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Circ Res. 1970;27:739-764
doi: 10.1161/01.RES.27.5.739
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571

Capillary Exchange Modeling

BARRIER-LIMITED AND FLOW-LIMITED DISTRIBUTION

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ABSTRACT

In the well-perfused visceral organs, active flow occurs in most capillaries, and they are packed closely. In this situation, lateral diffusion equilibration is relatively rapid and the distribution of exchanging materials is governed chiefly by the permeability of the capillary walls. We modeled extravascular distribution of exchanging substances from this kind of capillary and illustrated the changes expected in the outflow profile with increasing permeability, the evolution from the barrier-limited to the flow-limited case. We then examined the two extremes of the assemblies of such capillaries in an organ. In one, the large-vessel transit times are constant and the capillary transit times account for the outflow distribution of the vascular reference substance; in the other, the capillary transit times are constant but the large-vessel transit times vary. The barrier-limited and flow-limited cases corresponding to these are very different. In the case intermediate between these two extremes, the transit times in both the large vessels and the capillaries in the organs vary. If the organ is functionally homogeneous, the distribution of capillaries supplied by each large vessel is the same, and the situation may be described by a product distribution. The formulation for this intermediate case may then be used both to quantify capillary permeability and to describe the distributions of large-vessel and capillary transit times.

ADDITIONAL KEY WORDS

multiple indicator dilution method
transcapillary exchange
diffusible indicators
capillary permeability
well-perfused visceral organs
spatially distributed models
assemblies of large-vessel transit times
assemblies of capillary transit times

■ Physiologists have long used models of the exchange of materials in capillaries to provide a basis for interpreting experimental data and as a means of obtaining a quantitative description of the factors important in this exchange. This description is valid only so long as the model used is an accurate reflection of the experimental situation. Our purpose in this paper is to model the characteristics of transcapillary exchange in a barrier-limited capillary and to explore how variations in the lengths of such capillaries would be expected to affect observations derived from a whole organ. We define a barrier-limited capillary as one which is surrounded by a small volume of tissue, with a depth such that the material which enters this space immediately equilibrates within it in a direction perpendicular to the capillary. This kind of equilibration is a physical possibility in the well-perfused visceral organs, because of the size ranges and times involved (1), but it could not occur in poorly perfused tissues such as skin and resting muscle, where the diffusion

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This work was supported by the Medical Research Council of Canada and the Quebec Heart Foundation and a special grant from the Elliott-Cerini Foundation. Dr. Ziegler is the recipient of a Fellowship from the Medical Research Council of Canada.

Received December 30, 1969. Accepted for publication August 10, 1970.

distances are large. We describe how the characteristics of the exchange vary as the permeability of the capillary to the indicator increases, and particularly examine the approach to the case in which the permeability becomes so large that the equilibration between intravascular and extravascular concentrations occurs at each point along the length. We then use this model of a single capillary in conjunction with two well-defined distributions of capillary transit times in an organ, which represent extremes in the possible spectrum, to demonstrate how these distributions contribute to the shapes of tracer outflow concentration curves for a "diffusible" substance (i.e., one which exchanges across the capillary walls) and for its appropriate reference substance (one which is distributed in the same phase of blood as is the diffusible indicator and which is confined to the vessels during its transit through the organ). We examine how the shapes of the outflow curves for diffusible substances change as we use indicator substances for which the capillary permeability is progressively greater. Finally we proceed from these cases to a more general model of the distribution of capillary and large-vessel transit times in well-perfused organs.

We have oriented the description of this modeling in such a fashion as to facilitate its use in the interpretation of the results of multiple indicator dilution experiments (2). In these, a diffusible tracer and its reference are injected simultaneously and normalized outflow dilution curves are obtained. The results of our modeling will be directly applicable to such experiments if we assume that the displacements between the outflow patterns of the two substances result solely from the passage of a portion of the diffusible substance across the capillary walls into an extravascular space, where it sojourns for a while before returning to the capillary.

Lumped Models

Three lumped models of a capillary with varying permeability which have been quoted and used extensively in the past bear upon the present modeling and therefore deserve review and comment prior to formulation of the model we wish to present, a spatially distributed model of a capillary with limitation in permeability at the wall. In none of these has length been explicitly defined as a variable. In each case, therefore, the model has been defined by an ordinary differential equation.

1. *Kety's Model.*—Kety treated as a single element a capillary together with the adjacent tissue with which the diffusible material exchanges (3). Consider that Q_r is the total amount of diffusible material in the region; F_c is the flow of blood in the capillary; C_a, C_v, and C_r are arterial, venous, and regional concentrations; and t is time. Then, by use of the Fick equation

$$\frac{dQ_r}{dt} = F_c(C_a - C_v). \qquad (1)$$

To calculate F_c without measuring directly the rate of accumulation of material, Kety defines the unmeasured concentration, C_r, in the region (the quotient of Q_r and the volume of tissue including blood, V_r) to be the product of the measured venous concentration and the average ([tissue including blood]/blood) partition coefficient λ_r, i.e.,

$$C_r = Q_r/V_r = \lambda_r C_v. \qquad (2)$$

This relation corresponds to the assumption that there is a single value for C_r over the whole tissue region at any one time (i.e., nowhere in the tissue will there be concentration gradients). Equation 1 becomes, on substitution, a first-order ordinary differential equation and the outflow response to the sudden introduction of an amount of material q_0 is consequently defined to be

$$C_v(t) = \frac{q_0}{\lambda_r V_r} e^{-(F_c/\lambda_r V_r)t}. \qquad (3)$$

A substance confined to the vascular space will not behave like this. It will travel along the capillary with a finite velocity and will emerge after a transport lag (4). Physically, the diffusible indicator can behave in the way described by equation 3, as a single "washout" with no appearance lag, only if there is instantaneous equilibration of the material

both along the length of the capillary and in the lateral direction (5).

For our present paper, the more pertinent part of the Kety modeling is the attempt to deal with nonequilibration. He introduced a new constant, m, defined as the extent to which "equilibration" between blood and tissue is achieved, in such a manner that

$$\frac{dQ_v}{dt} = F_c\, m\, (C_a - C_v). \qquad (4)$$

The attempt to introduce a permeability phenomenon in this way is internally inconsistent with the implication of equation 2 that diffusion is everywhere instantaneous and that there exists a single C_v. The use of the constant m cannot change the Kety model in any essential way. When the implications of restricted capillary permeability are considered in detail, it is apparent that diffusion equilibration cannot everywhere be instantaneous, and that to achieve a complete description of the system one must use a spatially distributed model, i.e., the equations must be partial differential equations.

2. *Models of Renkin and of Crone.*—These authors modeled the loss of diffusible material from a single capillary (6, 7). They assumed that diffusible material which had left the capillary was immediately and completely sequestered, so that none of it could return to the capillary lumen and that the rate of loss of this material was proportional to the remaining concentration at each point. From these assumptions they showed that

$$C_v = C_a\, e^{-\frac{PS_c}{F_c}}, \qquad (5)$$

where P is the permeability in cm • sec^{-1}, and S_c is the surface area of the capillary in cm^2.

In each case they applied the results of this final common equation to data acquired from whole organs, and the implicit assumption underlying this application is that the transit time through each capillary is the same. Renkin compared the concentrations of ^{42}K at the outflow from an isolated perfused muscle to that at its inflow during steady infusion. Crone, on the other hand, recognized that the dispersing characteristics of the circulation through an organ are such that it is logical to compare the effluent concentrations of diffusible label with that of a simultaneously injected reference substance, as Chinard et al. (2) had done. To use the above relation, he set the outflow concentration of the reference substance equal to C_a, that of the diffusible substance equal to C_v, and computed a value for extraction E (i.e., $[C_a\text{-}C_v]/C_a$) for each sample; and from this using the equivalent form of equation 5,

$$PS_c = F_c \ln\left(\frac{1}{1\text{-}E}\right), \qquad (5A)$$

a value PS_c for each sample. Crone expressed the opinion that material which did leave the capillary would return later in time (even though the return was not permitted in his modeling) and that consequently more reliable values for PS_c would be obtained from the early parts of the curve, from appearance to peak, when the proportion of returning material would be expected to be small. He showed data on the brain in which the extraction was approximately constant in the region from appearance to peak (8). More recently, Alvarez and Yudilevich (9) have tried to refine this comparison procedure by examining the ratio of the diffusible to reference substance over only the very earliest parts of the curves, i.e., by utilizing only the initial samples containing diffusible and reference substances. We shall examine the implications of these maneuvers during the development of our own modeling.

It is apparent that this model of permeability-limited distribution from a single capillary is not complete, since the return of material to the lumen has been neglected. We therefore formulate here a spatially distributed model of a capillary, which includes this return. Our model is not general in that we describe a special case, a capillary situated in a well-perfused organ.

A Distributed Model

Derivation of the Equations for a Single Capillary.—The model to be described may be termed a barrier-limited capillary with no

longitudinal diffusion. Transport along the capillary is assumed to occur only as the result of bulk flow along the capillary. The capillary is assumed to be situated in a well-perfused organ, one with a dense capillary network in which there is flow in all of the capillaries. The half distance between the capillaries is assumed to be so small that the time for equilibration of the concentration of diffusible substance in the lateral direction is a negligible fraction of the time of transit along the capillary, i.e., that the diffusible substance in the extravascular space equilibrates virtually instantaneously in the lateral direction. There will therefore be considered to be no diffusion gradient in the extravascular space perpendicular to the capillary. It is to be noted that this model will have possible application only in the well-perfused visceral organs. It could not be applied to poorly perfused tissues, such as skin or resting skeletal muscle, where there must be a diffusion gradient in the extravascular space, because of the large intercapillary distances and the large number of capillaries in which there may be no flow.

Consider a capillary of length L in which blood flows with a velocity W, which is enfolded by an extravascular space and separated from it by a permeability barrier at the wall. Because of the assumed instantaneous lateral equilibration within the extravascular space, this permeability limitation will be the dominating feature of the model. Now let

$u(x,t)$ = the concentration in the capillary at some point along the length x at time t;
$z(x,t)$ = the concentration in the extravascular space at some point along the length x at time t;
A = the volume per unit length for the capillary;
B = the volume per unit length for the extravascular space, A and B be constant along the length;
$B/A = \gamma$, and
λ = the partition coefficient for the diffusible substance in extravascular tissue to that in the reference vascular fluid at equilibrium, as suggested by Perl and Chinard (5). Note that the λ is not being used in the same sense as it was by Kety, where it was the average ([tissue including blood]/blood) partition coefficient.

We can then formulate, in the manner outlined in reference 4, an equation of mass continuity

$$\frac{\partial u}{\partial t} + W\frac{\partial u}{\partial x} + \gamma\frac{\partial z}{\partial t} = 0. \qquad (6)$$

We must now assume a rate equation describing the exchange of materials across the capillary wall. In the past this exchange has always been regarded as passive. More recently, Crone has demonstrated that in cerebral capillaries initial tracer glucose efflux rates demonstrate a saturation phenomenon (10), and that there is a stereospecificity of glucose efflux, the D-isomer leaving at an appreciable rate, the L-isomer not leaving at all during one passage through the brain (personal communication). The possibility exists that a concentrative membrane carrier transport system will be described in a capillary in the future (11). Both for this reason and for convenience in our later development, we have used two rate constants, a k_1 for efflux and a k_2 for influx. Using procedures analogous to those in reference 12 we find

$$\frac{\partial z}{\partial t} - k_1 u + k_2 z = 0. \qquad (7)$$

The assumption underlying the development of this equation is that the unidirectional flux is, in each instance, proportional to the concentration rather than the amount of material in the compartment from which it originates. If the concentration dependence of influx and efflux is the same, and a single rate constant, k, can then be used in the kinetic description, equation 7 becomes

$$\frac{\partial z}{\partial t} - ku + \frac{kz}{\lambda} = 0. \qquad (7A)$$

Alternatively, we may use the PS_e notation to derive an equation analogous to that developed by Renkin and Crone. Assume that the diffusible substance enters and leaves the

capillary passively and that BL is the volume of the extracellular space. Then we find

$$\frac{\partial z}{\partial t} - \frac{PS_c}{BL}\left(u - \frac{z}{\lambda}\right) = 0. \qquad (7B)$$

Whence the equivalent forms of the rate constants in the equations 7 are

$$k_1 = k = PS_c/BL; \text{ and } k_2 = k/\lambda. \qquad (7C)$$

Solution of the Equations for a Single Capillary.—Eliminating z from equations 6 and 7 we find

$$\frac{\partial^2 u}{\partial t^2} + W\frac{\partial^2 u}{\partial x \partial t} + (k_1\gamma + k_2)\frac{\partial u}{\partial t} + k_2 W\frac{\partial u}{\partial x} = 0. \qquad (8)$$

Now apply the Laplace operator with respect to time,

$$L[f(x,t)] = \int_0^\infty f(x,t)\, e^{-st}\, dt = \bar{F}(x,s).$$

The transformed equation becomes

$$\frac{d\bar{U}(x,s)}{\bar{U}(x,s)} = \frac{-[s^2 + (k_1\gamma + k_2)s]\, dx}{W(s + k_2)},$$

whence

$$\bar{U}(x,s) = \bar{U}(0,s)e^{-\frac{sx}{W}\frac{(s + k_2 + k_1\gamma)}{(s + k_2)}}. \qquad (9)$$

Assume that into the initially empty capillary of length L a quantity of diffusible material is suddenly introduced at the time 0+ and at the end $x = 0$. Then

$$\bar{U}(0,s) = \frac{q_0}{F_c}$$

and

$$\bar{U}(x,s) = \frac{q_0}{F_c}\, e^{-\frac{sx}{W}\frac{(s + k_2 + k_1\gamma)}{(s + k_2)}}. \qquad (10)$$

We will now examine four cases:

I. $k_1 = k_2 = 0$. This case corresponds to the appropriate reference substance, a substance which does not leave the capillary and is distributed in blood in the same way as is the diffusible substance.

$$\bar{U}(x,s) = \frac{q_0}{F_c}\, e^{-\frac{sx}{W}}. \qquad (11)$$

The term $\exp(-sx/W)$ introduces only a time displacement, a transport lag. The solution to this case is therefore

$$u(x,t) = \frac{q_0}{F_c}\,\delta\left(t - \frac{x}{W}\right). \qquad (11A)$$

The reference material propagates along the capillary with the velocity of flow and emerges at the time $t = L/W$, as an undistorted impulse function, in this model. This time is termed the capillary transit time, τ.

II. k_1 finite. $k_2 = 0$. In this case, none of the diffusible material returns from the extravascular space. All the material which enters the extravascular space is sequestered or metabolized there.

$$\bar{U}(x,s) = \frac{q_0}{F_c}\, e^{-\frac{k_1\gamma x}{W}}\, e^{-\frac{sx}{W}}. \qquad (12)$$

$$u(x,t) = \frac{q_0}{F_c}e^{-k_1\gamma\frac{x}{W}}\;\delta\left(t - \frac{x}{W}\right). \qquad (12A)$$

The output from the end of the capillary is

$$u(L,t) = \frac{q_0}{F_c}e^{-k_1\gamma\tau}\,\delta(t - \tau). \qquad (12B)$$

The output is a damped wave, emerging at the time of transit of the capillary. The material which emerges at the outflow consists only of throughput material, material which has not left the capillary.

Now let us examine the solution when the permeability notation has been used. Then

$$u(L,t) = \frac{q_0}{F_c}\, e^{-\frac{PS_c\gamma\tau}{BL}}\,\delta(t - \tau).$$

The ratio $AL/\tau = F_c$, the flow rate through the capillary, and hence

$$u(L,t) = \frac{q_0}{F_c}e^{-\frac{PS_c}{F_c}}\;\delta(t - \tau). \qquad (13)$$

The following relation between the diffusible substance and the reference substance results, in this case:

$$\frac{u(L,t)_{diff}}{u(L,t)_{ref}} = e^{-\frac{PS_c}{F_c}}. \qquad (14)$$

This case is the one Crone examined. The last equation is the form he used to examine his data, the comparison of simultaneously ob-

served normalized outflow concentrations for the diffusible and reference substances (7). The ratio of these concentrations, at the end of a single barrier-limited capillary, is indeed $\exp(-PS_c/F_c)$, when none of the exchanging material returns to the capillary lumen. Note that it may be difficult to apply the expression in this form to a dilution curve if the capillaries in the organ being examined vary in length and therefore in surface area.

III. k_1 and k_2 both finite.

$$\overline{U}(x,s) = \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}}\left(\frac{r}{r+k_2}\right)$$

$$= \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}}\left(1-\frac{k_2}{r+k_2}\right)$$

$$= \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}}\, e^{\frac{k_1\gamma k_2 x/W}{(r+k_2)}} \cdot (15)$$

Now expand the last term on the right, using Maclaurin's series. Then

$$\overline{U}(x,s) = \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}}\left[1+\frac{k_1\gamma k_2 x/W}{1!\,(s+k_2)}+\frac{(k_1\gamma k_2 x/W)^2}{2!\,(s+k_2)^2}+\ldots\right]$$

or

$$\overline{U}(x,s) = \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}} + \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}} \sum_{n=1}^{\infty} \frac{(k_1\gamma k_2 x/W)^n}{n!(s+k_2)^n} \cdot (16)$$

Noting that the inverse Laplace transform

$$L^{-1}\left(\frac{1}{(s+a)^n}\right) = \frac{1}{(n-1)!} t^{n-1} e^{-at},$$

we find

$$u(x,t) = \frac{q_0}{F_c} e^{-k_1\gamma\frac{x}{W}} \delta\left(t-\frac{x}{W}\right) + \frac{q_0}{F_c} e^{-k_1\gamma\frac{x}{W}} \sum_{n=1}^{\infty} e^{-k_2(t-x/w)} \frac{(k_1\gamma k_2 x/W)^n (t-x/W)^{n-1}}{n!\quad (n-1)!} S(t-x/W), \qquad (17)$$

where $S(t-x/W)$ is a step function at time $t=x/W$, so that $u(x,t)=0$ for $t<x/W$. At the outflow from the capillary,

$$u(L,t) = \frac{q_0}{F_c} e^{-k_1\gamma\tau}\ \delta(t-\tau) + T(L,t),$$

where

$$T(L,t) = \frac{q_0}{F_c} e^{-k_2 t}\ e^{-\tau(k_1\gamma-k_2)} \sum_{n=1}^{\infty} \frac{(k_1\gamma k_2\tau)^n\ (t-\tau)^{n-1}}{n!\quad (n-1)!} S(t-\tau). \quad (17A)$$

The step function will be carried forward implicitly in the rest of the development but will not be written.

The first term on the right-hand side of equation 17A is an impulse function delayed by time τ, and damped by $\exp(-k_1\gamma\tau)$. The exponent in the damping factor is the product of the efflux rate constant k_1, the ratio of the volume of the extravascular space to the volume of the intravascular space, and the transport lag τ. This first term is the solution to case II, and once again it represents material which has arrived at the outflow without traversing the capillary barrier. The second term is an infinite series. It represents material which has left the capillary and later returned, and which then has emerged at the outflow. For the sake of brevity we shall call the first term a spike and the second term, $T(L,t)$, a tail function. The tail function in equation 17A may also be transformed so that it includes a first order modified Bessel

function as follows:

$$T(L,t) = \frac{q_0}{F_c} e^{-k_2 t} \, e^{-\frac{L}{W}(k_1\gamma - k_2)} \, k_1\gamma k_2 \frac{L}{W} \sum_{n=0}^{\infty} \frac{1}{n!\,(n+1)!} \left(k_1\gamma k_2 \frac{L}{W}\left(t - \frac{L}{W}\right)\right)^n$$

$$= \frac{q_0}{F_c} e^{-k_2 t} \, e^{-\frac{L}{W}(k_1\gamma - k_2)} \, k_1\gamma k_2 \frac{L}{W} \left(\sqrt{k_1\gamma k_2 \frac{L}{W}\left(t - \frac{L}{W}\right)}\right)$$

$$\frac{2\sqrt{k_1\gamma k_2 \frac{L}{W}\left(t - \frac{L}{W}\right)}}{2} \sum_{n=0}^{\infty} \frac{1}{n!\,(n+1)!} \left(\frac{2\sqrt{k_1\gamma k_2 \frac{L}{W}\left(t - \frac{L}{W}\right)}}{2}\right)^{2n}$$

$$= \frac{q_0}{F_c} e^{-k_2 t} \, e^{-\frac{L}{W}(k_1\gamma k_2)} \sqrt{\frac{k_1\gamma k_2 \frac{L}{W}}{t - \frac{L}{W}}} \, \mathrm{I}_1\left(2\sqrt{k_1\gamma k_2 \frac{L}{W}\left(t - \frac{L}{W}\right)}\right); \qquad (18)$$

where $\mathrm{I}_1(y)$ is a modified first-order Bessel function, with argument y.

In the permeability notation

$$u(L,t) = \frac{q_0}{F_c} e^{-\frac{PS_c}{F_c}} \delta(t-\tau)$$

$$+ \frac{q_0}{F_c} e^{-\frac{PS_c}{F_c}\frac{1}{\lambda\gamma}\frac{t}{\tau}} e^{-\frac{PS_c}{F_c}\left(1-\frac{1}{\lambda\gamma}\right)} \sqrt{\frac{\left(\frac{PS_c}{F_c}\right)^2 \frac{1}{\lambda\gamma}\frac{1}{\tau}}{t-\tau}} \, \mathrm{I}_1\left(2\sqrt{\left(\frac{PS_c}{F_c}\right)^2 \frac{1}{\lambda\gamma}\left(\frac{t}{\tau} - 1\right)}\right). \qquad (19)$$

When the rate constants k_1 and k_2 are small (i.e., when the permeability is relatively small), the tail function may be computed as in equation 17A or equations 18 and 19. In the latter case, the ordinary series definition of the Bessel function is adequate. However, when the rate constants k_1 and k_2 are large and the value of the argument y in the Bessel function $\mathrm{I}_1(y)$ is greater than 12, these forms fail to converge quickly. The tail function is then best computed by using the asymptotic form of the Bessel function. For the convenience of the reader the two forms of the Bessel function are displayed below:

$$\mathrm{I}_1(y) = y/2 + \frac{(y/2)^2}{1!\;2!} + \frac{(y/2)^8}{2!\;3!} + \ldots$$

$$= \frac{e^y}{\sqrt{2\pi y}} \left(1 + \frac{(4-1)}{4y \cdot 1} + \frac{(4-1)\;(4-9)}{(4y)^2 \cdot 2} + \frac{(4-1)\;(4-9)\;(4-25)}{(4y)^3 \cdot 3} + \ldots \right).$$

The model solved here has been examined by others. Sangren and Sheppard examined the same problem, and offered a solution (13). Their final equation for the impulse response contains an error. Sheppard subsequently rectified this error in his book (14) and provided a solution which is reproduced by equations 17 and 18.

The physical implications of this model have not previously been elucidated. In the present paper three new aspects in particular are explored: the kinds of physiological situation in which the model may be applicable, the approach of the model to the flow-limited case as the permeability of the capillary is increased, and the use of the single capillary model in multicapillary modeling to provide a basis for examining the problem of whether the modeling can be used to interpret the data from multiple indicator dilution

experiments carried out in well-perfused organs.

IV. k_1 and k_2 both approach infinity. Assume that k_1 and k_2 approach infinity while the ratio k_1/k_2 remains constant and that the value of s in the denominator of the exponent of equation 10 may be neglected as k_2 approaches infinity. Then

$$\bar{U}(x,s) = \frac{q_0}{F_c} e^{-\left(1+\frac{k_1\gamma}{k_2}\right)\frac{sx}{W}}. \qquad (20)$$

At the end of the capillary

$$u(L,t) = \frac{q_0}{F_c}\,\delta\left(t - \left[1+\frac{k_1\gamma}{k_2}\right]\tau\right). \qquad (21)$$

This asymptote of the barrier-limited permeability spectrum is the flow-limited case we described previously (4). In this case the diffusible substance travels along the capillary as a delayed wave. Whereas the reference travels as an impulse with a velocity W, the diffusible substance travels as an impulse with the velocity $W/\left(1+\frac{k_1\gamma}{k_2}\right)$.

Conservation of Matter in a Single Capillary.—If our mathematical formulations are correct, we should be able to show from the analytical solution for the outflow concentration of the diffusible substance that the total amount of material leaving the system is q_0. The equation describing this is

$$F_c\int_0^\infty u(L,t)\ dt = F_c\,\frac{q_0}{F_c}\int_0^\infty e^{-k_1\gamma t}\,\delta(t-\tau)\ dt + F_c\int_0^\infty T(L,t)\ dt$$

$$= q_0\ e^{-k_1\gamma\tau} + F_c\int_0^\infty T(L,t)\ dt.$$

Now

$$\int_0^\infty T(L,t)\ dt = \frac{q_0}{F_c}\,e^{-\tau(k_1\gamma-k_2)}\sum_{n=1}^{\infty}\frac{(k_1\gamma k_2\tau)^n}{n!\ (n-1)!}\int_\tau^\infty e^{-k_2 t}\ (t-\tau)^{n-1}\ dt$$

$$= \frac{q_0}{F_c}\left(1-e^{-k_1\gamma\tau}\right).$$

Hence, as expected

$$F_c\int_0^\infty u(L,t)\ dt = q_0. \qquad (22)$$

Mean Transit Time along the Single Capillary, for Reference and Diffusible Substance.—Zierler, reasoning from the general approach of moments, has predicted that if all of the outflow curve for a diffusible substance is accessible experimentally, the volume calculated for that substance will represent its volume of distribution, and this volume will be independent of the permeability of the capillary (15). If our mathematical formulations are correct, the special case which we have studied will fulfill these requirements. The mean transit time through each capillary is defined to be, for each substance,

$$t_c = \frac{F_c\int_0^\infty tu(L,t)\ dt}{F_c\int_0^\infty u(L,t)\ dt}.$$

The denominator is seen on inspection to be q_0. Hence, for the reference substance

$$t_{c_{ref}} = \frac{F_c}{q_0}\int_0^\infty \frac{q_0}{F_c}\,t\ \delta(t-\tau)\ dt = \tau. \qquad (23)$$

For the diffusible substance

$$t_{c_{diff}} = \frac{F_c}{q_0}\int_0^\infty \frac{q_0}{F_c} t\, e^{-k_1\gamma\tau}\,\delta(t-\tau)\,dt + \frac{F_c}{q_0}\int_0^\infty t\; T(L,t)\;dt.$$

The second integral is

$$\int_0^\infty t\; T(t)\;dt = \frac{q_0}{F_c} e^{-\tau(k_1\gamma - k_2)} \sum_{n=1}^{\infty} \frac{(k_1\gamma k_2\tau)^n}{n!\;\;(n-1)!}\int_\tau^\infty t\, e^{-k_2 t}\;(t-\tau)^{n-1}\,dt.$$

Whence

$$t_{c_{diff}} = \tau + \frac{k_1\gamma\tau}{k_2}\ . \qquad (24)$$

The difference between the transit times of the diffusible and reference substances is $k_1\gamma\tau/k_2$; in the passive case, when $\lambda = 1.0$, and $k_1 = k_2$, it is $\gamma\tau$. The corresponding vascular volume of distribution V_c is $F_c\tau$; the pericapillary extravascular volume of distribution, $F_c k_1\gamma\tau/k_2$; and in the passive case, where $k_1 = k$, and $k_2 = k/\lambda$, the latter is $F_c\lambda\gamma\tau = BL$, as expected. The calculated extravascular volume is independent of the permeability of the capillary for all cases other than zero permeability. The flow F_c used to calculate this volume should correspond to the phase of distribution of the diffusible substance in blood. If it is plasma, F_c should be a flow of plasma; and if it is blood water, F_c should be a water flow.

Change in the Outflow Profile from the Single Capillary as Substances with Increasing Permeability are Examined.—The outflow profile of a diffusible substance from a single barrier-limited capillary consists of a damped impulse function, which emerges at the capillary transit time τ, followed by a tail function which is spread out in time. Prior to the time τ, nothing appears at the outflow. The tail function is zero until the time τ, becomes finite thereafter, and contains two major terms, a decreasing exponential $\exp(-k_2 t)$ and a first-order modified Bessel function, a function which increases progressively as the value of the argument increases. The area under the impulse function decreases, as dictated by the damping term, as a substance is introduced to which the capillary is more permeable. Although it is obvious that the area under the tail function simultaneously increases, it is difficult to perceive how this function changes in form. We have therefore computed a series of numerical examples to illustrate this change in form. We have used two different values of the γ ratio, 3.0 and 10.0; λ is assumed to be 1.0 and $k_1 = k_2 = k$. The value $\gamma = 3.0$ corresponds roughly to that which would be found in a solid visceral organ for an extracellular substance such as sucrose; and the value $\gamma = 10.0$ corresponds to the value for a substance such as labeled water, which would distribute into the total water of the organ. Capillaries with equivalent permeabilities are compared in these two instances, i.e., the damping factors in the first terms of equations 17 and 19, $\exp(-k_1\gamma\tau)$ and $\exp-(PS_c/F_c)$, are made equal. In each of the two corresponding cases $k_1\gamma = PS_c/V_c$; and so when γ is changed, k_1 is changed reciprocally to preserve the value of PS_c/V_c. When the capillary is a right circular cylinder of radius r, $S_c = 2\pi rL$, $V_c = \pi r^2 L$, and $k_1\gamma = 2P/r$.

Figure 1 illustrates the results of these computations. The top panels correspond to the case in which $k = 0$. The reference impulse emerges at the normalized transit time 1.0 with undiminished area and there is, of course, no tail function. In the lower panels the mean transit time of the diffusible substance is fixed by the value for γ. When the major proportion of the outflow profile is localized to the spike, the tail function has a large dispersion and appears as a low magnitude single exponential with a large time constant. As the permeability is increased the proportion of the output emerging as the damped spike diminishes progressively until it becomes an insignificant fraction. The tail

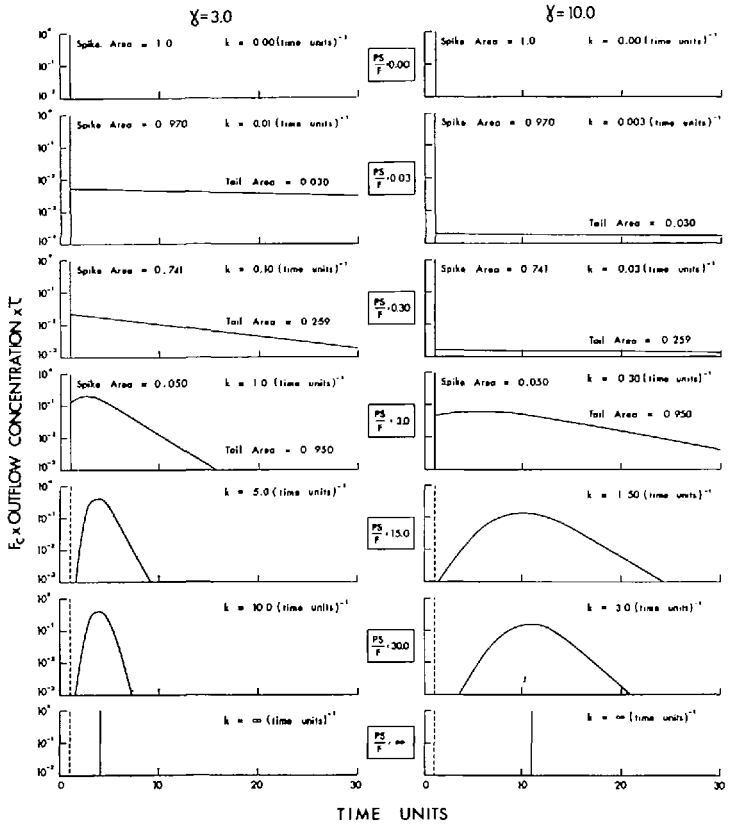

FIGURE 1

Outflow profile for substances undergoing passive barrier-limited distribution in response to a unit input. The profiles are normalized so that the area under each is unity. The abscissa is normalized to t/τ, and the ordinate correspondingly becomes $F_o\tau\ u(L,t)$. The abscissa scale is linear; the ordinate scale, logarithmic. Separate sets of data are displayed for the γ values 3.0 and 10.0. In each case, capillaries with equal PS_c/F_o values are displayed in these semilogarithmic plots. The time scale is t/τ. The permeability values increase from the top to the bottom of the illustration, and the lowest panels display the asymptotic case, flow-limited distribution. The first part of the illustrated output, in the cases with low permeability, is an impulse function with a normalized area, $\exp(-PS_c/F_o)$. It is difficult to illustrate this form, which theoretically has an infinitely large magnitude and infinitesimally small duration. We have simply placed a vertical line at the site of the function and have placed on the illustration a number representing its normalized area. When the spike area is less than 0.01 of the total, we have used a broken rather than a solid line.

function reshapes into a peaked function with less and less dispersion and finally asymptotes to the flow-limited case, a spike of unit area, at the normalized abscissal time $(1+\gamma)$. The time of the peak of the tail function is imperceptibly different from that of the initial spike until a preponderant part of the area is localized to the tail function. The peak then begins to shift to the right in time, to increase in magnitude, and to approach the position of the delayed impulse function.

In the experimental situation, if the permeability is very low, the low magnitude exponential tail function may not be easily resolvable and the outflow profile may appear to consist only of an impulse at the time τ with area $\exp(-k_1\gamma\tau)$. Chinard et al., in their multiple indicator dilution studies in the kidney, observed low recoveries at the outflow of labeled albumin with respect to labeled red cells when they considered only the early extrapolated parts of the curves (16). A mechanism such as the one we have just described may account for their observations when it is distributed over the whole labeled albumin dilution curve.

Form of the Concentration Profile within the Capillary and within the Extravascular Space.—The outflow profile is the result of what has occurred previously in time along the length of the capillary. To gain some understanding of these events, it is appropriate to examine the concentration profiles within the capillary and the extravascular space. We must first develop an expression for $z(x,t)$. Applying the Laplace transformation to equation 7 we find

$$\bar{Z}(x,s) = \frac{k_1 \bar{U}(x,s)}{(s+k_2)} \qquad (25)$$

Substituting the expression for $\bar{U}(x,s)$ from equation 25, we find

$$\bar{Z}(x,s) = \frac{k_1}{(s+k_2)} \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}} e^{\frac{k_1\gamma k_2 x/W}{s+k_2}}$$

$$= k_1 \frac{q_0}{F_c} e^{-\frac{sx}{W}} e^{-k_1\gamma\frac{x}{W}} \sum_{n=0}^{\infty} \frac{(k_1\gamma k_2 x/W)^n}{n!\,(s+k_2)^{n+1}}, \qquad (25A)$$

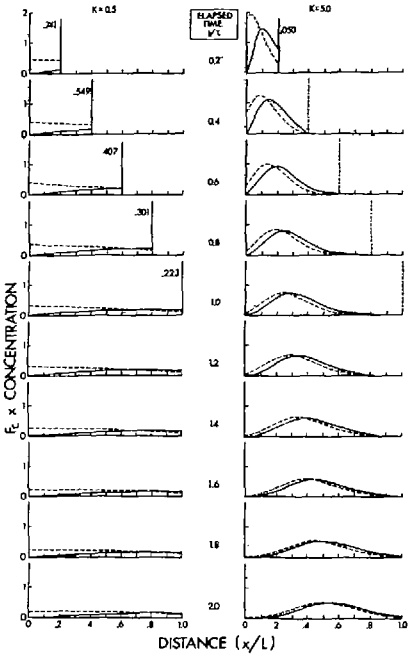

FIGURE 2

Concentration profiles in space. The distance axis in the illustration is normalized so that the abscissa is x/L. The ordinate is either $F_c u(x,t)$ or $F_c z(x,t)$. The case is taken in which $\lambda = 1.0$, $k_1 = k_2 = k$, and $\gamma = 3.0$. The time scale has been normalized to t/τ, and the changes in the length profiles (intravascular and extravascular) are illustrated at normalized time intervals of 0.2, for both a small rate constant ($k = 0.50$), and a moderately large rate constant ($k = 5.0$). The intravascular profile is the solid line, and the extravascular profile, the broken line. The impulse function (vertical line) remains intravascular during its propagation along the capillary in these instances. The number on each panel represents the proportion of the total material introduced, which is still traveling in the damped impulse function. When this area is less than 0.01 of the total, the impulse function is illustrated by a broken, rather than a solid, vertical line.

whence

$$z(x,t) = k_1 \frac{q_0}{F_c} e^{-\frac{x}{W}(k_1\gamma - k_2)} e^{-k_2 t} \sum_{n=0}^{\infty} \frac{(k_1\gamma k_2 x/W)^n}{n!} \frac{(t-x/W)^n}{n!} S(t-x/W) \quad (26)$$

$$= k_1 \frac{q_0}{F_c} e^{-\frac{x}{W}(k_1\gamma - k_2)} e^{-k_2 t} I_0\left(2\sqrt{k_1\gamma k_2 \frac{x}{W}\left(t-\frac{x}{W}\right)}\right) S(t-x/W) \quad (26A)$$

$$= k_1 \frac{q_0}{F_c} e^{-\frac{PS_c x}{F_c L}\left(1-\frac{1}{\lambda\gamma}\right)} e^{-\frac{PS_c}{F_c \lambda\gamma}\frac{t}{\tau}} I_0\left(2\sqrt{\left(\frac{PS_c}{F_c}\right)^2 \frac{1}{\lambda\gamma}\frac{x}{L}\left(\frac{t}{\tau}-\frac{x}{L}\right)}\right) S(t-\tau x/L). \quad (26B)$$

The adjacent profile in the capillary is

$$u(x,t) = \frac{q_0}{F_c} e^{-k_1\gamma\frac{x}{W}} \delta\left(t-\frac{x}{W}\right) + \frac{q_0}{F_c} e^{-\frac{x}{W}(k_1\gamma - k_2)} e^{-k_2 t} \sqrt{\frac{k_1\gamma k_2 \frac{x}{W}}{t-\frac{x}{W}}} I_1\left(2\sqrt{k_1\gamma k_2 \frac{x}{W}\left(t-\frac{x}{W}\right)}\right) S(t-x/W) \quad (27)$$

$$= \frac{q_0}{F_c} e^{-\frac{PS_c}{F_c}\frac{x}{L}} \delta\left(t-\frac{x\tau}{L}\right) + \frac{q_0}{F_c} e^{-\frac{PS_c}{F_c}\frac{x}{L}\left(1-\frac{1}{\lambda\gamma}\right)} e^{-\frac{PS_c}{F_c}\frac{1}{\lambda\gamma}\frac{t}{\tau}} \sqrt{\frac{\left(\frac{PS_c}{F_c}\right)^2 \frac{1}{\lambda\gamma}\frac{1}{\tau}\frac{x}{L}}{\tau\left(\frac{t}{\tau}-\frac{x}{L}\right)}} I_1\left(2\sqrt{\left(\frac{PS_c}{F_c}\right)^2 \frac{1}{\lambda\gamma}\frac{x}{L}\left(\frac{t}{\tau}-\frac{x}{L}\right)}\right) S(t-\tau x/L). \quad (27A)$$

It is again difficult to perceive the form of these two profiles. To illustrate how these two profiles change as a function of time we have computed a set of illustrative numerical examples (Fig. 2). These demonstrate that when the rate constant is small, a major part of the material remains confined to the impulse function within the capillary and emerges at the outflow in the impulse function, i.e., it has not entered the extravascular space. The material which has left the capillary emerges at the outflow as the tail function. When the rate constant is much larger, the loss from the intravascular impulse function is so large that the area under it becomes negligible during its passage along the capillary. The exchanging material spreads into the extravascular space and appears to move along toward the exit, both inside the capillary and in the extravascular space, with the passage of time. The extravascular concentration profile for the exchanging material $z(x,t)$ appears to fall behind that of the intravascular material $u(x,t)$ in space. The mode of representation used (which neglects the direction normal to the length) is suitable because instantaneous lateral equilibration is assumed to occur within each compartment, i.e., no lateral concentration gradient is assumed to be present. The discontinuity between the intravascular and extravascular concentration profiles is situated at the capillary barrier.

In the flow-limited case (where k_1 and k_2 approach infinity) the transform $\bar{Z}(x,s)$ is obtained by substituting equation 20 into

equation 25. If $k_1 = k_2$, the corresponding expression for the extravascular concentration becomes

$$z(x,t) = \frac{q_0}{F_e}\ \delta\left(t - [1+\gamma]\frac{x}{W}\right).$$

This is equal to the concomitant intravascular concentration. Therefore, in the flow-limited case the impulse propagates as a delayed wave which extends through both vascular and extravascular spaces.

If, at any time after injection, $R_e(t)$ is the total remaining in the system, both within the capillary and within the extravascular space, the fraction of the material remaining is

$$\frac{R_e(t)}{q_0} = 1 - \frac{F_c}{q_0}\int_0^t u(L,t)\ dt.$$

The expression on the right is analogous to $[1-H(t)]$ as defined by Zierler for a whole organ (17). In contrast to that for the whole organ, the above expression for the single capillary is an idealized one, in that inflow and outflow channels have not produced delay in and distortion of the observed data.

Step Response of the Single Capillary.— When the input to the capillary is a step function, the output is the time integral of the impulse response. In the permeability notation, the output is

$$u(L,t) = \frac{q_0}{F_c}\ e^{-\frac{PS_e}{F_c}}\,S(t-\tau) + \frac{q_0}{F_e}\ e^{-\frac{PS_e}{F_e}\left(1-\frac{1}{\lambda\gamma}\right)}\int_\tau^t e^{-\frac{PS_e}{F_e}\frac{1}{\lambda\gamma}\frac{t}{\tau}}\sum_{n=1}^{\infty}\left(\frac{\left(\frac{PS_c}{F_c}\right)^2\frac{1}{\lambda\gamma}\frac{1}{\tau}}{n!\quad(n-1)!}\right)^n (t-\tau)^{n-1}\ dt. \qquad (28)$$

When none of the extravascular tracer returns to the vessel, the first term, the step function of magnitude $\exp(-PS_e/F_c)$, emerging at the transit time τ, represents the outflow profile. Renkin has utilized only this first term of the solution, in his interpretation of ^{42}K outflow profiles from isolated perfused skeletal muscles(6).

Multicapillary Modeling

One of the major problems in interpreting the experimental results obtained by the multiple indicator dilution method is that of reconciling models of the distribution of diffusible substances in a single capillary with data obtained as summated outflows from many capillaries in an organ. Here we attempt to deal with the problem in a preliminary manner by examining how variations in the distribution of capillary transit times will affect the relation between a diffusible substance and a reference substance, when each capillary behaves in a barrier-limited fashion. To do this we assume temporarily that the transfer characteristics of the larger vessels are such that they impose a simple transport lag on the observed pattern, with no distortion of the shape of the observed curve. This ideality cannot be true (18), but it will be used for the present.

Many kinds of distributions of capillary transit times are possible. For the purposes of the present study, three kinds are considered. Two well-defined cases, extremes in the spectrum, are examined first. In the initial case, the time spent in the large vessels is assumed constant and the distribution of outflow arrivals of the reference substance is assumed to result solely from varying capillary transit times. In the second, the time spent in each capillary is assumed to be constant, and the distribution of outflow arrival times for the vascular reference is assumed to result from varying times spent in the large vessels. In the third, combinations of capillary and large-vessel transit times are considered, and the first two cases are shown to be particular extremes of this more general case. We shall use computed illustrations to demonstrate the two extremes. For the purpose of this development and in the illustrations, we have assumed that $\lambda = 1.0$. In this development we

have assumed that each unit (capillary and its associated extravascular space) is relatively independent of its neighboring unit. This may be a relatively realistic assumption for diffusible substances whose extravascular space of distribution is the extracellular space. For substances entering cells freely, however, the assumption of infinitely rapid lateral diffusion in the extravascular space will interconnect the units in a complex manner. It is difficult to deal with this interconnection in the absence of specific knowledge of the spatial distribu-

$C(t)$ = $Q(t)/F$, the concentration of label appearing at the outflow; and

t_0 = the common time spent in large vessels or, alternatively, the common start time for capillary traversal, if all the large vessel transit times are placed at the beginning, for this analysis.

Then

$$C(t) = \frac{1}{F}\int_{(L/W)_{min}}^{L/W} F_o\, u(L,t-t_0)\, n(L/W)\, d(L/W). \qquad (29)$$

tions and directions of flows in capillaries. For the present, it has been neglected.

1. *Varying Capillary Transit Times, with Constant Large-Vessel Transit Times.*—For the purposes of this analysis let us assume that the velocity of flow along each capillary is the same, that the diameter of each capillary is the same, and hence that the flow through each capillary is the same. The input of indicator into each capillary varies with its proportional flow and, in this situation, will be the same to each. Let

$n(L/W)\, d(L/W)$ = number of capillaries through which blood flows with transit time from (L/W) to transit time $(L/W) + d(L/W)$;

$(L/W)_{min}$ = the minimum capillary transit time;

$\int_0^\infty n(L/W)\, d(L/W) = N$, the total number of capillaries;

Nq_0 = q, the total input to the system;

NF_o = F, the total flow through the system;

$Q(t)$ = the quantity of label appearing at the outflow/time;

From this expression and our previous descriptions of the impulse response for a single capillary, we may now develop expressions for the outflow concentration-time profiles for the reference substance, for a substance undergoing barrier-limited distribution, and for a substance undergoing flow-limited distribution. Prior to this development, let us introduce a change of variables $t' = t - t_0$.

For the reference substance,

$$C(t)_{ref} = \frac{1}{F}\int_{(L/W)_{min}}^{L/W} q_0\, \delta\left(t' - \frac{L}{W}\right) n\left(\frac{L}{W}\right) d\left(\frac{L}{W}\right) = \frac{q_0}{F} n(t'). \qquad (29A)$$

The shape of the outflow distribution for the reference substances arises from the distribution of capillary transit times.

For the purpose of computing numerical illustrations, an arbitrary form closely approximating that found experimentally for indicator dilution curves, a random walk function (19), has been chosen. This is used, in all our illustrations, to describe the outflow profile for the reference substance. The form of the function is

$$Q(t)_{ref} = \frac{q}{(t_{ref} - t_a)} \frac{e^{-(1-m)^2/\chi^2 m}}{\chi\sqrt{\pi}\, m^{3/2}},$$

where $m = (t - t_a)/(t_{ref} - t_a)$.

The parameters which we have chosen for our illustrations are $q = 1$ (this is a unit input normalization); $t_a = 2.90$ seconds; $t_{ref} = 4.00$

seconds; and $\chi = 0.50$ (this value yields a linear downslope to the curve, on a semilogarithmic plot). For the particular case being considered at present, a t_0 value of 3.00 seconds has been selected, so that the mean capillary transit time is 1.00 second, for the reference substance.

For a substance undergoing barrier-limited distribution from the capillary lumen,

$$C(t)_{diff} = \frac{q_0}{F} e^{-k_1\gamma t'} n(t') + \frac{q_0}{F} e^{-k_2 t'} \int_{\tau_{min}}^{T} e^{-\tau(k_1\gamma - k_2)} n(\tau) \sum_{n=1}^{\infty} \frac{(k_1\gamma k_2\tau)^n}{n!} \frac{(t'-\tau)^{n-1}}{(n-1)!} d\tau \quad (29B)$$

$$= \frac{q_0}{F} e^{-k_1\gamma t'} n(t') + \frac{q_0}{F} e^{-k_2 t'} \int_{\tau_{min}}^{T} e^{-\tau(k_1\gamma - k_2)} n(\tau) \sqrt{\frac{k_1\gamma k_2\tau}{t'-\tau}} I_1\left(2\sqrt{k_1\gamma k_2\tau(t-\tau)}\right) d\tau. \quad (29C)$$

The first term corresponds to throughput material and the second to material which has left the capillary and subsequently returned. The capillary lengths and transit times vary, and so the use of the permeability notation (PS_c/F_c) is not suitable, since the parameter S_c in this expression becomes larger for the longer capillaries. The appropriate way to introduce the permeability is to use the relations: $k_1\gamma = 2P/r$; and $k_2 = 2P/\gamma r$. It is evident that the magnitude of the damping factor in the first term increases progressively with the time of capillary transit.

In Figure 3, we illustrate by a set of numerical examples the effect of increase in permeability on the two components of the outflow profile, throughput, and exchanging material. The throughput is not symmetrical to the curve for the reference substances on this semilogarithmic plot but departs progressively from it with time. For larger values of P, this first component becomes smaller and peaks earlier, and its downslope decays faster. As P is increased, the proportion of the curve contributed by the second component increases, the peak of this component is higher, and its downslope decays more rapidly.

For a substance undergoing flow-limited distribution into an extravascular space $(k_1 = k_2 = \infty)$,

$$C(t)_{diff} = \frac{q_0}{F} \int_{(L/W)_{min}}^{L/W} \delta\left(t' - [1+\gamma]\frac{L}{W}\right) n\left(\frac{L}{W}\right) d\left(\frac{L}{W}\right) = \frac{q_0}{F} \frac{n\left(\frac{t'}{1+\gamma}\right)}{1+\gamma}. \quad (29D)$$

This is the case which we previously described (4). It is illustrated in the lower panels of Figure 3.

The progressive change in shape of the curve for the diffusible substance, as the permeability is increased, is more easily evident in Figure 4, where the ordinate is rectilinear. The curves corresponding to $\gamma = 3.0$ and $\gamma = 10.0$ are displayed in the left-hand panels, for the present case, where the time spent in the large vessels is assumed to be constant, and the distribution of the outflow arrivals of the reference substance is assumed to be consequent to the distribution of capillary transit times. Similarly, the shape of the curve for a flow-limited substance changes progressively with changes in the value for γ. This change, described by equation 29D, is illustrated in the upper panel of Figure 5. The initial outflow delay increases, and the scaling factor producing diminution in magnitude and delay in the outflow increases, as γ increases.

There are two areas in which this flow-

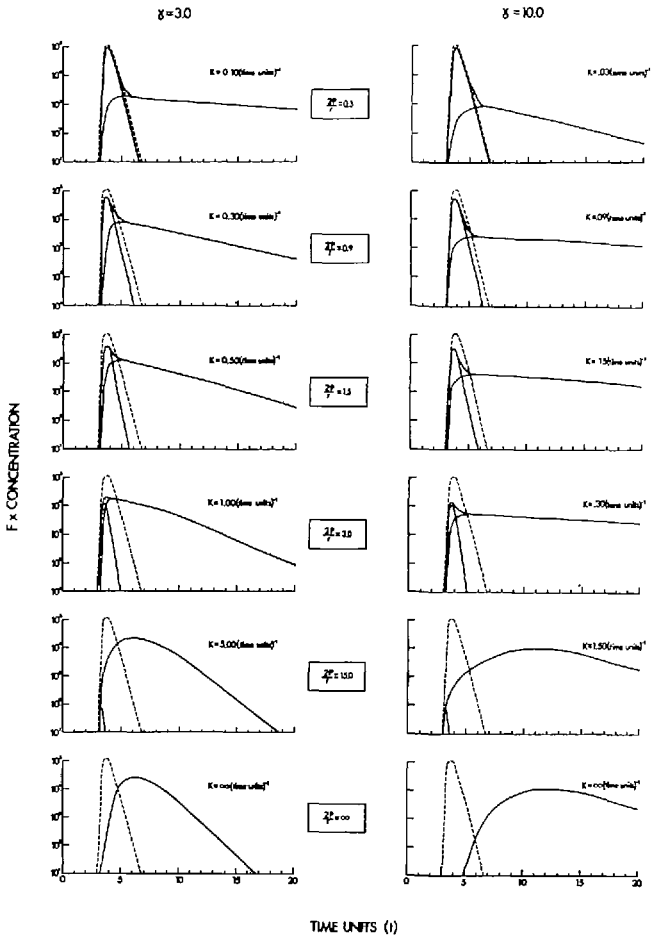

FIGURE 3

Outflow profiles for a barrier-limited substance, from an organ with variation in capillary transit times, but constant large-vessel transit times. We have assumed, in each case, that $k_1 = k_2 = k$. The panel on the left corresponds to $\gamma = 3.0$; and that on the right, to $\gamma = 10.0$. Each barrier-limited curve consists of a throughput component and an exchanging component, and the area under the total profile is unity. The permeability values used to compute corresponding panels with differing γ values are the same, in each case. The exchanging components, which depend upon the assembly of tail functions, differ, of course. The throughput curves are not symmetrical with the reference curves, in these semilogarithmic plots.

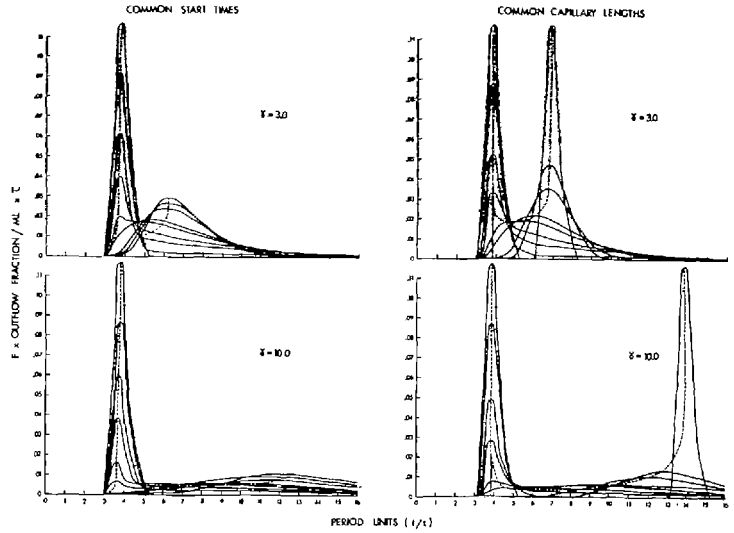

FIGURE 4

Progressive changes in the shapes of outflow dilution curves for a barrier-limited substance for $\gamma = 3.0$, and $\gamma = 10.0$. The asymptotic forms are, in each instance, the vascular reference substance and the flow-limited curve. The panel on the left corresponds to the case in which there is variation in the capillary transit times but the large-vessel transit times are constant, and that on the right to the case in which there is variation in the large-vessel transit times but the capillary transit times are constant. The broken lines represent the locus of the peaks of the curves. In the left-hand panels, the initial peak advances in time and a bimodal curve appears as the permeability is increased; finally the curve becomes unimodal, with a later peak. In the right-hand panels, the peak is always situated at the same time as that of the reference curve, when the permeability values are low. With increasing permeability values, the peak diminishes in magnitude and then is delayed, in relation to that of the reference substance. The curves remain unimodal throughout.

limited description appears to have biological application: the liver (4, 20), and the lungs (21). In each case, the terminal unit of the anatomical exchange bed is an anastomosing labyrinth with probable concurrent flow. In the liver the labyrinth is three dimensional and in the lungs, two dimensional.

2. *Varying Large-Vessel Transit Times, with Constant Capillary Transit Times.*—Let us once again assume that the velocity of flow among each capillary is the same, that the diameter of each capillary is the same, and hence that the flow through each capillary is the same. The input of indicator into each capillary varies with its proportional flow and, once again, will be the same to each. Now let

$r(t_0)\ dt_0$ = number of capillaries with start times (i.e., corresponding large vessel transit times) from t_0 to $t_0 + dt_0$;

$t_{n_{min}}$ = the minimum capillary start time;

$\int_0^\infty r(t_0)\ dt_0 = N$, the total number of capillaries; and

$t_\kappa = L/W$, the common constant transit time for each capillary.

Then

$$C(t) = \frac{1}{F}\int_{t_{0_{min}}}^{t-\frac{L}{W}} F_c\ u(L,t-t_0)\ r(t_0)\ dt_0. \quad (30)$$

From this expression and those for the impulse response of a single capillary, we may once again develop expressions for the reference substance, for a substance undergoing barrier-limited distribution, and for a substance undergoing flow-limited distribution.

For the reference substance,

$$C(t)_{ref} = \frac{1}{F}\int_{t_{0_{min}}}^{t-\frac{L}{W}} q_0\ \delta\left(t-t_0-\frac{L}{W}\right) r(t_0)\ dt_0$$

$$= \frac{q_0}{F} r(t-t_\kappa). \quad (30A)$$

The shape of the outflow dilution curve corresponds, in this instance, to the distribution of capillary start times, or large-vessel transit times.

For a substance undergoing barrier-limited distribution from the capillary lumen, we find

$$C(t)_{diff} = \frac{q_0}{F} e^{-k_1\gamma t_\kappa}\ r(t-t_\kappa)$$

$$+ \frac{q_0}{F} e^{-t_\kappa(k_1\gamma - k_2)} \int_{t_{0_{min}}}^{t-t_\kappa} r(t_0) \sum_{n=1}^{\infty} \frac{(k_1\gamma k_2 t_\kappa)^n}{n!} \frac{(t-t_0-t_\kappa)^{n-1}}{(n-1)!}\, dt_0 \quad (30B)$$

$$= \frac{q_0}{F} e^{-k_1\gamma t_\kappa}\ r(t-t_\kappa)$$

$$+ \frac{q_0}{F} e^{-t_\kappa(k_1\gamma - k_2)} \int_{t_{0_{min}}}^{t-t_0} e^{-k_2(t-t_0)}\ r(t_0) \sqrt{\frac{k_1\gamma k_2 t_\kappa}{t-t_0-t_\kappa}}\, I_1\left(2\sqrt{k_1\gamma k_2 t_\kappa\ (t-t_0-t_\kappa)}\right) dt_0. \quad (30C)$$

Once again the first term corresponds to throughput material and the second term to exchanging material which has left the capillary and subsequently returned. The transit time for every capillary is the same and so the expression $\exp(-k_1\gamma t_\kappa)$ is a constant. The throughput component is therefore a scaled reproduction of the dilution pattern of the reference substance. On a semilogarithmic plot it is symmetrical to the outflow curve for the reference substance (Fig. 6). The exchanging component, the assembly of tail functions, is dispersed in time in a manner similar to that for the previous case. As the permeability value increases, the proportion of material in the throughput peak decreases, and that in the exchanging fraction increases.

For a substance undergoing flow-limited distribution, we find

$$C(t)_{diff} = \frac{q_0}{F}\int_{t_{0_{min}}}^{t-\frac{L}{W}} \delta\left(t-t_0-[1+\gamma]\frac{L}{W}\right) r(t_0)\ dt_0$$

$$= \frac{q_0}{F} r(t-[1+\gamma]t_\kappa). \quad (30D)$$

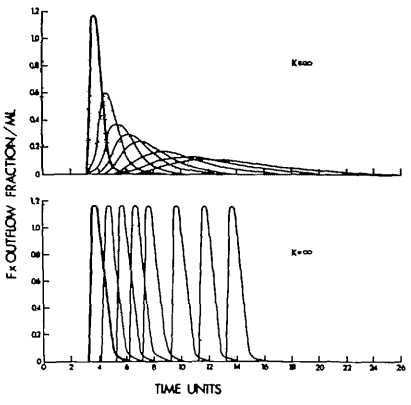

FIGURE 5

Flow-limited cases illustrated for γ values of 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 10.0. The top panel illustrates the progressive change in shape of the flow-limited curves when the capillary transit times vary but the large-vessel transit times are constant; and the bottom panel, the progressive delay but lack of change of shape or magnitude of the curves for the case for which the large-vessel transit times vary but the capillary transit times are constant.

This outflow curve reproduces that of the reference curve in magnitude, but it is delayed in all parts by the time γt_K. This asymptotic case differs completely from that for the case in which large-vessel transit times are constant but the capillary transit times vary. This behavior is demonstrated in the bottom panels of Figure 6 and in Figure 4, in which a set of barrier-limited curves with differing permeabilities have been aggregated on one plot together with the appropriate reference and flow-limited extremes, both for $\gamma = 3.0$ and $\gamma = 10.0$. No bimodal curves are encountered in this set of barrier-limited curves. The continual time displacement of the outflow curve, which occurs in this flow-limited case as the value for γ is increased, is displayed graphically in Figure 5, where it contrasts strongly with the flow-limited case in the instance in which outflow variation is the result of variation in the capillary transit times.

No instance of this kind of flow-limited phenomenon (i.e., time displacement of the reference profile) has been observed biologically and the absence of such observations leads one to suspect that the model has no biological counterpart. The chief interest of the present case therefore lies in the use of uniform capillary or source-sink transit times by other authors (3, 5-7, 9, 22) as the initial point from which they develop arguments relating to the interpretation of the manner in which permeability and diffusion phenomena contribute to the shaping of indicator dilution curves from whole organs. We have shown by illustrations that qualitative differences between this case, in which the capillary transit times are constant, and the first case, in which the large-vessel transit times are constant but the capillary transit times vary, do not become grossly apparent until the extremes, the asymptotic flow-limited cases, have been examined (compare Figures 3 and 6).

Graphic representation of the data from dilution experiments has served as a basis for making quantitative inferences in the past. The kinds of maneuvers which have been used bear examination, in terms of the foregoing development. Three chief types of plots have been used.

A. Ratio-Time Curves (23). The ratio $C(t)_{diff}/C(t)_{ref}$ is plotted against time. Figure 7 illustrates ratio curves corresponding to the two cases we have modeled, for $\gamma = 3.0$. For the low permeabilities, the forms of the two kinds of curves are distinctly different. When the capillary transit times vary, the curves start at finite values between 0 and 1, decrease to a minimum, and then increase rapidly. When $k_2 = 0$, there are no tail terms, and the ratio becomes a falling exponential (broken lines). When the capillary transit times are constant, the ratio curve initially assumes a value between 0 and 1 and later increases rapidly. When $k_2 = 0$, the ratio assumes a constant value, and the curve is simply a straight line. Curiously both kinds of curves, that with a minimum and that with no minimum, have been observed for the ratio ($^{42}K/^{131}I$-labeled albumin), in studies on the

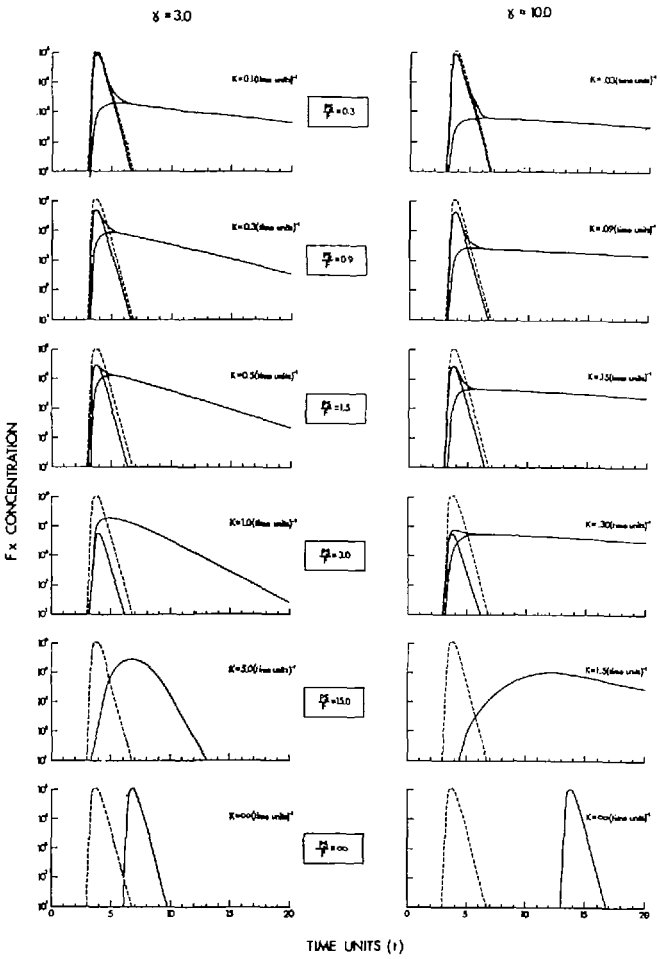

FIGURE 6

Outflow curves for a barrier-limited substance from an organ with constant capillary transit times and variation in large-vessel transit times. The panel on the left corresponds to $\gamma = 3.0$, and that on the right to $\gamma = 10.0$. Each barrier-limited curve consists of a throughput component and an exchanging component. The permeability values used to compute the profiles on corresponding panels with differing γ values were the same, and hence the throughput components, the assembly of damped spikes, were the same. These are symmetrical to the reference curves on the semilogarithmic plots. The exchanging components of the corresponding panels, which depend on the assembly of tail functions, differ, as expected.

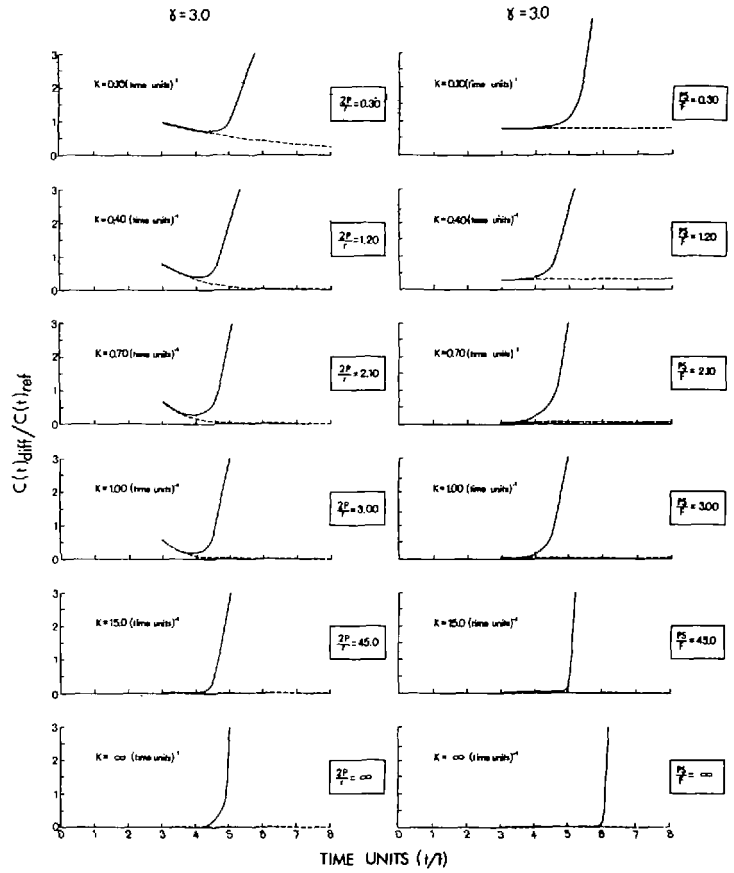

FIGURE 7

Ratio-time curves. On the left, the large-vessel transit times are constant and the capillary transit times vary; on the right, the capillary transit times are constant and the large-vessel transit times vary.

heart (9, 24). In this particular case, a proportion of the labeled potassium is irreversibly removed from the extravascular space, and the later values of the ratio are lower than they would otherwise be (20). For high permeability values the curves for the two kinds of capillary distributions become relatively alike. The ratio becomes zero for the initial samples, so long as the outflow appearance is delayed with respect to the vascular reference substance, and then increases rapidly, as $C(t)_{diff}$ assumes finite values. The outflow delay leading to ratio curves of this sort has been observed in dilution curves obtained from the liver (4, 20).

B. Extraction-Time Curves (7). The ratio

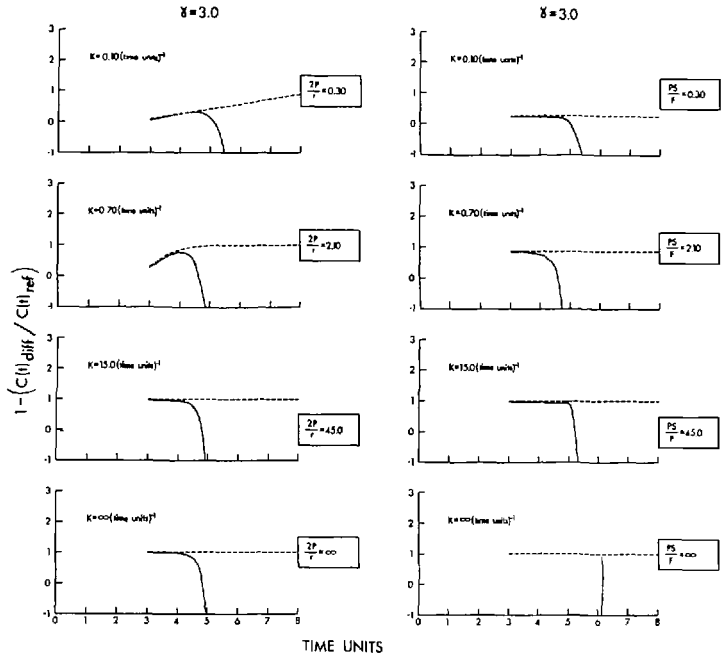

FIGURE 8

Extraction-time curves. The large-vessel transit times are constant and the capillary transit times vary, on the left; on the right, the capillary transit times are constant but the large-vessel transit times vary.

$[C(t)_{ref} - C(t)_{diff}]/C(t)_{ref}$ is plotted against time. Crone has termed this expression the extraction. In the manner in which it is used here it is an instantaneous value and does not, in general, correspond to the steady-state extraction values used for the estimation of hepatic or renal blood flow, during continuous infusion. These latter values represent, in terms of our preceding development, the steady-state response of a system to a step input when a portion of the material is being irreversibly removed from the system (either because $k_2 = 0$ or because material is being removed from the extravascular space). This distinction must be kept clear, in the mind of the reader. Figure 8 illustrates instantaneous extraction-time curves, for the two cases we have modeled. Once again the two cases yield distinctly different kinds of curves for low permeability values. When the capillary transit times vary but the start times are the same (left-hand panels), the curves start between 0 and 1, rise to a peak, and then decrease sharply. When $k_2 = 0$ and there are no tail terms, the ratio becomes a rising exponential (broken lines), which increases from its initial value to 1. When the capillary transit times are constant, the values remain fairly constant and then decrease rapidly. When $k_2 = 0$, the extraction is once again constant, and the curve becomes a straight line. For high permeability values the curves, as expected,

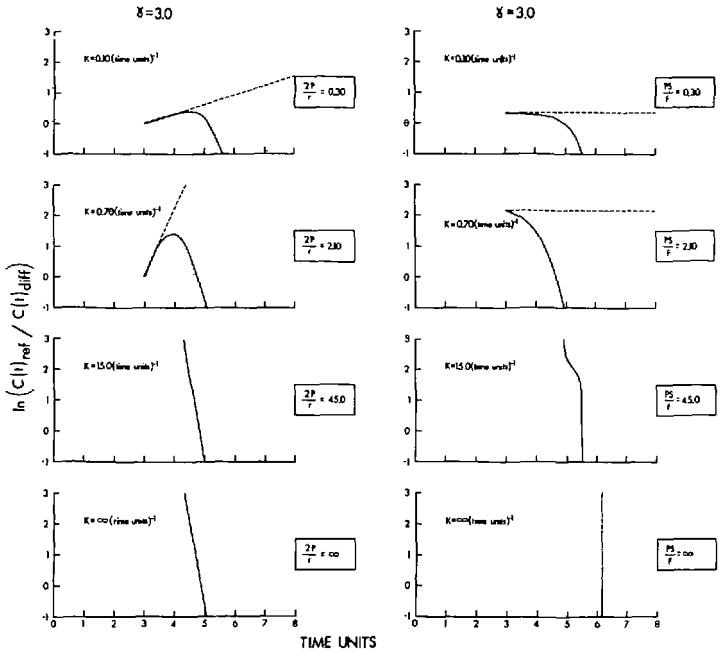

FIGURE 9

Log ratio-time curves. The large-vessel transit times are constant and the capillary transit times vary, on the left; the capillary transit times are constant but the large-vessel transit times vary, on the right.

become relatively like. The extraction becomes 1 and then decreases rapidly as $C(t)_{diff}$ assumes finite values.

C. Log Ratio-Time Curves (12). The value $ln\ [C(t)_{ref}/C(t)_{diff}]$ is plotted against time. Figure 9 illustrates cases corresponding to the two cases we have analyzed. At low permeability values, there are characteristic differences. When the capillary transit times vary but the start times are the same (left-hand panels), the curve starts at a value greater than zero, rises to a peak, and then decreases. When $k_2 = 0$ and there are no tail terms, the curve becomes a rising straight line, with the slope $k_1\gamma$ (broken lines). The initial values of the curve, for the case where k_2 is finite, asymptote to the broken line. When the capillary transit times are constant but the large-vessel transit times vary, the curve assumes an initial value and thereafter decreases below this value. When $k_2 = 0$, the natural logarithm of the ratio is constant and the curve is a horizontal straight line. At high permeability values, the initial values are, in each case, infinite when there is an outflow appearance delay for the diffusible substance. The values decrease rapidly thereafter.

3. *Varying Large-Vessel and Varying Capillary Transit Times.*—In this case, there will be a distribution of both capillary transit times and of large-vessel transit times, or wait times, i.e., a double distribution. Let us once again suppose, for simplicity, that the velocity of flow in each capillary is the same, that the

diameter of each capillary is the same, and hence that the flow through each capillary is the same, so that the input of indicator to each capillary will be the same. Let

$m\left(t_0, \frac{L}{W}\right) d\left(\frac{L}{W}\right) dt_0$ = the number of capillary equivalent pathways with wait times from t_0 to $t_0 + dt_0$ and with capillary transit times from L/W to $L/W + d(L/W)$.

Then

$$C(t) = \frac{1}{F}\int_{t_{0\min}}^{t_0}\int_{(L/W)_{\min}}^{L/W} F_c\, u(L,t-t_0)\, m\left(t_0, \frac{L}{W}\right) d\left(\frac{L}{W}\right) dt_0. \quad (31)$$

Corresponding expressions may now be developed for the vascular reference substance, for a barrier-limited substance, and for a flow-limited substance. For example, for the reference substance,

$$C(t)_{\text{ref}} = \frac{1}{F}\int_{t_{0\min}}^{t_0}\int_{(L/W)_{\min}}^{L/W} q_0\, \delta\left(t - t_0 - \frac{L}{W}\right) m\left(t_0, \frac{L}{W}\right) d\left(\frac{L}{W}\right) dt_0. \quad (31A)$$

This expression and the others which would evolve are rather too complex for use in the analysis of experimental data. The set of equations could be solved if the distribution $m(t_0, L/W)$ could be expressed as a product distribution $r(t_0) \cdot n(L/W)$. This is appropriate only in organs in which there is regional homogeneity, from the structural and functional point of view (for example, the heart). The inference of the use of the product distribution is that, even though the large vessel wait times differ, the distribution of capillary transit times for each terminal element of the vascular unit is the same. With its use equation 31 becomes

$$C(t) = \frac{1}{F}\int_{t_{0\min}}^{t_0}\int_{(L/W)_{\min}}^{L/W} F_c\, u(L,t-t_0)\, r(t_0)\, n\left(\frac{L}{W}\right) d\left(\frac{L}{W}\right) dt_0. \quad (32)$$

When $r(t_0) = \delta(t_0)$, equation 32 becomes the first case we examined (equation 29), the case in which the capillary transit times vary, but the start times are all the same. When $n\left(\frac{L}{W}\right) = \delta\left(\frac{L}{W}\right)$, equation 32 becomes the second case which we have examined (equation 30), the case in which the large-vessel transit times vary, but the capillary transit times are constant. The two cases examined are therefore asymptotic extremes of a series of possible product distribution functions. We have already examined these extremes and gained insight into their behavior. The intermediate situation may often be a closer approximation to the real situation.

For this intermediate case the expression for the outflow concentration time profile for the reference substance becomes

$$C(t)_{\text{ref}} = \frac{1}{F}\int_{t_{0\min}}^{t_0}\int_{(L/W)_{\min}}^{L/W} q_0\, \delta\left(t - t_0 - \frac{L}{W}\right) r(t_0)\, n\left(\frac{L}{W}\right) d\left(\frac{L}{W}\right) dt_0$$

$$= \frac{q_0}{F}\int_{t_{0\min}}^{t_0} r(t_0)\, n(t-t_0)\, dt_0. \quad (33)$$

The profile may therefore be represented as a convolution integral of the distribution of start times and the distribution of capillary transit times.

Expressions for a barrier-limited substance and for a flow-limited substance may then be derived by substitution of the appropriate expression for the "single capillary effect" $u(L,t-t_0)$ into equation 32. It may be possible to derive information from this more complex

case with suitable experimental information. If a flow-limited substance is defined experimentally by the superimposition of the outflow curves of molecular species with markedly different diffusion constants, the corresponding expression may allow us to derive the distributions of large-vessel and capillary transit times. This information, in turn, will provide the means necessary to obtain, from the analysis of simultaneous outflow dilution curves for a barrier-limited substance, numerical estimates of the pertinent parameters. It appears appropriate to delay a complete examination of this case so that it may be presented with an analysis of a suitable set of experimental data. It should be noted that the foregoing development has a certain amount of generality. For example, under circumstances in which the flow is slow and the diffusible material is one for which the capillary wall presents no barrier, the "single capillary effect" might best be represented by the convection diffusion model of Perl and Chinard, in which longitudinal diffusion is appreciable.

INFERENCES

We have developed a model of the kinetic processes underlying the distribution of substances from a barrier-limited capillary in a well-perfused organ. We have developed, by use of this model, two extremes in the kinds of distribution of transit patterns which might be expected in an organ. In one, the large-vessel transit times are considered constant, and the capillary transit times are considered to produce the form of the outflow distribution pattern for the vascular reference. The liver and the lung may belong predominantly to this pattern. In the other, the capillary transit times are considered constant, and the large-vessel transit times vary. No biological instance corresponding to the profile predicted for the flow-limited extreme of this model (in which no intercapillary connection is assumed) has been found. Most organs appear to belong to an intermediate category, in which there is variation in both capillary transit times and large-vessel transit times. It will be possible to analyze data by use of this more general pattern and to gain useful information.

Circulation Research, Vol XXVII, November 1970

Acknowledgment

We wish to thank Miss Margaret Mulherin, who with patience and care typed this manuscript.

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