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ON THE THEORY OF BLOOD-TISSUE EXCHANGE OF INERT GASES: VI.

VALIDITY OF APPROXIMATE UPTAKE EXPRESSIONS

MANUEL F. MORALES AND ROBERT E. SMITH
THE UNIVERSITY OF CHICAGO AND THE NAVAL MEDICAL RESEARCH INSTITUTE, BETHESDA, MARYLAND

It is shown that the equation of inert gas uptake by a distinct parallel tissue-blood arrangement coincides, under certain conditions, with two formulations which neglect the possible existence of a blood-tissue barrier. The first of these approximations is the classic von Schrötter equation in continuous form, whereas the second is the empirical one frequently used by contemporary authors. The condition for coincidence is that the product of permeability and blood-tissue exchange surface greatly exceed the rate of blood flow to the tissue. It is difficult to examine this condition at present because of a dearth of gas permeability measurements and because apparently there exist no measurements of surface and flow on the same tissue. A compilation is made of such values as are available, and it is found that on the assumption that gas permeabilities are of the order of 1×10^{-3} cm sec^{-1}, the conditions for neglecting the blood-tissue barrier may be met in many cases and certainly not met in many others. It is concluded that under these circumstances the more exact equations, taking into account the barrier, should be employed, at least until precise independent measurements justifying the approximations become available.

In a series of papers appearing during recent years, the present authors (1944a, 1944b, 1944c, 1945a, 1945b; hereinafter referred to as I, II, III, IV, and V, respectively) have endeavored to formulate a quantitative theory of inert metabolite uptake, taking into account all factors which in the light of present knowledge seem of first-order importance. No attempt has been made, however, to relate this development to more limited expressions, derived by other authors, in particular, to the early and classic one of H. von Schrötter (1906). It seems necessary to clarify the relationship at this time because at least some contemporary workers have regarded their von Schrötter-like expressions as conceptually different from ours. To anticipate the results of this paper, we shall say that in a "distinct parallel" system (IV), when the product of permeability and surface is much greater than the blood flow through a tissue, then the limiting form of our equation is essentially identical with the von Schrötter expression. This is a straightforward mathematical fact. Whether or not

this limiting condition is actually attained in real systems is a distinct question, and one which only experimental measurement can answer. In the authors' opinion, existing data are inadequate for the decision, although experiments now in progress* seem very promising.

There are possibly three fundamentally different arrangements of tissues with respect to the circulation (IV); of these, it will presently be obvious that the von Schrötter treatment is applicable only to one, namely, what we have called "distinct parallel". It is, therefore, the simplest case of this arrangement which we shall choose in order to demonstrate the relationship between the two mathematical descriptions. In the original von Schrötter treatment the possible difference in solvent power between the blood and tissues was neglected, but this is a matter easily corrected by dividing the tissue volume by a partition coefficient, α, which for inert gases is one or less than one.

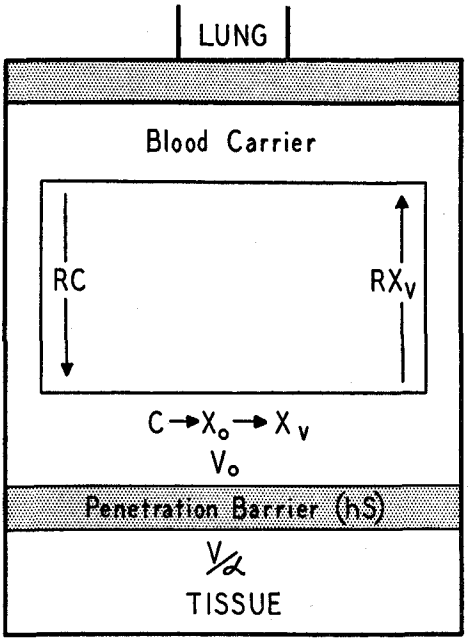

FIGURE 1. Model of a simple exchange system in which transport is via the vascular flow between the point of solute supply (e.g., the lung) and that of exchange (e.g., a tissue region of volume V and homogeneous with respect to its solution properties). In the von Schrötter case the barrier penetration factor hS is neglected.

* Experiments by Dr. Falconer Smith and his associates, aimed at the measurement of h for radioactive inert gases (plasma membrane of myxomycetes), are currently being conducted at the National Institute of Health.

We shall treat, as usual, the uptake of an inert metabolite at some localized region in the circulation, assuming that all blood leaving this region is charged with metabolite at a constant concentration, C. The problem will be to find the amount, ϕ, of this metabolite within a distant tissue region which is in diffusion contact with the blood (Figure 1). Let us denote by V_0 the volume of blood which flows through the tissue region in question during one circulation time, and by V the volume of the tissue. After the manner of von Schrötter (*loc. cit.*), we may now think of the transfer problem in the following approximate way: V_0 cm^3 of blood pick up V_0C gm of metabolite at the uptake region, and this amount is distributed *instantaneously* between blood and remaining tissue in proportion to their volumes, i.e., a fraction $V_0/(V_0 + V/\alpha)$, remains in the blood and a fraction, $(V/\alpha)/(V_0 + V/\alpha)$ is allotted the tissue. The V_0 cm^3 of blood now return to the uptake region and become re-saturated, the net amount picked up at this time being just equal to that which it gave up to the tissue. The cycle is then repeated. It is easy to see that the amount of metabolite in the tissue after n cycles is,

$$\phi(n) = V_0C\left\{\left(\frac{V/\alpha}{V_0 + V/\alpha}\right) + \left(\frac{V/\alpha}{V_0 + V/\alpha}\right)^2 + \cdots + \left(\frac{V/\alpha}{V_0 + V/\alpha}\right)^n\right\} = \frac{VC}{\alpha}\left\{1 - \left(\frac{V/\alpha}{V_0 + V/\alpha}\right)^n\right\}. \tag{1}$$

Expression (1) is essentially von Schrötter's final result. For comparison with our equations, however, a slight transformation is desirable. If we think in terms of an equivalent *continuous* circulation rate, R cm^3 sec^{-1}, through the tissue, it is clear that the volume of blood which has passed up to the time t is Rt; since V_0 cm^3 is the volume which passes per cycle, the number of cycles up to the time t is,

$$n = \frac{R}{V_0}t. \tag{2}$$

Using (2), we may re-write (1) as

$$\phi(t) = \frac{VC}{\alpha}(1 - e^{kt}); \tag{3}$$

$$k = -\frac{R}{V_0}\log_e\left(1 + \frac{\alpha V_0}{V}\right). \tag{4}$$

This same system may be treated more accurately by the simultaneous solution of two differential equation (I, IV). We shall de-

note the permeability of the blood-tissue barrier by h, and the exchange surface by S; x_0 will be the *average* metabolite concentration along the capillaries, x, the average in the tissue, and x_v, the concentration of metabolite in the blood leaving the tissue region. Now x_0, of course, will lie between C and x_v, its exact value depending on the instantaneous concentration gradient along the capillary. We shall take into account the existence of this gradient only phenomenologically, by assuming that over the course of the absorption,

$$x_0 = C - f(C - x_v); \quad f, \text{constant.} \tag{5}$$

Employing expression (5), the arterio-venous accumulation term, $R(C - x_v)$, becomes $(R/f)(C - x_0)$. In all past papers we have taken $f = 1$, whence the coefficient of $(C - x_0)$ was to be interpreted as the rate of blood flow. It is clear that if other values of f are chosen, the original equations and solutions still hold, provided the "R" is reinterpreted as $1/f$ times the true rate of blood flow. For example, if x_0 is to be the arithmetic mean of C and x_v, then $f = 1/2$, and R/f is twice the rate of blood flow.

It is not difficult in certain restricted cases to set up the partial differential equations for this system and so to deduce the axial concentration gradient theoretically. For example, if z measures distance along a capillary axis, ρ measures the radial distance from the capillary axis, $C_B(z, t)$ is the concentration of solute in the capillary, $C_T(\rho, z, t)$ is the concentration of solute in the (assumed) homogeneous tissue, D_T, the diffusion coefficient in the tissue, and ρ_0 is the radius of the capillary, then the governing equations are:

$$\pi\rho_0^2 \frac{\partial C_B}{\partial t} = R\frac{\partial C_B}{\partial z} - 2\pi\rho_0 h(C_B - C_T),$$

$$D_T \nabla^2 C_T = \frac{\partial C_T}{\partial t},$$

with the boundary condition that, $-D_T(\partial C_T/\partial\rho)_{\rho=\rho_0} = h[C_B - C_T(\rho_0)]$, and that C_T remains finite as $\rho \to \infty$. The advantage gained by attempting an exact solution of these equations may, nevertheless, be illusory, because there are available virtually no good measurements of the physical constants involved, and the detailed capillary geometry is much more complicated than this model suggests.

Adopting (5) we may write the differential equations of the system as,

$$V_0 \frac{dx_0}{dt} = \frac{R}{f}(C - x_0) - hS(x_0 - \alpha x); \tag{6}$$

$$V\frac{dx}{dt} = hS(x_0 - \alpha x)\,. \tag{7}$$

The solution of equation (6) and (7) is (I),

$$\phi_0(t) = V_0 x_0 = V_0 C\left\{1 + \frac{k_2 + \dfrac{2R}{V_0 f}}{k_1 - k_2}\,e^{k_1 t} - \frac{k_1 + \dfrac{2R}{V_0 f}}{k_1 - k_2}\,e^{k_2 t}\right\}; \tag{8}$$

$$\phi(t) = Vx = \frac{V}{\alpha}C\left\{1 + \frac{k_2}{k_1 - k_2}\,e^{k_1 t} - \frac{k_1}{k_1 - k_2}\,e^{k_2 t}\right\}; \tag{9}$$

where,

$$k = -\frac{\dfrac{R}{V_0 f} + \dfrac{hS}{V_0}\left(1 + \dfrac{\alpha V_0}{V}\right)}{2} \pm 1/2\left\{\left[\frac{R}{V_0 f} + \frac{hS}{V_0}\left(1 + \frac{\alpha V_0}{V}\right)\right]^2 - 4\frac{RhS}{fV_0 V}\right\}^{1/2}. \tag{10}$$

The plus or the minus sign before the second term of equation (10) corresponds arbitrarily, to k_1 and k_2. A comparison of (3) with (9) readily suggests that the physical assumptions which justify the von Schrötter expression, (3), are those which would cause one of the two exponentials in (9) to disappear. This reduction to one exponential could be effected by having $k_1 = k_2$; however, it can be shown that this equality would require certain terms in (10) to assume complex values, which requirement would be physical nonsense. The second, and only plausible, method is to have one of the two absolute values of k, say k_1, be much larger than the other, whereupon (9) becomes,

$$\phi(t) \cong \frac{V}{\alpha}C(1 - e^{k_2 t})\,. \tag{11}$$

For $|k_1| >> |k_2|$, it is apparent from (10) that,

$$\left[\frac{R}{V_0 f} + \frac{hS}{V_0}\left(1 + \frac{\alpha V_0}{V}\right)\right]^2 >> 4\frac{\alpha RhS}{fV_0 V}. \tag{12}$$

The structure of condition (12) suggests that it can be achieved either when $R/f >> hS$ or $R/f << hS$. To show this more clearly, we shall adopt the following notation: $R/f = X$; $hS = Y$; $(\alpha V_0/V) = r$; and

in the event that $X >> Y$, the small quantity $Y/X = \varepsilon$; in the converse case, $X << Y$, we have the small quantity, $X/Y = \eta$. We may then write from (10),

$$k_2(X >> Y) = -\frac{1}{2V_0}\left\{ X + Y(1+r) - X\left[1 + 2(1-r)\varepsilon + (1+r)^2\varepsilon^2 \right]^{1/2} \right\}; \tag{13}$$

$$k_2(X << Y) = -\frac{1}{2V_0}\left\{ X + Y(1+r) - Y(1+r)\left[1 + \frac{2(1-r)}{(1+r)^2}\eta + \frac{1}{(1+r)^2}\eta^2 \right]^{1/2} \right\}. \tag{14}$$

It can be stated on experimental grounds that we need not be concerned with values of $r > 1$. It will be noted that the special case, $r = 1$, is a critical one in both (13) and (14), but one which need not concern us here. When $r < 1$, it will be obvious to the reader from an inspection of expressions (13) and (14) exactly what numerical conditions are being assumed in retaining only the linear terms (in ε or η) in the binomial theorem expansion of the radical, yielding,

$$k_2 = -\frac{ahS}{V}, \tag{15}$$

when $R/f >> hS$, and

$$k_2 = -\frac{R}{V_0}\cdot\frac{1}{2f}\left[1 - \frac{1-r}{(1+r)^2} \right]; \text{ when } R/f << hS. \tag{16}$$

It is clear that (3) can be regarded as an approximation identical with (11) provided that we can show (4) to be essentially the same as (16). Exact coincidence cannot be expected because of the approximations already made. Nonetheless, it may be shown graphically (Fig. 2) as well as by expansion in a MacLaurin series that for $0 \leqq r \leqq 0.6$, the coefficient of $-R/V_0$ in (16) is not appreciably different from $\log_e(1 + r)$. The identity of (4) and (16) is thus reasonably complete for this range of r if we assume, as in the past, that the average axial concentration gradient is such as to make $f \cong 1$. To summarize, then, if in the differential equations for a distinct parallel system, (8), (9), it be assumed that, (a) there exists along the absorbing blood vessel a concentration gradient of the type $f \cong 1$, (b) $hS >> R$ (in such a way as to justify the expansion of

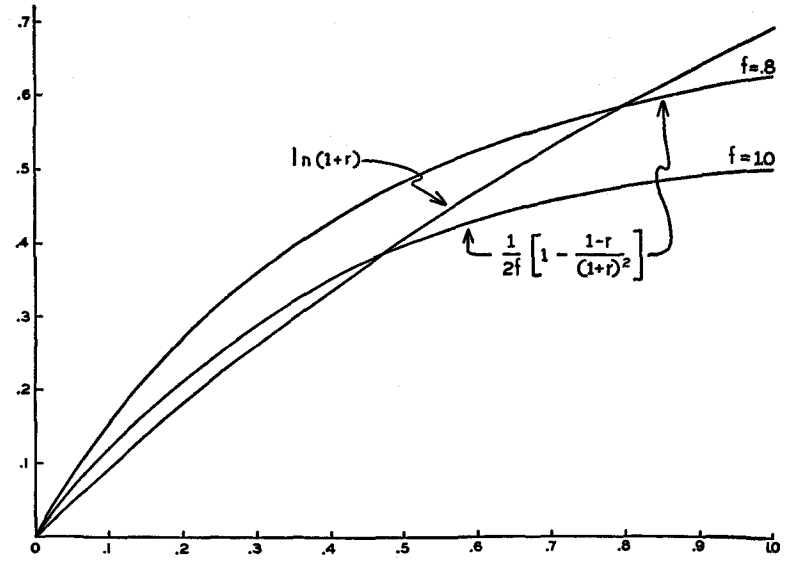

FIGURE 2. Graph to show approximate coincidence of the single exponent as derived in the von Schrötter theory ($1n(1+r)$) and in the limiting case of the differential equation method. The coincidence in the physiologically important range $0 < r < .6$ is seen to depend on f (see text), being best when $f = 1$, and increasingly poor as f decreases from unity.

the radical in (14)), and (c) $0 \leqq \alpha V_0/V \leqq 0.6$, then the uptake as a function of the time is given by von Schrötter's expression (3), (4).

In the absence of suitable experimental values of h, we can only speculate about the plausibility of the condition, $R/f << hS$. Let us divide this inequality by V_T, the tissue volume, and assume that $f = 1$. We may then fairly require that

$$\left[\frac{\frac{S}{V_T}}{\frac{R}{V_T}}\right] \quad h \text{ exceed at least 100 to justify (11) and (16).}$$

We have not found in the existing literature simultaneous measurements of blood flow and surface-volume ratios on any tissue. However, it may be seen from the data gathered in Table 1 that the ratio in question may be expected to lie between the two extremes, 277 h and 460,000 h. The decision regarding the validity of the von Schrötter type of approximation is thus seen to depend on accurate values of the permeability of the plasma membrane to gases. Such values are not abundant. In early rough calculations we, as well as others, have assumed values of the order of 1×10^{-5} cm sec^{-1}. Under these

circumstances it is clear that the ratio mentioned above would be much less than the requisite 100. It is probable, however, that the permeabilities are larger than 1×10^{-5}. From Krogh's measurements we (III) have calculated 7×10^{-3} and 3×10^{-4} cm sec^{-1} for O_2 and CO_2 respectively through the lung barrier. Recently, V. Wartiovaara

TABLE 1

Blood Flow and Capillary Surface per Unit Volume for Various Tissues

Tissue or Organ	Blood Flow/Volume (sec^{-1})	Surface/Volume (cm^{-1})
Guinea Pig Muscles:		
(resting)		3,8,32 (1)
(massage)		200 (1)
(working)		390 (1)
(maximum circulation)		750 (1)
(gastrocnemius)		186-254 (2)
(masseter)		304-507 (2)
Mouse Muscle:		
gastrocnemius		486-640 (2)
masseter		726-923 (2)
Guinea Pig Fat:		
Fat fat tissue		23.5 (3)
Lean fat tissue		64.1 (3)
Frog Muscle		190 (1)
Horse Muscle		240 (1)
Dog Muscle		590 (1)
Thyroid	.0933 (4)	
Kidney	.025 (4)	
Liver	.025, .006, .017 (4)	
Brain	.023 (4)	
Intestines	.012 (4)	
Spleen	.007 (4)	
Stomach	.004 (4)	
Hand	.0022 (4)	

The numbers in parenthesis refer to authorship of data:

(1) Krogh (1936)
(2) Sjöstrand (1937)
(3) Gersh and Still (1945)
(4) Best and Taylor (1943)

(1944) has measured the permeability of *tolypellopsis* for deuterium, and I. Holm-Jensen, A. Krogh and V. Wartiovaara (1944) that of certain plant tissues for various ions; all of these values are of the order of 1×10^{-3} cm sec^{-1}. Accepting 1×10^{-3} as a round number for h, we see that the extremes of the critical ratio are .277 and 460 — values which straddle 100. It would thus appear that whereas in certain cases the von Schrötter approximation might be quantitatively justifiable, in others it would be very poor indeed. Until tissue constants can be measured with greater precision, a preference must be given to the general differential equation formulations (I–V) which are capable of describing situations wherein penetration is strongly limiting, *as well as those situations where this is not so.*

In emphasizing the clear priority of H. von Schrötter with regard to equations of the type of (3) and (4), it also seems opportune to mention the important papers of T. Teorell (1937a, 1937b) on the kinetics of distribution of injected substances. So far as we are aware, Professor Teorell's work is the first rational attempt to describe the whole-body distribution process by means of an approximate system of differential equations. It is regretted that this paper had not come to our attention at the time the present work was begun.

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