 hr until equilibrium is reached. Indicators are tritiated inulin and ^{14}C labeled sucrose. At the end of the experiment the following data are obtained: Plasma inulin 1,000 cpm/ml, plasma sucrose 300 cpm/ml, muscle inulin 120 cpm/g, and muscle sucrose 60 cpm/g.

Calculate the volumes of distribution and the partition coefficients. Also give the interstitial fluid volumes assuming it to be plasma ultrafiltrate and that the plasma contained 5% albumin (see Ex. 1). Discuss the difference between Vd values for the two indicators.

5.3 For inert gas ^{85}Kr the concentration ratio $c_{plasma}/c_{red\ cells}$ is 0.65. Write the equation for the dependence of $\bar{\lambda}_{brain}$ on the hematocrit of the blood when you know that at hematocrit 0.40 the $\bar{\lambda}_{brain}$ is 1.06.

First write the equation

$$\lambda = \frac{\bar{c}_{brain}}{c_{blood}} = \frac{c_{brain}}{\text{Htc}\ c_{red\ cells} + (1 - \text{Htc})c_{plasma}}$$

chapter 6

Then insert $c_{plasma} = 0.65\ c_{red\ cells}$ so that c_{plasma} is eliminated. This equation is used to express λ_{brain} [0.40] as $[1/(0.40 + 0.60 \cdot 0.65)] \cdot c_{brain}/c_{red\ cells}$. As this λ value is 1.06 it follows that $c_{brain}/c_{red\ cells} = —$. Inserting this into the general equation gives

$$\lambda(\mathrm{Htc}) = \frac{—}{\mathrm{Htc} + (1 - \mathrm{Htc}) \cdot 0.65}$$

This example illustrates how one can utilize one experimental λ measured at a given hematocrit value for calculating other λ values if $c_{plasma}/c_{red\ cells}$ is known.

Note that the gross chemical composition of the gray and white matter of the brain is practically the same in various mammals including man. Hence λ_{area} and λ_{white} are also the same but $\bar{\lambda}$ is higher in man than in many of the other mammals because of the high percentage of white matter present.