A Concurrent Flow Model for Extraction during Transcapillary Passage

By James B. Bassingthwaighte

ABSTRACT
A model for capillary-tissue exchange in a uniformly perfused organ with uniform capillary transit times and no diffusional capillary interactions was designed to permit the exploration of the influences of various parameters on the interpretation of indicator-dilution curves obtained at the venous outflow following the simultaneous injection of tracers into the arterial inflow. These parameters include tissue geometric factors, longitudinal diffusion and volumes of distribution of tracers in blood and tissue, hematocrit, volumes of nonexchanging vessels and the sampling system, capillary permeability, \( P \), capillary surface area, \( S \), and flow of blood- or solute-containing fluid, \( F'_s \). An assumption of instantaneous radial diffusion in the extravascular region is appropriate when intercapillary distances are small, as they are in the heart, or permeabilities are low, as they are for lipophobic solutes. Numerical solutions were obtained for dispersed input functions similar to normal intravascular dye-dilution curves. Axial extravascular diffusion showed a negligible influence at low permeabilities. The "instantaneous extraction" of a permeating solute can provide an estimate of \( PS/F'_s \), the ratio of the capillary permeability-surface area product to the flow, when \( PS/F'_s \) lies between approximately 0.05 and 3.0; the limits of the range depend on the extravascular volume of distribution and the influences of intravascular dispersion. The most accurate estimates were obtained when experiments were designed so that \( PS/F'_s \) was between 0.2 and 1.0 or peak extractions were between 0.1 and 0.6.

KEY WORDS indicator dilution capillary membrane permeability mathematical analysis blood flow coronary artery myocardial metabolism isotope compartmental analysis blood-tissue exchange transport mechanisms

The purpose of this study is to demonstrate that under specific circumstances the permeability-surface area product of capillary membranes to hydrophilic solutes can be estimated from paired or multiple indicator-dilution curves.

The so-called instantaneous extraction, \( E(t) \), of a diffusable indicator can be calculated from the transport functions, \( h(t) \), or the normalized venous outflow concentration-time curves of an organ following the slug injection into the arterial inflow of a bolus containing a diffusible tracer, \( D \), and a nondiffusible reference tracer, \( N \). The formula proposed by Crone (1) is

\[
E(t) = \frac{h_N(t) - h_D(t)}{h_N(t)},
\]

where \( h(t) \) is the fraction of the injected dose appearing in the outflow per unit time. The extraction \( E(t) \) is related to the net average flux of diffusible tracer out of the blood. An interpretation of \( E(t) \) in terms of parameters influencing capillary-tissue exchanges can be made only by assuming specific geometric and functional relationships within the organ. When a specific value \( E \) of \( E(t) \) governed by the unidirectional flux from blood to tissue can be selected and when "back diffusion" or flux of permeant tracer from the extravascular region back into the flowing blood is negligible, then it is theoretically reasonable to estimate the product, \( PS \), of capillary permeability, \( P \), and capillary surface area, \( S \), from this \( E \).

\[
PS = -F'_s \log_e(1 - E),
\]

where \( F'_s \) is the flow of solute-containing mother fluid (defined explicitly in Eq. 13). It will be argued that the selected value \( E \) should be at or near the maximum value of \( E(t) \).

Eq. 2 was derived by Sangren and Sheppard (2) from a Krogh cylinder capillary-tissue model with a permeability barrier and arrived at independently by Renkin (3) and Crone (1). Eq. 2, which I
call the Renkin-Crone model, is not a complete model; it does not take into account the extravascular region and therefore does not describe conservation of mass of the permeating tracer. Nevertheless, it does represent a limiting behavior of other models (4-9) under conditions where (1) a permeability barrier controls the escape of tracer from the bloodstream, (2) there is no axial diffusion parallel to the flow stream, and (3) the extravascular volume of distribution is so large that no escaped tracer returns to the blood. Goresky et al. (5) have presented detailed descriptions and some limiting forms for the Sangren-Sheppard model. This model is based on the assumptions that the ratios of capillary surface area to intravascular volume and to extravascular volume are constant for all volume elements along a capillary and that there are no concentration gradients within either capillary or extravascular space in a direction perpendicular to the capillary axis.

Other models appear to be unsuitable for describing the permeation of capillary membranes by small hydrophilic solutes. Perl's "interpolation model" (6) is an approximation derived from the barrier-free convection-diffusion model of Perl and Chinard (10); there is a permeability barrier, but the mathematical expression for the transmission of tracer in the extravascular region does not lend itself to precise physical interpretation. Johnson and Wilson (7) simplified the Sangren-Sheppard model by assuming that not only radial but also longitudinal diffusion is infinitely rapid so that the extravascular compartment is a uniform mixing chamber. Schmidt's very complex model (8) provides solutions in only rather simple and not too useful cases. Levitt's model (11) incorporates intercapillary exchanges and radial diffusion but lacks a permeability barrier. Lee and Fronek (9) considered intercapillary distances to be infinite so that extravascular diffusion dominates their model's behavior. The single capillary Krogh cylinder model of Bassingthwaighte et al. (4) is, apart from Schmidt's, the most extensive of these models. It includes a permeability barrier, intravascular and extravascular axial diffusion and extravascular radial diffusion over finite intercapillary distances, permeability gradients along the capillary, and variable flow, but a great deal of time is required to compute the numerical solutions.

The present model is a variant of the Krogh cylinder model for describing capillary-tissue exchange in a well-perfused organ with parallel capillaries and short intercapillary distances. Although it is a simplification of a previously described model (4), it retains enough generality so that it can be simplified further to the form of other useful models (1-3, 5-7, 10). It provides solutions for a pair of tracers entering the capillary with concentrations $C_{in}(t)$. Within the capillary-tissue region there are (1) plug flow, finite axial diffusion (different for the two tracers), and instantaneous radial diffusion in the capillary, (2) an endothelial barrier with permeability to one tracer, which can vary along the length of the capillary, (3) a stagnant extravascular region with finite axial and infinite radial diffusion, and (4) explicit definitions of the volumes of distribution of the tracers in plasma, erythrocytes, and tissue. (5) Dispersion and delay in the venous outflow are also described. Reductions from the parent model (4) are: (1) radial diffusion in the extravascular space is assumed to be infinitely rapid (a logical simplification for analyzing data from well-perfused organs which permits much faster computation), (2) continuously variable flow is not considered, since its effects seem to be minimal, and (3) the pseudo-bolus flow approximation (plug flow with leakage upstream and downstream) is replaced by plug flow inside the capillary. The use of three longitudinal diffusion coefficients (for both a reference substance and the permeating tracer along the bloodstream and for the permeating tracer in the extravascular tissue) and finite capillary permeability (which can vary along the length of the capillary) are the important extensions beyond the models of Sangren and Sheppard (2, 5) and of Perl and Chinard (10).

The emphasis in the present model is on the whole-organ approach tempered by assuming homogeneous perfusion. In an organ composed of parallel capillaries with equal flows, permeabilities, and intercapillary distances, concentrations are symmetrical about the axes of the capillaries and net exchange between neighboring regions does not occur. Therefore, the model is more clearly applicable to mammalian myocardium which experiences relatively homogeneous flow than it is to skeletal muscle which is characterized by marked temporal variations and interregional differences in flow. (Although this model is a single capillary model mathematically, Goresky et al. [5, p 755] have preferred to call such a model a "multicapillary" model with "varying large-vessel transit times, with constant capillary transit times." ) The assumption of local homogeneity and no net exchanges is justified in the heart by the observation (12) that iodoantipyrine washout curves have shapes determined by flow and show no effects of
CAPILLARY EXTRACTION

485

intraorgan diffusion between inflow and outflow, unlike tritiated water washout curves, which show a small diffusional component at low flows. This model should be appropriate for describing transport of small hydrophilic solutes, including substances as rapidly permeating as antipyrine, but, because it is a single capillary model, it cannot be used for highly diffusible tracers undergoing intraorgan diffusional shunting.

To permit applications of the model to experimental data, the transport functions (probability density functions of transit times) of the arteries and veins, \( h_a(t) \) and \( h_v(t) \), were also modeled so that the investigator could examine the output of the whole system in response to any form of input, \( C_{in}(t) \). The transport function of the whole system is the convolution of the arterial, transcapillary, and venous transport functions:

\[
  h(t) = h_a(t) \ast h_{cap}(t) \ast h_v(t),
\]

where \( h_{cap}(t) \) is the impulse response of the capillary-tissue cylinder. The observed output, \( C_{out}(t) \), is the convolution of the input with the system transport function:

\[
  C_{out}(t) = C_{in}(t) \ast h(t) = \int_0^t C_{in}(\alpha) \ast h(t - \alpha) d\alpha,
\]

where \( \alpha \) is a variable used for the integration.

A particular aim of the present paper is to explore the appropriateness of Eq. 2 for calculating \( PS \) for extracellular tracers such as \(^{22}\text{Na}, \) sucrose, and inulin from the instantaneous values of \( E(t) \) in the myocardium. Previous modeling (4) has suggested that either \( E_{max} \), the maximum value of \( E(t) \) of Eq. 1, or \( E(t_p) \), the value at the time of the peak of the reference tracer curve, is more useful than the earliest values of \( E(t) \). There has been some question as to how much underestimation of \( PS \) might be caused by a diminution in \( E(t) \) due to return of escaped tracer from tissue back to blood (back diffusion). Martin and Yudilevich (13) attempted to correct for this source of error by extrapolating back to the time of first arrival of tracer in the outflow to obtain \( E(0) \). The important problem with their approach is that local perfusion is heterogeneous; therefore, the tracer emerging first almost certainly has come mainly from regions having higher than average flow and lower than average extractions; if \( E(0) \) and the average flow, \( F \), of the regional flows are used in Eq. 2, \( PS \) will be underestimated. Since pathways having local perfusion nearer to the average \( F \) will tend to have transit times closer to the mean transit time, it seems most pertinent to assess the accuracy of estimation of \( PS \) from \( E(t_p) \), although \( t_p \) normally precedes \( t \), or from \( E_{max} \), which occurs at an unspecified time normally near \( t_p \) and somewhat before \( t \). Also of practical importance is the assessment of the influence of indicator dispersion in arteries and veins. For these purposes an approximating model was developed; numerical solutions are presented to demonstrate the behavior over pertinent ranges for the important parameters.

List of Terms

\[ \beta_e \]
- Intravascular dispersive Peclet number, Eq. 33.

\[ \beta_p \]
- A permeation Peclet number, Eq. 32.

\[ C \]
- Concentration (moles or mmoles/ml).

\[ \Delta C \]
- Concentration difference between two locations.

\[ C_{in}(t) \]
- Concentration in the plasma in the inflowing blood.

\[ C_{out}(t) \]
- Concentration in the plasma in the venous outflow.

\[ C_{x}(x, t) \]
- Concentration in the extravascular volume of distribution, \( \psi \).

\[ c \]
- Capillary region.

\[ D_s, D_E \]
- Diffusion coefficients in the capillary plasma and the extravascular region, respectively (cm\(^2\)/sec).

\[ E(t) \]
- Instantaneous extraction calculated from outflow concentrations (dimensionless).

\[ F, F_0, F_1 \]
- Flow through the individual capillary (ml/sec).

\[ F_{1} \]
- Flow of solute-containing mother fluid (ml/g sec\(^{-1}\)), Eq. 13.

\[ h(t) \]
- Frequency distribution of transit times (sec\(^{-1}\)).

\[ h_a(t) \]
- \( h(t) \) for the bed lying between the injection site and the arterial inflow end of the capillary.

\[ h_{cap}(t) \]
- \( h(t) \) for the capillary tissue model for either a permeant or a nonpermeant solute.

\[ h_v(t) \]
- \( h(t) \) for the vascular bed lying between the capillary outflow and a downstream sampling point in the vein.

\[ h_n(t) \]
- \( h(t) \) for a nonpermeant substance.

\[ h_p(t) \]
- \( h(t) \) for a permeating solute.

\[ Hct \]
- Hematocrit, the fraction of the blood volume which is erythrocytes.

\[ j \]
- Index of the segment axially along the capillary-tissue hexagon.

\[ K \]
- Exchange coefficient (ml/sec), Eq. 18.
\( K_{rj} \) = Radial exchange coefficient in the \( j \) segments across the capillary membrane, Eq. 18.

\( K_{xc} \) = Axial exchange coefficient in the capillary, Eq. 20.

\( K_{xE} \) = Axial exchange coefficient in the extravascular region, Eq. 21.

\( L \) = Capillary length (cm).

\( N_r \) = Number of capillaries in the whole organ, Eq. 9.

\( n_x \) = Number of segments axially in which the capillary-tissue hexagon is divided for numerical purposes, usually 20-60.

\( P, P(x) \) = Permeabilities at the arterial and venous ends of the capillary, respectively.

\( \Delta q \) = Quantity of solute (mmoles) transferred from one region to another in one time step in a solution.

\( \Delta q_r, \Delta q_x \) = Reference to amounts transferred in the \( r \) and the \( x \) directions, Eqs. 25-28.

\( R \) = Half of the intercapillary distance with a hexagonal arrangement of parallel capillaries (cm).

\( R_r \) = Capillary radius (cm).

\( r \) = Radial distance from axis of capillary (cm).

\( \rho \) = Density (g/ml) of organ tissue excluding the blood contained in large vessels.

\( S \) = Capillary surface area (cm²/g) in tissue devoid of large nonexchanging vessels, Eq. 12.

\( S_r \) = Surface area of a single capillary (cm²) = \( 2\pi L R \) or \( \rho V_r S \).

\( t \) = Time (sec).

\( \sigma, \tau, \tau_r \) = Parameters defining a lagged normal density curve (sec) (27).

\( \tau_r \) = Capillary mean transit time (sec).

\( \tau_E \) = Mean transit time of tracer in extravascular region when blood-tissue exchange is barrier limited, Eq. 32b.

\( t_+ \) = Time infinitely soon after the beginning of a time step occurring just after the shift of the capillary fluid downstream by one segment.

\( t_-, t + \Delta t \) = Times just before a downstream shift of the intracapillary contents occurs at the end of each \( \Delta t \) in the numerical solution.

\( t_\sigma \) = Time of the peak of \( h_\sigma(t) \).

\( \Delta t \) = Duration of time step (sec).

\( v \) = A fractional volume of distribution (ml/ml).

\( v_r \) = Fractional volume of distribution (ml/ml of accessible intravascular "space" of blood) of permeant tracer in the blood = \( 1 - Hct(1 - u_{av}) \).

\( u_{av} \) = Fraction of the organ volume which is made up of blood in large nonexchanging vessels (ml blood/ml organ).

\( V \) = An actual volume (ml).

\( V_a \) = Volume (ml) of a single capillary-tissue hexagon of length \( L \).

\( V_r \) = Volume (ml) of a single capillary of length \( L \).

\( V_E \) = Volume (ml) of extravascular tissue in a single capillary-tissue hexagon = \( V_a - V_r \).

\( W \) = Total organ weight (g).

\( x \) = Distance along the capillary from inflow, \( x = 0 \), to outflow, \( x = L \).

\( \xi_r, \xi_E \) = Tortuosity coefficients (dimensionless) in capillary and extravascular region, respectively; \( \xi_r = 1 + 0.5Hct(1 - u_{av}) \).

The Model

The capillary-tissue component of the model is diagramed in Figure 1. It is considered to be part of an organ with arteries and veins. In experiments on an isolated organ, values can be obtained for the total flow, \( F_a \) (ml/sec), the organ weight, \( W \) (g), and the density, \( \rho \) (g/ml). Other experiments can provide values for the fraction of the organ volume consisting of the blood in the nonexchanging vessels, \( u_r \) (ml blood/ml organ), of the inflowing arterial and outflowing venous systems, for the fractional volumes of distribution of diffusible indicators in capillary blood, \( u_c \) (ml/ml), erythrocytes, \( u_{rbc} \) (ml/ml), and the extravascular region, \( u_E \) (ml/ml), for the capillary surface area, \( S \) (cm²/
g tissue excluding large vessels), and for the diffusion coefficients in the axial direction in plasma, \( D_c \) (cm²/sec), and extravascular tissue, \( D_E \) (cm²/sec). (Fractional volumes [dimensionless] are written with a lower case \( v \) and are subscripted.) When \( v_{rec} \) is not zero, the rate of exchange with the erythrocytes is assumed to be infinitely fast; the fraction of the blood in which solute is dissolved is \( v_e \), which is the volume of the plasma plus the fraction of the red cells accessible to the solute:

\[
v_e = 1 - Hct + v_{rec} \cdot Hct = 1 - Hct(1 - v_{rec}). \tag{5}
\]

where \( Hct \) is the small vessel hematocrit. Anatomic studies on the dog heart (14) provided values for the capillary radius, \( R_c \), of about 2 \( \mu \)m, the half-intercapillary distance, \( R \), of 9.5 \( \mu \)m, and capillary lengths, \( L \), of 400-1000 \( \mu \)m. With \( R = 9.5 \mu \)m, capillary density is 3200/mm².

The volumes (in ml, indicated by upper case \( V \)) of the capillary-tissue hexagon, \( V_h \), the capillary, \( V_c \), and the extravascular region, \( V_E \), are

\[
V_h = 2\sqrt{3} R^2 L, \tag{6}
\]

\[
V_c = \pi R^2 L, \tag{7}
\]

\[
V_E = V_h - V_r. \tag{8}
\]

Thus, the volume of solute-containing mother fluid in each hexagonal column is \( v_c V_c + v_E V_E \). The number of capillaries, \( N_c \), is

\[
N_c = W(1 - v_e)/\rho V_h, \tag{9}
\]

which introduces an insignificant error due to the difference in densities of blood and myocardium. The density, \( \rho \), was taken to be 1.063 g/ml (15). A value for \( v_e \) of 0.12 ml/ml was obtained by subtracting from the blood content of 0.15 ml/ml given by Hirche and Lochner (16) the 0.03-ml/ml small vessel volume estimated by Myers and Honig (17). The flow in each capillary, \( F_c \) (ml/sec), was

\[
F_c = F_r/N_c, \tag{10}
\]

and the capillary mean transit time, \( \bar{t}_c \), was

\[
\bar{t}_c = V_c/F_c = V_c N_c/F_a. \tag{11}
\]

The latter form emphasizes that \( \bar{t}_c \) is independent of an estimate of \( L \), which is subject to much uncertainty. Typical values for \( F_r/W \) of 1 ml/g min⁻¹ and \( R \) of 9\( \mu \)m gave a value for \( \bar{t}_c \) of about 2 seconds. If \( L = 500\mu \)m, then \( \rho N_c/W = 6 \times 10^4 \) capillaries/ml myocardium and \( F_c = 3 \times 10^{-8} \) ml/sec. Changes in the number of open capillaries and the intracapillary distances induced by increasing flow or perfusion pressure were not modeled explicitly, but they should be considered when fitting data from the heart (18, 19) and especially from the lung (20). The capillary surface area, \( S \) (cm²/g myocardium excluding large vessels), is

\[
S = 2\pi R_c L N_c \frac{W(1 - v_e)}{\rho \sqrt{3} R^2} \tag{12}
\]

and has values around 500 cm²/g. With this definition of \( S \), \( S \cdot P \) has the units ml/g sec⁻¹; thus, Eq. 2 is dimensionally balanced, since the units are the same as those for \( F_r^* \).

The flow of solute-containing fluid through the organ (from Eq. 5) is \( v_c F_a \), and \( F_r^* \) (ml/g sec⁻¹) is the flow of solute-containing fluid per gram of myocardium excluding large vessels:

\[
F_r^* = \frac{(1 - Hct + v_{rec} \cdot Hct) F_a}{W(1 - v_e)} = \frac{v_c F_a}{W(1 - v_e)} = \frac{v_c F_c}{\rho V_a} \tag{13}
\]

The concentrations, \( C \) (mmoles/ml), are axisymmetric: \( C_c \) is the concentration in capillary plasma and \( C_E \) is that in the extravascular region of volume \( V_E \) divided by the partition coefficient, \( v_e \), which is the ratio of the solubility of the permeating tracer in \( V_E \) to that in plasma. Thus, \( C_c - C_E \) is the driving force for solute movement. The tracer flux into the capillary within each element of length, \( \delta x \), at each position, \( x \), along the capillary from \( x = 0 \) to \( x = L \) at each time, \( t \), is given by

\[
v_c \pi R_c^2 L \frac{\partial C_c(x, t)}{\partial t} = D_c \frac{\delta^2 C_c}{\delta x^2} - v_c \pi R_c^2 L P(x) 2\pi R_c L (C_c - C_E) - v_c F_c L \frac{\partial C_c}{\partial x}; \tag{14a}
\]

the change in concentration is obtained by dividing Eq. 14a by the effective volume:

\[
\frac{\partial C_c(x, t)}{\partial t} = \frac{D_c}{\xi^2} \frac{\partial^2 C_c}{\partial x^2} - \frac{v_c}{\pi R_c^2} \frac{\partial C_c}{\partial x}; \tag{14b}
\]

where \( P(x) \) (cm/sec) is the permeability of the capillary endothelium at each point \( x \) and \( \xi \) is a tortuosity coefficient, the distance traveled by a tracer particle in going around cells or other obstructions relative to the distance along a straight line. The permeability-surface area product, \( P(x) \cdot 2\pi R_c L \), divided by the volume of distribution of tracer in the capillary blood, \( v_c \pi R_c^2 L \), gives the coefficient of the second term. Radial
diffusion is assumed to be instantaneous in both capillary and extravascular regions so that $\frac{\partial C_r}{\partial t}$ and $\frac{\partial C_f}{\partial t}$ are zero. The tissue concentration, $C_r$, is derived in a fashion analogous to that used to derive Eq. 14:

$$\frac{\partial C_r(x, t)}{\partial t} = \frac{D_r}{\xi_r^2} \frac{\partial^2 C_r}{\partial x^2} + \frac{2\pi R_c LP(x)}{v_r V_r} [C_r(x, t) - C_f(x, t)].$$

(15)

The permeability, $P$, was considered either to be constant or to increase or decrease linearly with distance along the capillary:

$$P(x) = P_0 + \frac{x}{L} (P_L - P_0)$$

(16)

where $P_0$ and $P_L$ are the permeabilities at the arterial and venous ends of the capillary. $P(x)$ can be any arbitrary nonnegative function.

In the tissue, tracer was assumed to move solely by diffusion. Values for the axial diffusion coefficient, $D_r$, and the tortuosity factor in the tissue, $\xi_r$, were taken from Page and Bernstein (21) and Suenson et al. (22) or calculated from the free diffusion coefficients assuming that the ratios of free to intratissue diffusion, $D$, are similar to those observed by these authors for similar molecules.

"Instantaneous" radial diffusion is justified when intercapillary distances, $2R_c$, are short and on the basis that when angular diffusion equals radial diffusion the corners of the hexagon have concentrations very close to those at the midpoints of the sides and the column can be considered to be cylindrical (Gonzalez-Fernandez and Atta [23]).

Because of the axial diffusion terms and the variable coefficient, $P(x)$, in Eqs. 14 and 15, analytical solutions were not found. Numerical solutions were obtained after the axial capillary and the surrounding tissue had been divided into $n_x$ segments along the vessel. This procedure allowed Eqs. 14 and 15 to be reduced to approximating ordinary differential equations which could then be solved by a finite difference technique modified by the use of some analytical expressions. An important feature required to minimize errors in computed local fluxes was the technique of "sliding" the capillary core through the hexagon in finite steps as recommended by Stephenson (24). In this technique, the time step, $\Delta t$, for the computations is fixed by the spatial grid and the flow:

$$\Delta t = V_c/n_x F_c = \bar{v}_c n_x.$$

(17)

Use of a $\Delta t$ smaller than this value appears as a relative exaggeration of the diffusional fluxes. (This situation occurred in some solutions for the previous model [4]1.) The finite difference techniques for solving the equations were more accurate when $\Delta t$ was small; therefore, $n_x$ was made so large that the solutions remained unchanged when it was increased further. An $n_x$ of up to 60 was used, but 20 usually sufficed for the solutions to be presented. Fluxes, $\Delta q/\Delta t$ (mmoles/sec), were calculated using Fick’s first law:

$$\Delta q/\Delta t = K \Delta C,$$

(18)

where the coefficient of exchange, $K$ (ml/sec), is comprised of a diffusion coefficient times an area divided by a distance and $\Delta C$ is a concentration difference. For the radial exchange coefficient between the capillary and the immediately surrounding segment of tissue, the exchange rate, $K_r$, is the permeability–surface area product of the $j$th segment:

$$K_r = \frac{2\pi R_c LP(x)}{n_x}$$

(19)

$$j = 1, n_x.$$

Eq. 19 is a steady-state equation and can be considered to be reasonable in the presence of changing concentrations in capillary and tissue on the basis that the time to reach steady state in a 0.3μ thick aqueous sheet (approximately equivalent to the capillary endothelial membrane) is about 0.05 msec ($[\Delta r]^2/2D = [0.3 \times 10^{-4}]^2/2 \times 10^{-5} = 0.05$ msec).

The longitudinal diffusional exchange rate, $K_x$, between capillary segments of length $L/n_x$ was

$$K_x = D_c \pi R_c^3 (1 - Hct + urbcHct)$$

$$\frac{\xi_r^2 L / n_x}{\xi_r^2 L / n_x},$$

(20)

which assumes that the cross-sectional area of the capillary available for axial exchange is $\pi R_c^2 v_r$, if diffusion occurs through plasma and the fraction, $urbc$, of the erythrocyte with which tracer rapidly equilibrates. The tortuosity factor, $\xi_r$, has been set at $1 + 0.5 \times Hct \times (1 - urbc)$ to take into account its dependence on hematocrit as suggested by La Force and Fatt (25).

Intracapillary dispersion analogous to that produced by a combination of laminar streaming with a convex velocity profile plus cross-stream or random mixing was produced simply by raising $D_c$ for...
CAPILLARY EXTRACTION

both the reference and the permeating tracer to values higher than those for molecular diffusion. Such values of $D_c$ can be considered the sum of "turbulent diffusion" (26) plus molecular diffusion.

The rate of exchange between tissue segments was

$$K_{xF} = \frac{D_c V_v n_x}{\xi^2 L^2}, \quad (21)$$

where the area for exchange is $V_v$ times the cross-sectional area $V_s/L$, the diffusion distance is again $L/n_x$, and $\xi$ is the tortuosity.

No net exchanges were allowed at the boundaries between neighboring hexagons (at $r = R$ and at $x = 0$ and $L$), since $\partial C/(\partial r$, $\partial C/(\partial x$, and $\partial C/(\partial x$ were zero, emphasizing the assumptions that neighboring capillaries had the same starting and ending points and that their flows were concurrent and of equal velocity. Indicator input and output were via flow alone, and intravascular diffusional exchanges at the entrance and exit were considered to be negligible.

The numerical method was based on the assumption that the velocity profile in the capillary was flat. The technique of sliding the intracapillary fluid downstream in a stepwise fashion was accomplished as follows: at the beginning of each computational time step, the intracapillary concentration $C_c$ in the $j^\text{th}$ segment was replaced by that immediately upstream as if the capillary contents suddenly slipped one segment length downstream.

$$C_{c,j}(t_+) = C_{c,j-1}(t_-), \quad (22)$$

where $j$ is the index of the segment along the vessel and the negative and positive subscripts indicate times just before and just after time $t$ at the beginning of a time step. $C_{c,j}(t_+)$ is $C_{c,j}(t_-)$ when the input is directly into the capillary or it is the output of the arterial segment, $C_{c,j}(t_-)$, which is $C_{c,j}(t_+)$ when the input is into the capillary or it is the output of the arterial segment. This technique separates the handling of the terms containing $\partial C/\partial t$ and $\partial C/\partial x$.

During each $\Delta t$ the diffusional exchanges occur. The rate of mass accumulation in each segment of capillary blood was given by the net rate of addition of mass by convection plus the net additions due to axial diffusion and permeation of the capillary wall:

$$C_{c,j}(t + \Delta t) = C_{c,j}(t) + \frac{\Delta t n_x}{V_v} \cdot \left[ K_{x,j}[C_{c,j-1}(t) - 2C_{c,j}(t) + C_{c,j+1}(t)] + K_{r,j}[C_{c,j}(t) - C_{c,j}(t_-)] \right], \quad (23)$$

Eq. 23 is the finite difference form of Eq. 14b: $C_{c,j}(t + \Delta t)$ is the concentration at the end of the interval just prior to the next time step. The time derivative of $C_c$ at the $j^\text{th}$ location along the $x$ axis is $C_c(t + \Delta t) - C_c(t)$; the second derivative $\partial^2 C_c/\partial x^2$ is given by $(C_{c,j-1} - 2C_{c,j} + C_{c,j+1})$. The tissue exchanges with intracapillary fluid are governed by $K_{c,j} - C_c(t)$ or $K_{r,j} - C_{c,j}(t_-)$. The final flow term of Eq. 14b was approximated by the stepwise sliding at the beginning of each time interval, $\Delta t$. During the time step $\Delta t = F_v/n_x$, the flow moves $F_v \cdot \Delta t \, \text{ml}$, which is exactly the volume of the segment $V_v/n_x$.

In the tissue, only diffusional exchanges were considered. Thus, for the $j^\text{th}$ tissue compartment, the conservation of mass expressed in Eq. 15 was put in finite difference form analogous to that in Eq. 23:

$$C_{t,j}(t + \Delta t) = C_{t,j}(t) + \frac{\Delta t n_x}{V_v} \cdot \left[ K_{x,t}[C_{t,j-1}(t) - 2C_{t,j}(t) + C_{t,j+1}(t)] + K_{r,t}[C_{t,j}(t) - C_{t,j}(t_-)] \right], \quad (24)$$

This finite difference method is accurate when $\Delta t$ is small and $n_x$ is large. To shorten computation times, Eqs. 23 and 24 were modified to take advantage of analytical calculations at each time interval, permitting the use of fewer segments and larger values of $\Delta t$. Thus, momentarily ignoring the axial movement of indicator, the transport of tracer across the capillary membrane, $dq_r/\partial t$, is given by the simultaneous equations:

$$\frac{dq_{r,j}}{\partial t} = \frac{V_v C_v}{n_x} \cdot \frac{dC_{c,j}}{\partial t} = K_{r,j}[C_{c,j}(t) - C_{c,j}(t_-)], \quad (25a)$$

$$\frac{dq_{r,j}}{\partial t} = \frac{V_v V_k}{n_x} \cdot \frac{dC_{t,j}}{\partial t} = K_{r,t}[C_{t,j}(t) - C_{t,j}(t_-)], \quad (25b)$$

whose solution for the interval $\Delta t$ is

$$\Delta q_{r,j} = \frac{V_v C_v}{n_x} \left\{ 1 - \exp \left[ -\Delta t K_{r,j} \left( \frac{n_x}{V_v C_v} + \frac{n_x}{V_v V_k} \right) \right] \right\}. \quad (26a)$$

$$\Delta q_{r,j} = -\Delta q_{r,j}, \quad (26b)$$

where $\Delta q_r$ is the amount traversing the membrane during the interval $t$ to $t + \Delta t$. Similarly, if the radial exchanges are momentarily ignored, the
longitudinal exchanges between a capillary compartment and its neighbors upstream and downstream can be calculated analytically.

\[ \Delta q_{x_j} = \frac{v_x V_x}{2n_x} \left[ 1 - \exp \left( -\frac{2\Delta t \cdot K_{x} n_x}{v_x V_x} \right) \right] \]

\[ \cdot \left[ C_{x-1}(t_x) - 2C_{x}(t_x) + C_{x+1}(t_x) \right]. \] (27)

An analogous expression was used for the nonpermeating reference tracer for which the diffusivity (turbulent plus molecular) was given by \( D_{nt} \), which is different from \( D_n \) and entry into erythrocytes was prohibited.

For diffusional exchanges between the \( j^{th} \) and the \((j-1)^{th}\) and \((j+1)^{th}\) extravascular compartments, the calculations are similar.

\[ \Delta q_{x_j} = \frac{v_x V_x}{2n_x} \left[ 1 - \exp \left( -\frac{2\Delta t \cdot K_{x} n_x}{v_x V_x} \right) \right] \]

\[ \cdot \left[ C_{x-1}(t_x) - 2C_{x}(t_x) + C_{x+1}(t_x) \right]. \] (28)

Then,

\[ C_r(t+\Delta t_+) = C_j(t_+ \cdot \frac{n_x}{v_x V_x} (\Delta q r_j + \Delta q x_j). \] (29)

\[ C_{x}(t+\Delta t_+) = C_{x}(t_+ \cdot \frac{n_x}{v_x V_x} (\Delta q r_{x} + \Delta q x_{x}). \] (30)

Eqs. 26-28 were not solved as simultaneous equations throughout the whole matrix, but they were solved separately. This approach is reasonably accurate when the terms in the first set of brackets in Eqs. 27 and 28 are less than 0.1; they are only about 0.02 when \( n_x \) is 20 or more and \( D_r \) and \( D_x \) are less than 10^{-8} cm/sec. These equations were modified at the ends of the cylinder so that no exchanges occur with the 0^{th} or \((n_x + 1)^{th}\) compartments.

**ACCURACY OF COMPUTATION**

Using the parameter values given in the preceding section, solutions showed some differences with different small values of \( n_x \). However, changing \( n_x \) when it was over 20 did not change the curves. Larger diffusion coefficients necessitated larger values for \( n_x \). Solutions were also compared with the Sangren-Sheppard model by putting \( D_{x}, D_{nx} \), and \( D_x \) equal to zero with \( P(x) = \) a constant. With \( PS/F_s' \) of 0.1, 1.0, and 10, the solutions for outflow concentration at a time 10\( t_0 \) differed at each point by less than 1% from the analytical solution (5), and the differences were less at shorter times, attesting to the numerical accuracy in this limiting case.

The finite difference method allows rapid computation, permits the use of a variety of input functions (pulse, step, or an experimental curve) with equal ease, and lets permeability be varied along the capillary as described in the preceding section or with time if desired.

To approximate experimental situations most closely, it was felt desirable to use an input function which matched realizable experimental input functions to the heart. For this purpose, the transport function, \( h_n(t) \), between the injection site and the entrance to the capillary was described by a lagged normal density curve (27), a unimodal density function having variable relative dispersion, skewness, and delay. This input form can be considered to describe either the dispersion in the arterial inflow to a single capillary or the variation in path lengths leading to a large number of identical capillaries. The use of a dispersed input does allow the influence of return of tracer from tissue to blood (often called back diffusion) on calculated extractions, \( E(t) \), to be seen more realistically.

The third component of the transorgan transport function, Eq. 3, is the transport function of the venous system, \( h_v(t) \). It was modeled using an overdamped fourth-order differential operator described previously (28). Thus, the venous outflow concentration, \( C_{out}(t) \), was the convolution of the capillary outflow, \( C_{x}(t) \), with \( h_v(t) \).

**COMPUTATIONS**

Solutions to the model were obtained from a FORTRAN program in a medium speed digital computer (Control Data Corporation model 3300) operating under a time-sharing monitor. Program control was via SIMCON (29), an input-output control program devised for simulation studies which permits changing of the parameters in the model or the input functions and the choice of variable to be displayed on an oscilloscope (Tektronix model 564) where single or multiple solutions (Figs. 2-7) were photographed with a Polaroid model C30 camera.

**Results**

**RESPONSES OF THE MODEL TO VARIOUS INPUT FUNCTIONS**

Figure 2 shows the responses of the capillary-tissue model, undistorted by any dispersion or delay in the venous outflow, for three different forms of the input curve, \( C_{in}(t) \). In the top section, \( C_{in} \) was a pulse 1 second in duration. The output curve for the reference tracer, \( h_n(t) \), was an identical undeformed but delayed pulse. The output permeant tracer curve, \( h_p(t) \), had two components. The first
CAPILLARY EXTRACTION

**FIGURE 2**

Responses of capillary-tissue model to three input functions (see text). Parameters were: \( R_c = 1.62 \), \( L = 400 \), \( R = 7.5 \), \( v_e = 0.15 \), \( W = 1.0 \) ml/g min\(^{-1} \), \( F = 1.063 \) g/ml, \( P = 2 \times 10^{-4} \) cm/sec, \( v_e = 0.32 \), \( n = 50 \), \( Hct = 0.5 \), \( v_r = 0 \), \( D_c = D_E = 0 \). Parameters of the lagged normal density curve input used in the middle section of the figure were \( a = 0.81 \) seconds, \( \tau = 1.0 \) seconds, and \( t_e = 2.5 \) seconds. \( PS = 0.59 \) ml/g min\(^{-1} \) and \( PS/F, \) \( 1.39 \).

component was a pulse about 60% lower than \( h_v(t) \) due to escape of tracer into extravascular tissue. There was a slight rise in \( h_v(t) \) during this phase because of return of escaped tracer. The second component was a very low long tail due to the remainder of the returning tracer; it is an almost monoexponentially decaying curve scarcely distinguishable from the baseline. The semilogarithmic plots of the impulse responses of the model of Goresky et al. [5] should be perused for a detailed display of solutions to this particular limiting case with \( D_p = D_E = 0 \), which is the Sangren-Sheppard model [21]. The extraction, \( E(t) \), calculated by Eq. 1 was about 0.6; it diminished slightly because of tracer return during the 1-second pulse, and, when \( h_v(t) \) became zero at the end of the pulse, it became incalculable. In all figures, \( E(t) \) is plotted only when values are positive. \( E(t) \) becomes negative when the reference tracer concentration falls below that of the permeant tracer during the tails of all curves. The slopes of these tails can be used to estimate \( PS/v_eV_E \) in the barrier-limited case, as Perl (6) showed, but the negative values of \( E(t) \) during the tails are too dependent on the form of \( C_{in}(t) \) and on other factors to be useful.

With the lagged normal density curve as the input (Fig. 2, middle), the curve for the reference tracer at the venous end of the capillary, \( C_{rv} \), again had exactly the same shape as the input curve but was delayed. The concentration of the permeant tracer at the venous end of the capillary, \( C_{rv} \), although similar in shape to \( C_{rv} \) in its initial portion, had a very slow prolonged decay. The extraction, \( E(t) \), became negative about 8.5 seconds after injection and was not plotted.

The response to a step input is the integral of the response to the impulse and is really the cumulative residence time distribution function, \( H(t) \), as defined by Zierler (30). For the reference tracer, \( H_v(t) \) became constant at 1.0 as soon as it appeared, but \( H_v(t) \) rose slowly as tracer returned from \( E(t) \) to diminish slowly over the more than 200 seconds required for the input and output concentrations to become equal and the tissue to become saturated with tracer.

**EFFECT OF PERMEABILITY ON EXTRACTION**

In Figure 3 (left) the responses to a dispersed input are shown for the nondiffusible tracer, \( h_v(t) \), and for the permeating tracer, \( h_v(t) \), at five different permeabilities, \( P \), from 0.5 to \( 8 \times 10^{-5} \) cm/sec. Axial diffusion was zero. Taking the surface area, \( S \), as \( 607 \) cm\(^2\)/g, from Eq. 12, \( PS \) values ranged from 0.18 to 2.91 ml/g min\(^{-1} \). At low values of \( P \), the calculated extraction, \( E(t) \), was low and constant in its early portion. At the highest permeability shown, \( P = 8 \times 10^{-5} \) cm/sec, the extraction was near 100% and remained high until back diffusion occurred causing \( E(t) \) to diminish rapidly to zero. At all values of \( P \), for these cases with \( D_E = 0 \), the initial values were the highest; some downslope of \( E(t) \) at early times was most readily discernible when \( E_{max} \) was about 50%. Since experimental accuracy limits the usable range of values of \( E \) from about 5% to 75% in the heart, to extend the range of estimable permeabilities beyond a single decade, one must vary the flow.

Rous and co-workers (31) and more recently Wiederhielm (32) have shown that the permeability at the venous ends of capillaries can be up to 10 times greater than that at the arterial ends. Figure 3 (right) shows that the early values of \( E(t) \) are insensitive to such gradations in permeability and give a measure only of the average \( P \). Two solutions for which the average permeability along the length of the capillary was \( 2 \times 10^{-6} \) cm/sec are shown; one solution was obtained with the permeability constant along the length of the capillary and the other with the permeability at the venous end 80 times that at the arterial end. The two solutions were no different in their early portions. A minor effect of increased venous permeability was slightly earlier back diffusion from tissue to blood which
gave the curve of \( E(t) \) the appearance of having a slightly smaller volume of distribution; the cause is the relative increase in \( C_p(x = L) \) compared with \( C_p(x = 0) \) which promotes relatively early escape of tracer from the extravascular region into the outflow.

**Effect of Membrane Contact Time and Capillary Volume on Extraction**

An enlargement of the total capillary volume while flow remained constant resulted in a prolonged capillary transit time, \( T_c \), which is the contact time for fluid and membrane, increased the probability of escape from blood to tissue, and therefore increased the early values of \( E(t) \). From Eqs. 6–11, \( T_c \) can be expressed to show which variables are involved:

\[
T_c = \frac{\pi R_c^4(1 - u_c)W}{2\sqrt{3} R^2 F_a p} = \frac{\pi R_c}{2\sqrt{3} R^2 F_a p/u_c}. \tag{31}
\]

Estimates of \( P \) from observed values of \( E \) are not only dependent on the obvious and easily measured variables \( F_a \), \( p \), and \( W \) but also on variables for which accurate values are not readily obtained. Underestimation of large vessel volume, \( u_c \), causes overestimation of \( N_c \) and \( S \) and underestimation of \( P \). Solutions for varied \( u_c \) are shown in Figure 4 (top left). A fivefold range of values of \( u_c \) resulted in 10% changes in \( E_{max} \), suggesting that over the more probable range of \( u_c \), from 0.05 to 0.12, the errors are not likely to be very large.

Accuracy of estimation of \( R_c \) is quite important. Underestimation of capillary radius means underestimation of surface area, \( 2\pi R_c L \), and overestimation of linear velocity of the blood, \( F_c/\pi R_c^2 \), and therefore, for any observed value of \( E(t) \), results in rather significant overestimation of the true permeability. With \( R_c \) ranging from 1.6\( \mu \) to 2.6\( \mu \), initial extractions were from 0.52 to 0.70 and the actual permeability–surface area products were from 0.44 to 0.71 ml/g min\(^{-1} \) (Fig. 4, top right). If an average value for surface area of 500 cm\(^2 \)/g myocardium had been assumed, the estimates of \( P \) would have ranged from 1.47 to 2.38 \( \times \) 10\(^{-5} \) cm/sec, although \( P \) was actually 1.5 \( \times \) 10\(^{-5} \) cm/sec for these solutions.

The estimates are very nearly as sensitive to errors in intercapillary distance, \( 2R \). The hexagon volume, \( V \), is proportional to \( R^3 \) (Eq. 6a), and therefore only a 10% overestimate in \( R \) results in an 18% underestimate in \( N_c \) and \( S \) (cm\(^3 \)/g) or a 21% overestimate in \( P \) from the observed extractions. This sensitivity of \( P \) to errors in estimates of \( R, R_c \), and \( u_c \) has discouraged most investigators from estimating \( P \) and has led them, quite sensibly, to report their results simply in terms of the \( PS \) products.

Eq. 31 states that \( L \), capillary length, does not influence \( T_c \); hence, error in \( L \) ordinarily has no
Effects of contact time and exchangeable intravascular volumes on extraction. With $F_c/W = 1 \text{ ml/g min}^{-1}$, $v_w = 0.15$, $R_r = 2\mu$, $Hct = 0.5$, $v_{ec} = 0$, $P = 1.5 \times 10^{-4} \text{ cm/sec}$, and $\rho = 1.063 \text{ g/ml}$, $S = 607 \text{ cm}^3/l$, $P_S/F' = 1.28$.

**Top Left:** Increasing the fractional volume, $v_w$, of the nonexchanging arteries and veins from 5% to 25% of the organ volume reduced the functional myocardial mass and the number of capillaries and resulted in a 13% diminution in $E_{\text{max}}$.

**Top Right:** With $v_w = 0.15$, $R_r$ was increased from 1.6$\mu$ to 2.6$\mu$ in steps of 0.25$\mu$, resulting in reduced intravascular velocity and increased capillary surface area, which thereby caused $E_{\text{max}}$ to increase from 0.52 to 0.70. Other parameters were the same as they were for the top left section of this figure.

**Bottom Left:** Increasing hematocrit from 30% to 50% with $v_{ec} = 0$ decreased plasma volume and resulted in an increase in $E_{\text{max}}$ from 0.48 to 0.60. $v_w = 0.15$; other parameters are the same as they are for the top left section.

**Bottom Right:** With Hct constant at 0.50, increasing the rapidly exchangeable fraction of the erythrocyte from 0 to 0.8 reduced $E_{\text{max}}$ from 0.60 to 0.40; this situation is the same as that which occurs when plasma flow is increased 80% or Hct is reduced to 0.10.

---

Effect on the interpretation of $E(t)$. A doubling of the value for $L$ in the model halves $N_c$ and doubles $F_c$ leaving $I_c$ constant and the probability of escape of tracer from blood to tissue unchanged. When axial diffusion is important, changing $L$ will have an effect, because the ratio of convective to diffusive velocities as shown by the axial Peclet number, $(F_c/\pi R^3)/(D_r/L)$, will be changed. This effect was evident in the pulse responses of the parent model (ref. 4, Fig. 7) where $E(t)$ showed markedly increasing early values when $D_r/L$ was very high (10$^{-1}$ cm/sec) and the Peclet number was low.

$F'_r$, the flow of solute-containing mother fluid per unit tissue mass, is calculated by Eq. 13 on the assumptions that there is instantaneous radial mixing within the capillary blood and that the erythrocyte membrane is not acting as a barrier between plasma and the intraerythrocyte space defined by $v_{ec}$. With $v_{ec} = 0$, no tracer entered erythrocytes and therefore $E_{\text{max}}$ increased with increasing $Hct$ and diminishing $F'_r$ (Fig. 4, bottom left). Increasing $v_{ec}$ increases $F'_r$ substantially at normal hematocrits and decreases $E_{\text{max}}$ (Fig. 4, bottom right). When $v_{ec}$ is large, changing Hct has little effect. However, even for antipyrine, when $v_{ec}$ is slightly larger than the erythrocyte water content (33), the effects of changing Hct are of consequence for accurate interpretation of mean transit time estimations (12, 20). On the other hand, for most of the small hydrophilic solutes for
which the estimation of $E(t)$ is fruitful, the permeability of the red cell membrane is so low that the exchange is negligible when the solutes are injected into the arterial inflow without preequilibration with erythrocytes, so that $v_{ec}$ is effectively zero, as described by Goresky et al. (34). The fractional exchange rate for completely barrier-limited escape across the capillary membrane is $P_{2\pi R_c L/\nu_c V_c} = 2P/\nu_c R_c$, the capillary permeability-surface area product divided by the capillary volume of mother fluid. The bottom sections of Figure 4 show that increasing the solute-containing volume diminishes the fractional extraction.

EFFECT OF THE extravascular VOLUME OF DISTRIBUTION

Figure 5 shows curves of $E(t)$ for increasing values of $v_E$ with $F_c'$ and all other parameters held constant but with axial diffusion. The initial value for $E(t)$ was 0.62 in this case for large and small $v_E$. But, as predicted by Johnson and Wilson (7), with small values of $v_E$ the return of tracer was so early that $E(t)$ had plateaus too short to be readily measurable. Larger values of $v_E$ provided values of $E(t)$ with longer plateaus from which relatively reliable estimates of $E_{max}$ could be obtained; the curves are similar to the experimental curves obtained by Crone (35), Yudilevich et al. (19), and Guller et al. (36). For any given $v_E$ the plateaus of $E(t)$ were longest when the extractions were small (e.g., Fig. 3, left).

LONGITUDINAL DIFFUSION OR DISPERSION

For the solutions presented so far, the coefficients for longitudinal diffusion in tissue, $D_{c0}$, and in the capillary, $D_{cN}$, have been zero. Figure 6 (left) shows solutions with and without axial diffusion (dotted and solid lines, respectively). $D_{cN}$ and $D_{cP}$, representing overall diffusivities (molecular plus turbulent) for reference and permeant tracers, of $2 \times 10^{-5}$ cm$^2$/sec resulted in lowering the peak heights of $h_N(t)$ and $h_P(t)$. Without axial diffusion the initial value of $E(t)$ was $E_{max}$; with axial diffusion initial values of $E(t)$ were low and rose to a later $E_{max}$ (dotted line), which was slightly lower than $E_{max}$ without axial diffusion.

With $D_{c0} > D_{cN}$, late portions of $E(t)$ were unaffected, but early negative values indicated a very brief precession of the more diffusible tracer along the capillary itself, an observation which could only be made experimentally with a very refined sampling system. In Figure 6 (right), solutions at two low permeabilites ($PS/F'_c = 0.20$ and 0.40) with $D_{cN} = 1.0 \times 10^{-5}$ cm$^2$/sec and $D_{cP}$ having values of 0, 0.8, 1.6, and $2.4 \times 10^{-5}$ cm$^2$/sec are shown. Diffusion coefficients were given these unusually high values to exaggerate the results for illustrative purposes. These curves need to be interpreted while keeping in mind that, for these solutions, the velocity profile in the capillary was flat and therefore the “diffusion” produced axial dispersion. For each set of four curves, higher $D_{cP}$ reduced the peak of $h(t)$ because of increased longitudinal dispersion of the bolus of permeant tracer. When $D_{cP}$ was high, $E(t)$ showed a maximum at the time of the peak of $h_N(t)$. With $D_{cP} < D_{cN}$, $h_P(t)$ was less dispersed than $h_N(t)$ so that the apparent early values of $E(t)$ were very high, as shown, and a minimum was obtained at the time of the peaks of $h(t)$. Thus, the relative amounts of dispersion undergone by the boluses of reference and permeating tracer determine the shape of $E(t)$. Although it is not realistic for the nonpermeant tracer to have a greater molecular diffusivity than does the permeant tracer, Taylor (37) has shown that with a parabolic velocity profile a bolus of highly diffusible solute will, because of interlaminary radial diffusion, become less dispersed than will a less diffusible substance; this situation is approximated with a flat velocity profile by setting $D_{cN} > D_{cP}$. The initially decreasing values of $E(t)$ observed by Lassen and Crone (38) may be attributable to such radial diffusion, but it is most likely...
that such diffusion occurs primarily in vessels larger than capillaries.

\[ E(t) \text{ and } PS/F' \]

The relationships between the theoretically expected extractions and the primary governing parameters, \( P \), \( S \), and \( F' \), are presented in dimensionless form in Figure 7 (left) by plotting \( \log(1 - E(t_{eq})) \) vs. \( PS/F' \). In the absence of longitudinal diffusion, the standard equation (Eq. 2) is the broken line, which assumes no back diffusion and also describes the initial extractions predicted by the models of Martin and Yudilevich (13) and of Johnson and Wilson (7). Estimates of \( PS/F' \) from \( E \) using Eq. 2 are too low when \( PS/F' \) is high because of tracer return (back diffusion).

The crosses shown in Figure 7 (left) above the solid line represent the relationships occurring when the nonpermeating tracer becomes more dispersed than the permeant one. These relationships would apply when intravascular dispersion is dominated by radial diffusion in the presence of a parabolic velocity profile (Taylor's effect). Below and to the left of the solid line are the relationships when the dispersion of permeating tracer is the greater (open circles). These relationships occur when axial diffusion dominates, which can really be expected only when the velocity profile is flat. If the relative dispersions of \( h_N \) and \( h_0 \) occurring during transorgan passage could be estimated, then at least partial correction for the resultant distortion of \( E(t) \) could be made. These sources of deviation from Eq. 2 are illustrated in Figure 7 (right). The important point is that the general relationships portrayed in Figure 7 are applicable no matter what mechanisms are involved in producing the dispersion of the tracers. This statement must be qualified by emphasizing that it applies to a homogeneously perfused organ. Other explanations for an initially rising \( E(t) \) are available in multicapillary systems; the most likely is that the capillaries with the highest flow have the shortest transit times and the lowest extractions, giving low initial values of \( E(t) \).

**EFFECT OF DISPERSION IN THE VENOUS OUTFLOW ON E(t)**

In each experiment the importance of dispersion in the venous outflow and the sampling system should be assessed. Although theoretically one can deconvolute to correct for the distortions by the sampling system, this procedure is usually impractical, especially when the experimental concentration-time curves have been sampled at intervals of a second or more. Moreover, deconvolution cannot correct for venous dispersion, since the venous transport function, \( h_U(t) \), is never known exactly; only the total intravascular \( h(t) \) from injection to sampling site is known. The purpose of Figure 8 is to show that venous dispersion can mask the information contained in \( E(t) \) and is likely to do so when the extravascular volume of distribution, \( V_E \), is small.

**Effects of longitudinal intracapillary diffusion. Left:** Finite axial intravascular dispersion (dotted lines) of both tracers, permeant and nonpermeant, gave lower values for the early part of \( E(t) \), although \( E_{max} \) was very nearly as high (0.615 compared with 0.633) as it was when dispersion was zero (solid lines). **Right:** When the reference tracer became more dispersed than the permeating tracer, \( E(t) \) was initially high and decreased to a temporary minimum. When the permeating tracer was relatively more dispersed, \( E(t) \) rose gradually to peaks that were slightly greater than the value of \( E_{max} \) obtained when axial dispersion was zero for both tracers. The values of \( E(t) \) at the first nodes at 5.4 seconds were 99% of \( E_{max} \) obtained with \( D_{u2} = D_{u1} = 0 \). See text.

*Circulation Research, Vol. 35, September 1974*
Effects of back diffusion and axial dispersion on estimates of PS. Left: The broken line is the classical calculation, Eq. 2. With a limited extravascular region, $v_E = 0.2$, tracer returns, reducing $E(t_n)$ (solid line). Axial intravascular dispersion of reference and permeant tracers causes small changes in $E(t)$, which result in substantial errors in estimating PS only at low PS/F.' Right: Ratio of PS/F,' estimated by Eq. 2 to actual PS/F,' in eight situations (four differing axial dispersion effects at each of two extravascular volumes of distribution). The “ideal” line at 1.0 would occur with $v_E = \infty$; smaller values of $v_E$ deviate more from the ideal. Lines A (no intravascular dispersion) and C (equal dispersion of permeant and reference tracers) approach the ideal at low PS/F,' but C deviates more than A at high PS/F,'. Relatively greater dispersion of the permeant tracer (lines B and circles in the left section of figure) gives increased $E(t_p)$ and slight overestimation of PS at low PS/F,'. Relatively greater dispersion of the nonpermeant (Taylor diffusion) does the opposite (lines D and crosses in the left section).

Effect of dispersion in the venous outflow. The capillary outflow is convoluted with venous transport functions, $h_v(t)$, representing volumes of outflow veins that are small ($t_v = 1$ second) and large ($t_v = 10$ seconds). The dispersion occurring with large venous transit times resulted in lower apparent values of $E_{max}$ and underestimation of PS. The reduction in $E_{max}$ was small when $v_E$ was large, giving minimal back diffusion, but the diminution of $E_{max}$ and particularly $E(t_p)$ was substantial when $v_E$ was small. Four cases are shown in Figure 8: large and small $v_E$ and short and long venous mean transit times. The model for $h_v(t)$ was a fourth-order overdamped differential operator (28) with a relative dispersion of 0.30 and a skewness of 1.0; PS/F,' = 1.0, PS/$v_E V_E = 0.07$/sec, and $D_C V = D_C P = 5 \times 10^{-4}$ cm$^2$/sec. With this linear operator providing $h_v(t)$, the venous dispersion is identical for the permeant and the nonpermeant tracer. When $v_E$ was large (left) back diffusion was minimal, and $E(t)$ had a relatively long flat plateau. The plateau was significantly lengthened when $t_v$ was lengthened from 1 second to 10 seconds, but its $E_{max}$ of 0.615 was virtually uniminished in comparison with the $E_{max}$ of 0.618 when $t_v$ was 1.0 second. In contrast, when $v_E$ was small (0.08, Fig. 8, right), earlier back diffusion reduced $E_{max}$ to 0.600, even with a $t_v$ of 1 second. With a $t_v$ of 10 seconds, the effects were...
important; although $E_{\text{max}}$ was computed to be 0.597 in this idealized situation, this maximum occurred at about $t = 5$ seconds, which is a time when the venous outflow concentrations are still so low as to be almost unmeasurable experimentally. By $t = 7.5$ seconds, $h_v$ had risen to 10% of peak height, but $E(t)$ had diminished to about 0.56, which would give a 15% underestimate of $PS$. Therefore, minimization of venous and sampling system volumes is advisable.

**Discussion**

Description of the behavior of the present model has three purposes. The first is to emphasize that it is important not merely to consider the idealized capillary-tissue model but also to consider the total organ so that one can attempt to define the parameters of a model in terms of the experimentally accessible information. The second is to illustrate transient responses of a model of passive capillary-tissue exchange whose primary new features are axial diffusion, permeability which varies along the length of the capillary, and arterial and venous transport function influences. The third is to show that the classical equation, $PS = -F_{g'} \log(1 - E)$, can be applied over a limited range of $PS/F_{g'}$ values in the ideal situation. Some of the principles involved have been previously reviewed (39).

**REDUCTION TO OTHER MODELS**

Although this model is overly simple, it has the virtue that when it is simplified further it can be reduced to other models of proven value. The model is dependent on radial intratissue diffusion being rapid compared with the permeation of the capillary membrane, as shown in Figure 9. When there is no axial diffusion ($D_e = D_{cv} = D_{c0} = 0$) and the permeability is finite, this model becomes the Sangren-Sheppard model (2, 5). With the further assumption of infinite permeability, this model asymptotes to the delayed wave flow-limited extreme described by Goresky (40). With $D_e = D_f$, and $P = \infty$, the model is identical to that of Perl and Chinard (10) and simplifies to a first-order mixing chamber when $D_e = D_f = \infty$. With $D_e = \infty$ and $P(x)$ finite and constant, the model is identical to that of Johnson and Wilson (7). Our model does not reduce to that of Lee and Fronek (9) by using zero longitudinal diffusion, since they used finite radial diffusion with infinite intercapillary distances.

**GEOMETRICAL LIMITATIONS OF THE MODEL**

Being based on the assumption that the capillaries have synchronized starting points, equal flows, and constant intercapillary distances and lengths, the model is somewhat too simple and permits no exchange of solute between regions having different velocities or directions of flows. Studies by Thompson et al. (41) and Yipintsoi et al. (42) have shown that the flow in an organ even as homogeneously constructed as the heart is still not uniformly distributed. In addition, there must be nonuniformity of permeability and of capillary radii or surface area for exchange. Levitt (11) has taken a step in the right direction in developing a model with offset starting points, but it has the weakness that capillary interactions are considered to occur via a uniformly mixed extravascular space,
which is unreasonable. The model of Goresky et al. (5) of noninteracting parallel units with differing capillary transit times is more likely useful for slowly permeating solutes. Some idea of nonuniformity of flow can be obtained from washout curves for highly diffusible substances such as antipyrine and water by assuming monoexponential washout and applying the graphical analysis of Van Liew (43), but those studies yield no idea of variability in PS. In recent studies Crone and Garlick (44) observed the washout of sucrose, mannitol, and inulin from the gastrocnemius muscle following a 90-120-minute period of equilibration. They observed that the fractional escape rate (FER) of each of these substances decreased with time, but more so for the small molecules than for the large. At early times the FER was in approximately the same proportion as the diffusion coefficient, suggesting that there was no restriction to diffusional exchange. But at later times the ratio of the FER for sucrose and that for inulin was near unity; this finding could conceivably be explained on the basis that the escape of the two substances at these late times was from regions of low flow and that their washout was flow limited, so that a difference in their diffusibilities had no effect. These observations can also be partially explained as a variation in position of the starting and terminating points of adjacent capillaries, for such a configuration results in some net diffusional exchange between tissue regions supplied by the adjacent capillaries and will cause a more rapid initial washout of the more diffusible tracer. A further possibility is that sucrose enters the sarcoplasmic reticulum, although inulin does not, so that in the late phase of washout the FER for sucrose is slowed by the traversal of the sarcolemma.

Such observations conflict with the assumption on which the models of Johnson and Wilson (7) and Levitt (11) are based. They argued that the extravascular space should be considered to have a uniform concentration because of the variation in starting points, capillary lengths, and intercapillary distances. If this assumption were reasonable, three experimental observations should be apparent. First, Crone and Garlick (44) should have observed constant ratios of fractional escape rates. Second, outflow dilution curves following slug injection of tracers should show precession of the more highly diffusible tracer, but none has been apparent (12, 19, 36, 45, 46). Third, the curves of $E(t)$ should be negative or very low in the first sample and should rise in the first few seconds, as can be seen in the parent model when the diffusion coefficient was high (ref. 4, Fig. 8). But the usual observations are fairly flat $E(t)$ curves (19, 36, 45, 46), some of which diminish (38). Rising values of $E(t)$ have been seen for sodium (36) and potassium (47, 48) on most curves; the most likely explanation is heterogeneity of flow. A point in favor of some interaction between capillaries is the observation from this laboratory by Yipintsoi and Tancredi (unpublished) showing that extraction of tritiated water is only 90% and virtually constant at different flows but still less than 1.0 with $v_C V_d u_b V_e$. The assumption of uniform tissue mixing can be provided in the present model by infinitely rapid axial diffusion in the tissue ($D_e = \infty$). But for the blood-perfused dog heart and probably for most high-flow organs, axial diffusion seems to have a negligible effect; for example, Yipintsoi and Bassingthwaighte (12) have shown that the basic shape, relative dispersion, and skewness of the washout curves of iodoantipyrine are independent of the flow. Curves obtained at different flows were superimposed on each other when they were plotted as the residue versus $t/t_e$, which cannot occur when there are any barrier limitations or unless longitudinal diffusion is either negligible or infinite. The shape similarity cannot occur with any variability in the ratio of tracer movement by convection versus diffusion.

Exploration of the model's behavior at various flows is based on an assumption of constant capillary density. In the heart, the increase in capillary density with an increase in flow is not great (18), but in skeletal muscle many more capillaries are open during exercise than at rest. The flow-dependent geometry could in part be taken into account by reducing intercapillary distances and increasing capillary radii at higher flows, as Roughton (49) suggested. Such geometrical changes could provide a partial explanation for the observations by Renkin (3), Yipintsoi et al. (18), Trap-Jensen and Lassen (50), and others, that estimates of PS are higher at higher flows. In addition, at low flows back diffusion is relatively important in reducing $E(t)$, causing PS to be underestimated. Yet another possibility is that regional flows are more homogeneous at high flows, which tends to reduce interactions between capillaries and raise $E(t)$. Although opposed by our interpretation of the iodoantipyrine washout data (12), one could argue that apparent increases in PS with increasing $P$ might also be due in part to axial diffusion of tracers in the plasma.
for if the flow has a flat or partially flattened velocity profile (Coulter and Pappenheimer [51]) or is turbulent (Aris [52]), then the more diffusible (permeating) tracer will tend to spread axially more than the reference (nonpermeating) tracer and will reduce the early values of \( E(t) \), as has been observed (36, 47, 48); the effect is greater at low flows.

The assumption of negligible radial concentration gradients, \( \frac{\partial C}{\partial r} = 0 \), is reasonable with a half intercapillary distance, \( R_c \), of 8–10 \( \mu \). Solutions of the parent model (4), where nonzero values of \( \frac{\partial C}{\partial r} \) were accounted for, are shown in Figure 9, using tissue diffusion coefficients, \( D_r \), and \( D_e \), of 1 \( \times 10^{-4} \) cm\(^2\)/sec for the radial and axial directions, an intercapillary distance of 20 \( \mu \), and a capillary radius of 4 \( \mu \). The solutions showed negligible gradients radially, in spite of the extraordinarily high permeability (\( P = 2.5 \times 10^{-3} \) cm/sec) and the low diffusion coefficient, because although the ratio \( P/[D_e/(R - R_c)] \) was high (1.5) the relaxation time for radial diffusion \( (R - R_c)^2/2D_r \) was short (0.18 seconds) compared with the capillary transit time of 0.66 seconds. Gonzalez-Fernandez and Atta (23) showed that angular diffusion led to negligible concentration gradients along the sides and into the corners of a hexagonal column, justifying the present use of the diffusion relaxation time radially in a cylinder. This result was anticipated by Johnson and Wilson (7), Blum (53), Pollock and Blum (54), and Knisely et al. (55), who ignored radial gradients in their modeling, but this assumption should not be made for tracers of lower diffusibility or organs with larger intercapillary distances. The work of Aroesty and Gross (56) supports our assumption that intracapillary radial diffusion times are negligibly short.

**USE OF \( E_{\text{max}} \) FOR ESTIMATING PS**

Yudilevich and co-workers (13, 19, 46) have used an extrapolation method in an attempt to estimate the extraction, \( E(0) \), in the first sample containing a measurable concentration of the reference tracer. Because the first values are influenced by factors such as axial diffusion and heterogeneity of flow, because, as Perl (6) has observed, there is no unequivocal method for extrapolating curves such as those in Figure 6 to the appearance time, and because \( E_{\text{max}} \) is by definition greater than or equal to \( E(0) \), then \( E_{\text{max}} \) or \( E(t_p) \) is more likely to represent the extraction at the average flow whenever there is heterogeneity of regional perfusion. Use of the earliest values of \( E(t) \) to calculate PS almost inevitably leads to its underestimation, since the measured average flow is less than the local flow through the regions with the shortest transit times. Because the initial portions of the outflow dilution curves from low-flow regions are obscured by the tails of the curves emerging from high-flow regions, it is impossible to be certain which value of \( E(t) \) represents a region of local flow equal to the average flow, but it is most logical to assume that regions with transit times for the reference tracer close to the average transit time (which is about 20% beyond the time of peak of \( h(t) \) [27]) have flows close to the average flow, \( F_r^* \). On this basis, \( E(t_p) \) or \( E_{\text{max}} \) has a value closer to the average than does \( E(0) \). Furthermore, one may reasonably suspect that, if \( E_{\text{max}} \) occurs prior to \( t_p \), the time of the peak of \( h(t) \), it underestimates the average regional extraction and gives underestimates of PS.

When \( E(t) \) shows long plateaus the problem is minimized. When \( PS/F_r^* \) is low and heterogeneity of flow is not extreme, an average \( E \) and average \( F_r^* \) give good estimates of the average PS. Crone’s early experiments on the permeability of the brain capillaries to glucose and fructose (35) showed values of \( E \) of less than 0.40 which remained level for several seconds, a situation in which his calculation of PS by Eq. 2 was completely appropriate.

**EXPERIMENTALLY ACCESSIBLE RANGE OF \( PS/F_r^* \)**

Perhaps the most important conclusion to be made from these model solutions is that the range over which \( PS/F_r^* \) can be examined for any given organ is not very large. Considering that even for water \( h_p(t_p)/h(t_p) \) is seldom less than 10% (12), the values of \( E_{\text{max}} \) over 75% probably cannot be depended on to provide reliable estimates of PS. If the range of usable values of \( E_{\text{max}} \) is from 5% to 75%, then \( PS/F_r^* \) can range only from 0.05 to 2.0 (Fig. 7). For the heart, where blood flows are probably between 0.50 and 1.5 ml/g min\(^{-1}\) in vivo and between 0.5 and 3 ml/g min\(^{-1}\) in isolated preparations, then the range of values of PS that can be examined is perhaps a hundredfold from 0.03 to 3 ml/g min\(^{-1}\). With a surface area of about 500 cm\(^2\)/g, this range would mean permeabilities of 0.10 to 10 \( \times 10^{-4} \) cm/sec. There seems to be no possibility of using \( E_{\text{max}} \) for finding specific values for permeability of myocardial capillaries to inert gases, antipyrine, or other lipid soluble substances which move rapidly through capillary endothelial cells, since with \( E_{\text{max}} \) over 0.75 the return of tracer from the extravascular region renders Eq. 2 inadequate and more importantly the much increased probability of interregional diffusion probably in-
validates the principle of independence of neighboring capillaries. At the other extreme, the permeability to large hydrophilic solutes, which permeate by traversing the interendothelial cellular clefts, can only be estimated if \( h_{o}(t) \) and \( h_{b}(t) \) are measurably different, which probably means that the extraction is 5% or more.

These considerations can be expressed more or less quantitatively in terms of the present model or others. Perl’s approach (6, 10) provides a good starting point, using ratios of convective and diffusive (or permeative) velocities. His interpolation model (6) includes longitudinal dispersion, which results in rising early values of \( E(t) \) at values of \( PS/F_{t} \) higher than 0.5, just as is shown in Figure 6. Perl discussed his model’s behavior in terms of \( F_{c}/\nu_{c}v_{c} \) sec\(^{-1} \) (where \( S_{c} \) is \( 2\pi R_{c}L \), the surface area of an individual capillary). A dimensionless parameter may be more useful: \( PS_{c}/(\nu_{c}V_{c}) \)/(\( F_{c}/v_{c} \)) is the capillary transit time, \( \tau_{c} \), divided by a time constant for reflux from tissue to blood; it provides a measure of the importance of back diffusion in reducing \( E_{\text{max}} \), from its ideal value of \( 1 - \exp(-PS/F_{t}) \). This number emphasizes radial exchange versus flow: its reciprocal is a “permeation” Peclet number, \( \beta_{p} \), which is a connective intracapillary velocity, \( F_{c}/\pi R_{c}^{2} \), divided by a radial transmembrane permeation velocity, \( PS_{c}/[\pi (R_{c}^{2} - R_{e}^{2})\nu_{c}] \).

This expression can be simplified:

\[
\beta_{p} = \frac{F_{c}/\pi R_{c}^{2}}{PS_{c}/[\pi (R_{c}^{2} - R_{e}^{2})\nu_{c}]} = \frac{F_{c}/V_{c}}{PS_{c}/\nu_{c}V_{c}} = \frac{F_{c}/V_{c}}{PS_{c}/\nu_{c}V_{c}} = \frac{F_{c}/V_{c}}{PS_{c}/\nu_{c}V_{c}} (32a)
\]

The latter form is \( F_{c} \) times \( PS \) times the ratio of extravascular to intravascular volumes of distribution. Use of this Peclet type of criterion ignores axial diffusion. Perl (6) made use of the initial clearance, \( EF_{t} \), from blood into the extravascular region to show that \( \beta_{p} \) can be used to define a limit of adequacy of Eq. 2. Using his Tables 1 and 2, with \( PS/F_{t} = 1.0 \) and \( \nu_{c}V_{c}/\nu_{c}V_{c} \) and \( \beta_{p} \) having the rather small value of 4.0, \( E_{\text{max}} \) was reduced by 7% because of returning tracer; the error in estimating \( PS \) from Eq. 2 would be 14%. The error would be less at lower values of \( PS/F_{t} \) and at higher values of \( \nu_{c}V_{c}/\nu_{c}V_{c} \) and \( \beta_{p} \). Since capillary volume is approximately 2.5% of tissue volume and extracellular space in the heart is 20–30%, values of \( \nu_{c}V_{c}/\nu_{c}V_{c} \) might be closer to \( 25 - 2.5Hct(1 - Hct) \) or \( 22.5/1.5 = 15 \). Then one could permit values of \( PS/F_{t} \) as high as 3.75, and still Eq. 2 would err by only 14%. In practice, usable estimates of \( E_{\text{max}} \) can probably not be obtained with values of \( PS/F_{t} \) greater than 3.0 because of perfusion heterogeneity and intravascular dispersion.

The permeation Peclet number, \( \beta_{p} \), is also the ratio of the time constant of escape of extravascular tracer with pure barrier limitation (\( \tau_{c} = \nu_{c}V_{c}/PS_{c} \) = \( [\nu_{c}V_{c}/\nu_{c}V_{c}]PS_{c} \) to capillary transit time (\( \tau_{c} = V_{c}/F_{c} = \nu_{c}V_{c}/PS_{c} \)):

\[
\beta_{p} = \frac{\tau_{c}}{\tau_{c}}. (32b)
\]

At very low values of \( PS/F_{t} \), tracer washout from the organ, after the passage of the intravascular bolus, would be monoeXponential with time constant \( \tau_{c} \). At infinitely high \( PS/F_{t} \), the washout time constant would be more nearly \( \nu_{c}V_{c}/PS_{c} \), the total volume of distribution in the hexagonal unit divided by the flow in the capillary. (Both of these rates are conceptually equivalent to the rate of washout from a uniformly mixed volume.) At intermediate values of \( PS/F_{t} \), the washout time constant is longer than the longer of these two extremes. That is, in the absence of axial diffusional effects, the fractional escape rate of extravascular tracer is always equal to or less than the lesser of \( 1/\tau_{c} \) and \( \nu_{c}F_{c}/(\nu_{c}V_{c} + \nu_{c}V_{c}) \), for the washout is limited by one or other or both of the processes. In absolute terms, an increase in flow increases the FER, except in the barrier-limited extreme.

(These considerations are based on the idea that the solute is more or less evenly distributed throughout its volume of distribution. When \( PS/F_{t} \) is rather high, more than 10, and therefore beyond the range where Eq. 2 is useful, then axial gradients influence the FER, such that at early times when the indicator is predominantly at the upstream end of the tissue region the FER is less than the rate obtained with uniform tracer distribution and at late times when the tracer is predominantly at the downstream end the FER is greater than that with uniform distribution. Axial diffusion evens out the tracer distribution and strongly reduces the trend toward a temporal rise in FER, particularly in the late phase where in combination with escape into the outflow and diffusion in the upstream direction it lends to maintenance of an intratissue concentration profile of constant shape [concentration decreasing exponentially from the downstream toward the upstream end] and of diminishing magnitude and gives a constant FER and purely monoeXponential washout.)

Axial diffusion in the tissue has a negligible effect on computed values of \( E(t) \) when \( PS \) is small.
Intravascular dispersion does not only reduce $E_{\text{max}}$ as Perl suggested (6). As is shown in Figures 6 and 7, intravascular dispersion influences the shape of $E(t)$, either raising or lowering values of $E_{\text{max}}$ and $E(t_p)$, depending on whether the permeating tracer is dispersed more or less than the reference tracer. The pertinent intravascular Peclet number for axial dispersion is:

$$\beta_e = L^2/D_c \Delta t_e .$$

The changes in $E(t_p)$ can be expressed approximately as a function of $(D_{\text{cp}}/D_{\text{cn}} - 1)/\beta_{\text{cn}}$, where the subscripts $D$ and $N$ denote permeant, $D$, and nonpermeant, $N$, tracers. When the permeant and nonpermeant tracers are dispersed equally, there is no effect on $E(t)$. When $D_{\text{cp}} > D_{\text{cn}}$ as in plug flow, the function is positive, showing that $E(t_p)$ is increased; the smaller $\beta_{\text{cn}}$ or the lower the velocity, the larger is the increase. When $D_{\text{cp}} < D_{\text{cn}}$, the reference tracer is dispersed more (Taylor effect), and $E(t_p)$ is reduced. Greater exactitude is not easily obtained, since the amount of change in $E(t)$ also depends on the extraction itself. The rate of escape from blood to tissue could be considered as another permeation Peclet number, the ratio of convective velocity to the escape velocity from the capillary:

$$\beta_{\text{PC}} = \frac{V_c V_e / \rho V_e PS}{I_c} = \frac{V_c V_e / \rho V_e F'_e}{P_c} = \beta_{\text{SN}} ,$$

which points out the nature of the long familiar ratio, $PS/F'_e$. Using $PS/F'_e$ in an expression for $\Delta E(t_p)$, the change in $E(t_p)$ due to intravascular dispersion is

$$\Delta E(t_p) = \text{constant} \cdot \frac{(D_{\text{cp}}/D_{\text{cn}} - 1)}{\beta_{\text{cn}}} \cdot e^{-PS/P'_e} ,$$

which will be useful over at least a small range of values of $E(t_p)$. In the example given in Figure 6 (right), the constant has a value of about 10, but insufficient exploration has been done to define the precision of this value over wide ranges of conditions.

Thus, one can see that the presence of intravascular dispersion vitiates the use of $E(0)$, the first calculable values of $E(t)$, for estimating $PS$. Therefore, we have focussed on $E(t_p)$ and $E_{\text{max}}$ as the useful points on the curve. In general these two have similar values, and for practical purposes one averages through a few points to either side. $E(t_p)$ has the virtue of occurring at a recognizable time: it is easy to locate and estimate even in the presence of noise.

The above argument is even more relevant in the presence of perfusion heterogeneities, when one can expect the earliest part of the output curve to come from regions of higher than average flow. This problem might be partially circumvented if experiments are done at the highest flows obtainable under carefully regulated physiological circumstances, assuming that organ perfusion is relatively homogeneous at high flows. The remaining problem is whether permeability actually changes between low flows and high flows. Ideally one would like to maintain capillary pressures at a normal level while achieving the highest possible flows.

In summary, this study provides justification for the use of the instantaneous extraction technique for the estimation of capillary permeability–surface area products when $PS/F'_e$ falls within a limited range. Back diffusion of tracer and axial diffusion can be expected to influence $E(t_p)$ and $E_{\text{max}}$ in a predictable fashion so that certain corrections can be applied to the classical equation $PS/F'_e = -\log_e[1 - E(t_p)]$ to obtain reasonably accurate estimates of $PS$.

**Acknowledgment**

Mr. J. Dunnette and Mr. T. J. Knopp helped in obtaining the computer solutions, and Mrs. Jane Irving prepared the manuscript. Dr. T. Yipinsei was a helpful critic during the evolution of the modeling. Dr. John L. Stephenson’s advice concerning the use of $\Delta t - V_c / (F'_e N_c)$ for the numerical solutions is very much appreciated. Dr. W. Perl and Dr. C. A. Goresky contributed most helpful criticisms of the manuscript in its various stages.

**References**

8. *Schmidt GW: Mathematical theory of capillary exchange as
35. Crone C: Facilitated transfer of glucose from blood into brain tissue. J Physiol (Lond) 181:103-113, 1965
47. Tancredi RG, Yipintsoi T, Richmond DR, Bassingthwaighte JB: Estimation of myocardial cell permeability to potassium in the intact heart (abstr). J Clin Invest 49:958a, 1970
A Concurrent Flow Model for Extraction during Transcapillary Passage

JAMES B. BASSINGTHWAIGHTE

Circ Res. 1974;35:483-503
doi: 10.1161/01.RES.35.3.483

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/35/3/483

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/