A Convection-Diffusion Model of Indicator Transport through an Organ

By William Perl, Ph.D., and Francis P. Chinard, M.D.

ABSTRACT

A model for interpretation of extravascular indicator dilution experiments is proposed, in which the indicator is assumed to enter the blood-tissue exchange region through vascular sources, to equilibrate instantaneously and locally between blood and tissue at the capillary-cell level, and, while maintaining this local equilibration, to be transported to vascular sinks by simultaneous diffusion and convection at a more macroscopic distance level. The model has the mathematical form of the time-dependent Fick diffusion equation to which a convection term was added. The model contains as opposite limiting cases the washout-type models and a recently proposed delayed wave model of the indicator dilution process. The various features of the extravascular indicator outflow pattern—appearance time, modal time, semi-log downslope, and dispersion about the mean—are described in terms of two parameters: (1) a diffusion parameter, square of source-to-sink distance divided by diffusion coefficient of the indicator in the tissue; (2) a convection parameter, the blood flow divided by steady-state solubility volume of distribution of the indicator in the tissue. In contrast to the preceding opposite limiting cases, the present model accounts plausibly for extravascular indicator experiments in dog kidney.

ADDITIONAL KEY WORDS indicator curve outflow pattern microcirculation transport kinetics blood flow kidney anesthetized dogs T-1824 sodium creatinine tritiated water tritium gas krypton diffusion convection

Extension of the indicator dilution experiment of Stewart (1) and Hamilton (2) by the addition of extravascular indicators to the bolus of solution injected into the inflow to an organ has necessitated corresponding extensions of the theory (3-12). Although the classical theorems for obtaining flow of carrier fluid and volume of distribution of an indicator from its outflow pattern remain essentially valid for extravascular indicators, numerous other details of the shape of the outflow pattern differ from indicator to indicator and from organ to organ. Models devised to infer (1) permeability, from upslopes of outflow patterns in various organs other than the kidney (13, 14), (2) "clearance" or "washout" flow per unit volume, from downslopes in the lung (15-17), or (3) relative appearance times and shapes of entire outflow patterns in the liver (18-21) were found inapplicable to the kidney (12). The inexplicable features in the kidney include the following experimental facts: (1) the appearance times and modal, or peak value, times for highly diffusible extravascular indicators...
such as tritium gas and krypton are earlier or coincidental with those for vascular indicators such as T-1824 labeled albumin; (2) the relative downslopes of extracellular indicators (creatinine) and intracellular indicators (water) are not in proportion to their volumes of distribution.

Qualitative suggestions for interpreting the preceding early time phenomena in terms of a "diffusion bypass" were made (12, 22-24). In another connection, a quantitative formulation of transport of diffusible substances in perfused tissues was proposed as a generalization of Fick's partial differential equation of diffusion (25). The present study combines the preceding approaches in an attempt to explain the shape of the venous outflow patterns of highly diffusible extravascular indicators in the kidney. The resulting model turns out to include as opposite limiting cases the hitherto unrelated "washout" type model (15-17) and the delayed traveling wave model (18-21).

The present model is designed to apply only to extravascular indicators, such as the inert gases, labeled water, and creatinine. It does not apply to vascular indicators, such as labeled albumin or red cells.

**Principal Symbols**

- $a$, cm$^2$, cross-sectional area in basic unit
- $a_n$, $n$th exponential amplitude in equation A21
- $A$, cm$^2$, facial area of tissue slab
- $B$, ratio of diffusion coefficient in tissue to diffusion coefficient in water
- $C$, amount/cm$^3$, concentration
- $d$, infinitesimal element of, differential
- $D$, cm$^2$/sec, diffusion coefficient
- $e$, base of natural logarithms
- $E$, amount/sec, flux of indicator out of tissue slab
- $f$, cm$^3$/sec, rate of vascular fluid flow through basic unit
- $F$, cm$^3$/sec, rate of vascular fluid flow through tissue slab
- $I$, amount/sec, flux of indicator into tissue slab
- $i$, amount/sec, flux of indicator in basic unit
- $k_1$, sec$^{-1}$, smallest rate constant in sum-of-exponential representation of theoretical indicator curve; linear downslope on semi-log plot of experimental outflow pattern
- $L$, cm, thickness of tissue slab
- $m$, amount, amount of indicator
- $s$, sec$^{-1}$, Laplace transform frequency variable
- sinh, cosh, hyperbolic sine, cosine
- $t$, sec, time
- $t_0$, sec, catheter dead time
- $t_1$, sec, catheter exponential lag time
- $t'$, sec, catheter corrected time, equation 38
- $v$, cm$^3$, volume of tissue in basic unit
- $V$, cm$^3$, volume of tissue slab
- $w$, cm$^3$, concentration of indicator in renal venous whole blood divided by amount of indicator injected, equation 30
- $w'$, cm$^3$, catheter corrected $w$, equation 35
- $x$, cm, distance in source-sink direction
- $X$, nondimensional distance, equation A2
- $\beta$, Peclet number, equation 28
- $\delta$, Dirac delta, or impulse, function
- $\partial$, partial differential
- $\Delta t$, standard deviation of time, equation 39
- $\Delta x$, standard deviation of distance
- $\lambda$, partition coefficient
- $\bar{\lambda}$, average partition coefficient
- $\mu$, micron unit of distance
- $\rho$, fraction of injected indicator recovered
- $\tau$, nondimensional time, equation A3
- $\nu$, cm/sec, velocity of propagation of concentration wave in basic unit
CONVECTION-DIFFUSION MODEL OF OUTFLOW PATTERN

\[ \infty, \text{ infinity} \]

Subscripts

- \( a \): appearance
- \( b \): effluent vascular fluid (blood)
- \( c \): convection, also catheter in equation 32
- \( d \): diffusion
- \( e \): equation 33
- \( f, 1, 2 \): vascular fluid, interstitial, intracellular phases
- \( l \): lower
- \( r \): reference phase
- \( s \): upper
- \( 0, 1, 2, 3, 4 \): "snapshot" times of progress of bolus of indicator, Fig. 2
- \( + \): just to right of slab boundary face
- \( - \): just to left of slab boundary face

Methods

Indicator injected as a bolus\(^1\) subdivides at the branchings of the large arterial vessels into component boluses in proportion to flow.

\(^1\)The term bolus refers to the indicator contained in the injected solution rather than to the solution itself.

The component boluses are assumed to travel nondispersively and to reach the blood-tissue exchange region simultaneously, i.e., the contribution of all non-exchanging vessels to the dispersion of indicator is neglected. The boluses emerge into the blood-tissue exchange region from vascular sites, denoted as sources. Immediately after emergence the boluses are assumed, following Goresky (18-21), to distribute themselves locally over intercapillary distances into the volume of distribution that would be available to them in a steady-state condition, with equilibrium partition coefficients. The equilibrated boluses then are transported by two mechanisms, (1) diffusion and (2) bulk movement (convection) by the capillary blood flow, into the nearest available venular non-exchange vessels, denoted as the sinks. The boluses, which are now dispersed by diffusion, are successively rejoined and carried without further dispersion to the output location.

A specific but idealized vascular geometry is assumed (Fig. 1). Consider the blood-tissue exchange region to be a slab of tissue with sources distributed over the \( x = 0 \) face and sinks distributed over the \( x = L \) face. Each source is connected to an oppositely situated

\[ C_{e}(x, t) \]

\[ C_{M}(x, t) \]

\[ C_{A}(x, t) \]

**FIGURE 1**

Cross-section view of half a source-exchange-sink unit. The unit repeats indefinitely in the y- and z-direction to give slab (planar) geometry. (a) Straight-through capillary geometry: convective flux \( j_{c} \), blood flow \( f \), and diffusive fluxes \( j_{d} \), \( j_{d} \) are all in the same direction. (b) Diffusion-bypass capillary geometry: convective flux \( j_{c} \) is in the direction of blood flow \( f \); diffusive fluxes \( j_{d} \), \( j_{d} \), \( j_{d} \) are in source-sink direction.

_Circulation Research, Vol. XXII, February 1968_
sink by a "capillary." Thermodynamically associated with each capillary are several extravascular tissue phases, for example, interstitial tissue and intracellular tissue. The simultaneously entering boluses of the indicator are assumed to equilibrate instantaneously in a direction, denoted lateral, which is perpendicular to the source sink or x-direction. Equilibration means equalization of the electrochemical potential so that the indicator concentrations in the phases in the lateral direction are related by constant partition coefficients. That is, the electrochemical potential is constant in all tissue phases at given x, but it varies with x and t. Because of the variation of the concentration component of the potential with x, indicator diffuses in the x-direction. Simultaneously in the vascular phase, the indicator is carried convectively by the vascular fluid. Any tendency for the potentials in the several phases at a given x to become unequal due to (1) convective movement of indicator which occurs only in the vascular phase, and (2) unequal diffusion flux densities in the several phases is immediately counteracted by the assumed instantaneous lateral equilibration. This assumption is equivalent to the view that the three-dimensional diffusion of a bolus of indicator from source to sink can be regarded as composed of a relatively quickly completed two-dimensional diffusion perpendicular to the source-sink direction and a relatively slowly completed one-dimensional diffusion in the source-sink direction. Finite permeability barriers which would slow the lateral equilibration appreciably are not allowed in the present model. However, the limiting case of zero permeability, that is, no entry into a tissue phase, is allowed. For example, an extracellular indicator would have instantaneous lateral access to its extracellular volume of distribution but zero access to the intracellular tissue phase.

The preceding summary of assumptions underlying the model represents, of course, a highly idealized picture of the progress of a bolus of diffusible indicator through an organ. For example, the assumption of a lateral diffusion time that is small relative to the source-sink diffusion time may fail because the lateral diffusion distance is not small relative to the source-sink distance, or also because of finite permeability barriers which slow down lateral equilibration. Again the contribution of the non-exchange arterial and venous vessels to the dispersion of the indicator, neglected here, would be expected to be comparable to that contributed by the blood-tissue exchange region if the volume contained by these vessels were comparable to the volume of distribution of indicator in the blood-tissue exchange region. The assumption of planar geometry for sources and sinks, made for mathematical simplicity, may be substantially less realistic than, for example, spherically outward diffusing geometry. The very concept of simple Fick diffusion with a single diffusion constant may be inapplicable if the tissue is too heterogeneous at the source-sink distance level. Thus, while quantitative solutions of the mathematical problem posed by the present model are derived, their application to biological situations can be made only with the usual extreme caution. We proceed with the mathematical formulation of the model.

A field point of view is adopted (25) in which physiological quantities in the tissue are considered to vary continuously in both space and time. The capillaries connecting the sources and sinks are, to begin with, considered as "straight through" [Fig. 1(a)]. Each source-capillary-sink combination constitutes a vascular phase in which plug flow of fluid at volume rate \( f \) (cm\(^3\)/sec) is assumed. The vascular and extravascular phases have cross-sectional areas \( a_1 \), \( a_2 \), and \( a_3 \) (cm\(^2\)). The preceding arrangement repeats with sufficient regularity, statistically or otherwise, in the plane perpendicular to the x-direction, so that one-dimensional planar solutions for the slab as a whole exist. In effect, the tissue is regarded on the present model as an assembly of basic units. Each basic unit consists of a vascular source, a capillary plus thermodynamically associated tissue, and a vascular sink. All basic units are assumed to behave...
CONVECTION-DIFFUSION MODEL OF OUTFLOW PATTERN

identically with respect to transport of indicator. The presently derived indicator curve is then essentially the response of one basic unit to input of a bolus of the indicator into it.

Consider a volume element of tissue \( dv = dx \), composed additively of the various tissue phases

\[
dv = dv_f + dv_1 + dv_2
\]

(1)

This volume element contains an amount \( dm = Cdv \) of indicator, where \( C(x, t) \) (amount/cm\(^3\)) denotes the average concentration of indicator in the tissue at distance \( x \) and time \( t \). This amount is distributed additively among the tissue phases as

\[
dm = Cdv = C \left( dv_f + dv_1 + dv_2 \right)
\]

(2)

where \( C_f, C_1, \) and \( C_2 \) are the respective concentrations in the tissue phases. A reference phase (such as plasma, plasma water, etc.) is assumed, which is in thermodynamic contact with phases \( f, 1, \) or \( 2 \), and in which the indicator concentration is \( C_r(x, t) \). Average and individual tissue-to-reference partition coefficients are defined as

\[
\lambda = C/C_r
\]

(5)

\[
\lambda_j = C_j/C_r, \quad j = f, 1, 2
\]

(6)

Division of equation 3 by \( Cdv \) relates these partition coefficients as

\[
\lambda = \lambda_f \left( dv_f/dv \right) + \lambda_1 \left( dv_1/dv \right) + \lambda_2 \left( dv_2/dv \right).
\]

(7)

In accordance with the assumption of instantaneous lateral equilibration, \( \lambda_f, \lambda_1, \) and \( \lambda_2 \) are taken as equilibrium partition coefficients. In addition, chemical homogeneity of the tissue is assumed, so that \( \lambda_f, \lambda_1, \) and \( \lambda_2 \) are constant throughout the tissue, although the various concentrations vary with \( x \) and \( t \). The average tissue-to-reference coefficient \( \bar{\lambda} \) is a weighted average of \( \lambda_f, \lambda_1, \) and \( \lambda_2 \), the weights being the respective local proportions of the tissue phases. Physical homogeneity of the tissue is assumed, that is,

\[
dv_f/dv = V_f/V, \quad j = f, 1, 2
\]

(8)

where \( V_f, V_1, \) and \( V_2 \) are the vascular, phase 1, and phase 2 volumes which additively compose the entire tissue volume \( V \). Equations 7 and 8 yield

\[
\bar{\lambda} V = \lambda_f V_f + \lambda_1 V_1 + \lambda_2 V_2
\]

(9)

which defines the solubility volume of distribution of the indicator in the tissue, with respect to the reference phase. Equations 1-9 constitute the so-called local flow-limited assumption; namely, solubility (more generally electrochemical) equilibrium exists within the volume element \( dv \) at all times. This assumption, which implies no diffusional or permeability limitation to transport at the level of size of \( dv \), is the same that Kety formulated for a tissue as a whole (26). In contrast to Kety's case, the present treatment yields a diffusional limitation for the tissue as a whole.

The average tissue-to-vascular fluid partition coefficient \( \lambda \) is defined by equations 5 and 6 as

\[
\lambda = C/C_f = \bar{\lambda}/\lambda_f
\]

(10)

(if vascular fluid is chosen as the reference phase, then \( \lambda = \bar{\lambda} \)). The convective flux of indicator \( j_c \) (amount/sec) crossing a plane of area \( a = a_f + a_1 + a_2 \) at distance \( x \) is, using equation 10,

\[
j_c = fC_f = fC/\lambda.
\]

(11)

The diffusion flux \( j_d \) (amount/sec) crossing the area \( a = a_f + a_1 + a_2 \) at distance \( x \) is

\[
j_d = fD_f \left( \partial C_f/\partial x \right) - a_1 D_1 \left( \partial C_1/\partial x \right) - a_2 D_2 \left( \partial C_2/\partial x \right)
\]

(12)

where \( D_f, D_1, \) and \( D_2 \) (cm\(^2\)/sec) are the diffusion coefficients of the indicator in the respective tissue phases. This diffusion is kept one-dimensional, that is, the component fluxes on the right-hand side of equation 12 are kept "in phase" by the condition of instantaneous lateral equilibration. Thus, equations 12, 6, 5, 8, 2, and 1 give

\[
j_d = -a D \partial C/\partial x.
\]

(13)
where
\[
D = \left( a_1 \lambda_1 D_1 + a_1 \lambda_2 D_2 + a_2 \lambda_3 D_3 \right) / \lambda
\]
\[
= \left( \lambda_1 V_1 D_1 + \lambda_1 V_2 D_1 + \lambda_2 V_2 D_2 \right) / \left( \lambda_1 V_1 + \lambda_1 V_2 + \lambda_2 V_2 \right)
\]
defines the diffusion coefficient for the composite tissue as a weighted average, according to solubility volume, of the diffusion coefficients in the tissue components.

Conservation of mass in \( dv \) requires that the time rate of increase of the amount of indicator in \( dv \) equals minus the space rate of change of the total flux through \( dv \), or
\[
\frac{\partial (dm)}{\partial t} = - \frac{\partial}{\partial x} \left( f_a + f_v \right).
\]
By equations 4, 11, and 13, this equation becomes
\[
a \frac{\partial C}{\partial t} dx = aD \frac{\partial^2 C}{\partial x^2} dx - \frac{f}{\lambda} \frac{\partial C}{\partial x} dx.
\]
The vascular fluid flow per unit area of tissue is expressed as
\[
f/a = F/A = FL/V,
\]
where \( F \) (cm³/sec) is the vascular fluid flow to the entire slab of tissue, of volume \( V = AL \). Division of equation 16 by \( adx \) and substitution of equation 17 give the partial differential equation used (25)
\[
\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - \frac{FL}{\lambda V} \frac{\partial C}{\partial x}.
\]
The same equation holds for \( C_1, C_2 \), or \( C_3 \), by equations 5 and 6. Equation 18 is assumed to be linear (parameters are independent of concentration), with coefficients constant in space (tissue is homogeneous) and in time (tissue is in a steady state).

The boundary condition at \( x = 0 \) is that the given input flux of indicator \( I(t) \) (amount/sec) at \( x = 0_\) denotes just outside the slab at \( x = 0 \) equals the amount transported into the slab by convection and diffusion, or (\( 0_+ \) denotes just inside the slab at \( x = 0 \))
\[
I(t) = (F/\lambda) C(0_+, t) - AD \left( \frac{\partial C}{\partial x} \right)_{0_+}.
\]
Only the case of impulse (\( \delta \)-function) injection of an amount \( m \) of indicator is considered, or
\[
I(t) = m \delta(t).
\]
Equations 19 and 20 imply that after deposition of the amount \( m \) just inside the slab at \( t = 0 \), no further flux of indicator occurs at the \( x = 0 \) face of the slab. The rationale for this boundary condition is that the sources and sinks are considered to be arrayed on alternate parallel planes spaced a distance \( L \) apart. The outflow in both directions from any plane of sources into the planes of sinks on both sides is, by symmetry, equivalent to the condition of zero flux at \( x = 0 \).

The boundary condition at \( x = L \) is that the flux of the indicator at \( x = L_\) (just inside the slab)
\[
E(t) = (F/\lambda) C(L_+, t) - AD \left( \frac{\partial C}{\partial x} \right)_{L_+}
\]
equals the flux of indicator at \( x = L_+ \) (just outside the slab)
\[
E(t) = (F/\lambda) C(L_+, t).
\]
The concentration of indicator in the vascular fluid varies continuously at exit from just inside to just outside the slab, since no diluting or concentrating mechanism exists at this location. Hence, by equation 10,
\[
\lambda C_f(L, t) = C(L_+, t) = C(L_+, t).
\]
Hence subtraction of equation 22 from 21 gives as the boundary condition at \( x = L \)
\[
\left( \frac{\partial C}{\partial x} \right)_{L_-} = 0.
\]
\{ The given input flux at \( x = 0_\) can also be expressed as a product of flow and concentration, \( I(t) = FC_0/(0_-, t) \). This concentration, however, because of instantaneous local equilibration with the tissue, would change discontinuously to a lower concentration \( C_f(0_+, t) \) just after entrance to the slab. The difference \( F \left[ C_f(0_-, t) - C_f(0_+, t) \right] \) is just the diffusion term in equation 19. A reverse discontinuity at the exit to higher concentration cannot occur on physical grounds. \}

The initial condition is that no indicator

\[ \text{PERL, CHINARD} \]

\[ \text{Circulation Research, Vol. XXII, February 1968} \]
is present initially within the slab, or
\[ C(x, 0) = 0. \]  \hspace{1cm} (25)

Remarks

By expressing \( z \) as a fraction of source-sink distance \( L \) in equation 18, the present model is seen to contain two parameters: a diffusion time
\[ t_d = \frac{L^2}{D} \]  \hspace{1cm} (26)
and a convection time
\[ t = \frac{\lambda V}{F}. \]  \hspace{1cm} (27)

The convection time \( t \) is also the centroid, or mean transit time, of the indicator curve by the general volume theorem of indicator dilution theory (3, 7, 12). The nondimensional ratio of these parameters,
\[ \beta = \frac{t_d}{t} = \frac{L^2}{DT} = \frac{FL^2}{\lambda DV}, \]  \hspace{1cm} (28)
is denoted as the Peclet number in the heat and mass transfer literature (27-29). The present Peclet number differs from the literature Peclet number by the presence of the partition coefficient \( A \).

The types of solution of equation 18 depend on \( \beta \). They are indicated schematically as a "snapshot" of a bolus of indicator at several times in its progress through the tissue (Fig. 2). Concentration of indicator is plotted above the \( x \)-axis in the vascular phase and below the \( x \)-axis in the extravascular phase. The following three cases are considered:

(1) \( \beta \to \infty \); diffusion is negligible relative to convection (Fig. 2, a). This is the delayed traveling wave case of Goresky (18-21). At time \( t_0 \) the bolus, assumed "rectangular," exists at concentration \( C_f \) in the vascular fluid, just before entrance into a volume \( V \) of tissue, and it is traveling with the vascular fluid velocity. At time \( t_1 \) the bolus has just entered the exchange region and has equilibrated laterally with an extravascular volume. If this volume is taken for convenience as equal to the vascular volume, with a one-to-one average partition coefficient, or \( A V = 2V_f \), then the indicator concentration in the vascular bolus is now \( C_f/2 \), and in the extravascular

---

\textsuperscript{2}Diffusion refers to source-to-sink diffusion. In all cases the diffusion involved in the local lateral equilibration is considered instantaneous.
The mass of the indicator is divided equally between vascular and extravascular boluses, that is, the longitudinal "thickness" of bolus is unchanged at entrance into the exchange region (assuming no change of vascular fluid cross-sectional flow area at entrance into the exchange region). The vascular and extravascular boluses travel together and in unchanged form (time $t_2$) to the exit of the exchange region. The rate of travel is half the vascular fluid velocity; that is, the relevant solution of equation 18 with $D = 0$ is $C(x - vt)$, a concentration wave of unchanged shape propagating with velocity

$$v = FL/\lambda V = (FL/V_f)(V_f/V).$$

The second form in equation 29 shows that the velocity of propagation of the concentration wave is less than the vascular fluid velocity by the ratio, in the present example one half, of the vascular volume $V_f$ to the solubility volume of distribution $\lambda V$. The mechanism of this reduction in velocity of propagation is the continuous in-and-out lateral movement of indicator, constituting a "slippage" with respect to the vascular carrier fluid (18). At time $t_0$ the bolus has just emerged from the exchange region, at unchanged concentration $C_f/2$ and with twice the pre-entrance longitudinal "thickness" because of the lateral outflow from the extravascular volume at exit. Thereafter (time $t_4$) the bolus travels unchanged in form at the vascular fluid velocity.

(2) $\beta = 1$; diffusion is comparable to convection (Fig. 2, b). After entering the slab at time $t_0$, the bolus disperses in the source-sink direction. The dispersion is not symmetric, however, but it is less toward the front of the bolus than toward the rear because of the rear-to-front continual transfer of indicator by the vascular convective movement combined with instantaneous lateral equilibration. Although theoretically the leading edge of the bolus extends to $x = L$ and the trailing edge to $x = 0$, the main parts of the bolus travel with a reduced velocity approximating that of case (1) above. This reduced velocity has the consequence of allowing more time for source-sink diffusion to disperse the bolus, as compared to travel at the vascular fluid velocity. This crucial feature is illustrated later for the experimental results.

(3) $\beta \rightarrow 0$; convection is small relative to diffusion (Fig. 2, c). The bolus at entry into the exchange region equilibrates rapidly not only laterally but also longitudinally to uniform concentration throughout the tissue. Thereafter, the vascular fluid acts as a "slow leak" and "washes out" the indicator by first-order kinetics. This is the flow-limited case postulated by Kety (26).

The dispersion of the indicator curve on the present model is due to a combination of source-to-sink diffusion and the convective rate at which vascular fluid washes out the indicator. Where convection is relatively rapid, between cases (1) and (2), the dispersion at output is due mainly to source-to-sink diffusion. Where convection is relatively slow, between cases (2) and (3), the dispersion at output is due mainly to the rate at which vascular fluid washes out the indicator. Dispersion due to non-uniform distributions of capillary lengths, source-sink distances, and non-exchange vessel lengths is neglected in the present model.

The capillaries in the blood-tissue exchange region need not be "straight through" (Fig. 1, a). If, for example, all capillaries and associated tissue phases have the same U-shape (Fig. 1, b), only a constant additional convective component of indicator flux, perpendicular to the source-sink direction, is introduced. This additional flux component does not alter the source-to-sink diffusional or convective flux components, and hence it does not alter the model solutions based on equation 18. Furthermore, a random network of capillaries connecting the sources and sinks should also not alter, in the first approximation, the applicability of equation 18, provided the network has statistically constant properties in the directions perpendicular to the
source-sink direction. On the present model for extravascular indicators, it is the geometric regularity of the arrangement of sources and sinks which imposes a corresponding regularity on the diffusion of the indicator. The capillaries play only a subsidiary role. They do not guide the extravascular indicator as they do a vascular indicator. Rather, their function with respect to extravascular indicator is to impart to it an average convectional movement in the source-to-sink direction. Locally, the direction of capillary fluid flow need not be the same as the source-to-sink direction in order for the one-dimensional formulation (equation 18) to be applicable. The preceding remarks can be formulated mathematically and provide the rationale for applying the present model to vascular beds of the diffusion bypass type, such as exist in the kidney (12, 22-24).

**Theoretical Results**

The partial differential equation 18, subject to the boundary conditions 19, 20, 24, and the initial condition 25, was solved by standard methods (Appendix) to yield a family of indicator curves. Denote by \( C_S(t) \) [\( = C_f(L, t) \) in equation 23] the concentration of the indicator in the effluent vascular fluid. The two-parameter family of indicator curves \( C_S(t, t_s, t) \) can be presented nondimensionally as a single-parameter family in two ways. In the first way, \( 100 t_s (F/m) C_S \) is plotted against \( t/t_s \), which yields a curve of area = 100 and centroid at \( t/t_s = 1/\beta \). In the second way, \( 100 t (F/m) C_S \) is plotted against \( t/t_s \), which yields a curve of area = 100 and centroid located at \( t/t_s = 1/\beta \). These two methods differ by a scale transformation; namely, multiply the abscissas and divide the ordinates in the first method by \( \beta \) to obtain the respective coordinates in the second method. Semi-log plots of the preceding curve families are given in Figures 3 and 4 (the constancy of area of all curves is not evident on a semi-log plot but only on a rectangular plot). Specific features of these curves are discussed later.

**Experimental Results**

To test the model, four multiple indicator experiments on dog kidney were analyzed (Table 1; these are unpublished experiments of Chinard, Enns, and Nolan, except for experiment 3, run a, (12), which is recalculated here). The detailed methodology is given elsewhere (12, 31). In brief, 0.3 to 0.7 ml of an aqueous solution containing tracer amounts of several indicators is injected rapidly (<0.5 sec) into the left renal artery. During the next 15 seconds (experiment 1) or 60 seconds (experiments 2, 3a, 3b) 30 equally spaced samples of blood are collected from the left
Comparison of theoretical indicator curves and experimental outflow patterns (experiment 1, Table 1). Theory: solid lines = theoretical curves for various $\beta$, broken line = locus of theoretical peak values; abscissa = time in units of mean transit time $t$; ordinate = logarithm of effluent concentration normalized to area = 100 on rectangular plot. (See text, equation 30.) Experiment: open circles = THO; solid triangles = cold creatinine (80 mg injected); crosses = T-1824 labeled albumin. (For abscissa and ordinate see text, equations 30-37.) Flagged points represent extrapolation for recirculation.

Multiple indicator outflow pattern of a dog kidney, experiment 2. Ordinate = logarithm of
renal vein. The indicators used, in various combinations, and their approximate distribution properties are:

T-1824 (Evans Blue), which binds to serum albumin, is confined predominantly to the vascular volume.

Creatinine, which is distributed into extracellular fluid, is not reabsorbed significantly from tubular fluid and remains extracellular. Radioactive sodium ion, $^{23}$Na, which distributes itself into extracellular fluid, is reabsorbed predominantly from proximal tubular fluid and enters the tubule cells.

Tritiated water, THO, and deuterated water, DHO, distribute themselves in total tissue

---

**FIGURE 6**

Enlarged portion of Figure 5 which also includes open triangles, $^{22}$Na. Dashed lines = catheter corrected patterns, omitted for clarity in $T_k$, $^{38}$Kr, and $^{22}$Na patterns.

---

$1000 \times$ concentration of the indicator in whole blood divided by the amount of the indicator injected, unit $(1000 \text{ m})^{-1}$; abscissa = time from injection, given in seconds. Crosses = T-1824 labeled albumin; solid triangles = $^{14}$C-creatinine; open circles = DHO; solid circles = $^{38}$Kr; open squares = tritium gas, $T_t$. Prolongations of straight lines represent recirculation corrections.
water and are reabsorbed from tubular fluid.

The radioactive inert gases—krypton, $^{85}$Kr, and tritium, $T_2$—distribute themselves into all components including lipids.

The experimental outflow pattern for each indicator was expressed as

$$w(t) = C_b(t)/m,$$  \(30\)

where $C_b(t)$ is the concentration of indicator in the renal venous whole blood sample drawn at time $t$ after injection of the amount $m$. Semi-log plots of the outflow patterns in experiment 2 are shown (Fig. 5). The initial portions of the outflow patterns are shown enlarged in Figure 6. The dashed curves were corrected for catheter distortion, as described later. The outflow patterns were corrected for recirculation in the conventional manner by extending the initial linear downslope portion of the experimental data. The resulting set of values, also denoted as the outflow pattern $w_t(t)$, was the basis of the subsequent calculations. The conventional information (Table 1, columns 2-7) was derived as follows (12).

**Column 2.** Blood flow $F$, divided by recovery $\rho$ of the indicator, was obtained from

$$\rho_m = F \int_0^\infty C_b \, dt$$

$$F/\rho = 1 / \int_0^\infty w \, dt.$$  \(31\)

**Columns 3 and 4.** In the absence of independent knowledge of recovery $\rho$, a "most plausible" set of values of blood flow $F$ was derived from the $F/\rho$ data. (The derived values of $F$ are used only to compute the distribution volume $XV$. They are not used as a test of the model.) The general assumptions were: (1) recovery is unity for T-1824; (2) a decrease of $F/\rho$ for an extravascular indicator relative to T-1824 is interpreted as an average decrease in blood flow for the extravascular indicator, rather than an increased recovery relative to T-1824. This interpretation is plausible because the extravascular indicator takes a longer time to flow out of the organ than the vascular indicator. During this time the blood flow through the organ may be decreasing because of the experimental procedure (injection of the indicator and pumping of blood samples). Also analytical problems and the recirculation extrapolation render the recovery of the extravascular indicators less certain than for T-1824. The lowest $F/\rho$ for a group of similarly extravascular indicators (similar mean transit times) was taken as the blood flow for the group. Thus in experiment 1 the creatinine recovery was assumed equal to 0.80, and the resulting blood flow, 4.52 ml/sec, was assumed the same for THO. (Three significant figures are given only for computational purposes.) In experiment 2 the T-1824 blood flow, 4.74 ml/sec, was assumed for creatinine and $^{22}$Na. This value, however, would give a recovery higher than unity for $T_2$. Hence a recovery of unity was assumed for $T_2$, and the resulting blood flow, 3.53 ml/sec, was assumed the same for DHO and $^{85}$Kr. Similar considerations were made for experiment 3.

**Column 5.** The mean transit time $t$ is given by

$$t = t_0 - t_\infty,$$  \(32\)

where

$$t_0 = \int_0^\infty t \, w \, dt \int_0^\infty w \, dt,$$  \(33\)

and $t_\infty$ is a "catheter effect" mean transit time, taken as the sum of a dead time $t_0$ and an exponential lag time $t_1$. (20)

$$t_1 = t_0 + t_\infty.$$  \(34\)

The evaluation of $t_0$ and $t_1$ is described in connection with column 8. Their numerical values are indicated for each experiment (Table 1).

**Column 6.** The solubility volume of distribution $XV$ is the product of corresponding values in columns 4 and 5.

**Column 7.** The initial semi-log downslope $k_1$ was measured as 0.693/half-life on a real time semi-log plot of the data (Fig. 5; the catheter distortion correction does not affect this value; see equation 35 below) and multiplied by the mean transit time (column 5).
The value in parentheses is a theoretical value obtained from Figure 7 by use of the \( \beta \)-value of column 8.

**Column 8.** The parameter \( \beta = L^2/D \) of the present model was obtained by graphical comparison “by eye” of the theoretical curves and the experimental outflow patterns in the nondimensional plots of Figures 4 and 9-12. To make this plot the outflow pattern was first corrected for catheter distortion of curve shape according to Goresky and Silverman (20) who investigated catheters similar to those used in the present experiments. The quantity

\[
w' (t') = w (t) + t_1 dw (t)/dt
\]

was calculated, where

\[
t' = t - t_0
\]

and \( t_0, t_1 \) are the catheter parameters of equation 34. The ordinate \( 100 \left( F^2 / \rho \right) t_0 w' \) was then plotted against the abscissa

\[
t'/t = (t - t_0) / (t_1 - t_0 - t_1)
\]

to give a curve of area = 100 (on a rectangular plot) and centroid located at the unit abscissa.

The catheter parameters \( t_0 \) and \( t_1 \) were determined as follows: the catheter response to a step function can be represented with sufficient accuracy (20) as a delay, or dead time, \( t_0 \), followed by an exponential rise of rate constant \( 1/t_1 \). Estimates of \( t_0 \) from \( t_1 = \) catheter volume/sample pump rate and plausible estimates of \( t_1 \) (shown later) yielded negative
initial values of \( t'/t \) by equation 37. This result indicated too great an uncertainty in knowledge of the catheter volume and of the injection time and duration. Therefore, a self-consistent evaluation of \( t_0 \) and \( t_1 \) was made from the experimental outflow pattern itself. The dead time \( t_0 \) was taken as the earliest appearance time of any of the indicators, as estimated by extrapolation from the earliest measured values. The estimates of \( t_0 \) for the different indicators did not differ greatly. The exponential lag time \( t_1 \) was taken, for present purposes, as one half of the reciprocal of the initial semi-log downslope of the T-1824 curve. The rationale here is that the steepest observed downslope for all indicators is that for T-1824; the reciprocal of this downslope \( t \) (T-1824) represents, approximately, a lag time for the external catheter, internal large vessels, and internal capillaries, considered crudely as systems in series. Thus \( t \) (T-1824) represents an upper bound for the external catheter lag time \( t_1 \). A lower bound is zero. In the absence of further information, the average of these two bounds is the best estimate of \( t_1 \). The preceding estimates of \( t_0 \) and \( t_1 \) probably include to some extent the catheter effect of the large vessels, which is desirable for the present model. The present evaluations of \( \beta \) in column 8 are dependent mostly on the outflow patterns after the peak values, which are not sensitive to choice of \( t_0 \) and \( t_1 \).

**Column 9.** The diffusion time parameter \( L^2/D \) is given by the product of corresponding values in columns 8 and 5.

**Column 10.** An upper estimate \( L_u \) of diffusion distance was derived from the value in column 9 and from an upper estimate \( D_u \) of the diffusion coefficient (Table 2). The upper estimate \( D_u \) was taken as the diffusion coefficient of the tracer indicator in water at 37°C. For T-1824 the value for serum albumin given in (32) was used. For \( ^{22}Na^+ \) the value given for NaCl in (32) was used. The value for creatinine (molecular weight = 113) was obtained by interpolation on a plot of values in (32) against the reciprocal of the square root of molecular weight. The assumed equal value for THO and DHO was obtained as the average of the values interpolated at 37°C for all studies of self-diffusion coefficients of THO, DHO, and \( ^{3}H.O \) given in (33). No significant distinction between the values for THO and DHO could be made. The value for \( ^{85}Kr \) was obtained as \((4/85) \times D (He, 37°C)\).

![Figure 7](image-url)

**Theoretical ratio of final semi-log downslope \( k_f \) to outflow per unit solubility volume \( F/\lambda V = 1/\beta \); abscissa \( \beta = L^2/Di \).**

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>( T )</th>
<th>( D_u )</th>
<th>( ^{65}Na^+ )</th>
<th>THO</th>
<th>DHO</th>
<th>( ^{85}Kr )</th>
<th>( T_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-1824</td>
<td>0.085</td>
<td>1.3</td>
<td>2.0</td>
<td>3.1</td>
<td>3.1</td>
<td>1.4</td>
<td>2.9</td>
</tr>
<tr>
<td>( D_1 )</td>
<td>0.028</td>
<td>0.43</td>
<td>0.67</td>
<td>1.0</td>
<td>1.0</td>
<td>0.47</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*See text for references.*
CONVECTION-DIFFUSION MODEL OF OUTFLOW PATTERN

with $D$ (Hg, 37°C) = 8.3 (34). The value for $T_2$ was obtained as $(2/6)^{1/2} \frac{D}{H_2, 37°C}$ with $D$ (Hg, 37°C) = 5.07 (34).

Column 11. A lower estimate $L_i$ of diffusion distance was derived from the value in column 9 and a lower estimate $D_i$ of diffusion coefficient (Table 2). The lower estimate $D_i$ was taken as $D_i/3$ (26, 35, 36).

Discussion of Theoretical Results

Figure 3 shows the effect of varying the convection rate parameter $F/\lambda V = 1/t$ at fixed diffusion rate parameter $D/L^2$. Figure 4 shows the effect of varying $D/L^2$ at fixed $F/\lambda V = 1/t$. The features peculiar to the present model are best exhibited by Figure 4. In this plot both items of classical information, the flow $F$ and the mean transit time $t$, are “normalized out,” the former by making the area under each curve = 100, the latter by expressing time in units of $t$. The Peclet number $\beta$ represents in order of magnitude the ratio of the convective flux density to the diffusive flux density. As $\beta$ varies from 0 to $\infty$, the theoretical indicator curves vary in shape from a single decay exponential to a $\delta$-function (Fig. 4).

The curve for $\beta = 0$, considered for convenience as corresponding to infinitesimal convection rate and finite diffusion rate (approximated by the $\beta = 1$ curve in Figure 3), results from the relatively rapid and uniform diffusive filling by the indicator, after $\delta$-function injection, of its volume of distribution in the tissue slab. The infinitesimal convective flow of fluid then “washes out” the indicator from this volume by first-order kinetics without appreciably disturbing the uniform indicator concentration, which is maintained by diffusion. This limit represents the perfusion, or flow, limit of compartment kinetics for the whole tissue (26). The initial discontinuity of the curve in Figure 4 appears because of the infinite compression of the time scale in this case (infinitesimal convection means $t = \lambda V/F \to \infty$). On the time scale of Figure 3 the initial portion of the $\beta = 0$ curve up to its maximum value (approximated by the $\beta = 1$ curve) occupies about 0.5 $L^2/D$ sec (see Modal time below). Thereafter it takes an infinite time for the infinitesimal fluid flow to “wash out” the indicator.

The $\beta = \infty$, or “infinite convection-finite diffusion” indicator curve, is $\delta \left[ \left( t/t_0 \right) - 1 \right]$ in Figure 4 and $\delta \left( D t/L^2 \right)$ in Figure 3. This is the delayed traveling wave solution (18, 19) discussed later.

The general shape features of the theoretical indicator curves comprise an appearance time that is well defined, a relatively rapid rise to a maximum, a slower fall to a final exponential decrease, and an over-all dispersion about the mean transit time. The timing and prominence of each of these characteristics depend on both parameters of the model or, equivalently, on their ratio $\beta$ and on either parameter. These features are discussed in turn.

Appearance Time.—The effluent concentration remains almost zero for a time and then starts an increasingly rapid rise (Fig. 8). If the appearance time $t_a$ is defined arbitrarily as the time for the effluent concentration to rise 1 or 2 percent of its maximum value, then from the present model solutions this time is approximately as follows:

$$t_a = 0.04 \frac{L^2}{D} = 0.04 \beta t$$

$$t_a = 0.25 \frac{L^2}{D} = 0.25 t$$

$$t_a = 0.01 \frac{L^2}{D} = 0.5 t$$

$$t_a = 0.006 \frac{L^2}{D} = 0.6 t$$

$$t_a = (1 - 4.292 \beta^{-1}) t$$

in which equation 38(e), $100 < \beta < \infty$, (e)

in which equation 38(e), $100 < \beta < \infty$, (e)

Modal Time and Peak Value.—The modal, or peak value, time in the small convection limit $\beta \to 0$ is of the order 0.5 $L^2/D$. (An asymptotic formula is given in the Appendix, equation A24.) This time is that given by pure diffusion theory for the concentration at $x = L$ to rise to about 98 percent of its final equilibrium value (Appendix, equation A26). This result again illustrates the small perturbation action of convection as a slow leak.
superimposed on a concentration distribution determined essentially by diffusion. As $\beta$ increases, the modal time occurs sooner on the $Dt/L^2$ time scale (Fig. 3), but later on the $t/\ell$ time scale (Fig. 4). In the all-convection limit $\beta \to \infty$, the modal time approaches the mean transit time $t$. The locus of peak values is shown (Fig. 4) as the dot-dash curve.

Semi-Log Downslope.—At long time $t$ all theoretical indicator curves approach the exponential form $a_t e^{-k_1 t}$ (Appendix, equation A21; the subscript 1 denotes the “slowest” exponential). The model thus lends support to the conventional procedure for recirculation correction of prolonging the straight-line portion of the semi-log plotted outflow pattern. The straight-line portion starts increasingly later, however, as $\beta$ increases. The comparison with the experiment (Fig. 4) shows that this straight-line portion is reached by the extravascular indicators before recirculation sets in. The present model throws some light on the question of whether the semi-log downslope measures an $F/XV$ (11, 17, 37).

The rate constant $k_1 \approx F/XV$ at $\beta = 0$ and becomes increasingly larger than $F/XV$ as $\beta$ increases (Fig. 7). The reason for this increase of $k_1$ relative to $F/XV$ is that the convective flow "piles up" the indicator at $x = L$ above what would be there if the then remaining amount in the slab were uniformly distributed. Because the same total amount of indicator is to be removed as at $\beta = 0$, the result is a faster fractional rate of removal.

Dispersion about the Mean.—The root-mean-square, or standard, deviation of the theoretical indicator curves, denoted by $\Delta t$, is given by equations A32, A33 in the Appendix

$$\Delta t = \left[ (t - t)^2 \right]^{1/2} = t \left[ \frac{2}{\beta} \left( 1 - \frac{1}{\beta} + e^{-\beta x} \right) \right]^{1/2} ,$$

which approaches, in the all-convection limit,

$$\Delta t/t \to \left( \frac{1}{\beta} \right)^{1/2}, \beta \to \infty$$

and, in the all-diffusion limit, after expanding $e^{-\beta}$ to the third power in $\beta$ and simplifying,

$$\Delta t/l \to \left( 1 - \frac{1}{3} \beta \right)^{1/2}, \beta \to 0 .$$

The limiting expression 40 agrees with the well-known relation for the one-dimensional diffusional spread of an initially $\delta$-function distribution of substance which is moving as a whole with group velocity $v$. An observer moving with velocity equal to the group velocity sees, at a time $t$ after introduction of the $\delta$-function, a spatial standard deviation given by the well-known relation for one-dimensional free diffusion, $\Delta x = (2Dt)^{1/2}$. In the all-convection limit $\beta \to \infty$, $D \to 0$, and for the $\delta$-function injection, equation 18 has the previously noted solution $\delta[t - (\lambda V/FL)x]$. For $x = L$, the limiting relationships

$$t = l, \nu = L/t$$

hold. Hence an observer of the indicator curve at $x = L$ sees a temporal standard deviation

$$\Delta t = \Delta x/\nu = (2Dt)^{1/2}$$

which, since $\beta = L^2/Dt$, reduces to expression 40. As $\beta$ decreases from $\infty$, the exact equation 39 gives a smaller dispersion than expression 40 because the diffusion-impervious boundaries of the slab exert a confining tendency on the indicator, as compared to the free diffusion implied in expression 40.

Discussion of Experimental Results

The deficiencies of the delayed wave model and the washout model with respect to the kidney are illustrated for experiment 2 (Figs. 5 and 6). The delayed wave model predicts earlier appearance times, faster rise times, and earlier modal (peak value) times for indicators with smaller volumes of distribution. (The bolus travel time in the blood-tissue exchange region is $\lambda V/F$; see equation 29.) Thus T-1824 should be less delayed than creatinine, which in turn should be less delayed than water, krypton, and tritium (Table 1, column 6, experiment 2). In contrast, the experiment (Figs. 5 and 6) shows about the same appearance times for all indicators, faster rise times for tritium and krypton than for water and creatinine, equal modal times for creatinine

Circulation Research, Vol. XXII, February 1968
CONVECTION-DIFFUSION MODEL OF OUTFLOW PATTERN

and water, and a decrease of modal time from water to krypton to tritium.

The delayed wave model predicts that the semi-log downslope \( k_1 \) of an extravascular indicator should have no causal relation to blood flow per unit volume of distribution, that is, to \( 1/I = F/AV \). The washout model predicts that these two quantities should be equal, that is, that \( k_1 t = 1 \). The experiment shows that \( k_1 \) is close to \( 1/t \) for the most highly diffusible indicator, tritium (Table 1, column 7, experiment 2, \( k_1 t \) (tritium) = 1.1), and that there is a systematic increase of \( k_1 \) relative to \( 1/t \) from tritium to krypton to water (\( k_1 t = 1.1, 1.2, \) and 1.4, respectively).

The preceding divergencies, although not large, are highly reproducible experimentally. Their existence should not be affected by inaccuracy in correcting for catheter distortion (dashed lines, Fig. 6) or for recirculation (prolongation of straight portions, Fig. 5). Interpretation of the experimental data on the present model is made next.

Consider first experiment 1 (Fig. 4). The THO and creatinine data agree well with the theoretical curves for \( \beta = 2 \) and \( \beta = 8 \) (interpolated by eye). The first one or two points are probably too close to the time origin because the catheter dead time parameter \( t_0 \) was overestimated somewhat by being taken as the appearance time (see equation 37). The ratio \( (L^2/D)_{\text{crea}}/(L^2/D)_{\text{THO}} = 33.2/17.0 = 2.0 \) (Table 1) does not differ greatly from the inverse ratio of their diffusion coefficients \( D_{\text{crea}}/D_{\text{THO}} = 2.4 \) (Table 2; corresponding values of diffusion coefficient are divided; that is, it is assumed that the tissue value of the diffusion coefficient is in the same ratio to the water value for each indicator). A similar value of diffusion distance is thus indicated for both substances, despite major differences in their volumes of distribution, in agreement with the transport process envisaged by the model. The absolute magnitude of the derived diffusion distance (Table 1, columns 10 and 11) is thought to be plausible as a source-to-sink distance in kidney cortex. The sources postulated by the model comprise those portions of the vascular volume in which a net blood-to-tissue flow of indicator takes place as the indicator is carried along by the blood flow. The source strength would be proportional to the fractional rate per unit vascular volume, at which the concentration in an intravascular bolus of the indicator would equilibrate with the extravascular indicator concentration. The source strength would be low where the velocity of the blood carrying the bolus was high, as in the arterial vessels, and would be high where the blood velocity was low, as in the capillaries. In the kidney the sources should consist predominantly of the glomerular capillary volume, in accordance with established ideas as to where transcapillary equilibration of concentration of small molecules first occurs. The sinks postulated by the model comprise those portions of the vascular volume where, after local blood-tissue equilibration of concentration of the indicator has been completed, the blood velocity has increased sufficiently that the local intravascular concentration of indicator becomes independent of the local extravascular concentration of the indicator. In the kidney the sinks may be approximately identified with the junctional vascular volume between the peritubular capillary network and the interlobular veins. The source-to-sink distance in kidney cortex should then be, because of the regularity of arrangement of the vascular architecture (38) (sink centers half-way between source centers) and the diffuse nature of sources and sinks, somewhat less than half the distance between glomeruli. In dog kidney the center-to-center distance between glomeruli is about 500 \( \mu \) [2 \( \times \) 100 glomeruli in 40 cm\(^2\) of kidney cortex (38)]. The diameter of a glomerulus is about 150 \( \mu \). The derived diffusion distance in the range 120-230 \( \mu \) is compatible with the preceding considerations.

The source-to-sink diffusion distances derived for creatinine and THO appear considerably lower than the mean length of the peritubular capillaries between efferent arterioles and venules. This result is permitted by the model (the capillary fluid velocity need not be in the same direction as the diffusive...
flux density of indicator; see Model section) and agrees with the "diffusion bypass" hypothesis. This hypothesis was advanced (22) to account for the earlier appearance of tracer sodium and water relative to creatinine in the urinary excretion pattern, after simultaneous injection into the renal artery. The hypothesis was that a diffusible indicator such as sodium could "be brought by way of the blood stream to the proximity of the thin segment or collecting tubules and there cross into the tubular lumen" (22). Blood-to-blood bypasses, as well as tubular lumen-to-lumen bypasses in the kidney cortex, were since postulated for oxygen (12, 23) and for water, alcohols, and inert gases (12, 24).

The rise time of THO is actually faster than for creatinine in experiment 1 (Fig. 8). Real time theoretical curves for $\beta = 1, 2$ and $\beta = 5, 10$ and $\beta = 4.15$ sec (solid lines) were constructed from the theoretical nondimensional curves (Fig. 4) to bracket the experimental results (Table 1, columns 5 and 8, experiment 1). The comparable theoretical curves ($\beta = 2, \beta = 5$, Fig. 8) indicate a precession of THO over creatinine. This result is an independent consequence of the model since the curve-fit to determine $\beta$ depended on the data points mostly outside the early time region. In the early time region the experimental data are subject to considerable uncertainty, and the catheter corrections are largest. The theoretical appearance times of THO and creatinine (Fig. 8) may be calculated by semi-logarithmic interpolation from equations 38 and the respective $L^2/D$ values (Table 1) as:

$$t_a (\text{THO}) = 0.038 \times 17.0 = 0.65 \text{ sec}$$
$$t_a (\text{creat.}) = 0.028 \times 33.2 = 0.93 \text{ sec}.$$}

The first factor of the preceding products contains primarily the effect of the convection parameter $F/\lambda V$ on the appearance time. (There is also a secondary influence of $L^2/D$.) Convection alone, as in the Goresky model, would cause creatinine to appear sooner than THO since the solubility volume of distribu-

---

**FIGURE 8**

Comparison of theoretical and experimental results on rectangular plot in real time. Solid lines = theoretical curves for $\beta = 5$ and 10 and dashed lines = theoretical curves for $\beta = 1$ and 2 of Figure 4, converted to real time by use of the experimental mean transit times of creatinine and THO, Table 1, column 5, experiment 1; data points = catheter distortion corrected values of experiment 1; solid triangles = creatinine (flagged points are in recirculation corrected region); open circles = THO. (For abscissa and ordinate see text, equations 30 to 37.)

_Circulation Research, Vol. XXII, February 1968_
**CONVECTION-DIFFUSION MODEL OF OUTFLOW PATTERN**  

The theoretical considerations on dispersion about the mean can be illustrated by the experimental results. The standard deviation calculated directly from the THO outflow pattern is $\Delta_t_{\text{exp}} = 6.7$ sec. With $t = 8.50$ sec and $\beta = 2$ (Table 1, columns 5 and 8, experiment 1), the model yields $\Delta t = 8.5$ sec by the approximate equation 40. A maximum estimate of the standard deviation that results from ignoring the Goresky delay effect and using $t_L = 1.83$ sec, $L = 133 \, \mu$, $D = 1.0 \times 10^{-6}$ cm$^2$/sec in equation 43 is 0.83 sec. (This is a maximum estimate because $L = 133 \, \mu$ is a minimum estimate for the average capillary length which should be used.) This estimated value is far less than $\Delta t_{\text{exp}} = 6.7$ sec. For creatinine, $\Delta t_{\text{exp}} = 2.1$ sec, $\Delta t = 1.9$ sec by the exact equation 39, and $\Delta t = 2.1$ sec by the approximate equation 40, and the maximum estimate with no Goresky delay is 0.61 sec. We conclude that the Goresky delay effect is essential in providing sufficient time for source-to-sink diffusion to account for the dispersion of extravascular indicators.

The dispersion of the T-1824 outflow pattern in experiment 1 was 0.8 sec, or about one-third the creatinine dispersion and one-eighth the THO dispersion. The contribution of the non-exchange vessels to the T-1824 dispersion should be substantially less than 0.8 sec. This contribution should be present in the experimental creatinine and THO dispersion, but it was neglected in the present model. This neglect appears to be justified, particularly for THO. The contribution of the exchange vessels to the T-1824 dispersion should, on the present model, not be present in the creatinine or THO dispersions as the extravascular indicators are assumed not guided by the capillaries in the exchange region.

The T-1824 data (Fig. 4) are only qualitative, as the catheter correction was in general of the same order as the original data ordinates. Despite this, a significant conclusion is possible: the T-1824 data appear to fit a theoretical curve for $\beta = 10$. The resulting diffusion distance, however, in the range 23-39
μ (Table 1, columns 10 and 11, experiment 1) appears both incompatible with the diffusion distances for creatinine and THO and independently implausible anatomically. Alternatively, a minimum estimate for β, corresponding to \( L = 120 \mu \) and \( D = 0.085 \times 10^{-6} \text{ cm}^2/\text{sec} \), is \( \beta_{\text{min}} = 93 \). The T-1824 data appear too greatly dispersed to fit a theoretical curve of this or greater β value \( [\Delta t_{\text{exper.}} = 0.8 \text{ sec}; \Delta t (\beta = 93, t = 1.83) = 0.3 \text{ sec by equation 39}] \). The catheter uncorrected T-1824 data show the same behavior. It is concluded that the present model does not apply to the T-1824 outflow pattern.

The preceding negative conclusion for T-1824 is compatible with the present model. T-1824 is bound to serum albumin and hence is largely constrained to follow the anatomical capillaries. A distribution of peritubular capillary lengths (more precisely, of capillary traversal times for albumin-T-1824 complexes) appears anatomically to exist in kidney cortex. This distribution should contribute substantially to the dispersion of the T-1824 outflow pattern (see above). If, despite this contribution to the dispersion, the T-1824 data coincided with a plausible theoretical curve, the model, which does not allow such contribu-

![Figure 9](http://circres.ahajournals.org/)

**FIGURE 9**

Comparison of theory and experiment for experiment 2. Crosses = T-1824 labeled albumin; solid triangles = \(^{14}\text{C-creatine}\); open triangles = \(^{38}\text{Na}\).

![Figure 10](http://circres.ahajournals.org/)

**FIGURE 10**

Same as Figure 9. Open circles = DHO; solid circles = \(^{85}\text{Kr}\); open squares = \( T_h \). Other details are in legend to Figure 4.
tion, would be contradicted. Similar considerations apply to other vascular indicators such as labeled red cells. Thus the present model is self-consistent in being applicable to extravascular indicators but not to vascular indicators in a dog kidney.

Consider next experiments 2, 3a and 3b (Table 1, Figs. 9-12). All normalized outflow patterns agree fairly well with one or another theoretical curve. The creatinine, DHO, and T-1824 results are much the same as for experiment 1. The diffusion distance for creatinine and DHO is somewhat larger than in experiment 1, which may be correlated with the larger derived values of the various volumes (Table 1, column 6; the DHO volume in experiment 2 appears anomalously low).

The $^{22}\text{Na}$ diffusion distance, 162-281 µ, is about the same as for creatinine and DHO. This is plausible because its volume of distribution is intermediate between that of creatinine and water, and the extent of its reabsorption from the tubules is similar to that of water. The reabsorption feature might be expected to result in greater diffusion distances for $^{22}\text{Na}$ and DHO than for creatinine. The slight tendency discernible in this direction (Table 1) is probably not significant at the present level of experimental accuracy.

Of greater significance in view of the consistent though small differences among the normalized outflow patterns (Figs. 9-12) are

![Figure 11](image)

*Comparison of theory and experiment for experiment 3, run (a). Legend as in Figure 8.*

![Figure 12](image)

*Comparison of theory and experiment for experiment 3, run (b). Legend as in Figure 8.*
the approximately equal diffusion distances for \(^{85}\text{Kr}\) and \(\text{T}_2\) relative to the larger diffusion distance for DHO (Table 1, columns 10 and 11). The following two possibilities are offered in explanation.

1) The ratio \(B = D_{(kidney\ cortical\ tissue)}/D_{(water)}\) may be less for DHO than for \(^{85}\text{Kr}\) or \(\text{T}_2\). The value \(B = 1/3\) used as a lower bound (Table 2) is based on measurements in connective tissue and in muscle for \(\text{O}_2\) (35) and \(\text{CO}_2\) (36) which give \(B = 1/3\) to 2/3, and measurements in blood serum for \(\text{H}_2\), \(\text{O}_2\), \(\text{N}_2\) (39) which give \(B = 3/4\). These gases are lipid soluble, as are \(^{85}\text{Kr}\) and \(\text{T}_2\), so that the lipid component of the cell membranes should not be a direct factor (a solubility barrier) in reducing their diffusion coefficients relative to those in water. For DHO, however, the membrane lipid should offer a solubility barrier to diffusion and result in a value of \(B\) less than that for \(^{85}\text{Kr}\) or \(\text{T}_2\). If, for example, the value \(B_{(^{85}\text{Kr})} = B_{(\text{T}_2)} = 2/3\) is assumed, then experiment 3a yields the diffusion distance \(L = 96\ \mu\text{m}\) for \(^{85}\text{Kr}\) and \(\text{T}_2\). This same diffusion distance for DHO would be obtained for \(B_{(\text{DHO})} = 0.11\). It is not known whether this value is realistic.

2) Should \(D_{(tissue)}/D_{(water)}\) for DHO be greater than 0.11, then a larger diffusion distance for DHO than for \(^{85}\text{Kr}\) or \(\text{T}_2\) is indicated by the model. This situation could result from non-instantaneous local equilibration. If a slower local transcapillary equilibration for DHO exists relative to that for \(^{85}\text{Kr}\) or \(\text{T}_2\), the postulated sources for DHO would be diffusely spread over the glomerular capillary region, whereas the sources for \(^{85}\text{Kr}\) or \(\text{T}_2\) would be concentrated closer to the afferent arterioles. The presence of veins in apposition to the afferent arterioles and interlobular arteries would then make possible a shorter diffusional path for \(^{85}\text{Kr}\) and \(\text{T}_2\) than for DHO. (This argument suggests that the lipid component of membranes may slow down local equilibration of lipophobic molecules so that a uniform interchange with cells can be achieved with fewer capillaries.)

The split pathway feature in the kidney leading to two outputs, in blood and urine, should not greatly affect the present application of the model to the blood outflow pattern alone. For creatinine the two pathways are largely independent beyond the glomeruli so that the purely shape details of the normalized outflow pattern should be little changed by the urinary excretion. For water and sodium the urinary excretion is small so that the over-all input-output situation is still largely single input-single output. Reabsorption and secretion should affect only the glomerular filtrate fraction of the injected amount of these indicators. With respect to this fraction, reabsorption should produce only local regions of inhomogeneity of concentration (likewise for secretion) which would show up in the outflow pattern primarily as a volume (transit time) effect.

Concluding Remarks

A model was presented where an arterially injected bolus of diffusible, recoverable indicator is transported to the venous outflow as follows: (1) the indicator is divided into a number of boluses which appear at the vascular entrances (sources) to the blood-tissue exchange region almost simultaneously; (2) the boluses equilibrate instantaneously and locally over micron distances between blood and an extravascular volume characteristic of the indicator; (3) the locally equilibrated boluses diffuse in the direction of maximum negative activity (concentration) gradient toward venular exits (sinks). The diffusion takes place in the entire tissue accessible to the indicator, including the contained blood; (4) the indicator which happens to be in a region of moving blood (the vascular volume) is, in addition, transported by bulk movement, or convection, in a direction which locally need not be the same as that from source to sink; (5) the indicator arrives dispersed at the sinks; the dispersion is due to the diffusion component of the transport process.

The model is described mathematically by a partial differential equation, together with boundary and initial conditions and the auxiliary condition of instantaneous local
equilibration. Theoretical indicator curves are obtained, in which all the remaining mathematical information beyond the classical information of area and mean transit time is specified by a single additional parameter, \(L^2/D\), where \(L\) is the source-to-sink distance, and \(D\) is the diffusion coefficient of the indicator in the tissue.

The simultaneous inclusion of diffusion and convection transport mechanisms enables the model to bridge the gap between the opposite limiting cases of the washout-type model \([(\text{convection/diffusion}) \rightarrow 0]\) and the delayed wave model \([(\text{convection/diffusion}) \rightarrow \infty]\). The various features of the indicator curve—appearance time, modal or peak time, peak value, relation of semi-log downslope to blood flow per unit volume of distribution, the overall dispersion—can all be evaluated in terms of the combined and relative influence of diffusion and convection.

The model accounts plausibly for the outflow patterns of the extravascular indicators—creatinine, sodium, water, krypton and tritium gas—in a dog kidney. Inasmuch as length distribution in the capillary network is ignored, the model should not and, in fact, does not account plausibly for the vascular indicator, T-1824 labeled albumin.

Acknowledgments
We thank Drs. J. Murray Steele, Richard Effros, Melvin Silverman, Bernard Altshuler, and the referees of this paper for many useful comments. Andrew A. Perl assisted with the computations.

Appendix
Mathematical Solution of the Model
Equation 18 is written in nondimensional form as

\[
\frac{\partial \omega}{\partial \tau} = \frac{\partial^2 \omega}{\partial X^2} - \beta \frac{\partial \omega}{\partial X}, \quad (A1)
\]

\[
\bar{w}_b (s) = \tilde{\omega} (1, s) = \frac{4\beta e^{\beta/2} \alpha}{(\beta^2 + 4\alpha^2) \sinh \alpha + 4\beta \alpha \cosh \alpha}, \quad (A11)
\]

where

\[
X = x/L \quad (A2)
\]

\[
\tau = Dt/L^2 \quad (A3)
\]

\[
\omega (X, \tau, \beta) = (L^2F/\lambda Dm) C (x, t), \quad (A4)
\]

\[
w_b (\tau, \beta) = \omega (1, \tau, \beta) = (L^2F/\lambda Dm) \frac{C (L, t)}{(L^2/F/D) \omega}. \quad (A5)
\]

will be derived. Figure 3 is a plot of 100 \(w_b\) vs. \(\tau\) for various \(\beta\). Figure 4 is a plot of 100 \(\beta^{-1} w_b\) vs. \(\beta \tau = t/\ell\) for various \(\beta\). Figure 8 is a plot of 100 \((\beta \ell)^{-1} w_b\) vs. \(\beta \ell \tau = t\) for specific values of \(\beta\). The form A5 nondimensionalizes and normalizes the effluent concentration \(C (L, t)/\lambda = C_1 (L, t) = \omega (1, t)\) to unit area when plotted vs. \(\tau\); thus

\[
\int_0^\infty w_b (\tau) \, d\tau = 1. \quad (A6)
\]

Also, as will be verified, the centroid of the plot of Figure 4 is at unity for all \(\beta\), or

\[
\tau = \int_0^\infty \tau w_b (\tau) \, d\tau = 1/\beta. \quad (A7)
\]

The nondimensional boundary and initial conditions for \(\delta\)-function input are

\[
\delta (\tau) = \omega (0, \tau) - \beta^{-1} (\partial \omega/\partial X)_0 \quad (A8)
\]

\[
0 = (\partial \omega/\partial X)_1 \quad (A9)
\]

\[
0 = \omega (X, 0) \quad (A-10)
\]

Equations A1 and A8–A10 were solved by the standard Laplace transform method (40). The solution of the transformed equations, evaluated at \(X = 1\), is

\[
\bar{w}_b (s) = \frac{4\beta e^{\beta/2} \alpha}{(\beta^2 + 4\alpha^2) \sinh \alpha + 4\beta \alpha \cosh \alpha}, \quad (A11)
\]

where \(s\) is the (nondimensionalized) Laplace transform frequency variable and

\[
\alpha = (s + \beta^2/4)^{1/2}. \quad (A12)
\]

The inverse of equation A11 can be derived in two forms: a wave form suitable for cal-
culation at small values of time; and an exponential form suitable for calculation at large values of time. Equation A11 was first shifted by
\[
\text{inv } f(s + \omega) = e^{-\omega T} \text{inv } f(s)
\] (A13)
into the form
\[
\omega_b(\tau) = 4\beta_0 \beta / 2 e^{-\beta^2 / 4} \text{inv } \bar{v}
\] (A14)
where
\[
\bar{v} = \frac{s^4}{(4s + \beta^2) \sinh s^4 + 4s^4 \cosh s^4}.
\] (A15)
The wave form was derived by expressing the hyperbolic functions in exponential form, expanding in powers of \(e^{-s^2 / 4}\), retaining only the first power, and using a table of Laplace transforms [in (40), Table 2.2, item 12 and its derivative with respect to the parameter \(h\), in which \(D = x = 1\) and \(t = T\)]. The resulting first term of the wave form solution is
\[
\omega_b(\tau) = \beta e^y \left[ \frac{2}{(\pi \tau)^4} \left( 1 + \frac{\beta^2}{2 \tau} \right) e^{-\beta^2 / 4} - \beta \left( 4 + \beta + \beta^2 \right) \text{erfc } y \right],
\] (A16)
where
\[
y = (1 + \beta \tau) / 2 \tau^4,
\] (A17)
and \(\text{erfc } y\) is the complementary error function
\[
\text{erfc } y = \frac{2}{(\pi \tau)^4} \int_y^\infty e^{-x^2} dx
\] (A18)
\[
= -\frac{e^{-\nu}}{(\pi \tau)^4} \left( 1 - \frac{1}{2y^2} + \frac{3}{4y^4} - \ldots \right).
\] (A19)
For \(\beta < 10\) equation A16 was evaluated directly, and for \(\beta \geq 10\) the expansion A19 was used with standard mathematical tables (41, 42).

The exponential form of solution was derived by first locating the zeros of the denominator in equation A15. These occur at \(s_n^4 = \pm i \omega_n\), where
\[
\tan \omega_n = \Omega \omega_n / 4 \omega_n^2 - \beta^2.
\] (A20)

Each pair of values \(\pm \omega_n\) satisfying equation A20 corresponds to a simple zero of the denominator of equation A15 at \(s = s_n = -\omega_n^2\). At each zero the residue \(a_n\) of \(\bar{v}\) is evaluated as the numerator over the derivative by \(s\) of the denominator. The inverse of \(\bar{v}\) is then a sum of exponentials \(\sum a_n e^{-\omega_n^2 \tau}\). Substituting this sum into equation A14 yields
\[
\omega_b(\tau) = \sum_{n=0}^{\infty} a_n e^{-\omega_n^2 (\beta / 4) \tau}
\] (A21)
where
\[
a_n = \frac{2\beta_0 \beta / 2 e^{-\beta^2 / 4} \omega_n^2}{(\omega_n^2 - \beta - \beta^2 / 4) \cos \omega_n + (2 + \beta) \omega_n \sin \omega_n}.
\] (A22)

Four exponentials were determined in the calculations. These were sufficient to match the wave form solution A16 with \(\leq 1\) percent error at times \(\tau = 0.3, 0.06, 0.06, \ldots\), respectively, for \(\beta = 0.1, 1, 10\). For smaller \(\tau\) values the exponential form diverged and the wave form converged and was used. For larger \(\tau\) values the reverse obtained. For \(\beta \leq 0.5\) the first two exponentials of equation A21 sufficed for most of the time range of interest.

As \(\beta \to 0\) (the diffusion limit) the exponential form A21 approaches
\[
\beta^{-1} \omega_b \to e^{-\beta \tau} + 2 \sum_1 = (1) e^{-\omega_n^2 \tau + \ldots}.
\] (A23)

Equation A23 becomes a single exponential of rate constant \(\beta L^2 / D = F / \lambda V\) in the limit \(\beta = 0, \tau = \infty, \beta = t / t = \text{finite}\). The limiting behavior of the peak location and value as \(\beta \to 0\) is given by the first two terms of equation A23 as
\[
\tau_m = \pi t^{-2} \ln \left( 2\tau^2 / \beta \right)
\] (A24)
\[
\beta^{-1} \omega_{\text{m}} = e^{-\beta \tau_m}.
\] (A25)

The wave form of limiting solution as \(\beta \to 0\) is
\[
\beta^{-1} \omega_{\text{m}} \to e^{-\beta t_m} (e^{-\tau(1/4)} + e^{-\tau(1/4)} + e^{-\tau(2/4)} + \ldots).
\] (A26)

The solution A16 for arbitrary \(\beta\) reduces to the first term of equation A26 as \(\beta \to 0\). The order of magnitude of successive terms in the wave form solution for arbitrary \(\beta\) can be
guessed from this correspondence. [In equation A17 replace 1 by \((2n+1)^2 = 1^2, 3^2, 5^2, \ldots\).] For \(n \geq 20\) the wave form solution A16 suffices for most of the time range of interest. In the convection limit \(\beta \to \infty\), equation A16 approaches

\[
\beta^{-1} \omega_b \to (\beta/4\pi)^4 (1 + \frac{3}{2} u) e^{-\beta/4 (\omega^2 + \omega^4)},
\]

where

\[
u = 1 - \beta \tau.
\]

Equation A27 yields the Goresky solution \(\delta (1 - \beta \tau)\) in the limit \(\beta \to \infty\).

The appearance time as \(\beta \to \infty\) can be obtained from equation A27 as

\[
\beta \tau_0 = \frac{t_0}{1} = 1 - \frac{[(4/\beta) \ln (1/r)]^4}{3}.
\]

The limiting behavior of the peak location and value as \(\beta \to \infty\) is obtainable from equation A27 as

\[
u_m = 1 - \beta \tau_m \to 3/\beta
\]

\[
\beta^{-1} \omega_b (\beta \tau_m) \to (\beta/4\pi)^4 \cdot
\]

The mean value of \(\tau^n\) can be obtained from equation A11 as (7),

\[
\tau^n = \int_0^\infty \frac{\omega_b \, d\tau}{\int_0^\infty \omega_b \, d\tau}
\]

where \(\bar{\omega}_b (0) = \int_0^\infty \omega_b \, d\tau = 1\). The first mean, \(\tau\), is given by equation A7. The second mean, \(\bar{\tau}^2\), is given by text equation 39 according to

\[
(\Delta t/t)^2 = (\bar{\tau}^2 - \bar{\tau}^2)/\bar{\tau}^2.
\]

The higher means are increasingly more complicated functions of \(\beta\).

References


A Convection-Diffusion Model of Indicator Transport through an Organ
WILLIAM PERL and FRANCIS P. CHINARD

doi: 10.1161/01.RES.22.2.273

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 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/22/2/273

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/