Red Cell Permeability Effect on the Mean Transit Time of an Indicator Transported through an Organ by Red Cells and Plasma

By William Perl

ABSTRACT

When an indicator that permeates red blood cells with an equilibration time of the order of the mean transit time of the indicator through an organ is bolus injected solely into the plasma inflow to that organ, the mean transit time of the indicator is greater than it is when the indicator is injected pre-equilibrated between the plasma inflow and the red cell inflow. The mean transit time for equilibrated entry is in turn greater than that for indicator injected solely into the red cell inflow. A simplified method of calculation of this effect is given in the present paper; it requires only a model solution for the indicator steady state as distinguished from a more complicated time-dependent solution. The dependence of the effect on red cell membrane permeability allows this permeability to suitable indicators to be deduced. The method was applied to existing data on urea and thiourea passage through the dog kidney.

KEY WORDS stimulus-response theorem thiourea urea input-output analysis multiple indicator dilution dog kidney

Goresky et al. (1) have calculated from a specific transport model the indicator curve to be expected at efflux from an organ (dog liver) when a bolus of indicator (14C-thiourea) is injected solely into the inflowing plasma. This indicator curve is different in shape from that produced when the indicator is preincubated in blood and then injected simultaneously and at equilibrium concentrations into the plasma inflow and the red cell inflow. The difference depends among other things on the red cell permeability to the indicator. The primary purpose of these authors was to deduce this permeability from a curve fit of their measured curves to calculated indicator curves. The major part of their theoretical work represented solutions of their time-dependent model to yield detailed indicator curve shapes for comparison with their experimental curves. Moreover, they noted that not only the detailed shape but also the mean transit time of the calculated indicator curve for initially nonequilibrated entry depended on red cell permeability, and they regarded this result as one not widely recognized previously. The purposes of the present paper are to show that this mean transit time effect follows from existing mean transit time theorems (2), to give a simplified method of calculation using only the time-independent or indicator steady-state version of the model of Goresky et al. (1), and to indicate an application of this result to deduction of red cell membrane permeability (3).

Theory

The blood flowing through an organ (the system) consists of two absolutely and relatively moving phases, plasma and red blood cells. The red cells are in thermodynamic contact with the plasma, and the plasma is in thermodynamic contact with a stationary extravascular phase. The arterial blood inflow channel is considered as two inlets, one for plasma, and one for red cells. In the actual experiment that was performed, the amount \( m_0 \) of indicator is injected as a bolus into the arterial inflow in such a way that the fraction \( p_f = m_0 / m_{inj} \) enters the system in the plasma inflow and the remaining fraction \( 1 - p_f \) enters the system in the red cell inflow. Outflow detection of indicator is made by conventional sequential sampling of outflowing blood. The indicator concentration in each sample (amount/ml blood) divided by the total amount \( m_0 \) injected plotted against time from the start of injection is the indicator curve. The centroid (first time moment divided by the area) of the indicator curve minus the usually negligible centroid of the injected bolus is the mean transit time \( t \) (seconds) of the indicator.

The preceding actual experiment can be considered as the superposition of two separate experiments because of linearity of the system with respect to the indicator. In the first experiment, denoted by superscript \( p \), the amount \( m_{inj}^p \) of indicator is bolus injected into the plasma inflow, and no indicator is injected into the red cell inflow. The stimulus-response theorem (2) relates this bolus-injection experiment to an indicator steady-state experiment as follows:

\[
\frac{m_{inj}^p}{m_{inj}^p} = \int_0^\infty m^p(t) \, dt / m_{inj}^p.
\]
RED CELL PERMEABILITY TRANSIT TIME EFFECT

where the indicator transient residue \( m^+(t) \) is the total amount of indicator within the system at time \( t \) after the start of the bolus injection of \( m_0^+ \), and \( m_0^- \), the indicator steady-state residue, is the total amount of indicator within the system at a long time after the initiation of a constant infusion rate \( L^\text{w} \) (amount/sec) solely into the plasma inflow. Similarly, in the second experiment, denoted by superscript \( r \), the amount \( m_0^r \) of indicator is bolus injected into the red cell inflow, and no indicator is injected into the plasma inflow. The stimulus-response theorem gives

\[
\frac{m_0^r}{m_0^-} = \int_0^\infty \frac{m^+(t) dt}{m_0^+}. \tag{2}
\]

The sum \( m^+(t) + m^r(t) \) of the residues in these bolus injection experiments is the residue \( m(t) \) that would be obtained in the actual experiment in which the amount \( m_0^+ = m_0^r + m_0^- \) of indicator is bolus injected in the designated proportions. Thus,

\[
\frac{\int_0^\infty m(t) dt}{m_0^-} = \frac{m_0^+}{m_0} \int_0^\infty m^+(t) dt + \frac{m_0^r}{m_0^-} \int_0^\infty m^r(t) dt. \tag{3}
\]

The left side of Eq. 3 is the mean transit time \( \bar{t} \) measured in the actual experiment either by residue detection or by outflow blood detection (4-6). Eqs. 1-3 yield

\[
\bar{t} = \rho^+(m_0^+/L^\text{w}) + \rho^r(m_0^r/L^\text{w}), \tag{4}
\]

which is the desired mean transit time theorem.

The indicator steady-state factors within parentheses in Eq. 4 are evaluated by a specific model of the interior of the system. The model of Goresky et al. (1) is a Krogh cylinder in which indicator exchanges between the moving red cell phase and the moving plasma phase by a first-order permeability mechanism, and the moving plasma phase is, at any location along the cylinder, in lateral equilibration with a constant extravascular area of distribution. Longitudinal diffusion is assumed to be zero. The organ is idealized as a collection of identical Krogh cylinders in parallel with simultaneous starting points and negligible large vessel effects before and after the Krogh cylinders. This model yields (Appendix)

\[
\frac{\bar{t} - \bar{t}_\text{eq}}{\bar{t}_\text{eq} - \bar{t}} = \left[ \rho^+ \left( \frac{1 + \frac{\bar{t}_\text{eq}}{f H_e(1 - H_e)} - 1}{1 - e^{-\alpha}} \right) \right] \tag{5}
\]

where

\[
\alpha = \frac{PS}{F} \left[ \frac{1}{f H_e(1 - H_e)} + 1 \right]. \tag{6}
\]

and \( P \) (cm/sec) is the permeability coefficient of the indicator for the plasma-red cell barrier (the red cell membrane), \( S \) (cm\(^2\)) is the exchange area (total area of red cell membranes within the system), \( F \) (cm\(^3\)/sec) is the blood flow, \( f_\text{p} \) and \( f_\text{r} \) are the volumetric fractional water contents of plasma and red cells, respectively, \( H_e \) = red cell flow/(red cell flow + plasma flow) = \( F / (f_\text{p} H_e + f_\text{r}) \) is the external hematocrit as measured by flow collection of blood and subsequent hematocrit determination (\( H_e \) is assumed to be equal to the small vessel flow hematocrit. It is not equal to the small vessel volume hematocrit \( V_r/(V_r + V_p) \) = \( F_r L_r / (F_r L_r + F_p L_p) \) because the mean transit time \( \bar{t} \) of a red cell label is generally somewhat different [less] than the mean transit time \( \bar{t}_r \) of a plasma label.).

\[
\rho_\text{eq}^+ = \left[ 1 + \frac{f H_e}{f_\text{eq}(1 - H_e)} \right]^{-1} = \frac{F_{\text{eq}}}{F}, \tag{7}
\]

where \( F_{\text{eq}} \) is the plasma water inflow and \( F \) is the total water inflow (plasma water inflow plus red cell water inflow). Thus, Eq. 7 states that \( \bar{t}_\text{eq} \) results when the injected bolus of indicator is apportioned between the entering plasma and red cell phases in proportion to flow (of water). The second expression on the right of Eq. 5 vanishes for infinite permeability or \( PS/F \to \infty \). Although \( \bar{t}_\text{eq} \) is a Krogh cylinder in which indicator exchanges in lateral equilibration with a constant permeability, this \( \bar{t}_\text{eq} \) is in general different in value from the \( t_\text{eq} \) of a finite permeability indicator injected under the condition of Eq. 7, because \( \bar{t}_\text{eq} \) depends on the extravascular volume of distribution (Appendix) which is in general different for these two types of indicator. Even if \( \bar{t}_\text{eq} \) were the same for both types of indicator, the respective indicator curve shapes would in general still be different.

Eq. 5 reduces to the corresponding result derived by Goresky et al. (1) from the time-dependent solution of their model and demonstrates that the much simpler steady-state solution contains the mean transit time information. The result of Goresky et al. was derived for \( \rho^+ = 1 \) and \( \bar{t}_\text{eq} = \bar{t}_\text{eq} \). The correspondence of terminology is given in the Appendix.

Results

The right side of Eq. 5 with \( f_\text{e} = 0.96 \) and \( f_\text{r} = 0.74 \) was computed and plotted (Fig. 1) against \( PS/F \) for various values of \( H_e \) and for the extremum values \( \rho^+ = 0 \) (all indicator input into red cell inflow) and \( \rho^+ = 1 \) (all indicator input into plasma inflow). The variation of \( (\bar{t}_\text{eq} - \bar{t}_\text{eq})/(\bar{t}_\text{eq} - \bar{t}) \) = \( U \) with \( \rho^+ \) for given \( PS/F \) and \( H_e \) values is linear and can therefore be linearly interpolated between \( U_{\text{max}} (\rho^+ = 1) \) and \( U_{\text{min}} (\rho^+ = 0) \).

The interpolated value for \( U = 0 \) is \( \rho_\text{eq}^+ \) (Eq. 7), which corresponds to equilibrated entry \( \bar{t} = \bar{t}_\text{eq} \). For predominantly plasma entry of indicator or \( \rho_\text{eq}^+ < \rho < 1 \), the mean transit time is greater than that for equilibrated entry or \( \bar{t} > \bar{t}_\text{eq} \) and \( U > 0 \). The maximum effect occurs at a limiting hematocrit of 1, for which Eqs. 5 and 6 yield \( U \to \rho^+/(PS/F) \), shown in Figure 1 for \( \rho^+ = 1 \). For predominantly red cell entry of indicator or \( 0 < \rho < \rho_\text{eq}^+ \), the mean transit time is less than that for equilibrated entry or \( \bar{t} < \bar{t}_\text{eq} \) and \( U < 0 \). The minimum effect occurs at the minimum value of \( \alpha \) (Eq. 6) or \( (H_e)_{\text{min}} = [1 + (f_\text{r}/f_\text{p})^\gamma]^{-1} = 0.53 \).
which yields at $\rho^p = 0$ by Eq. 5 the curve shown in Figure 1. The present effect disappears at zero hematocrit, for which Eqs. 5 and 6 yield $U \rightarrow 0$ or the horizontal axis in Figure 1. As a function of $PS/F$ at a given $H_e$ and $\rho^p$, the maximum $U$ in absolute value occurs for zero permeability or $PS/F = 0$, which gives $\alpha = 0$ and $(1 - e^{0})/\alpha = 1$ in Eq. 5. These values of $U$ are indicated by the intercepts with the vertical axis in Figure 1. The effect of increasing $PS/F$ is to decrease the present effect, that is, $i \rightarrow i_{eq}$ and $U \rightarrow 0$.

## Discussion

The point of the mean transit time theorem (Eq. 4) is that it relates the mean transit time $\bar{t}$ of an indicator curve measured at outflow in a bolus-injection experiment to the steady-state amount of indicator within the system in a constant-infusion experiment. The constant-infusion experiment consists of infusing indicator at the rate $i_w$ into the blood inflow to an organ in such a way that the portions

\[ i_{w,p} = \rho^p i_w, \quad (8a) \]
\[ i_{w,r} = \rho^r i_w \quad (8b) \]

are infused respectively into the plasma inflow and the red cell inflow, where $\rho^p$ and $\rho^r$ are the respective portions injected into the plasma inflow and the red cell inflow in the bolus-injection experiment. Substitution of Eqs. 8 into Eq. 4 gives

\[ \bar{t} = m_w i_{w}, \quad (9) \]

where $m_w = m_{w,p} + m_{w,r}$. The right side of Eq. 9 expresses the steady-state indicator residue per unit input rate in the constant-infusion experiment performed under the conditions of Eqs. 8 that yields the mean transit time $\bar{t}$ in the divided bolus-injection experiment actually performed.

The resolution of the preceding constant-infusion experiment into two component constant-infusion experiments as expressed in Eq. 4 was made for convenience of evaluation and interpretation. The origin of the difference between the mean transit time $\bar{t}$ for arbitrarily nonequilibrated entry between plasma and red cells and the mean transit time $t_{eq}$ for equilibrated entry can be seen from consideration of Eq. 4 in the three cases: (1) solely plasma entry, (2) solely red cell entry, and (3) equilibrated entry. Consider first the condition of zero red cell permeability to indicator. Then, with solely plasma entry or $\rho^r = 0, \rho^p = 1 \rightarrow \bar{t} = t_{eq}$ is obtained which is intermediate between $t_{pev}$ and $t_{eq}$. Simply by the general algebraic property of Eq. 4 that for any $\rho^p < 1$ a value of $\bar{t}$ between $t_{pev}$ and $t_{eq}$ is obtained. For a nonzero red cell permeability, a similar argument applies except that the extreme values of $m_{w,p} / i_{w,p}$ for solely plasma entry and $m_{w,r} / i_{w,r}$ for solely red cell entry are respectively less than and greater than the previous extreme values for zero red cell permeability. Thus, with nonzero red cell permeability, the indicator infusing at constant rate $i_{w,p}$ solely into plasma can permeate into the red cell phase, which reduces the concentration of indicator in the plasma phase and in turn reduces the amount of indicator that can permeate into the extravascular phase. The increase in indicator...
steady-state residue from the red cell phase is not enough to make up for the decrease in residue from the vascular-plus-extravascular phase; hence, \( m_r^p / i_r^p \) with nonzero red cell permeability is less than \( m_r^p / i_r^p \) with zero red cell permeability. A similar argument holds for solely red cell entry (Appendix).

Chinard et al. (3, 7) have given arguments somewhat similar to those just presented in interpreting their indicator curves for urea, thiourea, and T-1824-albumin in the dog kidney. After solely plasma injection into the renal artery of a bolus of solution containing \(^{14}\)C-thiourea, the indicator curves were measured by sampling the renal vein blood outflow. At a hematocrit of 0.52, the mean transit times were \( t \) (thiourea) = 7.23 seconds, \( t \) (urea) = 5.54 seconds, and \( t \) (T-1824) = 3.67 seconds. At low hematocrits, the mean transit times of thiourea and urea were much closer together; moreover, they tended to converge on the mean transit time of creatinine. Since creatinine is generally regarded as an extravascular, extracellular indicator in the kidney (8) and the mean transit time of creatinine. Since creatinine is generally regarded as an extravascular, extracellular indicator in the kidney (8) and that the difference in their mean transit times arises from their different red cell permeabilities after solely plasma entry. Urea entry into red cells is assumed to be sufficiently rapid (~ 0.3 seconds) relative to its mean transit time so that \( t \) (urea) approximates the mean transit time \( t_{eq} \) for equilibrated entry. Substituting \( \rho^* = 1 \), \( H_e = 0.52 \), \( t_{eq} = 7.23 \), \( i_r^p = 5.54 \), and \( i_r^p = 3.67-0.73 \) into Eq. 5, where 0.73 seconds represents the statistically averaged difference between mean transit times of a plasma indicator and a red cell indicator (10), gives \( PS/F = 0.09 \). Other such data in Table 2 of reference 3 give \( PS/F \) values between 0 and 1. If the red cell permeability coefficient of thiourea is taken as \( P = 2 \times 10^{-6} \) cm/sec (room temperature value of 0.7 \( \times 10^{-6} \) in ref. 9 corrected to 37°C) and the surface-volume ratio of the dog red cell is assumed to be (90/67) \( \times 10^{-4} \) cm\(^{-1}\), the blood content of the kidney cortex 0.20 \( \times \) kidney weight, \( H_e \) 0.45, and blood flow/kidney weight 10 cm\(^3\)/sec 100 g\(^{-1}\), then \( PS/F = 0.03 \). Considering the various assumptions and approximations, the order of magnitude agreement between the two estimates of \( PS/F \) is considered satisfactory. More accurate tests of the present effect could be made at higher hematocrit (Fig. 1) and by systematically varying the blood flow and the entry apportionment between plasma and red cells. The present effect would appear to be useful in determining red cell membrane permeabilities in vivo to substances that equilibrate with red cells in times of the order of the mean transit time of the red cell through the system. Another example (1) is discussed in the Appendix.

The present method of calculating a mean transit time from an indicator steady-state solution rather than from an indicator transient solution is useful in diffusional or in convectonal-diffusional situations. For example, the mean transit time through a single inlet system in which the indicator can also diffuse upstream against the convectional inflow before entering the system (11) is easily derived by the present method (unpublished calculation). The present method has been independently noted and several examples given by Buffham and Kropholler (12).

**Appendix**

To evaluate the parenthetical factors in Eq. 4, the steady-state version of the model of Goresky et al. (1) is adopted for simplicity. More general models including various diffusional parameters are also feasible. The adopted model expresses convection-permeation mass balance in the indicator steady state in each moving phase in a volume element of length dx. Thus,

\[
F_w (dc_w/dX) + P (dS/dX) (c_w - c_r) = 0, \quad (A1)
\]

\[
F_r (dc_r/dX) - P (dS/dX) (c_w - c_r) = 0, \quad (A2)
\]

where \( c_w \) and \( c_r \) (amount/cm\(^3\) water) are the concentrations of indicator in plasma water and red cell water, respectively, \( F_w \) and \( F_r \) are the through-flow rates of plasma water and red cell water, respectively, and \( dS/dX \) is the element of exchange area between the plasma water phase and the red cell water phase in the volume element of nondimensionalized length \( dX = d(x)/L \), where \( X \) varies from 0 at the arteriolar end to 1 at the venular end of the Krogh cylinder. Adding Eqs. A1 and A2 and integrating with respect to \( X \) gives

\[
F_w c_w + F_r c_r = F_w c_{w_0} + F_r c_{r_0} = i_w, \quad (A3)
\]

where \( c_{w_0} \) and \( c_{r_0} \) are the given indicator concentrations at \( X = 0 \) in the plasma water inflow and the red cell water inflow, respectively. Subtracting Eq. A1/F\(_{pw}\) and Eq. A2/F\(_{nr}\) and integrating with respect to \( X \) gives

\[
c_w - c_r = c_{w_0} - c_{r_0} e^{-X}. \quad (A4)
\]

Integrating Eqs. A3 and A4 from \( X = 0 \) to \( X = 1 \) and solving simultaneously yields

\[
F_w \int_0^1 c_w \, dX = i_w + F_r (c_{w_0} - c_{r_0}) \gamma(\alpha), \quad (A5)
\]

\[
F_r \int_0^1 c_r \, dX = i_r - F_w (c_{w_0} - c_{r_0}) \gamma(\alpha), \quad (A6)
\]
where 

\[ \Gamma(\alpha) = (1 - e^{-\alpha})/\alpha \]  

(A7)

and \( \alpha \) is given by Eq. 6. The indicator steady-state residue is given by

\[ m_{ss} = \int_{0}^{L} c_{ww}(x) dV_{ww} + \int_{0}^{L} c_{ew}(x) dV_{ew} + \int_{0}^{L} c_{ew}(x) dV_{ww}, \]  

(A8)

in which \( dV_{ww} \), \( dV_{ew} \), and \( dV_{ew} \) are the volumes of plasma water, extravascular water, and red cell water, respectively, in the volume element of length \( dx \) in the Krogh cylinder. The assumption of Goresky et al. (1) of complete lateral equilibration of indicator between plasma and extravascular tissue at any distance \( x \) and zero longitudinal diffusion is expressed by the partition coefficient

\[ \lambda_{ew} = c_{ew}(x)/c_{ww}(x). \]  

(A9)

Cross-sectional uniformity of the Krogh cylinder gives

\[ dV/dx = V/L \]  

(A10)

for each of the three volume elements in Eq. A8, which therefore becomes, by Eqs. A9 and A10,

\[ m_{ss} = (V_{ww} + \lambda_{ew} V_{ew}) \int_{0}^{L} c_{ww}(x) dX + V_{ew} \int_{0}^{L} c_{ew}(x) dX. \]  

(A11)

The indicator steady-state residue \( m_{ss} \) for constant infusion solely into the plasma inflow corresponds to \( c_{ww} = 0 \) and \( i_{ss} = F_{ww} c_{ww} \) Eqs. A5, A6, and A11 then yield

\[ m_{ss} = \frac{(V_{ww} + \lambda_{ew} V_{ew})}{F_{ww}} \left( 1 + \frac{F_{ww}}{F_{ww}} \right) + \frac{V_{ew}}{F_{ww}} \left( 1 - \frac{F_{ww}}{F_{ww}} \right). \]  

(A12)

The indicator steady-state residue \( m_{ss} \) for constant infusion solely into the red cell inflow corresponds to \( c_{ww} = 0 \) and \( i_{ss} = F_{ew} c_{ew} \) Eqs. A5, A6, and A11 then yield

\[ m_{ss} = \frac{(V_{ww} + \lambda_{ew} V_{ew})}{F_{ww}} \left( 1 - \frac{F_{ww}}{F_{ww}} \right) + \frac{V_{ew}}{F_{ww}} \left( 1 + \frac{F_{ww}}{F_{ww}} \right). \]  

(A13)

Substituting Eqs. A12 and A13 into Eq. 4 and using

\[ F_{ww} = f_{w}(1 - H_{r} F_{r}), \]  

(A14)

\[ F_{ew} = F_{w} - F_{ww} = f_{w} H_{r} F_{r}, \]  

(A15)

gives, after some reduction, Eq. 5, with

\[ t_{eq} = (V_{ww} + \lambda_{ew} V_{ew} + V_{ew})/F_{ew}, \]  

(A16)

\[ t_{e} = V_{ew}/F_{ew}, \]  

(A17)

where \( V_{r} = V_{ew}/f_{r} \) is red cell volume and \( F_{r} = F_{ew}/f_{r} = \) red cell flow.

Eq. 4 can be written in the form

\[ t = \rho^{2} t_{max} + (1 - \rho^{2}) t_{min}; \]  

(A18)

where \( t_{max} \) is given by Eq. A12 and \( t_{min} \) is given by Eq. A13. With normal morphology of organs, \( t_{max} > t_{min} \).

With respect to entry conditions \( t \) varies linearly with \( \rho^{2} \) from \( t_{max} \) at \( \rho^{2} = 1 \) (solely plasma entry) to \( t_{min} \) at \( \rho^{2} = 0 \) (solely red cell entry). At the intermediate value \( \rho^{2} = \rho_{0}^{2} \) (equilibrated entry) given by Eq. 7, the mean transit time \( t = t_{eq} \) is obtained, where \( t_{max} > t > t_{min} \). The values of \( t_{max} \) and \( t_{min} \) vary with permeability \( PS \) which affects \( \Gamma \) in Eq. A7. At \( PS = 0, \Gamma = 1 \), the value of \( t_{max} \) increases to the absolute maximum value given by Eq. A12 of

\[ t_{max} = (V_{ww} + \lambda_{ew} V_{ew})/F_{ww}, \]  

(A19)

and \( t_{min} \) decreases to the absolute minimum value of \( t \) given by Eq. A17. Thus, with respect to permeability the maximum absolute magnitude of the present effect occurs for zero permeability (an antipermeability effect) and the absolute magnitude of the effect decreases toward zero as permeability increases toward infinity. The existence of the effect therefore depends basically on the difference in magnitude between \( t_{eq} \) and \( t_{e} \) as stated in the text.

The mean transit time \( t_{eq} \) for the case of equilibrated entry is seen from Eq. A16 to depend on the extravascular volume of distribution of the indicator. The mean transit time \( t_{eq} \) of a plasma indicator is defined in analogy to Eq. A17 as

\[ t_{eq} = V_{ew}/F_{ew}, \]  

(A20)

where \( V_{r} = V_{ew}/f_{r} = \) plasma volume and \( F_{r} = F_{ew}/f_{r} = \) plasma flow. For zero extravascular volume of distribution, \( V_{ew} = 0 \), Eqs. A16, A17, and A20 yield

\[ t_{eq} = t_{e} = (t_{e} - t_{e})(F_{ew}/F_{ew}). \]  

(A21)

If the red cells move with velocity equal to that of the plasma, so that \( t_{e} = t_{e} \), then by Eq. 5, \( t_{e} = (t_{e} - t_{e})(F_{ew}/F_{ew}) = 0 \) and the present effect disappears, regardless of \( PS/F \) or \( H_{r} \). Even if \( V_{ew} = 0 \), it is theoretically possible that \( t_{eq} = t_{eq} \) (see Eqs. A16 and A17), in which case again \( t - t_{e} = 0 \).

It is seen from Eq. A16 that \( t_{eq} \) is the mean transit time of an indicator that equilibrates instantaneously between plasma and red cells (\( PS = \infty \)) provided that the extravascular volume of distribution of this indicator is \( \lambda_{ew} V_{ew} \), that is, the same as that of the finite permeability test indicator which yields \( t_{eq} \) by virtue of equilibrated entry.

Individual outflow recoveries such as the recovery in the plasma outflow after injection into the red cell inflow and regional mean transit times such as the mean transit time of indicator through the plasma phase after injection into the red cell inflow can be obtained by similar indicator steady-state methods (2, 5).

The case of unequal permeability coefficients, \( P_{out} \) for plasma to red cell permeation and \( P_{in} \) for red cell to plasma permeation, and also unequal indicator concentrations at equilibrium in plasma water \( c_{ww} \) (eq) and in red cell water \( c_{ew} \) (eq) is obtained by replacing \( P \) in Eqs. A1 and A2 by \( P_{out} \) and replacing \( c_{ew} \) by \( c_{ew}/A \) where \( A = \lambda_{ew} P_{in} / P_{in} \) and \( c_{ww} = c_{ew} \) (eq) (eq). Then in the present solution \( f_{w}, F_{ew}, \) and \( V_{ew} \) are replaced, respectively, by \( A_{w}, A_{ew}, \) and \( A_{ew} V_{ew} \). Eqs. 5 and 6 with \( \rho^{2} = 1 \) and \( t_{e} = t_{e} \) or \( V_{ew}/F_{ew} = V_{ew}/f_{ew} \) reduce to the result of Goresky et al. (1). The correspondence of notation between that of Goresky et al. and the present paper is:

\[ k_{1} = P_{out} V_{ew}, k_{2} = t_{e}, \beta = V_{ew}/F_{ew}, \gamma = \lambda_{ew} V_{ew} / V_{ew} \]  

Goresky et al. (1975) in Figure 6 of reference 1 give the mean transit times for a solely plasma bolus injection.
into the dog liver portal vein: \( \bar{t} \) (Cr-labeled red cells) = 3.79 seconds, \( \bar{t} \) (H-labeled water) = 20.69 seconds, and \( \bar{t} \) (labeled thiourea) = 23.76 seconds when hematocrit = 0.21. Substituting \( \bar{t} \) = 3.79, \( \bar{t} \) = 20.69, and \( \bar{t} \) = 23.76 into Eq. 5 and assuming \( \beta^* = 1 \) and \( \bar{t} \) = \( \bar{t} \), so that \( \beta = f \beta^* (1 - H_e) = 0.20 \) and, by Eq. 5, \( \alpha = k_1 (1 + \beta) = 4.55 \), gives (1 - e^\(-\alpha\)) = 0.908. Solution of this last equation gives \( \alpha = 0.195 \) from which \( k_1 = 0.043 \) sec^-1. Goresky et al. found \( k_1 = 0.087 \) sec^-1 by curve fitting the complete thiourea indicator curve with their time-dependent model. Conversion of \( k_1 \) to \( P = k_1 V_r/S \) with \( S/V_r = 2.4 \times 10^5 \) (1) gives \( P = 1.8 \times 10^{-6} \) cm/sec using \( k_1 = 0.043 \) and \( P = 3.6 \times 10^{-6} \) cm/sec using \( k_1 = 0.087 \). Although the former value agrees somewhat better with the previously deduced value from reference 9, \( P = 2 \times 10^{-6} \) cm/sec, the agreement is probably fortuitous because the present method is very sensitive to \( \bar{t} - \bar{t} \). Thus, a decrease of \( \bar{t} \) (thiourea) by only 0.27 seconds to give 23.49 seconds would yield the value of \( k_1 = 0.087 \) found by Goresky et al. The present method therefore requires accurate measurement of \( \bar{t} - \bar{t} \).

**Acknowledgment**

I thank Dr. Carl A. Goresky for stimulating and helpful correspondence.

**References**

12. BUFFHAM BA, KROPHOLLER HW: Tracer kinetics: Some general properties, the mean residence time and applications to phase and chemical equilibria. Chem Eng Sci 28:1081-1089, 1973

Circulation Research, Vol. 36, February 1975
Red cell permeability effect on the mean transit of an indicator transported through an organ by red cells and plasma.

W Perl

*Circ Res.* 1975;36:352-357
doi: 10.1161/01.RES.36.2.352

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 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/36/2/352

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/