BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 14, 1952

A MATHEMATICAL THEORY OF CAPILLARY EXCHANGE AS A FUNCTION OF TISSUE STRUCTURE

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A mathematical theory of the process of the exchange of substances between the blood in the capillaries of a homogeneous tissue and the extracellular space, and between the extracellular space and the cells is developed. An ideal geometry of the tissue is assumed, based to some extent on recent anatomical work concerning the functional distinction between two types of capillaries, the arteriolo-venular and the true capillaries. Equations are developed relating the concentration in the arterial blood to the mean capillary concentration, the concentration at the wall of the capillary in the extracellular space, and the average concentration in the extracellular space, and also relating the cellular concentration to the average extracellular concentration. The solutions of the equations are given for certain special cases and numerical results obtained. It is shown that the average extracellular concentration is a sensitive function of the permeability of the capillary wall and also is strongly influenced by the diffusion coefficient of the extracellular space. Furthermore, it is shown that the speed with which the average extracellular concentration approaches the steady state is largely a function of the permeability of the capillary wall.

I. Introduction. Most cells of organisms with closed circulatory systems must depend upon the system to bring to their local environments materials necessary for their maintenance and to remove their diffusible products from such environments. Since most cells are separated from the blood and lymph capillaries by a connective tissue matrix (Gersh, 1952), the efficiency of the supply and removal of substances (for any given arrangement of the capillaries) must depend partially on the characteristics of the ground substance of the connective tissue, and upon the amount of substance through which diffusion may occur, relative to the amount of fibrous and other material which is inert with respect to diffusion.

The aim of the present work is to analyze the influence of the interstitial matrix and capillary permeability upon the exchange of substances between the cells and the blood. Many approximations and idealizations seem necessary to obtain results which may be compared with experiment.

However, as N. Rashevsky (1948) has pointed out in another connection, even if we knew exactly the geometry of a given tissue and knew precisely the blood flows, diffusion coefficients, etc. necessary for the calculation of the exchange relations, and could solve the exceedingly complex boundary. value problem so presented, the results would still be of limited usefulness. This is true because the geometry, etc. of the solved problem would be special cases of an almost unlimited number of possible geometries. The analysis which is developed here assumes as known certain tissue parameters and certain data concerning blood flow in the capillaries, which are known only inexactly, or not at all. However, these data seem necessary for a detailed study of the exchange relations and are definitely data which could be obtained by experiment. The need for such data may stimulate work aimed at obtaining them. But, even in the absence of exact measurements, certain relations become evident and certain tentative conclusions may be drawn.

In the following, a brief discussion is given of the labile character of the tissues and of the extracellular matrix, then blood-tissue fluid exchange is described. Next, consideration is given to some experimental and theoretical work on blood-tissue molecular exchange. This is followed by a consideration of the anatomy of the capillary bed. On the basis of the previous discussion, a tissue model is then presented and equations governing the blood-tissue exchanges are formulated. Some applications of the solutions are considered, and a discussion of various implications of the results is given.

II. The extracellular matrix and tissue changes. I. Gersh (1952) has recently discussed the characteristics of the ground substance of the connective tissue. The ground substance is shown to be labile, and its plasticity is related in some cases to the action of certain connective tissue cells. Changes in the ground substance organization are shown to be related to tumor growth, regeneration, cyclic effects of endocrine glands, capillary permeability, immunological phenomena, and to calcification of cartilage, bone, and teeth.

Other work (Ruzick, 1927; Hurst, 1933; Gellhorn and Regnier, 1936; Pearce, 1936; Lowry *et al.*, 1942a, b, 1946; Horvath, 1946; Berg, 1947; Rhoades, 1948) indicates that the local environment of cells may change as a result of aging, tumor growth, regeneration and irradiation, and that these changes may in some cases be correlated with the rate at which cells may exchange substances with the blood. In this connection the work of L. Friedman and E. O. Kraemer (1930) on the diffusion of various substances in gelatine gels may be mentioned. These workers found that the

magnitudes of the diffusion coefficients of several nonelectrolytes in a 10% gelatine gel were only about one-half of their values in pure water.

III. Blood-tissue fluid exchange. E. H. Starling (1895–96) formulated the hypothesis that the exchange of fluid between the blood and the interstitial spaces depends of the balance between the hydrostatic pressure excess of the blood, which tends to filter fluid into the tissues, and the colloid osmotic pressure excess of the blood, which tends to filter fluid from the tissue into the blood. The mechanism depends on the relative impermeability of the capillary wall to the blood colloids, and on the low hydrostatic pressure of the extracellular fluid. Both points are confirmed experimentally (Pappenheimer *et al.*, 1948, 1951; Field *et al.*, 1932; McMaster, 1946). The work of E. M. Landis (1927, 1934, 1946), J. F. Danielli (1940), and J. R. Pappenheimer *et al.* (*loc. cit.*) has confirmed the details of Starling's hypothesis.

While Starling's hypothesis, as discussed above, accounts for blood-tissue fluid exchange, and, together with a consideration of the lymphatic system, adequately accounts for the maintenance of blood volume, etc., the exchange of many substances between the blood and the extracellular spaces occurs so rapidly that only diffusion through the capillary wall seems to provide a mechanism which could give the required speed.

IV. Blood-tissue molecular exchange. That the process of filtration through the capillary wall of substances in solution in the blood plasma is not rapid enough to account for the observed rate of transfer across the wall follows directly from the estimates of the maximum filtration rates observed. Pappenheimer *et al.* (1951) calculate that the ratio of the rate of transfer by diffusion to the rate of transfer by filtration during very rapid filtration is about 116 for glucose, 83 for raffinose, and 27 for inulin, when the extracellular concentration is zero. The ratio becomes equal to unity only when the ratio of the concentration in the extracellular space to the concentration in the capillary is about 0.99 for glucose and raffinose and 0.96 for inulin. Furthermore, the work of C. Hyman *et al.* (1952) provides direct evidence that even when a tissue is becoming edematous the rate of capillary exchange is not measurably affected.

Much experimental work has been devoted to the features of blood-tissue exchange (Dominguez *et al.*, 1935–36; Manery *et al.*, 1939a, b, 1941a, b; Hevesy and Jacobsen, 1940; Hahn and Hevesy, 1941; Gellhorn *et al.*, 1944; Kruhøffer, 1946a, b; Flexner *et al.*, 1948; Morel and Marois, 1949; Jones, 1951; Pappenheimer *et al.*, *loc. cit.*; Renkin, 1952).

The experimental work mentioned above, with the exception of that of Pappenheimer *et al.* and of Renkin, was done with intact animals, and the

exchange relations observed are greatly complicated by the fact that various organs receive in any time interval very different amounts of blood per unit volume of the organ. Thus H. B. Jones (*loc. cit.*) gives as the volume of blood per unit volume of tissue per minute received by the various organs of a man of approximately 70 kg. weight: thyroid, 3.0 to 10.0; kidney, 5.0; brain, 0.50; marrow, 0.15; liver, 1.10; muscle, skin, fat, and bone, about 0.026. The work of Gellhorn *et al.* (1944) mentioned above also indicates that an injected substance is removed from the blood by the organs with the larger perfusion rates and restored to the blood as the substance is gradually transferred to the organs with the lesser perfusion rates. It seems apparent from this data on the blood perfusion rates of various organs that the large differences in these rates may mask changes due to other differences between the tissues of various organs. In experiments in which the blood concentration of an injected substance is followed in an intact animal such seems to be the case. Work such as that of Pappenheimer *et al.* (*loc. cit.*), which partially avoids these complications by perfusing a relatively homogeneous tissue, may provide data reflecting more clearly the influence of the capillary permeability and the extracellular matrix upon the blood-tissue exchange relations.

The experimental data on blood-tissue exchange is usually described quite accurately by a sum of exponential terms, with two such terms being sufficient in many cases, although occasionally one is adequate (Flexner *et al.*, *loc. cit.*), and sometimes as many as five terms are needed (Jones, *loc. cit.*).

The time constants of the exponential terms have been interpreted in terms of total capillary wall area, and the over-all permeability coefficients of the capillary wall, neglecting the distribution process in the tissue, and frequently neglecting the differences in the blood perfusion rates of the various tissues. Thus T. Teorell (1937a, b) reviewed the work of several earlier investigators and provided a theoretical model for blood-tissue exchange which does not distinguish between tissues with respect to their perfusion rates.

However, the work of I. Bloch (1941, 1943) and of R. Smith and M. Morales (1944a, b) and of M. Morales and R. Smith (1944, 1945a, b, 1948) does take into account in a detailed fashion many important tissue parameters and provides a rational interpretation of the experimentally determined coefficients. The work of Smith and Morales particularly seems to provide a rationale for the investigation of the exchange of lipid soluble substances which takes into account the most pertinent physiological factors.

The work of N. A. Michels (1936), B. W. Zweifach (1936–37, 1939, 1940a, b, 1950) and R. Chambers and B. W. Zweifach (1940, 1944, 1946, 1948, 1949) on the functional anatomy of the capillaries has made clear that the capillary bed of most tissues is composed of two types of capillaries, whose functional significance must be taken into account in any complete theory of the blood-tissue exchange.

V. The capillary bed. The work of Chambers and Zweifach (*loc. cit.*) has disclosed that, functionally, the capillary bed consists of central channels with side branches. Starting at the smallest arteriole, the central channel is composed of a metarteriole, with a discontinuous array of typical muscle cells along it, imparting vasomotion to the vessels which are about eight to fifteen microns in diameter. Next comes the proximal portion of the arteriolo-venular or a-v capillary with atypical muscle cells which cause changes in the diameter of the a-v capillary only under abnormal conditions. The distal portion of the a-v channel is invested with a coat of connective tissue. These a-v capillaries fuse to form nonmuscular venules about fifteen to twenty-five microns in diameter; these venules have a relatively heavy coat of investing connective tissue. Branching off the proximal muscular portion of the central channels are precapillaries which have a proximal muscle-invested portion about twenty to thirty microns in diameter. The true capillaries anastomose freely and return to the distal portion of the a-v channels or to the nonmuscular venules. The angle at which the first of the precapillaries branches from a given a-v capillary is more than ninety degrees. Later branches leave at successively smaller angles, and the true capillaries return to the a-v channels at a very slight angle. The junction of the a-v and precapillaries is marked by endothelial folds which act as sphincters, apparently controlling the flow into the true capillaries. The true capillaries show only passive changes in diameter, which result from changes in the blood flow through them. Figure 1, based on the work of Zweifach, gives a schematic representation of the capillary anatomy.

The a-v channel normally has a continuous rapid blood flow through it, subject to recurrent vasomotion which consists of an irregular series of partial contractions of the metarteriole and the precapillary sphincters at intervals varying from thirty seconds to three minutes. Even when active flow through the true capillary is cut off, the capillary still has a fluid in it.

The angle of branching of the precapillaries from the central channel, and the relatively large diameter of the proximal portion of the precapillary, is apparently such as to maintain within the true capillary a more or

less uniformly low hydrostatic pressure; perhaps less, for the greater portion of its length, than the colloid osmotic pressure of the blood.

Thus Zweifach and Chambers accept the general concept of Starling's hypothesis—that filtration from the capillaries occurs where the hydrostatic pressure exceeds the colloid osmotic pressure—but shift the locus of action so that filtration from the a-v capillary is believed to occur along most of its length, and absorption from the tissue spaces occurs along most of the length of the true capillary.

The ratio of the number of true capillaries to the number of a-v capillaries is a tissue characteristic and varies from less than 1 in the skin to more than 10 in the skeletal muscle (Zweifach, 1936–37).

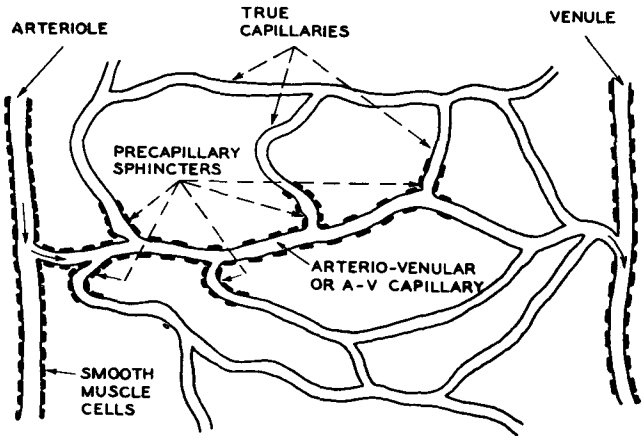

FIGURE 1. Schematic diagram of capillary bed

The unselective permeability of the capillary wall in most regions of the body is adequately explained by the "pore" theory (Chambers and Zweifach, 1947; Zweifach, 1940b; Pappenheimer *et al.*, *loc. cit.*). According to this, the endothelial cells of the capillary secrete a cement substance, which binds together the endothelial cells and constitutes a matrix between them which is porous. The matrix permits the passage of low molecular weight substances with little hindrance. A decrease in the calcium ion content or the pH of the perfusing fluid softens the cement and enhances its dissipation, and thus results in an increase in the rate of filtration and diffusion from the capillary. In addition to the layer of endothelial cells, the capillary wall has an endocapillary layer, which is very thin and noncellular, lining the inner surface. This may be a layer of adsorbed protein

(Zweifach, 1940b). A closely adhering, investing layer of argentophil fibrils, the pericapillary sheath, covers the outer surface of the capillary.

P. Rous *et al.* (1930, 1931), F. Smith *et al.* (1931, 1932), and Zweifach (1940) have observed what they interpret as an increase in the capillary permeability from the arterial to the venous end. Danielli and Stock (1944) have disputed the interpretation but not the observation. However, the reasoning of Danielli and Stock does not consider the functional anatomy of the capillary bed as outlined above, and hence must be questioned.

VI. A tissue model for blood-tissue exchange. On the basis of the foregoing discussion, an idealized model of a tissue will be constructed and the exchange between the blood and the tissue in such a model will be considered. The considerations are restricted to the exchange of substances which are lipid-insoluble. Substances which enter the red cells in appreciable amounts, which are appreciably adsorbed on blood proteins, or which undergo chemical changes at appreciable rates in either the blood or the extracellular spaces—all such substances require special considerations which would considerably complicate the equations to be developed and hence are excluded from the present treatment. Lipid-soluble substances may pass through the endothelial cells of the capillaries and also through the walls of the smaller arterioles and venules. Hence such substances are also excluded. The model applies only to a homogeneous tissue whose blood supply and ratio of extracellular to cellular phases are everywhere constant. The length of all capillaries, both a-v and true, will be taken as equal everywhere. The radii of the capillaries, and the number and location of the active capillaries will be assumed constant during the process considered.

Since the capillaries form an irregular network with the arterial end of one capillary likely to be adjacent to the venous end of another, only variations of concentrations in the extracellular spaces in a direction normal to the capillary axis are considered.

Furthermore, the filtration rate along the capillary will be taken as constant, positive along the length of the a-v capillary and negative along the length of the true capillary. This is perhaps partially justified by the observations of the gradient in capillary permeability mentioned above. Thus if the capillary becomes more permeable toward the venous end, the rate of filtration through the wall would be greater at the venous end, if the pressure were equal to that at the arterial end. But the pressure is lower, and hence, as an approximation, the filtration rate along the length of the capillary will be taken to be constant.

The number of parameters which must be taken into account is so large and the number of combinations of these occurring in the equations to be developed is so great that the Glossary of Symbols appended at the end of this work (see p. 258) may assist the reader in interpreting the equations.

Distances along both the a-v and true capillaries will be designated by z. The length L is defined as the average functional length of the a-v capillaries, i.e., the length along which exchange between the blood and tissue may occur at an appreciable rate. At the arterial end $z = 0$ and at the venous end $z = L$. The true capillaries form an irregular anastomosing network in which the length of any one capillary is not readily defined directly. But the ratio of the total length of all active true capillaries in a homogeneous tissue, i.e., those through which blood is flowing, to the total length of all a-v capillaries in the tissue could be determined. This ratio, which will be designated by A, and called the activity ratio, is assumed to be known. Then in our model we replace the actual distribution of capillaries by arrays consisting of one a-v capillary, of length L, and A true capillaries also all of length L, all in parallel. In the model, $z = 0$ where blood enters the true capillaries, and $z = L$ where blood flows out of them.

We asssume that the mean velocity of the blood entering the a-v capillaries in the homogeneous tissue is $v_1(0)$ and that entering the true capillaries is $v_2(0)$. Since we consider only substances in solution in the blood plasma, it is convenient to express the blood concentrations in terms of concentrations in the red cell-free, protein-free fraction $f_1(z)$ of the total blood volume which is in the a-v capillaries at any point z along the length of the capillary. Let $f_2(z)$ be the corresponding fractions of the blood in the true capillary. Since the blood entering the two types of capillaries may have different numbers of red cells per unit volume, even $f_1(0)$ and $f_2(0)$ may not be equal. Let r_1 and r_2 be the radii of the a-v and true capillaries, respectively.

We will assume that the bulk of the material filtered into or out of the capillaries is water, so that the changes in the volume of an element of blood or perfusate are due solely to water filtration. The product of the filtration constant by the net differences between the hydrostatic and osmotic pressures acting across the wall of the a-v capillary will be denoted by P_1. The corresponding quantity for the true capillary will be denoted by P_2. It is assumed that $P_1 > 0$ and $P_2 < 0$ for $0 \leq z \leq L$, where L is the length of the capillary. This assumption is in accordance with the concept of Zweifach and Chambers, discussed earlier, that filtration from the a-v capillary occurs along most of its length, and that ab-

sorption of fluid from the tissue spaces occurs along most of the length of the true capillaries.

Then the material balance equation for any element of length dz and volume $\pi r_1^2 dz$ along the a-v capillary is:

$$\pi r_1^2 d f_1(z)\, dz = [\pi r_1^2 f_1(z)\, v_1(z) - \pi r_1^2 f_1(z+dz)\, v_1(z+dz) - 2\pi r_1 P_1 dz]\, dt. \tag{1}$$

The term on the left-hand side of the equation gives the accumulation of the fluid in the volume $\pi r_1^2 dz$, and the terms on the right are, in order, the amount of fluid entering the element, the amount leaving the venous end, and the amount filtering through the capillary wall.

Simplifying (1) and using Taylor's theorem, we have

$$\frac{\partial f_1}{\partial t} = -\frac{\partial f_1 v_1}{\partial z} - \frac{2P_1}{r_1}. \tag{2}$$

We will consider only the case where filtration is constant with respect to time. Then the solution of (2) is

$$f_1(z)\, v_1(z) = f_1(0)\, v_1(0) - \frac{2P_1}{r_1} z. \tag{3}$$

Thus, according to the assumptions made, an element of fluid moves more slowly as it approaches the venous end of the a-v capillary. Similarly, we find for the true capillary,

$$f_2(z)\, v_2(z) = f_2(0)\, v_2(0) - \frac{2P_2}{r_2} z. \tag{4}$$

We now consider the variation along the length of the a-v capillary of a substance in the fluid of the blood. Let $K_1(z,t)$ be its concentration in the cell-free, protein-free fluid. The amount entering an element of volume of an a-v capillary, $\pi r_1^2 dz$, in time dt is

$$\pi r_1^2 f_1(z)\, v_1(z)\, K_1(z,t)\, dt. \tag{5}$$

The amount leaving the venous end of the element is

$$\pi r_1^2 f_1(z+dz)\, v_1(z+dz)\, K_1(z+dz,t)\, dt. \tag{6}$$

The net amount leaving through the capillary wall is

$$2\pi r_1 [(k_1 + d_1 P_1) K_1(z,t) - k_1' E_1']\, dz\, dt, \tag{7}$$

where k_1 and k_1' are, respectively, the average permeability coefficients for exit and entrance of the substance through the capillary wall (these coefficients may be different in the blood vessels of the brain and other special tissues), d_1 is the distribution ratio giving the ratio of the concentration of the substance in the filtrate to the concentration in the protein-free plasma, and E_1' is the mean concentration of the substance in the extracellular fluid at the wall of the a-v capillary. The amount of the substance accumulating in the element of volume is

$$\pi r_1^2 dz\, dK_1(z, t). \tag{8}$$

Since we have asumed that no inactivation or chemical changes occur in the blood, the material balance requires

$$\begin{aligned}\pi r_1^2 dz\, dK_1(z, t) = {} & [\pi r_1^2 f_1(z)\, v_1(z)\, K_1(z, t) \\ & - \pi r_1^2 f_1(z+dz)\, v_1(z+dz)\, K_1(z+dz, t)]\, dt \\ & - [2\pi r_1 (k_1 + d_1 P_1)\, K_1(z, t) - 2\pi r_1 k_1' E_1']\, dz\, dt.\end{aligned} \tag{9}$$

Simplifying this, we have

$$\begin{aligned}dz \frac{\partial K_1}{\partial t} = {} & f_1(z)\, v_1(z)\, K_1(z, t) - f_1(z+dz)\, v_1(z+dz) \\ & \times K_1(z+dz, t) - \frac{2}{r_1}(k_1 + d_1 P)\, K_1(z, t)\, dz + \frac{2}{r_1} k_1' E_1'(t)\, dz.\end{aligned} \tag{10}$$

Upon using Taylor's theorem and (3) we finally obtain

$$\frac{\partial K_1}{\partial t} = -f_1(z)\, v_1(z) \frac{\partial K_1}{\partial z} + \frac{2}{r_1}(P_1 - d_1 P_1 - k_1)\, K_1 + \frac{2}{r_1} k_1' E_1'(t). \tag{11}$$

Essentially the same considerations apply to the true capillary, except that the filtration here is assumed to occur from the tissue into the capillary. Hence the net amount of the substance leaving through the wall of the true capillary in time dt is

$$2\pi r_2 [k_2 K_2(z, t) - (k_2' - d_2 P_2) E_2'(t)]\, dz\, dt. \tag{12}$$

Here k_2 and k_2' are the average permeability coefficients for exit and entrance of the material through the true capillary wall, d_2 is the distribution ratio of the filtrate, and E_2' is the mean concentration outside of the wall of the true capillary. Thus, by the same reasoning that produced equation (11), we obtain an equation for $K_2(z,t)$. This is

$$\frac{\partial K_2}{\partial t} = -f_2(z)\, v_2(z) \frac{\partial K_2}{\partial z} + \frac{2}{r_2}(P_2 - k_2)\, K_2 + \frac{2}{r_2}(k_2' - d_2 P_2) E_2'(t). \tag{13}$$

We have neglected the radial concentration gradient in the capillary since it is likely to be very small.

We now consider the concentration of the substance in the extracellular and cellular phases. We use the previously defined activity ratio A and assume that each a-v capillary is surrounded by a cylinder of tissue of average radius AR. The average extracellular concentration in this cylinder will be called E_1 and the average intracellular concentration in the cells of this cylinder will be called C_1. Similarly we assume that each of the true capillaries in our model is surrounded by a cylinder of tissue of average radius R, with an average extracellular concentration E_2 and an average intracellular concentration C_2. If the number of a-v capillaries in an arbitrary volume V is N, and if we know A, L, and N, then the radii AR and R are given by the requirement that

$$V = [A^2R^2 + AR^2]\,\pi NL + B = \pi R^2 LN A\,(A+1) + B\,, \qquad (14)$$

where B is the volume occupied by the blood vessels larger than capillaries. The volume B is not likely to exceed about seven per cent of the total volume of any tissue. According to these definitions, $AR + R$ is an approximate measure of the average distance between a-v and true capillaries.

We will also assume that the amount of material removed from the tissue by the lymphatic system is negligible; hence the considerations are restricted to tissues in which the lymphatic drainage during the time considered is very small compared to the blood flow.

The gradient of concentration of the material in the extracellular phase at the surface of the a-v capillary is approximately (cf. Rashevsky, 1948, pp. 15–23)

$$\frac{2\,(E_1' - E_1)}{AR} \qquad (15)$$

where $AR/2$ is the approximate distance between the a-v capillary and the site where the true concentration may be supposed to be about equal to the average concentration. Then at the wall of the a-v capillary we have

$$[\,(k_1 + d_1P_1)\,K_{m1} - k_1'E_1'] = \frac{(E_1' - E_1)\,2\,D\,gl}{AR}\,, \qquad (16)$$

where K_{m1} is the mean concentration in the protein-free plasma, D is the diffusion coefficient in the substance of the extracellular space, g is a factor given by the ratio of the cell-free area through which diffusion may occur to the total area (normal to the gradient of the concentration), and l is the

ratio of the shortest distance between two points in the tissue to the distance which must be traveled between the two points without crossing any cell walls. The equation implies that the speed of diffusion in the extracellular space is very great relative to the speed of transport through the walls of the cells. Similarly, at the true capillary wall, we have

$$[k_2 K_{m2} - (k_2' - d_2 P_2) E_2'] = (E_2' - E_2) \frac{2 D g l}{R}. \tag{17}$$

The amount of the substance flowing into the cells in the region of the a-v capillary in time dt is approximately

$$\pi (A^2 R^2 - r_1^2) [h_1 E_1 - h_2 C_1] \frac{b s}{v} d z dt, \tag{18}$$

where h_1 and h_2 are permeability coefficients for entrance to and exit from the cells, s/v is the cell surface to volume ratio, and b is the fraction of the extravascular space occupied by cells. The expression implies that the speed with which the substance distributes itself inside of the cells is very great relative to the rate at which it crosses the cell wall. The amount of the substance flowing from the region surrounding the a-v capillary into the regions surrounding the true capillaries is given approximately by

$$(E_1 - E_2)\, 2 D g l \frac{2 \pi A R}{A R + R} d z dt. \tag{19}$$

Here

$$\frac{2 (E_1 - E_2)}{A R + R}$$

is the approximate gradient at the boundary of the region and $2 \pi A R dz$ is the approximate area normal to the gradient through which flow must occur.

The average net amount entering the region from the a-v capillary in time dt is

$$2 \pi r_1 [(k_1 + d_1 P_1) K_{m1}(t) - k_1' E_1'] d z dt. \tag{20}$$

The amount accumulating in the extracellular phase around the a-v capillary is

$$\pi (A^2 R^2 - r_1^2)\, a f_a d z d E_1, \tag{21}$$

where a is the fraction of the extravascular volume not occupied by cells, and f_a is the fraction of extracellular volume which is available for the distribution of the substance, i.e., not occupied by fibers or other material through which diffusion cannot occur.

Then the material balance requirement, together with (18), (19), (20), and (21), gives

$$\pi (A^2R^2 - r_1^2)\, a f_a d\, z dE_1 = -(E_1 - E_2) \frac{4\pi D g l A R}{AR + R} d\, z dt + 2\pi r_1 [(k_1 + d_1 P_1) K_{m1}(t) - k_1' E_1'] \dot{d}\, z dt - \pi (A^2R^2 - r_1^2) [h_1 E_1 - h_2 C_1] \frac{b s}{v} d\, z dt. \tag{22}$$

After cancellations and rearrangements, this becomes

$$\frac{dE_1}{dt} = -\frac{4 D g l}{a f_a (A^2R^2 - r_1^2)} \left(\frac{A}{A+1}\right)(E_1 - E_2) + \frac{2 r_1 (k_1 + d_1 P_1)}{a f_a (A^2R^2 - r_1^2)} K_{m1} - \frac{2 r_1 k_1'}{a f_a (A^2R^2 - r_1^2)} E_1' - \frac{b s h_1}{a f_a v} E_1 + \frac{b s h_2}{a f_a v} C_1. \tag{23}$$

Similarly, the amount of material flowing into the cells in the region of the true capillary in time dt is approximately

$$\pi (R^2 - r_2^2) [h_1 E_2 - h_2 C_2] \frac{b s}{v} d\, z dt. \tag{24}$$

The amount of material flowing from the region of the true capillary to the region of the a-v capillary is approximately

$$(E_2 - E_1)\, 2 D g l \frac{2\pi R}{AR + R} d\, z dt. \tag{25}$$

Here

$$\frac{2 (E_2 - E_1)}{AR + R}$$

is the approximate gradient at the boundary of the region and $2\pi R dz$ is the approximate area normal to the gradient through which flow must occur. The average net amount entering the region from the true capillary in time dt is

$$2\pi r_2 [k_2 K_{m2}(t) - (k_2' - d_2 P_2) E_2'] d\, z dt. \tag{26}$$

The amount accumulating in the extracellular phase around the true capillary is

$$\pi (R^2 - r_2^2)\, a f_a d\, z dE_2. \tag{27}$$

Then, since no material is inactivated in the region, (24), (25), (26), and (27) give

$$\pi (R^2 - r_2^2)\, a f_a d\, z dE_2 = - (E_2 - E_1) \frac{4\pi D g l R}{AR + R} d\, z dt + 2\pi r_2 [\, k_2 K_{m2}(t) - (k_2' - d_2 P_2) E_2']\, d\, z dt - \pi (R^2 - r_2^2)\, [\, h_1 E_2 - h_2 C_2] \frac{b\, s}{v} d\, z dt . \tag{28}$$

After cancellations and rearrangements, this becomes

$$\frac{dE_2}{dt} = - (E_2 - E_1) \frac{4 D g l}{a f_a (R^2 - r_2^2)(A + 1)} + \frac{2 r_2 k_2}{a f_a (R^2 - r_2^2)} K_{m2}(t) - \frac{2 r_2 (k_2' - d_2 P_2) E_2'}{a f_a (R^2 - r_2^2)} - \frac{b\, s\, h_1}{a f_a v} E_2 + \frac{b\, s\, h_2}{a f_a v} C_2 . \tag{29}$$

Equations (23) and (29) imply that no net exchange of material occurs between one array of our model, consisting of an a-v capillary and its associated true capillaries, and another such array.

The concentration of the substance in the cells of the two regions must now be considered. The amounts of material flowing into the cells of the two regions are given by (18) and (24). The consumption of the material by the cells in the a-v region is assumed to be

$$q_1 + q_2 (C_1 - C_0) , \tag{30}$$

where q_1 is the consumption in—say, moles per unit cell volume per unit time—and q_2 is a proportionality constant giving the change in the rate of consumption for a concentration different from some initial concentration C_0. Both q_1 and q_2 are negative for consumption. For production, q_2 will be assumed to be zero and q_1 positive. Then the amount of material produced or consumed in the a-v region is given by

$$\pi (A^2 R^2 - r_1^2)\, d\, z\, b f_b [\, q_1 + q_2 (C_1 - C_0)\,]\, dt , \tag{31}$$

where f_b is the fraction of the cellular volume which is available for the distribution and production of the substance. The amount accumulating in the cells is given by

$$\pi (A^2 R^2 - r_1^2)\, d\, z\, b f_b dC_1 . \tag{32}$$

Then (18), (31), and (32) give us

$$\pi (A^2 R^2 - r_1^2)\, d\, z\, b f_b dC_1 = \pi (A^2 R^2 - r_1^2)\, (h_1 E_1 - h_2 C_1) \frac{b\, s}{v}\, d\, z dt + \pi (A^2 R^2 - r_1^2)\, d\, z\, b f_b [\, q_1 + q_2 (C_1 - C_0)\,]\, dt . \tag{33}$$

Cancellation and rearrangement give us

$$\frac{dC_1}{dt} = \frac{s}{vf_b}[h_1E_1 - h_2C_1] + q_1 + q_2(C_1 - C_0) . \tag{34}$$

Similar considerations for the cells of the true capillary region give us

$$\frac{dC_2}{dt} = \frac{s}{vf_b}[h_1E_2 - h_2C_2] + q_1 + q_2(C_2 - C_0) . \tag{35}$$

We may now calculate the concentration of the substance in the venous blood leaving the capillary array. We will assume that edema is not developing. Hence the amount of fluid entering the array at any time must equal the amount leaving. Thus we have

$$\pi r_1^2 f_1(0)\, v_1(0) + A\pi r_2^2 f_2(0)\, v_2(0) = \pi r_1^2 f_1(L)\, v_1(L) + A\pi r_2^2 f_2(L)\, v_2(L) . \tag{36}$$

From (36), using (3) and (4), we obtain a relation which will be used later:

$$A = -\frac{r_1 P_1}{r_2 P_2}. \tag{37}$$

The amount of the substance leaving the a-v capillary in time dt is given by

$$\pi r_1^2 f_1(L)\, v_1(L)\, K_1(L, t)\, dt , \tag{38}$$

and the amount leaving the true capillaries of the array is

$$A\pi r_2^2 f_2(L)\, v_2(L)\, K_2(L, t)\, dt . \tag{39}$$

Then, after mixing the flows, the concentration of the protein-free venous plasma K_v is given by

$$K_v(t) = \frac{r_1^2 f_1(L)\, v_1(L)\, K_1(L, t) + A r_2^2 f_2(L)\, v_2(L)\, K_2(L, t)}{r_1^2 f_1(0)\, v_1(0) + A r_2^2 f_2(0)\, v_2(0)}. \tag{40}$$

VII. The transformation of the equations. The problem of the blood-tissue exchange has now been formulated in equations (11), (13), (16), (17), (23), (29), (34), and (35). These equations, together with (3), (4), and (40), are sufficient to determine the concentration of a substance in the venous blood, at the walls of the a-v and true capillaries, and in the cells of the two regions, as well as the average extracellular concentration in the two regions—all in terms of the concentration in the arterial blood, the

blood velocity in the two types of capillaries, and the various tissue parameters.

The solutions of the equations are most conveniently obtained by means of the Laplace transformation (Churchill, 1944). That is, we associate with each function $F(t)$ its Laplace transform $f(p)$, defined by

$$f(p) = \int_0^\infty e^{-pt} F(t)\, dt.$$

We will let x_i', x_i, y_i, w_i, and w_{mi} be the Laplace transforms of E_i', E_i, C_i, K_i, and K_{mi}, respectively, with $i = 1, 2$.

The transform of (11) is

$$pw_1 - K_0 = -f_1(z)\, v_1(z) \frac{dw_1(z,p)}{dz} + \frac{2}{r_1}(P_1 - d_1P_1 - k_1) w_1(z,p) + \frac{2k_1'}{r_1} x_1'(p), \tag{41}$$

where K_0 is the initial concentration in the capillary, assumed to be constant. Then

$$f_1(z)\, v_1(z) \frac{dw_1}{dz} = -\left[p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1)\right] w_1 + \frac{2k_1'}{r_1} x_1'(p) + K_0. \tag{42}$$

Let us put

$$\beta_1 = p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1) \qquad \text{and} \qquad \mu_1 = \frac{2k_1'}{r_1}.$$

Then, using (3), (42) becomes

$$\frac{dw_1}{-\beta_1 w_1 + \mu_1 x_1' + K_0} = \frac{dz}{f_1(z)\, v_1(z)} = \frac{dz}{f_1(0)\, v_1(0) - \frac{2P_1}{r_1} z}. \tag{43}$$

The solution of (43) is

$$\frac{w_1(z,p)\,\beta_1 - \mu_1 x_1' - K_0}{w_0(p)\,\beta_1 - \mu_1 x_1' - K_0} = \left(1 - \frac{2P_1 z}{r_1 f_{10} v_{10}}\right)^{\beta_1 (r_1/2P_1)}, \tag{44}$$

where $w_0(p)$ is the transform of the concentration in the protein-free plasma of the arterial blood, and $f_{10}v_{10} = f_1(0)v_1(0)$. The mean value of $w_1(z,p)$ along the a-v capillary is given by

$$\frac{w_{m1}(p)\,\beta_1 - \mu_1 x_1' - K_0}{w_0(p)\,\beta_1 - \mu_1 x_1' - K_0} = \frac{1}{L} \int_0^L \left(1 - \frac{2P_1 z}{r_1 f_{10} v_{10}}\right)^{r_1 \beta_1 / 2P_1} dz. \tag{45}$$

Calculating the integral, we finally have, putting

$$\gamma_1 = \frac{r_1}{2P_1}\left[p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1)\right] \qquad \text{and} \qquad \lambda_1 = \frac{2P_1L}{r_1 f_{10} v_{10}},$$

$$\frac{w_{m1}\beta_1 - \mu_1 x_1' - K_0}{w_0\beta_1 - \mu_1 x_1' - K_0} = \frac{1}{\lambda_1(1+\gamma_1)}\left[1 - (1-\lambda_1)^{1+\gamma_1}\right],$$

or

$$w_{m1} = \left(w_0 - \frac{K_0}{\beta_1}\right)\left(\frac{1-(1-\lambda_1)^{1+\gamma_1}}{\lambda_1(1+\gamma_1)}\right) + \frac{\mu_1}{\beta_1}x_1'\left(1 - \frac{1-(1-\lambda_1)^{1+\gamma_1}}{\lambda_1(1+\gamma_1)}\right) + \frac{K_0}{\beta_1}. \tag{46}$$

We will also need

$$w_1(L, p) = \left(w_0 - \frac{K_0}{\beta_1}\right)(1-\lambda_1)^{\gamma_1} + \frac{\mu_1}{\beta_1}x_1'(1 - [1-\lambda_1]^{\gamma_1}) + \frac{K_0}{\beta_1}. \tag{47}$$

The transform of (13) is

$$pw_2(z, p) - K_0 = -f_2(z)\, v_2(z)\frac{dw_2(z, p)}{dz} + \frac{2}{r_2}(P_2 - k_2)w_2(z, p) + \frac{2}{r_2}(k_2' - d_2P_2)x_2'(p). \tag{48}$$

Then

$$f_2(z)\, v_2(z)\frac{dw_2}{dz} = -\left[p - \frac{2}{r_2}(P_2 - k_2)\right]w_2 + \frac{2}{r_2}(k_2' - d_2P_2)x_2'(p) + K_0. \tag{49}$$

Putting

$$\beta_2 = p - \frac{2}{r_2}(P_2 - k_2), \qquad \mu_2 = \frac{2}{r_2}(k_2' - d_2P_2),$$

and using (4), we have

$$\frac{dw_2}{-\beta_2 w_2 + \mu_2 x_2' + K_0} = \frac{dz}{f_{20}v_{20} - \frac{2P_2}{r_2}z}, \tag{50}$$

where $f_{20}v_{20} = f_2(0)v_2(0)$. The solution of (50) is

$$\frac{w_2(z, p)\beta_2 - \mu_2 x_2' - K_0}{w_0(p)\beta_2 - \mu_2 x_2' - K_0} = \left(1 - \frac{2P_2 z}{r_2 f_{20} v_{20}}\right)^{\beta_2(r_2/2P_2)} \tag{51}$$

Equation (51) implies that the concentration of the substance in the protein-free plasma entering any true capillary is the same as that enter-

ing an a-v capillary. This is undoubtedly not correct, but may be approximately so, since many true capillaries originate fairly close to the arterial end of the a-v capillaries. The mean value of w_2 along the true capillary is

$$\frac{w_{m2}(p)\,\beta_2 - \mu_2 x_2' - K_0}{w_0(p)\,\beta_2 - \mu_2 x_2' - K_0} = \frac{1}{L}\int_0^L \left(1 - \frac{2P_2 z}{r_2 f_{20} v_{20}}\right)^{\beta_2 (r_2/2P_2)} dz\,. \tag{52}$$

The right-hand side is equal to

$$\frac{1}{\lambda_2(1+\gamma_2)}\left[1 - (1-\lambda_2)^{1+\gamma_2}\right], \tag{53}$$

where

$$\gamma_2 = \frac{r_2}{2P_2}\left[p - \frac{2}{r_2}(P_2 - k_2)\right] \quad \text{and} \quad \lambda_2 = \frac{2P_2 L}{r_2 f_{20} v_{20}}.$$

Then

$$w_{m2}(p) = \left(w_0 - \frac{K_0}{\beta_2}\right)\left(\frac{1-(1-\lambda_2)^{1+\gamma_2}}{\lambda_2(1+\gamma_2)}\right) + \frac{\mu_2}{\beta_2}x_2'\left(1 - \frac{1-(1-\lambda_2)^{1+\gamma_2}}{\lambda_2(1-\gamma_2)}\right) + \frac{K_0}{\beta_2}. \tag{54}$$

We will also need

$$w_2(L, p) = \left(w_0 - \frac{K_0}{\beta_2}\right)(1-\lambda_2)^{\gamma_2} + \frac{\mu_2}{\beta_2}x_2'\left[1 - (1-\lambda_2)^{\gamma_2}\right] + \frac{K_0}{\beta_2}. \tag{55}$$

The transforms of (16) and (17) are

$$\left[(k_1 + d_1 P_1)\,w_{m1} - k_1' x_1'\right] = (x_1' - x_1)\frac{2Dgl}{AR} \tag{56}$$

and

$$\left[k_2 w_{m2} - (k_2' - d_2 P_2)\,x_2'\right] = (x_2' - x_2)\frac{2Dgl}{R}. \tag{57}$$

Using the notations

$$\nu_1 = \frac{k_1' + \dfrac{2Dgl}{AR}}{k_1 + d_1 P_1}, \qquad \nu_2 = \frac{k_2' - d_2 P_2 + \dfrac{2Dgl}{R}}{k_2};$$

$$\rho_1 = \frac{2Dgl}{AR(k_1 + d_1 P_1)}, \qquad \rho_2 = \frac{2Dgl}{Rk_2};$$

we have for (56) and (57)

$$w_{m1} - \nu_1 x_1' + \rho_1 x_1 = 0\,, \tag{58}$$

$$w_{m2} - \nu_2 x_2' + \rho_2 x_2 = 0\,. \tag{59}$$

The transforms of (23), (29), (34), and (35), after the introduction of the E_0's and C_0's as the initial values of the extracellular and cellular concentrations, are:

$$px_1 - E_0 = -\frac{4Dgl}{af_a(A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right)(x_1 - x_2) + \frac{2r(k_1 + d_1P_1)}{af_a(A^2R^2 - R_1^2)} \times w_{m1} - \frac{2r_1k_1'}{af_a(A^2R^2 - r_1^2)}x_1' - \frac{bsh_1}{af_av}x_1 + \frac{bsh_2}{af_av}y_1; \tag{60}$$

$$px_2 - E_0 = -\frac{4Dgl}{af_a(R^2 - r_2^2)(A+1)}(x_2 - x_1) + \frac{2r_2k_2}{af_a(R^2 - r_2^2)}w_{m2} - \frac{2r_2(k_2' - d_2P_2)}{af_a(R^2 - r_2^2)}x_2' - \frac{bsh_1}{af_av}x_2 + \frac{bsh_2}{af_av}y_2; \tag{61}$$

$$py_1 - C_0 = \frac{sh_1}{vf_b}x_1 - \frac{sh_2}{vf_b}y_1 + \frac{q_1 - q_2C_0}{p} + q_2y_1; \tag{62}$$

$$py_2 - C_0 = \frac{sh_1}{vf_b}x_2 - \frac{sh_2}{vf_b}y_2 + \frac{q_1 - q_2C_0}{p} + q_2y_2. \tag{63}$$

The following notation will be used for the combinations of constants in (60) to (63):

$$\xi_1 = \frac{4glD}{af_a(A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right); \qquad \xi_2 = \frac{4glD}{af_a(R^2 - r_2^2)}\left(\frac{1}{A+1}\right);$$

$$\phi_1 = \frac{2r_1(k_1 + d_1P_1)}{af_a(A^2R^2 - r_1^2)}; \qquad \phi_2 = \frac{2r_2k_2}{af_a(R^2 - r_2^2)};$$

$$\psi_1 = \frac{2r_1k_1'}{af_a(A^2R^2 - r_1^2)}; \qquad \psi_2 = \frac{2r_2(k_2' - d_2P_2)}{af_a(R^2 - r_2^2)};$$

$$\sigma_1 = \frac{bsh_1}{af_av}; \qquad \sigma_2 = \frac{sh_2}{vf_b}; \qquad \omega = q_1 - q_2C_0.$$

Using these abbreviations in (60) to (63), we have

$$px_1 - E_0 = -\xi_1x_1 + \xi_1x_2 + \phi_1w_{m1} - \psi_1x_1' - \sigma_1x_1 + \sigma_2\frac{bf_b}{af_a}y_1, \tag{64}$$

$$px_2 - E_0 = -\xi_2x_2 + \xi_2x_1 + \phi_2w_{m2} - \psi_2x_2' - \sigma_1x_2 + \sigma_2\frac{bf_b}{af_a}y_2, \tag{65}$$

$$py_1 - C_0 = \sigma_1\frac{af_a}{bf_b}x_1 - \sigma_2y_1 + \frac{\omega}{p} + q_2y_1, \tag{66}$$

$$py_2 - C_0 = \sigma_1\frac{af_a}{bf_b}x_2 - \sigma_2y_2 + \frac{\omega}{p} + q_2y_2. \tag{67}$$

From (66) and (67), we have

$$y_i = \frac{\sigma_1 \frac{af_a}{bf_b} x_i + C_0 + \frac{\omega}{p}}{p + \sigma_2 - q_2}, \qquad i = 1, 2 . \tag{68}$$

Introducing (68) into (64) and (65), we get, after some rearrangements,

$$x_1\left(p + \xi_1 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2}\right) - \xi_1 x_2 - \phi_1 w_{m1} + \psi_1 x_1' - E_0\left\{1 + \frac{C_0}{E_0}\frac{bf_b}{af_a}\frac{\sigma_2\left(p + \frac{\omega}{C_0}\right)}{p(p + \sigma_2 - q_2)}\right\} = 0 , \tag{69}$$

$$x_2\left(p + \xi_2 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2}\right) - \xi_2 x_1 - \phi_2 w_{m2} + \psi_2 x_2' - E_0\left\{1 + \frac{C_0}{E_0}\frac{bf_b}{af_a}\frac{\sigma_2\left(p + \frac{\omega}{C_0}\right)}{p(p + \sigma_2 - q_2)}\right\} = 0 . \tag{70}$$

If we let

$$a_1 = p + \xi_1 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2},$$

$$a_2 = p + \xi_2 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2},$$

$$\beta_0 = E_0\left\{1 + \frac{C_0}{E_0}\frac{bf_b}{af_a}\frac{\sigma_2\left(p + \frac{\omega}{C_0}\right)}{p(p + \sigma_2 - q_2)}\right\};$$

then (69) and (70) become

$$a_1 x_1 - \xi_1 x_2 - \phi_1 w_{m1} + \psi_1 x_1' = \beta_0 , \tag{71}$$

$$a_2 x_2 - \xi_2 x_1 - \phi_2 w_{m2} + \psi_2 x_2' = \beta_0 . \tag{72}$$

Let us now introduce the symbols

$$\zeta_1 = \frac{1 - (1 - \lambda_1)^{1+\gamma_1}}{\lambda_1(1 + \gamma_1)}, \qquad \zeta_2 = \frac{1 - (1 - \lambda_2)^{1+\gamma_2}}{\lambda_2(1 + \gamma_2)},$$

$$Z_1 = \left[w_0 - \frac{K_0}{\beta_1}\right]\zeta_1\beta_1 + K_0 , \qquad Z_2 = \left[w_0 - \frac{K_0}{\beta_2}\right]\zeta_2\beta_2 + K_0 .$$

Using this notation in (46) and (54), and collecting the equations (58), (59), (71), and (72) for convenience of reference, we have:

$$x_1'(1-\zeta_1)\,\mu_1 - w_{m1}\beta_1 = -Z_1\,, \tag{73}$$

$$x_2'(1-\zeta_2)\,\mu_2 - w_{m2}\beta_2 = -Z_2\,, \tag{74}$$

$$\nu_1 x_1' - \rho_1 x_1 - w_{m1} = 0\,, \tag{75}$$

$$\nu_2 x_2' - \rho_2 x_2 - w_{m2} = 0\,, \tag{76}$$

$$\psi_1 x_1' + \alpha_1 x_1 - \xi_1 x_2 - \phi_1 w_{m1} = \beta_0\,, \tag{77}$$

$$\psi_2 x_2' - \xi_2 x_1 + \alpha_2 x_2 - \phi_2 w_{m2} = \beta_0\,. \tag{78}$$

These equations, (73) to (78), together with (40), (47), (55), and (68), are necessary and sufficient to determine the venous concentration, E_1, E_2, C_1, C_2, E_1', and E_2' in terms of the arterial concentration, the flow rates in the two types of capillaries, and the various tissue parameters.

Using (75) and (76) in (73), (74), (77), and (78) to eliminate w_{m1} and w_{m2} we obtain

$$x_1'[\mu_1(1-\zeta_1) - \beta_1\nu_1] + \beta_1\rho_1 x_1 = -Z_1\,, \tag{79}$$

$$x_2'[\mu_2(1-\zeta_2) - \beta_2\nu_2] + \beta_2\rho_2 x_2 = -Z_2\,, \tag{80}$$

$$x_1'(\psi_1 - \phi_1\nu_1) + x_1(\alpha_1 + \phi_1\rho_1) - \xi_1 x_2 = \beta_0\,, \tag{81}$$

$$x_2'(\psi_2 - \phi_2\nu_2) - \xi_2 x_1 + x_2(\alpha_2 + \phi_2\rho_2) = \beta_0\,. \tag{82}$$

VIII. The steady state. We may use equations (79) to (82) to get an estimate of the relative importance of the various parameters in their influence upon the steady state concentrations of a substance when the arterial concentration has been constant long enough for the steady state to be assumed.

We use the theorem that if a limit exists for a function $F(t)$ as t approaches infinity, then $pf(p)$ approaches the same limit as p approaches zero through positive values, where $f(p)$ is the Laplace transform of $F(t)$ and p is the transformation parameter (Doetsch, 1950, p. 458). Hence assuming the existence of a steady state, which seems plausible on physical

grounds, we have for (79) to (82), where the various functions of p, i.e., $a_1, a_2, \beta_0, \beta_1, \beta_2, \gamma_1, \gamma_2, \zeta_1$, and ζ_2 must be evaluated at the limit as $p \to +0$,

$$E_1'[\mu_1(1-\zeta_1) - \beta_1\nu_1] + E_1\beta_1\rho_1 = \lim_{p\to+0} - pZ_1, \tag{83}$$

$$E_2'[\mu_2(1-\zeta_2) - \beta_2\nu_2] + E_2\beta_2\rho_2 = \lim_{p\to+0} - pZ_2, \tag{84}$$

$$E_1'(\psi_1 - \phi_1\nu_1) + E_1(a_1 + \phi_1\rho_1) - E_2\xi_1 = \lim_{p\to+0} p\beta_0, \tag{85}$$

$$E_2'(\psi_2 - \phi_2\nu_2) - E_1\xi_2 + E_2(a_2 + \phi_2\rho_2) = \lim_{p\to+0} p\beta_0. \tag{86}$$

As an illustration, we will consider the production of a substance in the cells at a constant rate q_1 moles per cubic centimeter per second. Hence we take q_2 equal to zero. We will also take $k_1 = k_2 = k_1' = k_2'$, and $r_1 = r_2$; P_1, d_1P_1, P_2, and d_2P_2 will be neglected relative to k_1, since even during extremely rapid filtration into the tissue from the capillaries, k_1 is likely to be from twenty-five to two hundred times as large as P_1 or P_2. The exact ratio depends on the molecular weight of the substance, the ratio being higher for the lower molecular weights (Pappenheimer *et al.*, 1951). Since λ_1 and λ_2 are the ratios of the leakage through the capillary wall to the fluid flow into the capillary, we may put as a good approximation, when edema is not developing,

$$1 - \lambda_1 = e^{-\lambda_1} \quad \text{and} \quad 1 - \lambda_2 = e^{-\lambda_2}.$$

For while λ_1 and λ_2 may range from 0.001 to 0.2 (Danielli and Stock, *loc. cit.*), the higher values occur only during the rapid development of edema, and we restrict ourselves to the case of no net filtration into or out of the blood.

With these assumptions, we have the following values for the various coefficients in equations (83) to (86):

$$a_1 = \xi_1; \quad a_2 = \xi_2; \quad \lim_{p\to+0} p\beta_0 = \frac{bf_b}{af_a} q_1; \quad \beta_1 = \beta_2 = \frac{2k_1}{r_1};$$

$$\gamma_1 = -1 + d_1 + \frac{k_1}{P_1}; \quad \gamma_2 = -1 + \frac{k_1}{P_2}; \quad \zeta_1 = \frac{r_1 f_{10} v_{10}}{2Lk_1}\left(1 - e^{-2Lk_1/r_1 f_{10} v_{10}}\right);$$

$$\zeta_2 = \frac{r_1 f_{20} v_{20}}{2Lk_1}\left(1 - e^{-(2Lk_1/r_1 f_{20} v_{20})}\right);$$

$$\lim_{p\to+0} - pZ_1 = -K(0, \infty)\frac{f_{10} v_{10}}{L}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right);$$

$$\lim_{p\to+0} - pZ_2 = -K(0, \infty)\frac{f_{20} v_{20}}{L}\left(1 - e^{-(2Lk_2/r_1 f_{20} v_{20})}\right).$$

Let us also assume that $A = 1$; this may be approximately the case in mammalian skeletal muscle under the experimental conditions used by Pappenheimer *et al.* (*loc. cit.*), especially with the smaller perfusion rates. If we assume that $f_{10}v_{10} = f_{20}v_{20}$, then the coefficients of equations (83) and (84) become identical, as do those of (85) and (86), and $E_1' = E_2'$ and $E_1 = E_2$. This assumption is unlikely to be good, since according to the observations of Zweifach, $f_{20}v_{20} < f_{10}v_{10}$, but the lack of exact data on the relative flow rates, the fact that the assumption seems unlikely to affect the illustration qualitatively, and the simplicity gained seem to justify its use. Using these assumptions, equations (83) and (86) reduce, after some rearrangements, to

$$-E_1'\left\{\frac{r_1 f_{10} v_{10}}{2Lk_1}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right) + \frac{2Dgl}{Rk_1}\right\} + E_1 \frac{2Dgl}{Rk_1} = -K(0, \infty)\frac{r_1 f_{10} v_{10}}{2Lk_1}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right), \tag{87}$$

$$E_1' - E_1 = -q_1 b f_b \frac{R(R^2 - r_1^2)}{4 r_1 Dgl}. \tag{88}$$

Solving these for E_1' and E_1, we get

$$E_1' = K(0, \infty) + q_1 b f_b \frac{L}{f_{10} v_{10}}\left[\left(\frac{R}{r_1}\right)^2 - 1\right]\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right)^{-1}, \tag{89}$$

$$E_1 = K(0, \infty) + q_1 b f_b \times\left[\left(\frac{R}{r_1}\right)^2 - 1\right]\left\{\frac{R r_1}{4Dgl} + \frac{L}{f_{10} v_{10}}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right)^{-1}\right\}. \tag{90}$$

We now need numerical estimates of the various parameters. Mammalian striated muscle will be considered since this tissue is marked by large changes in activity. The average length of a capillary is about 0.7 mm. and the average radius is about 5×10^{-4} cm. (Rous *et al.*, 1930; Krogh, 1929). Jones (*loc. cit.*) gives the average perfusion rate of muscle as 0.01 to 0.030 volumes of blood per volume of tissue per minute. Pappenheimer *et al.* (1951) give an estimate of 70 cm.^{2} per gm. of muscle as the capillary wall area. This estimate is much smaller than those given by Krogh (*loc. cit.*). Using equation (14) with B, the volume of blood vessels larger than capillaries taken as 7% of the total volume, we obtain $R = 36.4 \times 10^{-4}$ cm. and $2N = 3.18 \times 10^5$ capillaries of both types per gm. Furthermore, we obtain $v_{10} = 1.33 \times 10^{-3}$ cm. per sec. for the blood velocity corresponding to a perfusion rate of 0.02 per minute. Taking f_{10} as 0.5, we have $f_{10}v_{10} = 0.67 \times 10^{-3}$ cm. per sec. Hence $L/f_{10}v_{10} \approx 100$.

However, the estimate of 70 cm.^{2} per gm. used in these calculations may be low. The value 140 cm.^{2} per gm. gives $L/f_{10}v_{10} \approx 50$. This value will be used in all calculations and graphs. Naturally, v_{10} depends on the activity, but since more capillaries open up during activity, and since the values of both E_1 and E_1' are more dependent upon the values assumed for R than those assumed for $L/f_{10}v_{10}$, we will keep this fixed and consider only variations in R, Dgl, and k_1.

The values of Dgl depend on the molecular weight of the substance considered, on the state of the extracellular matrix, and on the geometry of

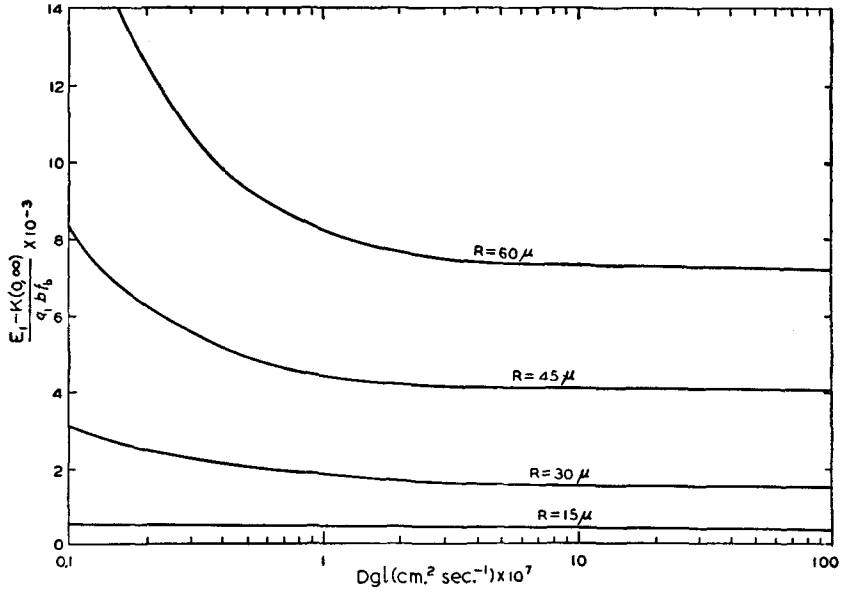

FIGURE 2. Graph of Equation (90). Values of parameters are: $L/f_{10}v_{10} = 50$ sec.; $r_1 = 5 \times 10^{-4}$ cm.; $k_1 = 10^{-4}$ cm. per sec.

the distribution of the cells in the tissue. The factor gl is likely to be about 0.1, since g is about 0.15 and l is about 0.66. The values of k_1 are dependent on the molecular weight of the substance considered, and upon the state of the capillary wall, which may be altered as a result of various physiological changes. The data of Pappenheimer *et al.* (1951) permit an estimate of k_1 to be made for various molecules. Thus for glucose, $k_1 \approx 10^{-4}$ cm. per sec., for sucrose, $k_1 \approx 0.6 \times 10^{-4}$, for raffinose $k_1 \approx 0.4 \times 10^{-4}$, for inulin $k_1 \approx 0.05 \times 10^{-4}$, and for NaCl, $k \approx 1.6 \times 10^{-4}$. We will consider variations in Dgl from 10^{-8} to 10^{-5} cm.^{2} per sec. and in k_1 from 10^{-5} to 10^{-3} cm. per sec.

Figure 2 shows the dependence of the ratio of $E_1 - K(0, \infty)$ to q_1bf_b

upon Dgl for four values of R. This ratio is much more dependent upon R than Dgl. Thus for a produced substance of about the molecular weight of glucose, the ratio is 400 for $R = 15\mu$, 1760 for $R = 30\mu$, 4000 for $R = 45\mu$, and 7300 for $R = 60\mu$.

Figure 3 shows the ratio of $E_1 - K(0, \infty)$ to $E_1' - K(0, \infty)$ as a function of Dgl for various values of R. Rather large differences between the average concentration and the concentration at the capillary wall may exist for the smaller values of Dgl if $K(0, \infty)$ is small. Thus if $K(0, \infty)$ is

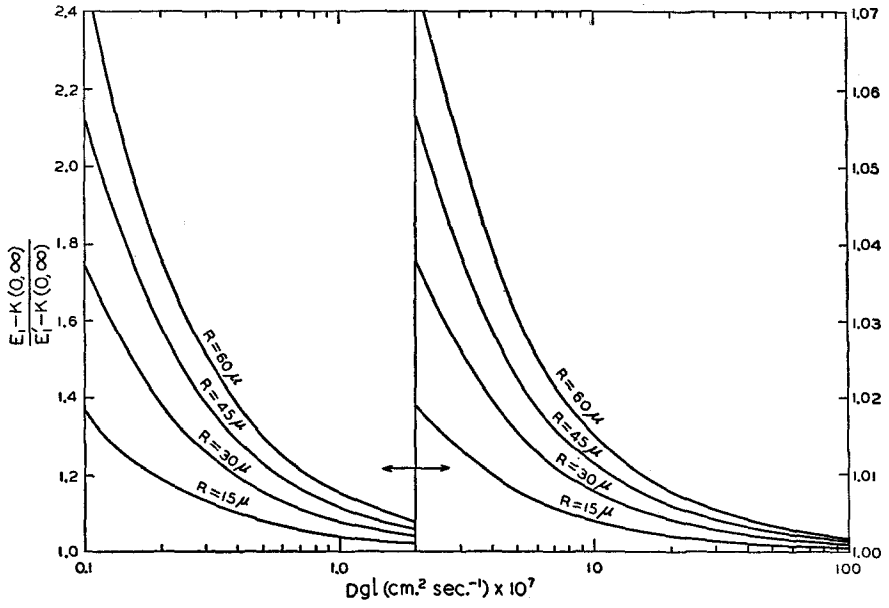

FIGURE 3. Graph of the ratio of equation (90) to equation (91). Values of parameters are: $L/f_{10}v_{10} = 50$ sec.; $r = 5 \times 10^{-4}$ cm.; $k_1 = 10^{-4}$ cm. per sec.

zero, the ratio of E_1 to E_1' for $Dgl = 10^{-7}$ cm.^{2} per sec. is 1.038 for $R = 15\mu$, 1.075 for $R = 30\mu$, 1.112 for $R = 45\mu$, and 1.150 for $R = 60\mu$.

Turning now to a consideration of the average intracellular concentration C_1, we have from either equation (34) or (68) that in the steady state with constant production q_1,

$$C_1 = q_1 \frac{v f_b}{s h_2} + \frac{h_1}{h_2} E_1 . \tag{91}$$

The variation in C_1 with constant q_1 is dependent on the average external concentration through the ratio of h_1 to h_2. If we assume that h_1 and h_2 are of the same order of magnitude, and that the cell radius is about 10^{-3} cm.,

then with $f_b \approx 0.5$ and $h_2 \approx 10^{-5}$ cm. per sec. we have, roughly, that the concentration in the cell at any time is about seventeen times that concentration produced in one second in unit volume by a source of strength q_1, plus the external concentration. The external concentration, as we have seen, is possibly several hundred to several thousand times the concentration which would be produced in a unit volume in one second by a source of strength q_1.

Hence it appears likely that the intracellular concentration of a substance produced in the cell may be influenced to a marked extent by the external concentration and thus by the diffusion coefficient of the extracellular material and the permeability coefficient of the capillary wall.

IX. Transient conditions. In order to investigate the influence of the diffusion coefficient of the extracellular material, and the permeability coefficient of the capillary wall upon the speed with which a substance introduced into the blood distributes itself, we will again resort to some drastic approximations. We will assume that $A = 1$, $k_1 = k_2 = k_1' = k_2'$, $r_1 = r_2$, $f_{10}v_{10} = f_{20}v_{20}$, and that $|\lambda_1| < < 1$ and $|\lambda_2| < < 1$. Using the last assumptions, we find that

$$\lim_{|\lambda_1|\to 0} \zeta_1 = \lim_{|\lambda_1|\to 0} \frac{1-(1-\lambda_1)^{1+\gamma_1}}{\lambda_1(1+\gamma_1)} = 1 \tag{92}$$

and

$$\lim_{|\lambda_2|\to 0} \zeta_2 = \lim_{|\lambda_2|\to 0} \frac{1-(1-\lambda_2)^{1+\gamma_2}}{\lambda_1(1+\gamma_1)} = 1\,. \tag{93}$$

The set of equations (79) to (82) now reduces to

$$-x_1'\beta_1\nu_1 + x_1\beta_1\rho_1 = -Z_1\,, \tag{94}$$

$$x_1'(\psi_1 - \phi_1\nu_1) + x_1(\alpha_1 - \xi_1 + \phi_1\rho_1) = \beta_0\,. \tag{95}$$

Let us consider the case in which the substance does not penetrate the cells, or penetrates them so slowly, relative to the speed of its distribution in the extracellular space, that we may assume that none of the material has entered the cells during the time required for a quasi-steady state to be attained in the extracellular space. Thus we assume that a substance is suddenly introduced into the blood in such a way that its arterial concentration remains constant. Then, if none of the substance was present initially, we have

$$Z_1 = \frac{K\beta_1}{p}; \qquad \beta_0 = 0 \tag{96}$$

where K is the constant arterial concentration.

Solving equations (94) and (95) for x_1 and x_1', using these assumptions, we have

$$x_1' = \frac{K[a_1 - \xi_1 + \phi_1\rho_1]}{p[\nu_1(a_1 - \xi_1 + \phi_1\rho_1) + \rho_1(\psi_1 - \phi_1\nu_1)]}, \tag{97}$$

$$x_1 = -\frac{K[\psi_1 - \phi_1\nu_1]}{p[\nu_1(a_1 - \xi_1 + \phi_1\rho_1) + \rho_1(\psi_1 - \phi_1\nu_1)]}. \tag{98}$$

By our assumptions we have $\sigma_1 \approx \sigma_2 \approx 0$, and we also assume, as before, that $|P_1| < < k_1$ and $|P_2| < < k_2$. Then the denominators of both equations (97) and (98) reduce to

$$p[\nu_1 p + \nu_1\phi_1\rho_1 - \phi_1\rho_1^2]. \tag{99}$$

We also have

$$a_1 - \xi_1 + \phi_1\rho_1 = p + \phi_1\rho_1 \tag{100}$$

and

$$\psi_1 - \phi_1\nu_1 = -\phi_1\rho_1. \tag{101}$$

Using (99), (100), and (101) in (97) and (98), we get

$$x_1' = \frac{K(p + \phi_1\rho_1)}{p[\nu_1 p + \nu_1\phi_1\rho_1 - \phi_1\rho_1^2]} \tag{102}$$

and

$$x_1 = \frac{K\phi_1\rho_1}{p[\nu_1 p + \nu_1\phi_1\rho_1 - \phi_1\rho_1^2]}. \tag{103}$$

Inverting these equations in p by routine methods of the Laplace transformation technique, we have, after some rearrangements,

$$E_1' = K\left\{1 - \frac{\rho_1}{1+\rho_1}\, e^{-t(\phi_1\rho_1)/(1+\rho_1)}\right\}; \tag{104}$$

$$E_1 = K\{1 - e^{-t(\phi_1\rho_1)/(1+\rho_1)}\}. \tag{105}$$

A check on the first of these equations is provided by a comparison of $E_1'(0)$ computed from equation (16) with $E_1'(0)$ computed from (104). Both computations give

$$E_1' = \frac{K}{\nu_1}. \tag{106}$$

We have from (105)

$$\frac{dE_1}{dt} = K\frac{\phi_1\rho_1}{1+\rho_1}\, e^{-t(\phi_1\rho_1)/(1+\rho_1)}, \tag{107}$$

and

$$\frac{dE_1(0)}{dt} = K\frac{\phi_1\rho_1}{1+\rho_1}. \tag{108}$$

Figures 4 and 5 show

$$\frac{1+\rho_1}{\phi_1\rho_1}$$

as a function of Dgl and k_1, respectively, for four values of R. These graphs give the time at which E_1 attains approximately 63% of the capillary concentration K, as well as the ratio of K to $dE_1(0)/dt$.

It may be noted that for a molecule of the weight of glucose, the time constant is 2.1 sec. for $R = 15\mu$, 10 sec. for $R = 30\mu$, 24 sec. for $R = 45\mu$, and 46 sec. for $R = 60\mu$. The time constant for the distribution process, for any fixed R, is markedly dependent on Dgl in the range 10^{-8} to 2×10^{-7} cm.^{2} per sec. and on k_1 in the whole range considered. Thus for

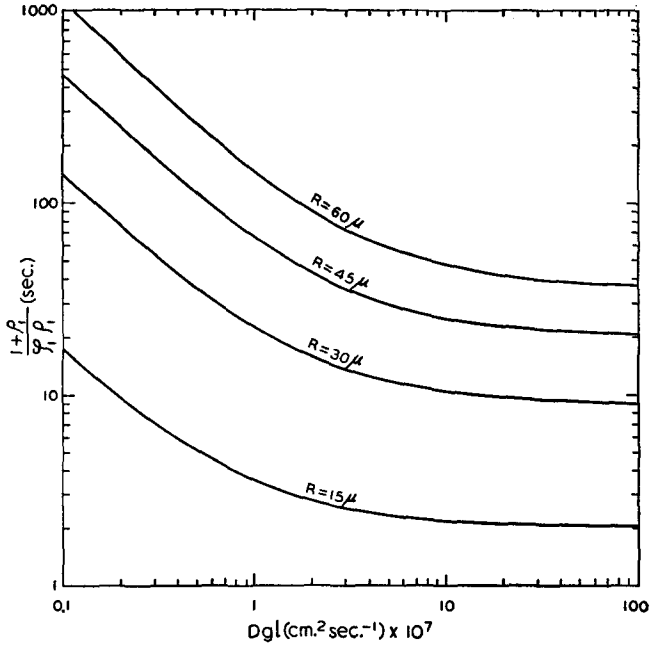

FIGURE 4. Graph of the reciprocal of the time constant of equation (105). Values of parameters are: $af_a = 0.1$; $r_1 = 5 \times 10^{-4}$ cm.; $k_1 = 10^{-4}$ cm. per sec.

molecules as large, or larger than, glucose the distribution time is very much dependent on the characteristics of the extracellular matrix. The permeability of the capillary wall greatly influences the distribution time for substances of any molecular weight.

However, the approximation that λ_1 and λ_2 are negligible compared to unity renders the treatment of doubtful value for more than the very start of the process of distribution, for these approximations, of course, imply that the concentration of the substance is everywhere the same along the length of the capillary and that the amount removed from the

blood is negligible compared to the amount flowing through the capillary in any given interval of time.

X. Discussion and conclusion. The treatment of capillary exchange developed above, while undoubtedly approximate and of limited validity, does indicate that both the diffusion coefficient of the extracellular matrix and the permeability coefficient of the capillary wall are important parameters in the distribution of substances in tissue. Changes in the diffusion

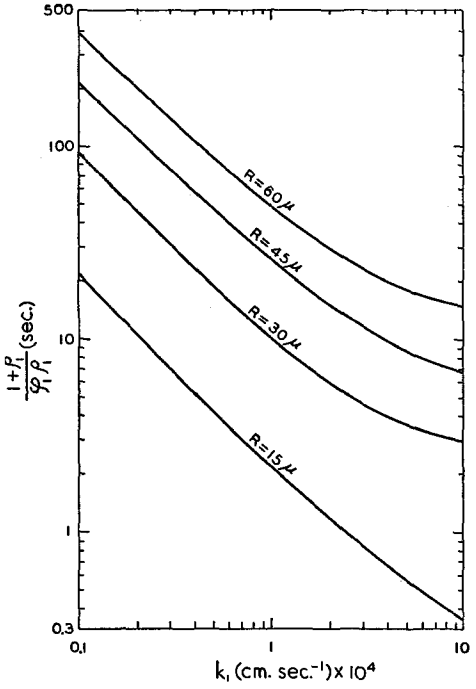

FIGURE 5. Graph of the reciprocal of the time constant of equation (105). Values of the parameters are: $af_a = 0.1$; $r_1 = 5 \times 10^{-4}$ cm.; $Dgl = 10^{-6}$ cm.^{2} per sec.

coefficient of the extracellular material are not so important as changes in the capillary permeability. Both parameters are subject to change, and changes in these parameters are followed by relatively large changes in both the steady state cellular and extracellular concentrations and changes in the initial rate at which a suddenly introduced substance distributes itself. Since the metabolism of cells is undoubtedly influenced greatly by the concentrations within them of various substances, it appears that significant changes in cell metabolism may occur as a result of alterations in either of these parameters.

The consequence of a change in the ratio of the number of true capillaries to the number of a-v capillaries has been investigated only in so far

as this may be correlated with changes in R. It is hoped that a more comprehensive investigation of this problem will form the subject of a later paper.

The writer wishes to acknowledge with gratitude his debt to the staff of the Committee on Mathematical Biology. Professor I. Opatowski has greatly helped the writer in developing the basic ideas which culminated in this work. Professor H. D. Landahl and Dr. George Karreman have, by helpful discussions, contributed considerably. The preparation of the manuscript has been the task of Mrs. Carlton Smith. The writer owes her a debt of gratitude which is difficult to express.

GLOSSARY OF SYMBOLS

A = the activity ratio, the ratio of the total length of all active true capillaries to the total length of all a-v capillaries in a homogeneous tissue, also the ratio of the number of active true capillaries to the number of a-v capillaries in the tissue model

AR = radius of cylinder of tissue associated with each a-v capillary

a = the ratio of the extracellular volume to the total extravascular volume

b = the ratio of the cellular volume to the total extravascular volume

C_0 = the initial intracellular concentration

C_1 = the average intracellular concentration in the region of the a-v capillaries at any time $t > 0$

C_2 = the average intracellular concentration in the region of the true capillaries at any time $t > 0$

D = the diffusion coefficient in the substance of the extracellular space

d_1 = distribution ratio, the ratio of the concentration in the filtrate from the a-v capillaries to the concentration in the protein-free plasma

d_2 = similar to d_1, but for the true capillaries

E_0 = initial extracellular concentration, assumed to be the same everywhere

E_1 = average extracellular concentration in the region of the a-v capillaries at any time $t > 0$

E_2 = average extracellular concentration in the region of the true capillaries at any time $t > 0$

E_1' = extracellular concentration at the wall of the a-v capillary at time $t > 0$

E_2' = extracellular concentration at the wall of the true capillary at time $t > 0$

f_1 = ratio of the volume of the cell-free, protein-free fluid of the blood to the total blood volume in the a-v capillary

$f_{10} = f_1(0)$

f_2 = similar to f_1 but for the true capillary

$f_{20} = f_2(0)$

f_a = ratio of the extracellular volume available for diffusion to the total extracellular volume

f_b = ratio of the cellular volume available for distribution of the substance to the total cell volume

g = ratio of the area normal to the concentration gradient in the extracellular space, through which diffusion may occur, to the total area

h_1 = permeability coefficient of the cell wall for entrance of the substance into the cell

h_2 = permeability coefficient of the cell wall for exit of the substance from the cell

K_0 = initial concentration of the substance in both the a-v and true capillaries, assumed to be constant

K_1 = concentration of the substance in the a-v capillary, $0 \leq x \leq L$, for the time $t > 0$

K_2 = concentration of the substance in the true capillary, $0 \leq z \leq L$, for time $t > 0$

K_{m1} = mean concentration in the a-v capillary for any time $t > 0$

K_{m2} = mean concentration in the true capillary for any time $t > 0$

K_v = venous concentration of the cell-free, protein-free fluid of the blood at any time $t > 0$

k_1 = permeability coefficient of the a-v capillary for exit of substance

k_1' = permeability coefficient of the a-v capillary for entrance of the substance

k_2 = similar to k_1, but for the true capillary

k_2' = similar to k_1', but for the true capillary

L = average length of the a-v and true capillaries, assumed to be equal

l = the ratio of the shortest distance between two points in the tissue to the average distance between the two points which must be traveled while not going through any cell

N = total number of a-v capillaries in an arbitrary volume of a homogeneous tissue

P_1 = product of the filtration coefficient by the net pressure acting across the a-v capillary wall, assumed to be constant along the length of the capillary and greater than zero

P_2 = product of the filtration coefficient by the net pressure acting across the true capillary wall, assumed to be constant along the length of the capillary and less than zero

p = Laplace transformation parameter with respect to t

q_1 = rate of production per unit volume, or rate of consumption per unit volume when concentration in cell is C_0

q_2 = rate of change of consumption with respect to the cellular concentration

R = radius of cylinder of tissue associated with each true capillary

r_1 = radius of the a-v capillary

r_2 = radius of the true capillary

s = average surface area of any cell of a homogeneous tissue

t = time

v = average cell volume

v_1 = velocity of the blood in the a-v capillary

v_2 = velocity of the blood in the true capillary

$v_{10} = v_1(0)$
$v_{20} = v_2(0)$
w_1 = Laplace transform of K_1
w_2 = Laplace transform of K_2
w_{m1} = Laplace transform of K_{m1}
w_{m2} = Laplace transform of K_{m2}
$w_0 = w_1(0,p) = w_2(0,p)$
x_1 = Laplace transform of E_1
x_1' = Laplace transform of E_1'
x_2 = Laplace transform of E_2
x_2' = Laplace transform of E_2'
y_1 = Laplace transform of C_1
y_2 = Laplace transform of C_2
z = distance along either a-v or true capillary, measured from arterial end

$$a_1 = p + \xi_1 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2}, \qquad a_2 = p + \xi_2 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2}$$

$$\beta_0 = E_0\left\{1 + \frac{C_0}{E_0}\frac{bf_b}{af_a}\frac{\sigma_2\left(p + \frac{\omega}{C_0}\right)}{p\,(p + \sigma_2 - q_2)}\right\}$$

$$\beta_1 = p - \frac{2}{r_1}(P_1 - d_1P_1 - K_1) = \frac{2P_1}{r_1}\gamma_1, \qquad \beta_2 = p - \frac{2}{r_2}(P_2 - k_2) = \frac{2P_2}{r_2}\gamma_2$$

$$\gamma_1 = \frac{r_1}{2P_1}\left[p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1)\right], \qquad \gamma_2 = \frac{r_2}{2P_2}\left[p - \frac{2}{r_2}(P_2 - k_2)\right]$$

$$Z_1 = \left(w_0 - \frac{K_1}{\beta_1}\right)\zeta_1\beta_1 + K_0, \qquad Z_2 = \left(w_0 - \frac{K_0}{\beta_2}\right)\zeta_2\beta_2 + K_0$$

$$\zeta_1 = \frac{1 - (1 - \lambda_1)^{1+\gamma_1}}{\lambda_1(1 + \gamma_1)}, \qquad \zeta_2 = \frac{1 - (1 - \lambda_2)^{1+\gamma_2}}{\lambda_2(1 + \gamma_2)}$$

$$\lambda_1 = \frac{2P_1L}{r_1f_{10}v_{10}}, \qquad \lambda_2 = \frac{2P_2L}{r_2f_{20}v_{20}}$$

$$\mu_1 = \frac{2k_1'}{r_1}, \qquad \mu_2 = \frac{2(k_2' - d_2P_2)}{r_2}$$

$$\nu_1 = \frac{k_1' + \frac{2Dgl}{AR}}{k_1 + d_1P_1}, \qquad \nu_2 = \frac{k_2' - d_2P_2 + \frac{2Dgl}{R}}{k_2}$$

$$\xi_1 = \frac{4Dgl}{af_a(A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right), \qquad \xi_2 = \frac{4Dgl}{af_a(R^2 - r_2^2)}\left(\frac{1}{A+1}\right)$$

$$\rho_1 = \frac{2Dgl}{AR(k_1 + d_1P_1)}, \qquad \rho_2 = \frac{2Dgl}{Rk_2}$$

$$\sigma_1 = \frac{bsh_1}{af_a v}, \qquad \sigma_2 = \frac{sh_2}{vf_b}$$

$$\phi_1 = \frac{2r_1(k_1 + d_1P_1)}{af_a(A^2R^2 - r_1^2)}, \qquad \phi_2 = \frac{2r_2k_2}{af_a(R^2 - r_2^2)}$$

$$\psi_1 = \frac{2r_1k_1'}{af_a(A^2R^2 - r_1^2)}, \qquad \psi_2 = \frac{2r_2(k_2' - d_2P_2)}{af_a(R^2 - r_2^2)}$$

$$\omega = q_1 - q_2C_0$$

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