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ON THE THEORY OF BLOOD-TISSUE EXCHANGES: I. FUNDAMENTAL EQUATIONS

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A mathematical analysis of the absorption of an inert gas by a heterogeneous system of n phases, e.g., a limb consisting of n tissues, is presented. The total uptake of gas, $\phi(t)$, up to time t is given in terms of arterial concentration, cardiac delivery, blood volume, and the volume, permeability, and partition coefficient of each tissue. The theory predicts how the uptake curve should change in shape under a variety of physiological conditions, and how from the numerical values of the constants the values of certain tissue constants, e.g. permeabilities, may be obtained.

Introduction. Many problems in the physiology of intact animals involve the absorption by the tissues of some substance which has entered the blood elsewhere. While experimental work along such lines can be and has been done with great care, the resulting data are not of the type that can be readily interpreted. Consequently, a need has arisen for a theoretical treatment of this subject. The present note is intended to submit such a consideration.

We will attempt here to treat the absorption of an inert gas in the blood by the tissues of a limb, and will use a vocabulary specific to this case. However, the mathematical results obtained are independent of vocabulary, and obviously could apply to anatomically different but functionally similar situations.

For the purpose of the analysis, we regard the limb to be constituted as follows: There exists a blood chamber of volume V_0 cm^3 (the blood volume). Into this chamber there is an inflow of blood at the rate of R cm^3 sec^{-1}; because blood and tissue fluid are practically incompressible, there is a liquid (blood + lymph) outflow also equal to R. The entering blood contains the gas in question at concentration C gm cm^{-3}. The (spatially) average concentration of gas in the blood chamber is x_0 gm cm^{-3}. In physiological contact with the blood chamber are n distinct tissues. The average concentration of gas in the i-th tissue is x_i gm cm^{-3}.

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The matter of penetration constants of the tissues deserves some attention here, even though the general aspects are thoroughly treated by Rashevsky (1938) to whose work the reader is referred. When the intracellular "solvent" is the same as the extracellular "solvent", then we write by Fick's Law,

$$\text{Penetration Rate}\ (\text{gm cm}^{-2}\,\text{sec}^{-1}) \quad K\frac{S_i\,p'_i}{\delta}(x_0 - x_i) \equiv h_i\,S_i(x_0 - x_i)\,, \tag{1}$$

where K is a constant of proportionality, S_i is the absorbing surface area in cm^2, δ is the thickness of the cell membrane, and p'_i is the partition coefficient of the gas between water and "membrane substance". The constants, Kp'_i/δ are lumped together into a single h_i cm sec^{-1}, which is then the *permeability* of the membrane. On the other hand, when the "solvents" of the two sides are different, then for the penetration rate we obtain:

$$\text{Penetration Rate} = \frac{K\,S_i\,p'_i}{\delta}\left(x_0 - \frac{p''_i}{p'_i}x_i\right) \equiv h_i\,S_i(x_0 - \alpha_i\,x_i)\,, \tag{2}$$

where α_i is the partition coefficient of the gas between the external medium and the intracellular solvent. For some of the tissues, e.g. adipose, which we will consider, it is necessary to use equation (2) rather than equation (1). It is perhaps superfluous to point out that in the first case, the steady state will be attained for $x_0 = x_i$, while in our case it is attained when $x_0 = \alpha_i x_i$, and generally speaking, the steady state concentration within the tissue will be different from the steady state concentration in the blood.

Derivation. The setting up of our differential equations follows easily from the principle of material balance, which holds for the blood chamber and each tissue independently. Thus:

$$\frac{d(V_0\,x_0)}{dt} = R\,C - R\,x_0 - \sum_{i=1}^{i=n} h_i\,S_i(x_0 - \alpha_i\,x_i)$$

$$\frac{d(V_i\,x_i)}{dt} = h_i\,S_i(x_0 - \alpha_i\,x_i) \qquad i = 1, 2, \cdots n.$$

The substitution, $y_0 = C - x_0$ and $y_i = C_i/\alpha_i - x_i$ $(i = 1, 2, \cdots n)$ renders the equations homogeneous and somewhat simplifies the solution. We have then instead the set:

$$-V_0\frac{dy_0}{dt} = R\,y_0 + \sum_{i=1}^{i=n} h_i\,S_i(y_0 - \alpha_i\,y_i) \tag{3}$$

$$V_i \frac{dy_i}{dt} = h_i S_i (y_0 - \alpha_i y_i) \qquad (i = 1, 2, \cdots n). \qquad (4)$$

We proceed to solve the set by the method of undetermined coefficients. The series:

$$y_i = \sum_{j=0}^{j=n} C_{ij} e^{-k_j t} \qquad (5)$$

will be a solution of equations (3) and (4) provided we can find appropriate expressions for the C_{ij} and the k_j. This can be done as follows. The solutions (5) must, by hypothesis, satisfy equations (3) and (4) identically, which means that after substitution is made the coefficients of $e^{-k_j t}$ must vanish. Thus from putting relation (5) into relation (4) we obtain the solutions:

$$C_{ij} = \frac{h_i S_i}{\alpha_i h_i S_i - V_i k_j} C_{0j} \qquad (i = 1, 2, \cdots n). \qquad (6)$$

On the other hand, we have yet to impose boundary conditions on equation (5). The two cases which concern the physiologist are absorption (when $t = 0$, $y_0 = C$, and $y_i = C/\alpha_i$) and desaturation, (when $t = 0$, $y_0 = 0$, and $y_i = 0$). Since our personal interest is in absorption, we will develop the equations for that case; however, it is clear that no mathematical difficulty is involved in the alternate conditions. For our case, then, when $t = 0$ relation (5) becomes:

$$\sum_{j=0}^{j=n} C_{0j} = C$$

and by (6),

$$\sum_{j=0}^{j=n} \frac{C_{0j}}{\alpha_i h_i S_i - V_i k_j} = \frac{C}{\alpha_i h_i S_i}, \qquad i = 1, 2, \cdots n. \qquad (7)$$

Equation (7) is therefore a linear set of $(n+1)$ equations which can be solved for the C_{0j} by the usual methods. Then from equation (6) all the other C_{ij} are obtainable. Determinantal solution for C_{0j} gives:

$$\begin{aligned} C_{0j} = {} & C (k_0 k_1 \cdots k_n)(V_1 V_2 \cdots V_n) \Delta_{ij} \Delta_{2j} \cdots \Delta_{nj} / k_j (\alpha_1 \alpha_2 \cdots \alpha_n) \\ & \times (h_1 h_2 \cdots h_n)(S_1 S_2 \cdots S_n)(k_0 - k_j)(k_1 - k_j) \cdots \\ & (k_n - k_j) \equiv A_{0j} C . \end{aligned} \qquad (8)$$

where there is no factor, $k_j - k_j$, in the denominator, and where,

$$\Delta_{ij} = \alpha_i\, h_i \left(\frac{S_i}{V_i} \right) - k_j ,$$

a function which we will have occasion to refer to later. Finally, putting equation (5) into equation (3), noting relations (6) and (8), we obtain the characteristic equation whose $(n+1)$ roots are the k_j:

$$V_0\, k_j + \sum_{i=1}^{i=n} \frac{\alpha_i\, h_i^2\, S_i^2}{\alpha_i\, h_i\, S_i - V_i\, k_j} - (R + \sum_{i=1}^{i=n} h_i\, S_i) = 0. \tag{9}$$

By the use of standard approximation methods, all the roots of equation (9) can be found once we have numerical values for V_0, R, α_i, h_i, V_i, and S_i. However, we may prove two useful facts about the roots of relation (9) without recourse to numerical methods.

I. *All the roots are positive.* This follows because if any one of them, say z, were negative, we could write the left hand member of equation (9) as:

$$F(z) = \left(\sum_{i=1}^{i=n} \frac{\alpha_i\, h_i^2\, S_i^2}{\alpha_i\, h_i\, S_i + V_i|z|} \right) - \left(V_0|z| + R + \sum_{i=1}^{i=n} h_i\, S_i \right) \cdot$$

The greatest value which the left-hand bracket could ever have would be, (for $|z| = 0$), $\sum h_i\, S_i$, whence the greatest value $F(z)$ could have would be $-(V_0|z| + R)$; thus $F(z)$ could never be 0, and therefore, contrary to our hypothesis k_j must always be positive.

II. *If the* $n+1$ *roots are, in descending order,* $r^{(n)}, r^{(n-1)}, \cdots r^{(0)}$ *and if the products,* $\alpha_i\, h_i \dfrac{S_i}{V_i}$ *are, in descending order,* $p^{(n)}, p^{(n-1)}, \cdots p^{(1)}$, *then these quantities fall into the sequence,* $r^{(n)} > p^{(n)} > r^{(n-1)} > p^{(n-1)} \cdots r^{(1)} > p^{(1)} > r^{(0)}$. For suppose that r'' and r' are roots such that $r'' > r'$. By hypothesis they both satisfy equation (9). On subtracting $F(r') = 0$ from $F(r'') = 0$, we obtain,

$$0 = V_0 + \sum_{i=1}^{i=n} \alpha_i\, h_i\, V_i \left(\frac{S_i}{V_i} \right)^2 \frac{1}{\left(\alpha_i\, h_i \dfrac{S_i}{V_i} - k'' \right)\left(\alpha_i\, h_i \dfrac{S_i}{V_i} - k' \right)} .$$

It must therefore be that some of the terms in the summation are negative, i.e., there is at least one tissue for which,

$$k'' > \alpha\, h \frac{S}{V} > k' .$$

Now imagine the roots k_j arranged in descending order, $r^{(n)} > r^{(n-1)} > \cdots > r^{(0)}$. By the reasoning just given, there must be a product, $\alpha\, h\, S/V$, between every two successive roots, but the number of such positions, n, is exactly equal to the number of tissues; thus if we adopt the notation, $p^{(n)} > p^{(n-1)} > \cdots > p^{(1)}$ for the descending sequence of products, we see that the two sequences must fall into the combined sequence, $r^{(n)} > p^{(n)} > \cdots > p^{(1)} > r^{(0)}$, and our theorem is proved.

From I and II it follows immediately that all the A_{0j} are positive, since all the k's are positive and since, by II, there are, for any k_j as many Δ_{ij}'s > 0 as there are $(k_i - k_j) > 0$, and as many Δ_{ij}'s < 0 as there are $(k_i - k_j) < 0$. However, the coefficients, C_{ij}/C, which we may call A_{ij}, need not be positive (see equation 6), nor must linear combinations of the A_{ij} necessarily be positive.

Next we turn to a consideration of the derivatives of k_j with respect to V_0, R, and the constants of the s-th tissue, α_s, h_s, V_s and S_s. These follow from equations (8) and (9). If by ω_j we denote the function:

$$\frac{1}{V_0 + \sum_{i=1}^{i=n} \alpha_i\, h_i\, V_i \left(\dfrac{S_i}{V_i} \right)^2 \Delta_{ij}^{-2}} > 0,$$

then we may write the various partial derivatives compactly as:

$$\frac{\partial k_j}{\partial R} = \omega_j > 0 \tag{10}$$

$$\frac{\partial k_j}{\partial (h_s S_s)} = \omega_j\, k_j^2\, \Delta_{sj}^{-2} > 0 \tag{11}$$

$$\frac{\partial k_j}{\partial \alpha_s} = \omega_j\, k_j\, V_s \left(\frac{S_s}{V_s} \right)^2 > 0 \tag{12}$$

$$\frac{\partial k_j}{\partial V_0} = -\,\omega_j\, k_j < 0 \tag{13}$$

$$\frac{\partial k_j}{\partial V_s} = -\,\omega_j\, k_j\, h_s^2 \left(\frac{S_s}{V_s} \right)^2 \Delta_{sj}^{-2} < 0\,. \tag{14}$$

The signs of these derivatives are evident enough. In connection with their numerical magnitudes it may be noted that all the derivatives are proportional to ω_j, a quantity which diminishes with increasing blood volume. The quantity, S/V, figures prominently in these functions, both by itself and where it appears in Δ_{ij}. Its presence stresses the physiological importance of the *shape* in which the tissue is disposed with respect to its blood supply.

The derivatives of the A_{ij} are complicated expressions whose signs and magnitudes cannot be ascertained from our work so far; consequently we have omitted them from this section.

We are now in a position to discuss the general solutions of the problem. Combining equations (5), (6), and (8) we obtain the concentrations of the gas in the blood and tissues as:

$$x_0 = C\,\{1 - (A_{00}\,e^{-k_0 t} + A_{01}\,e^{-k_1 t} + \cdots + A_{0n}\,e^{-k_n t})\}$$
$$x_1 = C\left\{\frac{1}{\alpha_1} - (A_{10}\,e^{-k_0 t} + A_{11}\,e^{-k_1 t} + \cdots + A_{1n}\,e^{-k_n t})\right\}$$
$$\cdots\cdots\cdots\cdots\cdots \tag{15}$$
$$x_n = C\left\{\frac{1}{\alpha_n} - (A_{n0}\,e^{-k_0 t} + A_{n1}\,e^{-k_1 t} + \cdots + A_{nn}\,e^{-k_n t})\right\}.$$

Multiplying each concentration by the corresponding volume, we obtain the total *amount* of gas in the limb:

$$\begin{aligned} V_0\,x_0 + V_1\,x_1 + \cdots + V_n\,x_n = C\,\Big\{ & V_0 + \frac{V_1}{\alpha_1} + \cdots + \frac{V_n}{\alpha_n} \\ & - (A_{00}\,V_0 + A_{10}\,V_1 + \cdots + A_{n0}\,V_n)\,e^{-k_0 t} \\ & - (A_{01}\,V_0 + A_{11}\,V_1 + \cdots + A_{n1}\,V_n)\,e^{-k_1 t} \\ & - (A_{0n}\,V_0 + A_{1n}\,V_1 + \cdots + A_{nn}\,V_n)\,e^{-k_n t} \Big\}. \end{aligned}$$

To expedite further discussion, we will adopt certain symbols for the quantities in this equation: We shall denote by

$$\phi = \text{total amount of gas in the limb} = \sum_{i=0}^{i=n} V_i\,x_i$$
$$\theta = \text{effective volume of the limb} = V_0 + \sum_{i=1}^{i=n} \frac{V_i}{\alpha_i}$$
$$Q_j = \text{the coefficient of the } j\text{-th exponential} = \sum_{i=0}^{i=n} A_{ij}\,V_i$$
$$\psi = \text{the variable sum} = \sum_{j=0}^{j=n} Q_j\,e^{-k_j t}.$$

Our equation then becomes simply:

$$\phi = C(\theta - Q_0\,e^{-k_0 t} - Q_1\,e^{-k_1 t} - \cdots - Q_n\,e^{-k_n t}) = C(\theta - \psi). \tag{16}$$

The solutions, $\phi(t)$, the total uptake, and $x_i(t)$ the uptake of the *i*-th tissue, are characterized by the following properties:

(1) They contain a number of exponential terms, $e^{-k_j t}$, equal to the number of tissues plus one.

(2) These exponential terms are all decaying terms, i.e., $k_j > 0$. The curves, $\phi(t)$ and $x_i(t)$ both approach asymptotes, $C\theta$ and C/α_i respectively.

(3) The coefficients of $e^{-k_j t}$, Q_j and A_{ij}, depend in general upon *all* the quantities, V_0, R, V_i, α_i, $h_i S_i$, and also on the shapes in which the tissue masses are disposed. Nothing is asserted about the signs of these coefficients.

(4) If the physical properties of the tissues are not radically different, then the mean value of the k's should be roughly equal to the mean value of $\alpha h S/V$ for the tissues. (The exact relationship is Theorem II.)

(5) The change in shape of $\phi(t)$ or $x_i(t)$ as V_0, R, V_i, α_i, or $h_i S_i$ is changed is governed mainly by the changes induced in the k_j's; therefor by equations (10) to (14), the curve approaches its asymptote *more rapidly* with increases in R, $h_i S_i$, or α_i, but it approaches it *more slowly* with increases in V_0 or V_i.

(6) Both ordinates $\phi(t)$ and $x_i(t)$ are proportional to the delivery concentration, C.

This concludes the purely mathematical considerations. The application to experimental data is considered elsewhere (Smith and Morales, 1944).

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