7

TRANSFER OF SUBSTANCES BETWEEN BIOLOGICAL COMPARTMENTS. SIMPLE DIFFUSION

This chapter and the following two chapters will be concerned chiefly with how solutes get from one place to another in physiological systems. Only the most elementary aspects of the problem will be presented here, for an extended discussion would require us to consider major portions of the fields of physiology, pharmacology, biochemistry, and biophysics.

7-1. Steady States and Equilibrium States

Throughout the subsequent discussion we shall be using the terms, "steady state" and "state of equilibrium" (or simply "equilibrium"). These terms are often confused or used as though they were synonyms. Since they have entirely different meanings, we must begin by distinguishing clearly between them. This is most easily done by means of the hydraulic analogy which is illustrated in Figure 7-1.

W and X are two reservoirs connected by an intervening pipe. Water can flow into W from a faucet, and out of either W or X by a drain. In the various diagrams the direction of flow is indicated by arrows. The reader should have no trouble in following the changes of inflow, flow between W and X, outflow, and amounts of water in the reservoirs, which are depicted in the diagrams. With respect to water, *reservoir W is in equilibrium with reservoir X when there is no net transfer of water between them, i.e.*, when the flow through the intervening pipe is zero. This may (Fig. 7-1d) or may not (Fig. 7-1b) coincide with a steady state. *Reservoir W is in a steady state when the quantity of water in W remains constant, i.e.*, when the flow into W exactly equals the flow out of W. Again, this may (Fig. 7-1d) or may not (Fig. 7-1c) coincide with equilibrium between W and X. When it does, we may speak of a *steady state of equilibrium*. Notice that the concept of equilibrium involves at least two regions so connected with each other that transfer can occur between them in both directions, whereas the concept of a steady state can be applied to a single region. Notice, too,

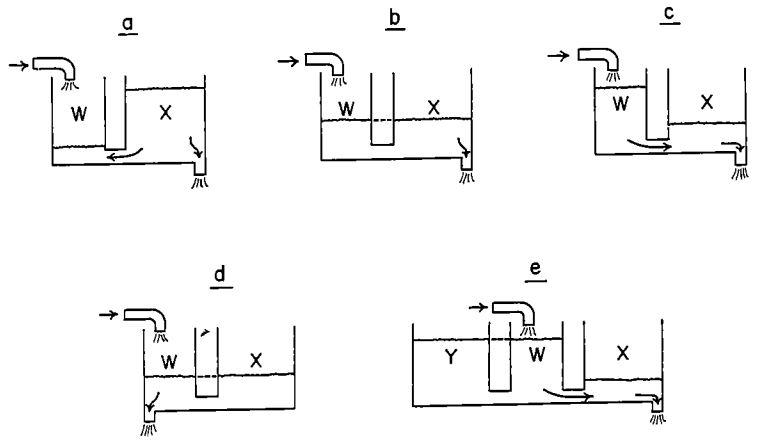

FIG. 7-1. Hydraulic Models to Illustrate the Terms "Steady State" and "Equilibrium"

Model a. Neither a steady state nor an equilibrium. *Model b*. W and X are in equilibrium with each other, but neither is in a steady state. *Model c*. (inflow equal to outflow). Both W and X are in a steady state, but they are not in equilibrium with each other. *Model d* (inflow equal to outflow). W and X are in a steady state of equilibrium. *Model e* (inflow equal to outflow). W, X, and Y are each in a steady state, but only W and Y are in equilibrium with each other.

that in a system with several reservoirs part of the system may be in equilibrium, or even, as in Figure 7-1e, a steady state of equilibrium (Y and W) when another part of the same system (W and X) is not in equilibrium. Ordinarily, however, when one part of a system is in a steady state so also are all other parts of the same system.

In accordance with the illustration just discussed, we shall now give more general definitions of equilibrium and of steady state.

Let S = the substance which is being transferred
W and X = two interconnected compartments
$(dQ_S/dt)_{W \to X}$ = the rate of transfer of S from W to X at time t
$(dQ_S/dt)_{X \to W}$ = the rate of transfer of S from X to W at time t
$dQ_{S \cdot W}/dt$ = the rate at which the quantity of S in W is changing at time t
$dQ_{S \cdot X}/dt$ = the rate at which the quantity of S in X is changing at time t

Then, W and X are in *equilibrium* with respect to S when there is *no net transfer of* S between them, *i.e.*, when $(dQ_S/dt)_{W \to X} = (dQ_S/dt)_{X \to W}$. W is in a *steady state* with respect to S when the *quantity of* S in W *remains*

constant, *i.e.*, when $dQ_{S \cdot W}/dt = 0$. In the steady state, the total quantity of S entering W per unit of time must be exactly equal to the quantity of S leaving W per unit of time. Similarly, X is in a steady state when $dQ_{S \cdot X}/dt = 0$.

Note carefully the distinction between $(dQ_S/dt)_{W \to X}$ which means the rate at which S *is being transferred from* W *to* X at time t, and $dQ_{S \cdot W}/dt$ which means the rate at which the quantity of S *present in* W is changing at time t. In the hydraulic system of Figure 7-1, the substance, S, whose transport was under scrutiny was water. But S might equally well be a solute, a radioactive isotope, or even an electric charge. And in general, W and X are not called reservoirs but rather pools or *compartments* as defined in the next section.

7-2. What Is Meant by the Term "Compartment"?

Suppose we have a rectangular chamber filled with a solution which is divided into two parts by an extremely thin barrier extending across the middle of the chamber (Fig. 7-2). Suppose further that the molecules of a particular solute, S, are able to cross the barrier either by going through holes or "pores" in the barrier or by traversing the substance of the barrier itself. Finally, suppose the solution on each side of the barrier is so well stirred that, when S is added to either side, it immediately reaches a uniform concentration on that side. However, because of the barrier, instantaneous mixing of the fluid on one side with the fluid on the other side does not occur, so that it takes a measurable time for S to approach a final steady state of equilibrium across the barrier. Under these circumstances

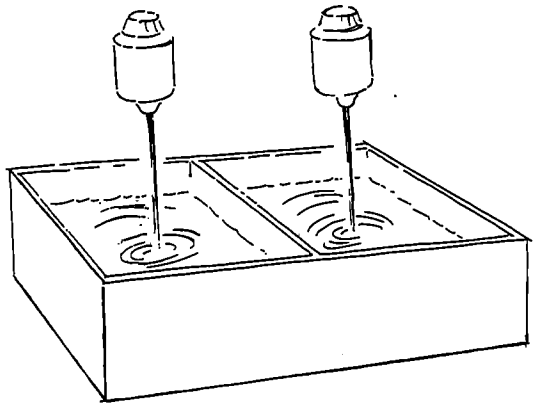

FIG. 7-2. Two Well-stirred Compartments, Separated by a Barrier

the reader will readily agree that the barrier divides the chamber into two distinct compartments. There they are! We could, if we wished, measure them—length, breadth, and depth. Like the compartments in a Pullman car or an egg box, they are real physical entities. Yet it is not their physical reality which identifies them as separate compartments in the sense in which we shall use the term; *it is rather the behavior of* S *in the system*. For example, suppose that the "barrier" were perforated so freely with big holes that mixing of S across it was complete before we could measure the concentration of S on either side. Then as far as our study of S is concerned, there would be only one compartment. At the other extreme, suppose the barrier were completely impermeable to S. Then also, as far as our study of S is concerned, there would be only one compartment, *i.e.*, the one into which S was originally placed. The other side might just as well not be there at all.* We are justified in talking about two compartments only when we can actually investigate the rate of transfer of S from one side to the other.

Let us take another example. If radioactive potassium ions are added to a well-shaken suspension of red blood cells in an isotonic fluid, the rate at which the radioactive potassium enters the red cells can be studied by removing aliquots from time to time and measuring the radioactivity in the centrifuged cells, or the supernatant fluid, or both. Now there are millions of individual cells in the suspension, each constituting a separate little physical chamber. But the technique of measurement allows us to study only what is going on in the group of red cells *taken as a whole*. There are, therefore, only two compartments—cells and surrounding fluid.

As a final extension of the meaning of the term "compartment" consider the chemical state of iodine in blood plasma. Some of the iodine is inorganic iodide ion, while some—in the thyroid hormone—is organic iodine, chiefly in thyroxine. No iodine is exchanged between these two forms except by complicated processes of hormone synthesis in the thyroid gland or hormone degradation in the tissues. For the mathematical description of iodine metabolism, it is convenient to regard inorganic iodide (everywhere in the body) and hormonal iodine (in all extrathyroidal tissues) as existing in two separate compartments, even though physically both forms of iodine occur together in plasma and in various other body fluids.

In accordance with the broadening of meaning illustrated by these examples, we may define the term "compartment" as follows:

> If a substance, S, is present in a biological system in several distinguishable forms or locations, and if S passes from one form or loca-

* In the present argument, we neglect any osmotic or electrostatic effects which S may produce across the barrier.

tion to another form or location at a measurable rate, then each form or location constitutes a separate compartment for S.

It may seem strange to lump different chemical forms and different locations together in this definition, but in fact the mathematical description of transformation from one compound to another is so similar to the mathematical description of transportation from one place to another that the apparent incongruity is justified. In most of this chapter, however, we shall be concerned only with the actual movement of substances from one place to another.

7-3. The Importance of Rapid Distribution within a Compartment. The Volume of a Compartment

The definition of a compartment given above is a definition of sheer convenience. It allows us to postulate as many compartments or as few compartments as are required for analyzing a given problem. But there is one important restriction implicit in the definition which limits our freedom to choose what we shall regard as a compartment: The S in one part of a compartment must be able to interchange rapidly enough with the S in all other parts of the same compartment so that for the particular problem at hand we do not have to worry about transport of S within the compartment. For if S were too slowly distributed, we would be forced to postulate not one but two or more different compartments. This does not mean that the concentration of S must necessarily be uniform throughout the compartment. It does mean that if a small increment of S is added to one part of the compartment, the added S must soon permeate the entire compartment so that the concentration of S in all parts will undergo the same proportional increase. For example, when the synthesis of thyroid hormone has been blocked by a drug such as thiourea, the actual concentration of iodide ion in the thyroid gland may be many times higher than in plasma. Yet the iodide ion in the thyroid exchanges so quickly and freely with the iodide ion in the blood stream that both may *usually* be regarded as belonging to the same iodide compartment. (For an example in which this is *not* true, see Exercise 6, Chapter 9.)

Since a single compartment may consist of regions with different solute concentrations, it becomes necessary to choose one of its regional concentrations as a reference standard and to pretend that the entire quantity of S in the compartment is at a uniform concentration equal to the real concentration of S in the reference region. This pretense allows us to define the *volume of the compartment* as the volume it would have if all of the S contained in it were actually distributed at a uniform concentration equal to that in the reference region. For example, suppose that 20 L. of extracellular fluid (represented by plasma) contained inorganic iodide at a concentration of 3 μg. per liter, and that 0.04 L. of thyroid gland contained inorganic iodide ion at a concentration of 300 μg. per liter. The total iodide in the iodide compartment would then be $(3)(20) + (300)(0.04) = 72$ μg. Now 72 μg. would have to be distributed through a volume of 24 L. to make a uniform concentration equal to the actual concentration in plasma, namely, 3 μg. per liter. We would say accordingly that the volume of the iodide compartment is 24 L. To be absolutely specific, we should say that the volume of the iodide compartment, *with respect to the iodide concentration in plasma*, is 24 L.; for in theory it would be equally correct to say that the volume of the compartment is 0.24 L. *with respect to the concentration of inorganic iodide in the thyroid gland*. But it is rarely necessary to make this distinction. When the reference concentration is not specified, it is commonly understood to be the concentration in plasma which can be sampled and analyzed directly. The imaginary compartment volume thus defined is really a "volume of distribution" (see Section 8-5).

Three processes contribute to the rapid distribution of various substances throughout various compartments. First, *stirring and mixing* by currents within a body of fluid. This is obviously important in the blood stream, in the lumen of the intestine, and presumably in certain other hollow viscera which contain fluid. Second, actual *transportation* of the substance by a flowing stream. It is the interconnection of remote regions by the all-pervading blood stream which allows us to regard "extracellular fluid" for many purposes as a single compartment. Both of these processes can distribute substances rapidly over considerable distances. In contrast the third process, *diffusion*, is quite effective in distributing solutes over very short distances, but is practically useless over long distances. To understand why this is true, we must examine Fick's law of diffusion.

7-4. Fick's Law of Diffusion

Consider an unstirred solution of a solute, S, maintained at constant temperature, in which the concentration of S is not uniform throughout the solution but varies from place to place. Consider a very small cubical volume of this solution, measuring dx by dy by dz units of length, at some point where there is a concentration gradient of S (Fig. 7-3). Let the concentration gradient be in the x direction so that one passes from a region of higher to a region of lower concentration as one proceeds in the direction of *increasing* distance along the x axis. Now, because of the random movements of thermal agitation, molecules of S will be entering and leaving the cube on all sides. Since there is no concentration gradient in the y direction, the mean concentration of S at the top face of the cube is equal to the mean concentration at the bottom face, so that on the average as many molecules of S traverse the cube from top to bottom as from bottom to top. There

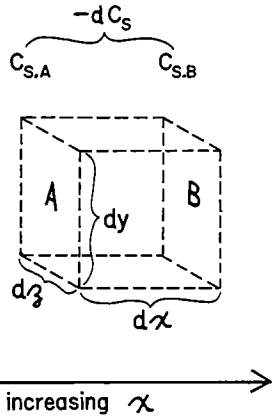

FIG. 7-3. An Infinitesimal Cube through Which Diffusion Is Occurring

The cube is so oriented that the concentration gradient for S, the diffusing solute, lies parallel to the x axis and perpendicular to faces A and B. For the rate of transfer of solute, (dQ_S/dt) to be *positive* in Equation 7-1, distance along the x axis must be measured in the direction of transfer, *i.e.*, from *left* to *right* in the figure (*arrow*). Accordingly, the *distance* at B is *greater* than the distance at A, so that the increment of distance, dx, is positive. But the *concentration* at B is *less* than the concentration at A, so that the increment of concentration, $-dC_S$ (which must be measured in the same direction), is negative.

is, therefore, no *net* movement of S in the y direction. The same is true of the z direction. But in the x direction, more molecules of S will happen to traverse the cube from face A to face B than in the opposite direction from face B to face A. (There is nothing mysterious about this. It is simply that at face A, where the concentration of S is higher than at face B, there are more molecules moving about in *all* directions than there are at face B.) As a consequence, there is a net transfer of S by diffusion in the x direction.

What factors will determine how many moles of S will be transferred from face A to face B per unit time? In other words, upon what will the net rate of transfer of S, (dQ_S/dt), depend? To begin with, it will be directly proportional to the concentration gradient, *i.e.*, to the *decrease* in concentration per unit *increase* in x. For our infinitesimal cube, this is $-dC_S/dx$. Notice that we cannot properly say that the rate of transfer is directly proportional to the concentration difference itself unless we regard the distance, dx, as fixed. It is the difference in concentration per unit of distance (the concentration *gradient*) which determines the rate of movement of S. If we *doubled* the distance over which the *same* concentration difference occurred, the gradient, and hence the rate of transfer of x, would be

cut in half. Next, the quantity of S transferred per unit of time is obviously directly proportional to the area through which the transfer is taking place. Double the area of faces A and B and the amount of S transferred from A to B will double. For our infinitesimal cube, the area is $(dy)(dz)$. With these factors identified, we can write an equation for rate of transfer, by defining an appropriate proportionality constant, D_S :

$$(dQ_S/dt) = D_S(dy)(dz)(-dC_S/dx) \tag{7-1}$$

Equation 7-1 is a general form of Fick's law of diffusion. It is closely analogous to the corresponding equation for the rate of transfer of heat along a temperature gradient. The proportionality constant, D_S, is called the *coefficient of diffusion* of S, or the *diffusivity* of S. In order to give a more well-defined meaning to diffusivity, let us solve Equation 7-1 for D_S :

$$D_S = \frac{dQ_S/dt}{(dy)(dz)(-dC_S/dx)} \tag{7-1a}$$

This makes it clear that D_S is equal to the number of moles of S which would diffuse in unit time across unit area when the concentration gradient is unity. Since the dimensions of D_S are $[L^2T^{-1}]$, its actual numerical value will depend upon what units of measurement are chosen for time and distance.

D_S varies with temperature, with the molecular weight of S, and with forces of interaction between molecules of S and molecules of the solvent which tend to impede the movement of S from one place in the solution to another. D_S also varies somewhat with the concentration of S, particularly when the concentrations are high (61). But the variation with concentration is usually small enough to be neglected in the ranges of concentration with which physiologists are concerned. In gases, diffusion is much more rapid than in liquids because the mean free path of a molecule between collisions is longer and the forces of interaction are weaker. *Graham's law*, which states that diffusivity is inversely proportional to the square root of molecular weight, is followed rather closely in gases but only approximately in liquids (57). For a comment on the relative rates of diffusion in gases and in liquids, see Exercise 2.

The validity of Equation 7-1 is not restricted to any particular pattern of diffusion or geometrical arrangement of concentration gradients, for it describes only what is happening in an infinitesimal volume of solution during an infinitesimal interval of time. In order to calculate the actual changes in concentration which occur through measurable distances and during finite intervals of time, we must use some integrated form of Equation 7-1. The technique of integrating such an equation is complex and need not concern us here, but it is important to realize that different integral

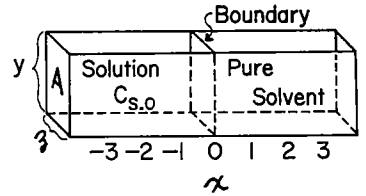

FIG. 7-4. Diffusion in a Finite System with Simple Geometry
The conditions illustrated are for time zero. The solution of Fick's general law of diffusion for this system is discussed in the text.

equations must be used for different geometrical arrangements. An equation which is valid for diffusion from a cylindrical volume cannot be used for diffusion from a spherical volume. Specific solutions for a number of geometrical arrangements have been worked out (25, 56, 61, 93). As an illustration, consider a uniform solution of S, at an initial concentration of $C_{S.0}$, adjacent to pure solvent in a long rectangular tube. At time zero, a sharp boundary between solution and pure solvent extends across the tube at right angles to its long axis at the point where x equals zero. The columns of both solution and solvent must be long enough so that no concentration changes will occur at the extremities of the tube during the time of observation (Fig. 7-4). For these conditions, Equation 7-1 may be simplified somewhat because throughout the entire system the diffusion gradients will remain parallel to the x axis. Accordingly we can replace the infinitesimal area $(dy)(dz)$ by the actual cross-sectional area of the tube, $A = yz$:*

$$(dQ_S/dt)_x = D_S A(-dC_S/dx) \tag{7-2}$$

where $(dQ_S/dt)_x$ is the quantity of solute diffusing per unit of time across the plane (of area A) which lies perpendicular to the diffusion gradient at a distance x units of length away from the initial boundary where $x = 0$.

For the arrangement of Figure 7-4, the integral form of Equation 7-2 is

$$C_{S.x.t} = (C_{S.0}/2)\left[1 - (2/\sqrt{\pi})\int_0^y e^{-v^2}dy\right] \tag{7-3}$$

where y is not a distance (as above) but is defined as

$$y = x/2\sqrt{D_S t} \tag{7-4}$$

* Equation 7-1 had to be written in terms of an infinitesimal area $(dy)(dz)$ because in the general case, the direction of the concentration gradient (which is always normal to a surface of equal concentration) may vary from point to point. For example, if S were diffusing outward from a spherical volume, the concentration gradients would be in the direction of the radii of the sphere which, of course, point in different directions.

and $C_{S.x.t}$ is the concentration of S at point x and at time t. $C_{S.0}$ is the concentration of S in the original solution.

Now the expression

$$(2/\sqrt{\pi})\int_0^y e^{-v^2}dy$$

is called the error function of y and may be symbolized by "erf(y)." It is closely related to the normal curve of error (normal curve of distribution), a fact which reminds us that the distribution of diffusing molecules is the result of random motions and accordingly follows statistical laws. Values of erf(y) for various values of y may be looked up, for example, in Dwight's *Mathematical Tables* (36). Alternatively, they may be calculated from a table of integrals of the normal curve by a method given in the *Handbook of Chemistry and Physics* (58). We may therefore simplify Equation 7-3 by writing it in the form

$$C_{S.x.t} = (C_{S.0}/2)\,[1 - \text{erf}(y)] \tag{7-5}$$

Combining Equations 7-4 and 7-5,

$$C_{S.x.t} = (C_{S.0}/2)\,[1 - \text{erf}(x/2\sqrt{D_S t})] \tag{7-6}$$

Now as t approaches infinity, $x/2\sqrt{D_S t}$ approaches zero, $1 - \text{erf}(x/2\sqrt{D_S t})$ approaches unity, and $C_{S.x.t}$ approaches $C_{S.0}/2$. Hence,

$$C_{S.x.\infty} = C_{S.0}/2 \tag{7-7}$$

Combining Equations 7-6 and 7-7 by eliminating $C_{S.0}$, and rearranging,

$$1 - (C_{S.x.t}/C_{S.x.\infty}) = \text{erf}(x/2\sqrt{D_S t}) \tag{7-8}$$

But the fraction $C_{S.x.t}/C_{S.x.\infty}$ is simply the fraction of the final equilibrium concentration at point x which has been attained at time t. If we symbolize this fraction as F_{eq}, we can rewrite Equation 7-8 as

$$1 - F_{eq} = \text{erf}(x/2\sqrt{D_S t}) \tag{7-9}$$

For any *particular* fraction of equilibrium, the error function will be a constant, and for any constant error function, $x/2\sqrt{D_S t}$ will likewise be a constant. Let us call this latter constant $K_{F_{eq}}$ so that

$$K_{F_{eq}} = x/2\sqrt{D_S t} \tag{7-10}$$

For any particular F_{eq} it is easy to obtain the numerical value for $K_{F_{eq}}$ from a table of the error function. Equation 7-9 shows that we must first locate the value of $1 - F_{eq}$ in the *body* of the table. Then by Equation 7-10 the corresponding *marginal* entry will be $K_{F_{eq}}$. To calculate the time, $t_{F_{eq}}$,

needed to attain the specified fraction of equilibrium, we must square both sides of Equation 7-10 and solve for t:

$$t_{F_{eq}} = (x^2/D_S)(1/2K_{F_{eq}})^2 \qquad (7\text{-}11)$$

Equation 7-11 states that the time needed for S to attain any specified fraction of its final equilibrium concentration is inversely proportional to the diffusivity of S and directly proportional to the *square* of the distance through which S must diffuse. It is for this reason that distribution of a substance solely by diffusion occurs rapidly enough over very short distances but is so slow as to be virtually useless over long distances. To get some feeling for the actual times and distances involved, let us work out a specific example.

Example

The diffusivity of nitrogen in water at 20°C. as tabulated by Hitchcock in Höber's *Physical Chemistry of Cells and Tissues* (57) is 2.02 (10^{-5}) cm² per second. If nitrogen is allowed to diffuse under conditions for which Equation 7-11 is valid, *i.e.*, conditions similar to those of Figure 7-4, how long will it take to achieve 95 per cent of equilibrium, $F_{eq} = 0.95$, at various distances from the original boundary?

In a table of the error function, we find that $1 - F_{eq} = 0.0500$ in the body of the table corresponds to $K_{F_{eq}} = 0.0443$ in the margin of the table. Substituting this value, and the value for D_{N_2} in Equation 7-11, and performing the indicated arithmetic, we obtain

$$t_{0.95} = 6.31(10^6)x^2$$

where t must be in seconds and x in centimeters because D was expressed in square centimeters per second. From this equation, it is easy to calculate values of $t_{0.95}$ for the values of x given in Table 7-1.

This example shows that by diffusion alone small molecules can achieve practically complete (95 per cent) equilibrium in a matter of seconds at distances of the order of cellular diameters and intercapillary distances. (For a more rigorous discussion, based upon diffusion from a cylindrical capillary, see Kety (64) and Roughton (93).) Indeed, the rate of distribution of essential metabolites by diffusion through cells and tissues is one of the most important factors which determines the optimal size of cells and the optimal spacing of capillaries. At distances of the order of 0.1 mm., 95 per cent of equilibrium is still achieved within a few minutes. But at distances much greater than a millimeter, the time to achieve 95 per cent of equilibrium by diffusion alone is to be reckoned in days. However, for two reasons these exemplary values for 95 per cent of equilibrium tend to overemphasize the ineffectiveness of diffusion as a distributing agency. In

TABLE 7-1

Time required to reach 95 per cent of equilibrium by diffusion through various distances in the system of Figure 7-4

Distance		x^2 (cm.²)	Time for 95% of Equilibrium at x			
μ	x (cm.)		$t_{0.95}$ (sec.)	min.	hr.	days
1	0.0001	$1(10^{-8})$	0.063			
3	0.0003	$9(10^{-8})$	0.57			
10	0.001	$1(10^{-6})$	6.3			
30	0.003	$9(10^{-6})$	57	1		
100	0.01	$1(10^{-4})$	630	11		
300	0.03	$9(10^{-4})$	5,700	95	1.6	
1,000	0.1	$1(10^{-2})$	63,000		18	
3,000	0.3	$9(10^{-2})$	570,000		160	6.6
10,000	1.0	1.0	6,310,000			73

the first place, over a considerable range of values of F_{eq} the time calculated for any particular value of D_S and any particular distance is roughly *inversely proportional to the square of the fraction of equilibrium not yet attained*, *i.e.*, inversely proportional to $(1 - F_{eq})^2$ (Exercise 4). For example, the time needed to attain 50 per cent of equilibrium at any given point is roughly 1/100 of the time for 95 per cent of equilibrium. In the second place, the times calculated above are for 95 per cent of equilibrium at a *single point* (or, more properly, a *single plane*) x cm. away from the initial boundary. But clearly the *average* fraction of equilibrium attained throughout the entire volume lying between the initial boundary and the plane at x is greater than 0.95 (Exercise 3).

7-5. Diffusion between Two Different Phases

If a diffusing substance must cross an interface between two different media, the absolute rate of diffusion but not the rate of approach to equilibrium, will be influenced by the *distribution ratio* for the substance between the two phases, *i.e.*, the ratio of concentrations at equilibrium.

Example

Figure 7-5 illustrates the diffusion of two different gases, A and B, from a gas phase into a liquid phase. For simplicity, let A and B have the same constant concentration, 3.0 mM. per liter in the gas phase, let the gas phase be well mixed, and let A and B have the same diffusivity in the liquid phase which is not stirred. Gas A has a solubility

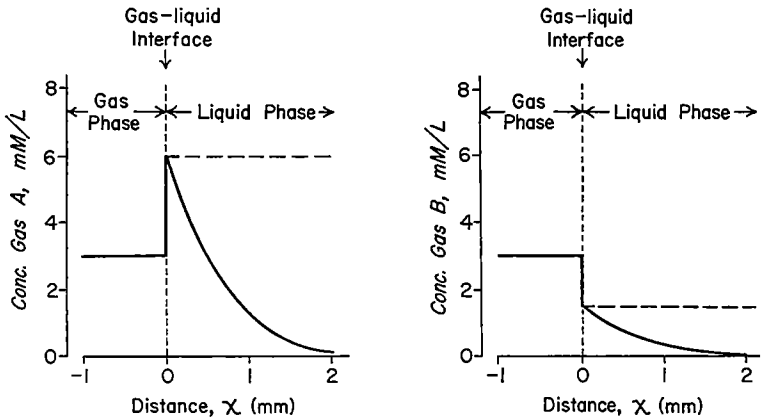

FIG. 7-5. Concentrations of a Gaseous Solute Diffusing Freely between a Gas Phase and a Liquid Phase

The gas phase is assumed to be well stirred; the liquid phase, unstirred. At the gas-liquid interface (at 0 mm.) it is assumed that equilibrium is established at once, so that the partial pressure of the diffusing gas in the gas phase is equal to its partial pressure in the liquid phase at the interface.

In the graph at the *left*, the solubility of gas A in the liquid is 2, so that at the interface the millimolar concentration suddenly doubles as one passes from gas phase to liquid phase. This provides a relatively high concentration gradient for diffusion through the liquid. In the graph at the *right*, the solubility of gas B in the liquid is 0.5 so that the concentration of gas B in the liquid at the interface is only one fourth as great as for gas A, and the concentration gradient for diffusion is therefore only one fourth as great. Note, however, that the proportion of the final equilibrium concentration in the liquid (*horizontal broken line*) attained by diffusion at a given distance from the interface is the same for both gases. For a given partial pressure in the gas phase, gas A diffuses into the liquid four times as fast as gas B. But the total quantity of gas A which must diffuse to reach equilibrium is also four times as great as for gas B. Hence the rate of approach to equilibrium is the same. (It is assumed in this example that the diffusivity of the two gases in the liquid is the same.)

in the liquid (*i.e.*, a liquid/gas distribution ratio or partition coefficient) of 2.0.* Gas B has a solubility of 0.5.

To begin with, consider the concentrations just *at* the boundary between gas and liquid. If we think of the boundary itself as a plane with no measureable thickness, we will see that equilibrium must be instantaneously established and continuously maintained between the last layer of gas phase before the boundary and the first layer of liquid phase after the boundary. Hence, the concentration of gas in the first layer of liquid, 6.0 mM. per liter for gas A, and 1.5 mM. per liter for gas B, will be equal to its concentration in the gas phase, here 3.0 mM. per liter, multiplied by its solubility. Thus the concentration gradient in the liquid is directly proportional to the solubility of the gas. By Fick's law, therefore, the moles of gas transferred by diffusion per unit of time must also be directly proportional to the solubility, and in this sense gas A diffuses into the liquid four times as fast as gas B. *Note well*, however, that to achieve its final equilibrium concentration throughout the liquid the *total amount* of gas A which must be transferred is *also* four times as great as for gas B. Consequently, when a gas diffuses into a liquid, the rate of approach to its equilibrium concentration in the liquid is *independent* of its solubility.

Although the rate of approach to equilibrium when a substance diffuses between *two* phases is independent of the distribution ratio, we shall see in the next section that distribution ratios may indeed influence the rate of equilibration when two phases are separated by a third phase.

* Note that for gases the terms *solubility*, *liquid/gas distribution ratio*, and *liquid/gas partition coefficient* are all synonymous.

7-6. Diffusion across Thin Membranes

We have already concluded that diffusion alone can maintain a practically even distribution of small molecules throughout such volumes as are contained within most single cells, although we have no right to assume a uniform concentration of such substances as oxygen and carbon dioxide which are very rapidly consumed by, or produced by, the cell. Diffusion can also account for the rapid distribution of solutes through the extracellular fluid between capillaries and cells. We must now consider the diffusion of substances across the intervening biological membranes such as the plasma membrane of cells. For simplicity the following discussion will be limited to the passive diffusion of uncharged solutes through homogeneous membranes. Whereas the conclusions which we reach from this simple approach will be applicable, with suitable qualifications, to the behavior of certain real membranes, the reader must realize that the whole subject of transport of substances across biological membranes by active and passive processes is exceedingly complex and that we are here deliberately avoiding its most engrossing intricacies.

Let us consider a homogeneous fluid compartment, W, separated from another homogeneous fluid compartment, Z, by a thin homogeneous membrane, M. Suppose first that W, Z, and M are all composed of the same medium, so that they are divided into two separate compartments and an intervening membrane only in our mind's eye (Fig. 7-6*a*). Then if a solute, S, is introduced into compartment W at the side farthest away from M, it will begin to diffuse without special hindrance across W, M, and Z at a uniform rate determined by a single coefficient of diffusion. Because the

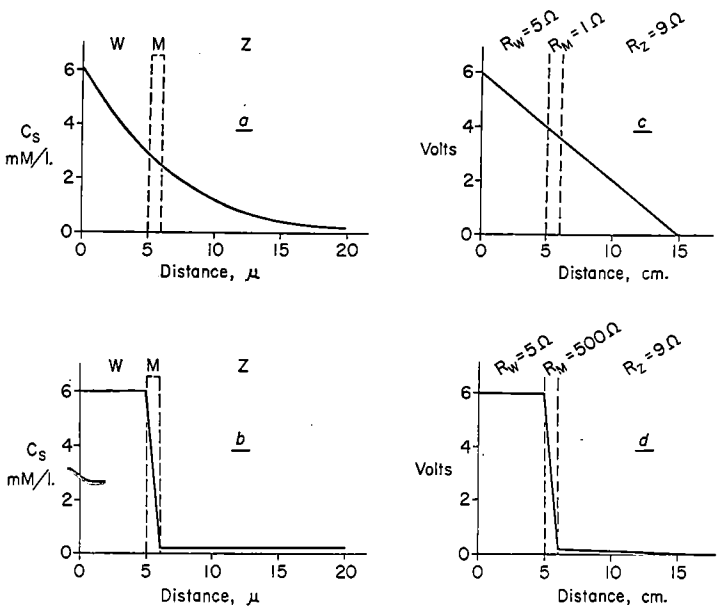

FIG. 7-6. A Membrane Viewed as a "Resistance" to Solute Flow

In *Graph a*, the thin membrane, M, offers no special hindrance to the diffusion of solute, just as in *Graph c* the short resistance, R_M, offers no special hindrance to the flow of current. But in *Graph b*, the thin membrane severely limits the rate of diffusion, just as in *Graph d* the short wire of high resistance limits the rate of current flow. In Graphs *b* and *d*, by far the greater part of the total gradient (of concentration or voltage) is across the rate-limiting segment of the system.

dimensions of the system are small, the concentration gradients will rapidly disappear as S becomes well distributed by diffusion throughout the whole system. Now let M assume more realistic properties as a membrane which considerably slows the diffusion of S, either because M has a limited total area of "pores" through which S can diffuse (83), or because the physicochemical nature of M impedes the progress of S across it. Then the total time needed for transfer of a given amount of S from W to Z will be substantially increased, so that the rate of change of Q_S in both W and Z will be small compared with the rate of distribution of S by diffusion throughout these compartments. As a result, both W and Z behave at all times as if they are well stirred, and the entire concentration gradient is practically confined to M (Fig. 7-6*b*). The situation is somewhat similar to the flow of electrons through a circuit in accordance with a voltage gradient supplied

by a battery. When the terminals of the battery are connected by three wires in series whose resistance per unit length is equally low, the voltage gradient is uniform through the whole circuit and electron flow is rapid (Fig. 7-6*c*). But when the middle wire is replaced by one with a considerably higher resistance, the time needed for transfer of a given number of electrons from one terminal of the battery to the other is much increased, and practically the whole voltage gradient occurs across the high resistance (Fig. 7-6*d*).

Now it can be shown that if a given difference of concentration is imposed between W and Z across M, and if M is sufficiently thin (say 10 μ or less) the quantity of S *entering* M per unit of time at its interface with W will very rapidly become practically equal to the quantity of S *leaving* M per unit of time at its interface with Z. (For a proof of this statement see Jacobs (61).) But if equal quantities per unit of time pass across both faces of M, the same quantity per unit of time must pass across *every* plane within M which lies parallel to the two interfaces. In other words, $(dQ_S/dt)_x$ is constant everywhere within M. But from Equation 7-2 it is evident that if $(dQ_S/dt)_x$ is constant, the concentration gradient in M, $(-dC_S/dx)_M$, must also be constant throughout M, and must therefore be equal to the total difference in concentration across M, $-\Delta C_{S.M}$, divided by the total thickness of M, Δx_M:

$$(-dC_S/dx)_M = -\Delta C_{S.M}/\Delta x_M = -(C_{S.M.Z} - C_{S.M.W})/\Delta x_M = (C_{S.M.W} - C_{S.M.Z})/\Delta x_M \quad (7\text{-}12)$$

where $C_{S.M.W}$ and $C_{S.M.Z}$ are the concentrations of S in the membrane at its interface with W and at its interface with Z, respectively.

Combining Equations 7-2 and 7-12 with the elimination of $-dC_S/dx$, we obtain the following equation for diffusion from W to Z across a thin membrane:

$$(dQ_S/dt)_M = (dQ_S/dt)_{W\to Z} = D_{S.M}A_M(C_{S.M.W} - C_{S.M.Z})/\Delta x_M \quad (7\text{-}13)$$

Equation 7-13 is a very useful simplification of Fick's law. Notice that it has to do entirely with what happens *in* the membrane. Notice in particular that $D_{S.M}$ is the effective diffusivity of S in the membrane, not in W or Z. If it is known that S diffuses through pores in the membrane which are filled with the same medium as W and Z, comparison of the diffusivity in the membrane, $D_{S.M}$, with the diffusivity in free solution provides a means of estimating what proportion of the total area of the membrane, A_M, is, in effect, available for free diffusion (83). But for the most part the plasma membrane of cells does not behave like a porous membrane, so that substances diffusing from the outside to the inside of cells presumably do so by dissolving in the substance of the membrane. For such membranes,

let $R_{S(M/W)}$ be the equilibrium distribution ratio or partition coefficient for S between M and W:

$$R_{S(M/W)} = (C_{S.M}/C_{S.W})_{eq} \tag{7-14}$$

where the subscript eq means "at equilibrium." Similarly,

$$R_{S(M/Z)} = (C_{S.M}/C_{S.Z})_{eq} \tag{7-15}$$

Then if we assume, as we did before, that equilibrium is always present at the interfaces, and that compartments W and Z are well stirred, we can apply Equations 7-14 and 7-15 directly to the interfaces:

$$C_{S.M.W} = R_{S(M/W)}C_{S.W} \tag{7-16}$$

and

$$C_{S.M.Z} = R_{S(M/Z)}C_{S.Z} \tag{7-17}$$

Substituting these values into Equation 7-13,

$$(dQ_S/dt)_{W\to Z} = D_{S.M}A_M(R_{S(M/W)}C_{S.W} - R_{S(M/Z)}C_{S.Z})/\Delta x_M \tag{7-18}$$

If W and Z are both aqueous media, it is likely that $R_{S(M/W)}$ and $R_{S(M/Z)}$ will be equal, so we may define

$$R_{S(M/aq)} = R_{S(M/W)} = R_{S(M/Z)} \tag{7-19}$$

Combining Equations 7-18 and 7-19,

$$(dQ_S/dt)_{W\to Z} = D_{S.M}A_MR_{S(M/aq)}(C_{S.W} - C_{S.Z})/\Delta x_M \tag{7-20}$$

There is evidence from many sources that the plasma membrane consists largely of lipid (31). According to Equation 7-20, the rate of diffusion of S across such a membrane should be directly proportional to the equilibrium distribution ratio for S between the membrane and the adjacent aqueous media. In a general way, this prediction is borne out by experiment. Compounds with a high oil/water partition coefficient (which is not necessarily identical with, but presumably similar to $R_{S(M/aq)}$) usually do penetrate cells more rapidly than compounds of similar molecular weight which are not as soluble in oil (31). This fact is very important, for the distribution of many drugs in the body is strikingly influenced by their relative solubility in aqueous and lipid media (see Section 10-17).

Equation 7-20 is a useful summary of how various important factors influence the rate at which a diffusing solute penetrates a membrane. But Equation 7-20 was derived from very simple, indeed naive, assumptions about the partitioning of a diffusing substance between the membrane and the adjacent aqueous media. By taking account of the successive energies of activation which a diffusing molecule must acquire first to pass from W to M, then to pass through M, and finally to pass from M to Z, Danielli has derived a considerably more elaborate theory of diffusion across nonporous membranes (28). According to Danielli's analysis, the rate of diffusion is not directly proportional to the distribution ratio, at least for substances which diffuse very slowly across the membrane. However, for present purposes we will neglect this important refinement of theory and we will continue to use Equations 7-18 and 7-20.

7-7. Practical Measures of Membrane Permeability

As it stands, Equation 7-20 is too complex for most biological applications. While it may be possible to measure the concentration of a substance in the two aqueous phases, and the area of the membrane across which diffusion is taking place, usually no reliable estimates can be made of $D_{S.M}$, $R_{S(M/aq)}$, or Δx_M. However, for any particular system, all three of these quantities can be assumed constant, and they may therefore be combined by defining a new *permeability constant*, $(k_{perm})_S$:

$$(k_{perm})_S = D_{S.M}R_{S(M/aq)}/\Delta x_M \tag{7-21}$$

Notice that $(k_{perm})_S$ has the dimensions of velocity: (LT^{-1}). We may now write Equation 7-20 in the simplified form:

$$(dQ_S/dt)_{W\to Z} = (k_{perm})_SA_M(C_{S.W} - C_{S.Z}) \tag{7-22}$$

$(k_{perm})_S$ can be calculated by measuring all of the other quantities in Equation 7-22. Thus, $(k_{perm})_S$ provides a practical measure of the relative ease with which different solutes can diffuse across a given membrane.

Still other measures of rates of diffusion across membranes are in use, particularly when the substance diffusing is a gas. For example, respiratory physiologists commonly prefer to think in terms of gradients of partial pressure rather than gradients of concentration. Furthermore, they prefer to express the quantity of a gas as its volume at standard temperature and pressure (std T,P), and the concentration of a gas, C_G, as volume of gas (std T,P) per volume of solution. Then according to Equation 2-27

$$\alpha_GP_G = C_G = V_{G(\text{std } T,P)liq}/V_{liq} \tag{7-23}$$

where α_G is the Bunsen solubility coefficient of gas G (Chap. 2). P_G is the partial pressure of G in atmospheres. Equation 7-2 may then be written

$$(dQ_G/dt)_x = AD_G\alpha_G(-dP_G/dx) \tag{7-24}$$

for gases in liquids, Q_G being in units of volume, or

$$(dQ_G/dt)_x = (\text{diffusion constant})\ A(-dP_G/dx) \tag{7-25}$$

where the *diffusion constant* is defined as

$$(\text{diffusion constant}) = \alpha_G D_G \tag{7-26}$$

and has the dimensions $[M^{-1}L^3T]$. The diffusion constant is the volume of gas (std T,P) diffusing per unit time across unit area in response to unit gradient of partial pressure. For a further note on this diffusion constant, see Exercise 1.

Finally, the *diffusing capacity* of the lung is used to describe the diffusion of gases between the alveoli and the blood across the alveolar-capillary "membrane" whose thickness and area are both unknown. The diffusing capacity for G is the total volume of G diffusing per unit time when the *mean difference* of partial pressure (*not* the gradient) between alveolar air and capillary blood is unity. The diffusing capacity has the dimensions $[M^{-1}L^4T]$. If the membrane through which G diffuses were simply an aqueous layer which permitted free diffusion, the diffusing capacity could be defined as

$$(\text{diffusing capacity}) = D_{G.\text{aq}} A_M \alpha_{G.\text{aq}} / \Delta x_M \tag{7-27}$$

an equation whose sole merit is its dimensional correctness. But it is far better to think of the diffusing capacity as merely an empirical measure of the rate at which a given gas diffuses across a membrane of unknown characteristics in response to unit difference of partial pressure.

This brief discussion of several measures of diffusion only begins to indicate the frustrating confusion of units, dimensions, and definitions which perplexes students in this field!

7-8. The Kinetics of Equilibration by Diffusion of a Solute between Two Compartments

Up to this point we have focused our attention upon the process of diffusion across a membrane. Very often, however, we are not as much concerned with what is happening in the membrane as we are with the resulting changes in the concentration of the diffusing solute in compartments W and Z. If the volume of compartment W, the volume of compartment Z, and the total amount of S in the whole system, $Q_{S.\text{tot}}$, all remain constant, we can easily derive equations for the concentration of S in W and the concentration of S in Z as functions of time. Figure 7-7 illustrates such a two-compartment system, together with the intervening membrane whose thickness, for convenience, has been greatly exaggerated. Actually, we shall assume that the membrane is so thin that it contains a negligible quantity of S. Since we shall be concerned only with a single solute, the subscript S will be omitted from the symbols used in the following derivation.

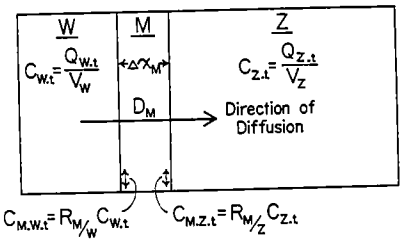

FIG. 7-7. Factors Concerned in the Kinetics of Diffusion of a Solute from W to Z across a Thin Membrane, M

It is helpful to begin by listing all of the *individual factors* which characterize the system.

1. The *independent variable* is time, t.
2. At any time, t, compartment W is fully characterized by
   - V_W, the volume of W (constant)
   - $Q_{W.t}$, the quantity of S in W (variable with time)
3. At any time, t, compartment Z is fully characterized by
   - V_Z, the volume of Z (constant)
   - $Q_{Z.t}$, the quantity of S in Z (variable with time)
4. At any time, t, the membrane, M, is fully characterized by
   - A_M, the area of M (constant)
   - x_M, the thickness of M (constant)
   - D_M, the diffusivity of S in M (constant)
   - $R_{M/W}$, the equilibrium distribution ratio for S between M and W (constant)
   - $R_{M/Z}$, the equilibrium distribution ratio for S between M and Z (constant)

Since the entire system consists of W, M, and Z, it is itself fully characterized at any time, t, by the nine factors listed above.

Next, we should list, as equations, all of the *relationships* which characterize the system. A general equation for diffusion of S across the membrane has already been derived. It is Equation 7-18:

$$(dQ/dt)_{W \to Z} = D_M A_M (R_{M/W} C_{W.t} - R_{M/Z} C_{Z.t}) / \Delta x_M \tag{7-18}$$

We are assuming that the total quantity of S, Q_{tot}, remains constant. Hence,

$$Q_{W.t} + Q_{Z.t} = Q_{\text{tot}} \tag{7-28}$$

The concentration of S in compartment W at any time, t, is

$$C_{W.t} = Q_{W.t} / V_W \tag{7-29}$$

Similarly, in compartment Z

$$C_{Z.t} = Q_{Z.t}/V_Z \tag{7-30}$$

Now the only process which is causing the quantities and concentrations of S in W and Z to change is the diffusion of S across the membrane. We have already assumed (in deriving Equation 7-18) that, with thin membranes, the rate of entry of S into M from W is at all times equal to the rate of exit of S from M into Z. (This assumption is, in fact, equivalent to the assumption stated above that the quantity of S within M is negligible.) Conservation of matter therefore requires

$$-dQ_W/dt = (dQ/dt)_{W\to Z} = dQ_Z/dt \tag{7-31}$$

Equation 7-31 simply states that the rate at which W is *losing* (negative sign) S, the rate at which S is *diffusing across* the membrane, and the rate at which Z is *gaining* S, are all equal. Now it should be obvious that at time infinity the gradient for diffusion across the membrane will have disappeared. There will then be no further net transfer of S, and the whole system will be in a steady state of equilibrium. Hence, at time infinity, Equation 7-31 becomes

$$-dQ_{W.\infty}/dt = (dQ/dt)_{W\to Z.\infty} = dQ_{Z.\infty}/dt = 0 \tag{7-32}$$

Finally, we must note the initial conditions* for the three variables: When $t = 0$, $Q_W = Q_{W.0}$, and $Q_Z = Q_{Z.0}$. Also, $R_{M/W}C_{W.0} > R_{M/Z}C_{Z.0}$. These boundary conditions show that the gradient for diffusion is from W to Z, and that at time zero there may already be some S present in Z. (Our derivation would be less general if we assumed that when $t = 0$, $Q_W = Q_{\text{tot}}$, and $Q_Z = 0$.)

We are now ready to derive an equation† for $C_{W.t}$ as a function of time. For this purpose, we are primarily interested in the changes taking place in compartment W, and consequently, we should like to eliminate, if possible, any dependent variables pertaining to M and Z by replacing them by corresponding variables for W. An obvious first step is to combine Equations 7-31 and 7-18 so as to replace $(dQ/dt)_{W\to Z}$ by its equivalent, $-dQ_W/dt$:

$$-dQ_W/dt = D_M A_M(R_{M/W}C_{W.t} - R_{M/Z}C_{Z.t})/\Delta x_M \tag{7-33}$$

Since Equation 7-33 is an equation for the decrease of the *quantity* of S

* *Boundary conditions* is the general term for any set of values of the dependent variables which characterize a particular system at specified values of the independent variables and which allow one to apply the solution of the differential equation to that particular system. But when, as in this example, the boundary conditions are given for time zero, they are almost always called *initial conditions*.

† A general method for deriving such an equation is discussed in Chapters 12–14.

in W, we would do well to replace the concentrations in the equation by their equivalents in terms of quantity as given in Equations 7-29 and 7-30:

$$-dQ_W/dt = D_M A_M[(R_{M/W}Q_{W.t}/V_W) - (R_{M/Z}Q_{Z.t}/V_Z)]/\Delta x_M \tag{7-34}$$

Equation 7-34 still contains a variable, $Q_{Z.t}$, which does not pertain directly to compartment W. This fault is easily remedied by solving Equation 7-28 for $Q_{Z.t}$ and substituting the result in Equation 7-34:

$$-dQ_W/dt = D_M A_M\left[\frac{R_{M/W}Q_{W.t}}{V_W} - \frac{R_{M/Z}(Q_{\text{tot}} - Q_{W.t})}{V_Z}\right]\Big/ \Delta x_M \tag{7-35}$$

Equation 7-35 now contains only $Q_{W.t}$ and t as variables. However, these variables are so surrounded by constants that it is a bit difficult to see what to do next. We may therefore resort to the simple device of defining certain new constants in terms of the old ones, being guided entirely by convenience. To indicate that these new *constants of convenience* have no clearly defined intrinsic meaning, we will employ for them the very colorless notation k_1, k_2, etc. Accordingly let us define

$$k_1 = D_M A_M/\Delta x_M \tag{7-36}$$

$$k_2 = R_{M/W}/V_W \tag{7-37}$$

$$k_3 = R_{M/Z}/V_Z \tag{7-38}$$

$$k_4 = k_3 Q_{\text{tot}} \tag{7-39}$$

Using these constants, we can rewrite Equation 7-35 in the form

$$-dQ_W/dt = k_1(k_2 Q_{W.t} + k_3 Q_{W.t} - k_4) \tag{7-40}$$

or, by further defining

$$k_5 = k_1(k_2 + k_3) \tag{7-41}$$

$$k_6 = k_1 k_4 \tag{7-42}$$

in the still simpler form

$$-dQ_W/dt = k_5 Q_{W.t} - k_6 \tag{7-43}$$

Now it is very easy to separate the variables in Equation 7-43 so that it can be integrated:

$$\int \frac{dQ_W}{k_6 - k_5 Q_{W.t}} = \int dt \tag{7-44}$$

The integral on the left can be found in any table of integrals. The integral on the right is elementary:

$$(1/-k_5)\ \ln\ (k_6 - k_5 Q_{W.t}) = t + k \tag{7-45}$$

where k is a constant of integration which can at once be evaluated from the initial conditions. When $t = 0$, Equation 7-45 becomes

$$k = (1/-k_5) \ln (k_6 - k_5 Q_{w.0}) \tag{7-46}$$

Combining Equations 7-45 and 7-46 by eliminating k,

$$(1/-k_5) \ln (k_6 - k_5 Q_{w.t}) = (1/-k_5) \ln (k_6 - k_5 Q_{w.0}) + t \tag{7-47}$$

or, multiplying both sides by $-k_5$,

$$\ln (k_6 - k_5 Q_{w.t}) = \ln (k_6 - k_5 Q_{w.0}) - k_5 t \tag{7-47a}$$

Taking antilogarithms,

$$(k_6 - k_6 Q_{w.t}) = (k_6 - k_5 Q_{w.0}) e^{-k_5 t} \tag{7-48}$$

Dividing both sides by k_5, and changing signs,

$$\left(Q_{w.t} - \frac{k_6}{k_5}\right) = \left(Q_{w.0} - \frac{k_6}{k_5}\right) e^{-k_5 t} \tag{7-48a}$$

Now Equation 7-48a is in a form made very familiar by the discussion in the previous chapter. Evidently $Q_{w.t}$ is decreasing toward an asymptote, $Q_{w.\infty}$, which is equal to k_6/k_5. Furthermore, the difference between $Q_{w.t}$ and the asymptote is decreasing exponentially at k_5 proportion per unit of time. It will now be interesting to replace these "constants of convenience" by the original factors they represent so that we can see which of the factors influence the asymptote and which the rate constant. From Equations 7-37 through 7-42

$$\begin{aligned} Q_{w.\infty} = k_6/k_5 &= \frac{k_1 k_4}{k_1(k_2 + k_3)} = \frac{k_4}{k_2 + k_3} = \frac{k_3 Q_{\text{tot}}}{k_2 + k_3} = \frac{Q_{\text{tot}}}{1 + (k_2/k_3)} \\ &= Q_{\text{tot}} \Big/ \left[1 + \left(\frac{R_{M/W} V_Z}{R_{M/Z} V_W}\right)\right] = Q_{\text{tot}} \Big/ \left[1 + \left(R_{Z/W} \frac{V_Z}{V_W}\right)\right] \end{aligned} \tag{7-49}$$

where

$$R_{Z/W} = R_{M/W}/R_{M/Z} = \frac{C_{M.\text{eq}}/C_{W.\text{eq}}}{C_{M.\text{eq}}/C_{Z.\text{eq}}} = C_{Z.\text{eq}}/C_{W.\text{eq}} = C_{Z.\infty}/C_{W.\infty} \tag{7-50}$$

Equation 7-49 shows that the *final equilibrium quantity* of S in W is determined by the total amount of S in the system, by its equilibrium distribution ratio between Z and W, and by the ratio of volumes of Z and W. Note that not a single characteristic of the membrane influences the asymptote, for we have even replaced the two distribution ratios by $R_{Z/W}$, the distribution ratio between Z and W. The lack of influence of the membrane on the final distribution is actually just what we ought to expect,

because we have assumed that it contains a negligible volume and a negligible quantity of S. It is not a third compartment; it is merely a barrier which slows the attainment of equilibrium—a kind of negative catalyst!

The rate constant, k_5, may be similarly decomposed into its component factors:

$$k_5 = k_1(k_2 + k_3) = \frac{D_M A_M}{\Delta x_M} \left(\frac{R_{M/W}}{V_W} + \frac{R_{M/Z}}{V_Z}\right) \tag{7-51}$$

which has the dimension (T^{-1}), as it should. From Equation 7-51 it is obvious that the *rate of approach to equilibrium* is influenced by *all* of the characteristics of the membrane, and, in addition, by the volumes of W and Z.

We may now substitute the original factors, identified in Equations 7-49 and 7-51, for the k-constants in Equation 7-48a:

$$\begin{aligned} \left[Q_{w.t} - \frac{Q_{\text{tot}} V_W}{V_W + R_{Z/W} V_Z}\right] = \left[Q_{w.0} - \frac{Q_{\text{tot}} V_W}{V_W + R_{Z/W} V_Z}\right] \\ \cdot \exp\left[-\frac{D_M A_M}{\Delta x_M} \left(\frac{R_{M/W}}{V_W} + \frac{R_{M/Z}}{V_Z}\right) t\right] \end{aligned} \tag{7-52}$$

But we originally set out to find an expression for the *concentration* of S in W at any time t. Equation 7-52 for the quantity of S may easily be converted to an equation for concentration by dividing both sides by V_W:

$$\begin{aligned} \left[C_{W.t} - \frac{Q_{\text{tot}}}{V_W + R_{Z/W} V_Z}\right] = \left[C_{W.0} - \frac{Q_{\text{tot}}}{V_W + R_{Z/W} V_Z}\right] \\ \cdot \exp\left[-\frac{D_M A_M}{\Delta x_M} \left(\frac{R_{M/W}}{V_W} + \frac{R_{M/Z}}{V_Z}\right) t\right] \end{aligned} \tag{7-53}$$

Notice that the expression $Q_{\text{tot}}/(V_W + R_{Z/W} V_Z)$ is the equilibrium concentration of S in W, $C_{W.\infty}$, which is being approached asymptotically as time increases:

$$C_{W.\infty} = Q_{\text{tot}}/[V_W + R_{Z/W} V_Z)] = Q_{\text{tot}}/(V_{\text{dist}}) \tag{7-54}$$

The denominator, $V_W + (R_{Z/W} V_Z)$, is thus the *volume of distribution* of S (Vdist) calculated with reference to its concentration in compartment W. In other words, $V_W + (R_{Z/W} V_Z)$ is the volume which would contain an amount of S equal to Q_{tot} at a uniform concentration of $C_{W.\infty}$.

Derivation of an explicit equation such as 7-53, in which every symbol has a clearly defined physical meaning, is always instructive and intellectually satisfying. But real membranes are structurally much more complex than the simple homogeneous model here assumed. So even if we had

detailed information about their physical properties, we might well find that Equation 7-53 was not really applicable to them. Therefore, in the next chapter we must turn to a less thorough and explicit, but more generally useful, analysis of the kinetics of transfer of substances between biological compartments.

EXERCISES. CHAPTER 7

Exercise 1

In textbooks of physiology it is commonly stated that in aqueous media carbon dioxide diffuses about 20 times as rapidly as oxygen. For example, Carlson, in the text by Ruch and Fulton (22), pages 796 to 797, states: "The intrinsic rate of diffusion of any substance is a function of its solubility, its molecular weight, and the permeability of the medium. Although a larger molecule than O_2, CO_2 is so highly soluble in the body fluids that it diffuses through the tissue 20 to 30 times as rapidly as O_2 does." What is the meaning of this statement?

Exercise 2

Forster (38) states, "Since the diffusion constant in air is about 1 million times that in saline . . . diffusion through 1 million microns (1 meter) of perfectly still gas would only demand a pressure difference equal to that normally associated with gas exchange across the pulmonary membrane." (It is assumed that the pulmonary membrane is 1 μ thick.) Is this statement justified?

Exercise 3

A. V. Hill (56) calculated the time needed for a sheet of muscle 1.0 mm. thick exposed to a constant concentration of oxygen on one side to attain by diffusion alone various average fractions of the equilibrium concentration of oxygen, the average being taken throughout the entire muscle. It was assumed that no oxygen was consumed by the tissue. For the diffusivity of oxygen in muscle he used the value $D_{O_2} = 4.5 \times 10^{-4}$ cm.^{2} per minute. Hill calculated that under these circumstances it would require 5 min. to reach an average of 53.4 per cent of the equilibrium concentration of oxygen throughout the tissue. Is this of the correct order of magnitude?

Exercise 4

Prove the validity of the statement made in the text (Section 7-4) that "over a considerable range of values of F_{eq} the time calculated for any particular value of D_S and any particular distance is roughly inversely proportional to the square of the fraction of equilibrium not yet attained, *i.e.*, inversely proportional to $(1 - F_{eq})^2$."

8

TRANSFER OF SUBSTANCES BETWEEN BIOLOGICAL COMPARTMENTS. GENERAL KINETICS

8-1. The Need for a More General Analysis of Transfer between Compartments

In Chapter 7 we undertook a detailed analysis of a particular mechanism —simple diffusion—by which a solute passes from one compartment to another. But it is often desirable to study the transfer of a drug, or a metabolite, or a radioactive isotope from one compartment to another without being concerned about the precise mechanism of transfer. For example, in the system discussed in Section 7-8 at the end of Chapter 7, if we knew Q_{tot} and if we were to measure the concentration of S in serial samples withdrawn from W and Z during the approach to equilibrium, we would be able to estimate V_W, V_Z, and $R_{Z/W}$. We could also calculate an exponential rate constant which would give us a very useful measure of the rate of approach to equilibrium, but would tell us nothing at all about the characteristics of the membrane. Indeed, the same kind of exponential approach to equilibrium can be caused by many processes other than simple passive diffusion (see Section 8-3). Therefore, it is desirable to undertake a more general analysis of the kinetics of transfer between compartments without reference to any particular mechanism of transfer. This analysis will then be applicable to a wide variety of problems.

8-2. Diagrams and Symbols for the Description of Transfer between Compartments

Figure 8-1 illustrates the kind of diagram and the symbols which will be used in the subsequent discussion. Each separate compartment is designated by a different capital letter and is represented in the diagram by a rectangle.* Each compartment is characterized by its volume V_A,

* The use of small rectangles for small compartments, large rectangles for large compartments often makes it easier to visualize the system. An even more elaborate