BULLETIN OF
MATHEMATICAL BIOLOGY
VOLUME 36, 1974

THE INTERACTION OF DIFFUSION AND PERFUSION IN HOMOGENEOUS TISSUE

T. R. HENNESSY*
Department of Applied Mathematics,
University of Cape Town, Cape Town,
South Africa

A mathematical model is proposed to examine the interaction between blood perfusion and gas diffusion in the uptake of inert gases in tissue. The standard Haldane perfusion model is contrasted with the Hills radial bulk diffusion model in a variety of homogeneous tissue types used in decompression theory. It is the intention of the present analysis to fix ideas on the role of diffusion, perfusion and axial concentration and quantitative studies are given and seem to show that Haldane's perfusion theory is at best a poor approximation even at asymptotic times. It is shown that a strong interaction exists between diffusion and perfusion in muscle tissue and neither approach adequately describes the actual uptake half-time of an inert gas.

1. Introduction. For many years there has been some doubt as to whether diffusion or perfusion is the dominant mechanism for uptake of inert gas in tissue.

A number of different mathematical models have been proposed, beginning with Zuntz (1897), von Schrotter (1906) and Haldane (1908). All these are similar and were based upon perfusion being the dominant mechanism. Haldane was the first to introduce the concept of a tissue half-saturation-time, which is defined to be that time for a tissue to receive one half the nett uptake of gas after a sudden change in arterial gas pressure. In this way various tissues become characterized by their half-times. For the rest of this paper

* Present Address: Department of Mathematics, Queen Elizabeth College, Campden Hill Road, London W8, England.

therefore, the early perfusion approach will be referred to as the Haldane model.

The most comprehensive review of early papers is that of Kety (1951), and since then a number of papers have appeared.

Perhaps the most important recent review is that of Hills (1970b) who in a remarkable paper shows that much of the present experimental data can be equally well correlated by a diffusion or perfusion theory approach. Perl (1962, 1963) also shows an interaction between diffusion and perfusion at large scale distances of 1 mm, for average rates of blood flow and intertissue diffusion. Thus, it seems that perfusion and diffusion mechanics are inextricably intertwined. The purpose of the paper will be to highlight this interaction and to define the conditions from a fundamental viewpoint.

The main features of all these models of gas transport through tissue appear to be a combination of some of the following dominant aspects:

(i) perfusion;
(ii) bulk diffusion;
(iii) fully transient;
(iv) axial as well as radial concentration dependence.

To a lesser extent additional features are present, and include a capillary permeability term (often used in place of true bulk diffusion) and anisotropy (diffusion velocity different in radial and axial directions).

Papers concerned with the uptake of a substance other than an inert gas introduce a number of other assumptions and boundary conditions, which will not be considered here.

Of the more recent papers concerned with gas transport through tissue, a number have appeared which all attempt to include some of the features (i) to (iv) above. These include Schmidt (1952, 1953), Thews (1953), Blum (1960), Perl *et al.* (1965), Johnson and Wilson (1966), Gonzalez-Fernandez and Atta (1968), Reneau *et al.* (1969), Bassingthwaite *et al.* (1970), Hills (1970a) and Levitt (1971). The most important paper prior to 1951 is probably that of Morales and Smith (1948), being the final paper in a set of six (including Smith and Morales, 1944a, 1944b) covering various models and approaches (1944–1948).

Schmidt and some of the latter authors attempt to treat (i), (iii) and (iv) but instead of (ii) use a capillary membrane property which is a first order approximation to bulk diffusion in the case of an inert gas. Table I gives a brief summary of recent approaches, most of which include an approximation to the axial dependent term (iv). Some are concerned with substances other than inert gases, but are included for interest.

However, in nearly all these earlier papers, very little attempt has been made

TABLE I

Summary of Various Mathematical Models of Transport in Tissue

	(i) Perfusion	(ii) Bulk diffusion	(iii) Fully transient	(iv) Axial dependence
Morales and Smith (1948)	Yes	1st Order	Yes	1st Order
Schmidt (1952, 1953)	Yes	1st Order	Yes	Yes
Sangren and Sheppard (1953)	Yes	1st Order	Yes	Yes
Thews (1953)	No	Yes	No	Yes
Blum (1960)	No	Yes	No	Yes
Bellman *et al.* (1960)	Yes	Yes	Yes	Yes
Johnson and Wilson (1966)	Yes	1st Order	Yes	Yes
Reneau *et al.* (1969)	Yes	Yes	Yes	Yes
Bassingthwaite *et al.* (1970)	Yes	Yes	Yes	Yes
Hills (1970a)	1st Order	Yes	No	Yes
Levitt (1971)	Yes	Yes	Yes	Yes
Haldane (1908)	Yes	No	Yes	No
Teorell (1937)	No	Yes	Yes	No
Roughton (1952)	No	Yes	Yes	No
Morales and Smith (1944–1948)	Yes	1st Order	Yes	No
Harris and Burn (1949)	No	Yes	Yes	No
Hills (1969)	No	Yes	Yes	No
Hills (1967)	No	Yes	Asympt.	No
Hennessy (1971b)	Yes	Yes	Yes	No
Perl *et al.* (1962, 1963, 1965)	Yes	Yes	Yes	No

Note: Not all models employ the same boundary conditions.

to extract and compare the crucial parameters from the mathematical model, viz: vascularity index, perfusion time scale and the diffusion time scale.

A very common approximation is to the bulk diffusion term, where gradients are simply replaced by their first order approximation, that is, the linear difference between two nearby concentrations divided by the distance between them. As Hills (1970a) has shown it is usually a poor approximation at small to medium times.

In some cases, the model is assumed non-transient. Whilst this approach is

reasonable for experiments which may be slowly varying, and/or of short duration, considerable errors will occur over saturation times.

At this stage it is perhaps pertinent to offer some justification for the emphasis on axial dependence, as shown in the first part of Table I. First of all there is no intuitive reason for omitting axial dependence in preference to bulk diffusion or perfusion. To see this, consider a long straight capillary surrounded by a tissue annulus. If the blood flow along the capillary is very fast, then one would expect that diffusion into the tissue would be the limiting factor, because the wall of the capillary would be effectively at uniform arterial inert gas pressure. In this case, axial dependence is negligible.

If, on the other hand, blood flow is very slow, then linear perfusion becomes the limiting mechanism, because one can now imagine that the tissue will absorb all the gas in the capillary leaving a zero concentration at the exit. Here once again, axial dependence falls away when considering the *overall* uptake of the tissue (which would be simply a linear growth rate). Clearly then between these two extremes, there may be a situation where radial and axial diffusion and perfusion interact and the length of the capillary then becomes important.

Gonzalez-Fernandez and Atta (1968) have shown the dependence of capillary length on oxygen extraction in the case of axial diffusion. With this model in mind, it can be appreciated that depending on the flow velocity (which can be made very low by the pre-capillary sphincters), an entire spectrum of behavior can be expected ranging from a linear uptake to straight annular diffusion. The interesting feature of this model is a complex feed-back effect as the gas diffuses into the annulus near the arterial end. As saturation progresses, the capillary gas tension will be depleted less and more gas will become available to saturate zones further downstream.

On heuristic grounds alone it seems reasonable to expect that the typical length of a capillary is attributable to some dependence on its gas transport properties. If the capillary length does not appear directly in the model, then it implies that the capillary is simply being treated as a *point source* of gas, in which case, spherical diffusion might just as well be invoked instead of cylindrical diffusion.

On the other hand, it may of course be possible that the capillary is indeed acting as a point source, by virtue of its length and distribution in the tissue.

In all the approximation shown in Table I there is hardly any rigorous justification for ignoring a term, based on an order of magnitude analysis. Of course in some cases no estimate of a physical quantity may be possible. In these situations, analysis of the order of magnitude of a term can often highlight an area of future experiment, and can also curtail the domain of validity of an existing model.

Thus the aim will be to focus attention on tissue structures, where all four of the above features assume importance. In doing so, the role played by perfusion and diffusion in tissue is seen in a clearer light than perhaps hitherto. The model to be described has been discussed by Reneau *et al.* (1969), Bassingthwaite *et al.* (1970) and Levitt (1971), although some boundary conditions and other features are different. Reneau's comprehensive analysis contains an oxygen consumption term and uses a modified alternating direction implicit numerical solution. His model also accounts for diffusion in the capillary (which can be shown to be negligible for an inert gas). The price paid for this sophistication was 10 hr of computing time to describe a physical process lasting a few seconds. Bassingthwaite *et al.* dispense with capillary radial diffusion, and use an explicit numerical method of solution. Levitt's model includes a special boundary condition, the effect of which renders the model unfortunately similar to that of using a Haldane approximation of assuming that the venous flow leaves in equilibrium with the tissue (a situation which is only approached at asymptotic times). In none of these models is there an order of magnitude analysis of the various terms and essential parameters. In particular the main difference between these models and the one to be studied is in the ratio of the diffusion time scale to perfusion time scale which here is assumed to be of the order one, where an interaction may be expected between perfusion and diffusion.

2. The Mathematical Model. Nearly all the models mentioned in Section 1 propose a structure based upon a single straight capillary of given characteristic length (l), radius (a), surrounded by a tissue annulus, of some realistic outer radius (b). This approach dates back to Krogh (1919a, 1919b).

Studies of a particular tissue show that whilst a, b and l all vary, they do so between definite limits. Therefore, there must exist a set of dimensions for a, b and l which characterize that particular tissue under a given metabolic state. Changing the latter may cause a and b to vary by opening up non-active capillaries, for example.

On the other hand it is noticed that capillaries are situated in an apparently random manner, where the end of one capillary may be placed near the beginning of another. Schmidt (1952) uses this argument to dispense with the axial extra-cellular concentration gradient.

Thus the question arises how does one justify allocating a typical tissue radius or length of capillary? It seems that the answer must be simply that there is at present no better tractable approach. In any case each capillary has to serve a definite *volume* of tissue in its immediate neighborhood; we merely specify it to be a circular cylindrical annulus on grounds of mathematical

convenience, and its apparent closeness to physical reality in specific tissues such as muscle. Contrast this approach with that of Hennessy (1971b) who supposed the extra-vascular space to be a solid cylindrical space, with no direct reference to the capillary structure. However, in this paper we make an attempt to relate the capillary dimensions with actual observation in tissue (Krogh, 1919a).

Moreover, as Gonzalez-Fernandez and Atta (1972) have shown, negligible error is made by choosing a circular cylindrical annulus in preference to a hexagon of equal area cross-section. Larger errors can occur if square or triangular tissue structures are present. In these cases, the cylinder must be considered a first approximation.

It is now necessary to describe the extra capillary space from the point of view of a diffusion medium. If this space is purely interstitial then diffusion will be very rapid (about 1-sec saturation time) as Roughton (1952) has shown. If of course the tissue has a low vascularity index α $(=a/b)$, then the saturation time rises considerably, but still well away from the very large times known to exist. On the other hand the tissue is actually a heterogeneous diffusion medium since the diffusion coefficient is believed to be the 10^4 times smaller in cytoplasm (Hills, 1967). Because of this dominance for cellular diffusion, it seems reasonable to suppose that the interstitial space is effectively fully stirred.

However, we are then forced to give this space a precise volume in the tissue annulus, which will complicate the model considerably. To avoid this, we assume that the annular tissue cylinder is an entirely cellular space, as envisaged by Hills (1966). Any actual interstitial diffusion which may be present may be included in a heuristic sense by adjusting (reducing) the vascularity ratio α or the capillary length. If on the other hand the cellular content of the annulus is sparse, then an entirely new model must be reworked. In other words, we are assuming effectively that the *inert gas capacity* of the interstitial space is much less than the cellular content of the tissue annulus, a fact born out by observation in many tissues, for example skeletal muscle.

The outer boundary and sides of the annular cylinder are supposed impermeable by symmetry. It is not difficult to show that the effect of axial diffusion down the capillary (Taylor, 1953) is quite negligible compared with perfusion (Blum, 1960). Also, radial diffusion may be supposed "instantaneous" compared to the other terms. Thus the blood is assumed to be a fully stirred fluid in the radial direction as it travels through the capillary. There is a continual loss of gas en route down the capillary and thus the concentration is axially dependent. Figure 1 describes the model with its main parameters.

We suppose that blood (taken to be a Newtonian fluid, for purposes of defining a volume flux) flows uniformly through the capillary with velocity V. It

carries an inert gas, whose arterial tension is fixed at p_a (atmospheres), derived from the exposure to an hyperbaric environment. Initially the region is at a tension p_0. Let S_b and S_c be the gas solubility in blood and cells (g gas/ml blood or cells/atmosphere at 37°C), and $S_p = S_c/S_b$.

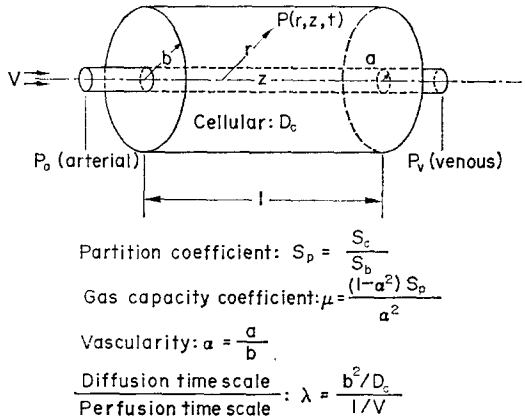

Figure 1. The proposed model of transient inert gas transport in cellular tissue, which includes perfusion, diffusion and axial dependency. The main parameters of the model are included

We denote the gas tension in the blood by $p_b(z, t)$ and in the cellular tissue $p_c(r, z, t)$. Notice that p_b only depends on z, because of rapid stirring in the r direction.

Applying a mass balance to a disc of fluid in the capillary and taking the limit, we obtain

$$\frac{\partial p_b}{\partial t} = -V \frac{\partial p_b}{\partial z} + \frac{2D_c S_p}{a} \left(\frac{\partial p_c}{\partial r}\right)_{r=a} \tag{1}$$

where D_c is the diffusion coefficient of inert gas in cellular tissue ($cm^2\ sec^{-1}$). Also the diffusion equation holds in the cellular space

$$\frac{\partial p_c}{\partial t} = \frac{D_c}{r} \frac{\partial}{\partial r} \left(r \frac{\partial p_c}{\partial r}\right) + D_c \frac{\partial^2 p_c}{\partial z^2}, \tag{2}$$

subject to

$$\frac{\partial p_c}{\partial r} = 0, \quad r = b, \quad 0 \leqslant z \leqslant l, \quad t \geqslant 0,$$

$$\frac{\partial p_c}{\partial z} = 0, \quad z = 0, l, \quad a \leqslant r \leqslant b, \quad t \geqslant 0,$$

and

$$\begin{aligned} &p_b = p_c, \quad r = a, \quad 0 \leqslant z \leqslant l, \\ &p_b = p_c = p_0, \quad a \leqslant r \leqslant b, \quad 0 \leqslant z \leqslant l, \quad t = 0, \\ &p_b = p_a, \quad z = 0, \quad t > 0. \end{aligned} \tag{3}$$

The mass uptake of inert gas is given by

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \pi a^2 V S_b [p_a - p_b(l, t)]. \tag{4}$$

The average tissue gas tension is perhaps a more convenient variable than M, and is given by

$$p = M/[\pi a^2 l S_b + \pi(b^2 - a^2) l S_c], \tag{5}$$

and thus

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{V/l}{\left[1 + \dfrac{(1 - \alpha^2)}{\alpha^2} S_p\right]} [p_a - p_b(l, t)]. \tag{6}$$

Notice that if V becomes very large, then $p_b(l, t) \to p_a$, which reduces to straight diffusion into the cellular annulus, and in the limit, using (1), we have

$$\frac{\mathrm{d}p}{\mathrm{d}t} = -\frac{2D_c}{a} \frac{S_p}{\left(1 + \dfrac{1 - \alpha^2}{\alpha^2} S_p\right)} \left(\frac{\partial p_c}{\partial r}\right)_{r=a}. \tag{7}$$

This is essentially Hills (1966) equation for pure radial diffusion into an annulus and will only be valid for $V \gg l$.

Transform to dimensionless variables:

$$\begin{aligned} &r = br', \qquad z = lz', \qquad t = \frac{b^2}{D_c} t', \\ &\frac{p_b - p_0}{p_a - p_0} = p_b', \qquad \frac{p_c - p_0}{p_a - p_0} = p_c', \\ &\frac{p - p_0}{p_a - p_0} = p'. \end{aligned} \tag{8}$$

Substitute into (1), (2) and (6) to obtain, after discarding primes,

$$\frac{\partial p_b}{\partial t} = -\lambda \frac{\partial p_b}{\partial z} + \frac{2S_p}{\alpha} \left(\frac{\partial p_c}{\partial r}\right)_{r=a} \qquad 0 \leqslant z \leqslant 1, t > 0, \tag{9}$$

where

$$\lambda = \frac{b^2/D_c}{l/V} = \frac{\text{diffusion time scale in cells}}{\text{perfusion time scale for capillary}},$$

a parameter used by Perl (1963) to discuss the interaction between perfusion and diffusion at the macroscopic level, and

$$\frac{\partial p_c}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial p_c}{\partial r}\right) + \beta\frac{\partial^2 p_c}{\partial z^2}, \tag{10}$$

$$0 < \alpha \leqslant r \leqslant 1, \qquad 0 \leqslant z \leqslant 1, \qquad t > 0,$$

where $\beta = b^2/l^2$. Finally, we have

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{\lambda}{1+\mu}[1 - p_b(1, t)], \tag{11}$$

where

$$\mu = \frac{(1-\alpha^2)S_p}{\alpha^2} = \frac{\text{gas capacity of cells}}{\text{gas capacity of blood}}.$$

We have used b rather than a to reduce r and t to dimensionless variables. This is because it is conceptually more appropriate to consider the diffusion time scale as b^2/D_c rather than a^2/D_c. The latter term is simply the diffusion time scale across the radius of a capillary which of course does not consist of cellular material. The quantity a^2/D_c must rather be regarded as a constant physical parameter of the tissue structure (because it is known that a varies only slightly in a given tissue under different conditions of stress). On the other hand b^2/D_c is the diffusion time scale of the tissue and is a measure of the time for diffusion processes to occur in the extra-vascular space normal to the capillary.

If V is large, than $\lambda \gg 1$ and (11) will become in the limit the dimensionless equivalent of (7),

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{-2S_p}{\alpha(1+\mu)}\left(\frac{\partial p_c}{\partial r}\right)_{r=\alpha}. \tag{12}$$

Consider the parameter $\beta = b^2/l^2$. Typical values of b are 15–30 μm, whereas l is normally 0.4 to 1 mm (Krogh, 1936).

Thus $\beta < 0.005$, and so the last term on the right-hand-side of (10) may be ignored, over a wide range of vascularities, providing always that the tissue remains a homogeneous and purely cellular. This approximation has the same effect as if the longitudinal diffusion coefficient is zero.

The boundary conditions become

$$\begin{aligned}
&\frac{\partial p_c}{\partial r} = 0, \quad r = 1, \quad 0 \leqslant z \leqslant 1, \quad t \geqslant 0,\\
&p_b = p_c, \quad r = \alpha, \quad 0 \leqslant z \leqslant 1,\\
&p_b = p_c = 0, \quad \alpha \leqslant r \leqslant 1, \quad 0 \leqslant z \leqslant 1, \quad t = 0,\\
&p_b = 1, \quad z = 0, \quad r = \alpha, \quad t > 0.
\end{aligned} \tag{13}$$

Notice that we must relax the condition

$$\frac{\partial p_c}{\partial z} = 0 \quad \text{on} \quad z = 0, 1, \qquad \alpha \leqslant r \leqslant 1, \qquad t \geqslant 0,$$

since otherwise the equations (9), (10) become overdetermined. The reason for this is that since the z dependence has been removed from (10), it is no longer possible to specify a zero gradient at $z = 0, 1$. On the other hand the problem is still z dependent by virtue of (9) and (13). Thus $(\partial p_c/\partial z)_{z=0,1}$ will in general be non-zero, thereby implying a loss of gas from each end. However, this loss is quite negligible, as can be seen by inspecting the dimensionless mass flux from one face in the worst case:

$$\frac{b^2}{l^2} \operatorname*{Max}_{\alpha \leqslant r \leqslant 1} \left(\frac{\partial p_c}{\partial z}\right)_{z=0,1} \leqslant \beta,$$

which has been supposed $\ll 1$. Here we are assuming that the dimensionless quantity $\partial p/\partial z \sim 1$ for all time. The same assumption applies to $\partial^2 p/\partial z^2$, to enable the last term on the right-hand-side of (10) to be discarded. Clearly these assumptions are not true at small times following the step change in arterial tension and it is a separate study to examine the effects of these terms at small times. However, if the terms were included, an analytic approach becomes unfeasible and a finite difference formula would be required which would also introduce its own errors at small times. Thus failing an analytic solution, it seems difficult to establish accurately the effect of these assumptions. It is thus supposed that any sharp discontinuities are soon smoothed out as time proceeds, and that these dimensionless terms remain of order one.

The Laplace Transform is applied to the set of equations (9), (10), (11) and the boundary conditions (13). Solution is straightforward with the results set out in the following form (s is the Laplace Transform parameter):

$$\bar{p}_b(z, s) = \frac{1}{s} \exp\left\{-\frac{sz}{\lambda}\left[1 - \frac{2S_p}{\alpha\sqrt{s}} \frac{f(\alpha, s)}{g(\alpha, s)}\right]\right\}, \tag{14}$$

$$\bar{p}_c(r, z, s) = \bar{p}_b(s) \frac{g(r, s)}{g(\alpha, s)}, \tag{15}$$

and

$$\bar{p}(s) = \frac{\lambda}{1 + \mu} \frac{1 - s\bar{p}_b(1, s)}{s^2}, \tag{16}$$

where the functions f and g are defined as

$$\begin{aligned} f(r, s) &= I_1(r\sqrt{s})K_1(\sqrt{s}) - I_1(\sqrt{s})K_1(r\sqrt{s}), \\ g(r, s) &= I_0(r\sqrt{s})K_1(\sqrt{s}) + I_1(\sqrt{s})K_0(r\sqrt{s}). \end{aligned} \tag{17}$$

K is the modified Bessel function of the second kind. We are of course primarily interested in evaluating the average inert gas pressure of the tissue region given by (16). Unfortunately inversion of this function analytically is not possible, because the singularities are isolated essential and the residue cannot be obtained in terms of recognizable functions. This can be seen by attempting to form the Laurent expansion at the singularity points given by $g(\alpha, s) = 0$.

Thus a numerical inversion technique must be employed to invert (16).

3. The Perfusion Approach. At this stage it is of interest to show how the Haldane perfusion dominated approach can be deduced from the present model. The basic step is to assume that diffusion is unimportant in the extra-vascular space (assuming an "aqueous" $D \sim 10^{-5}$ cm^2/sec). This is another way of stating that the diffusion time scale is very much less than the perfusion time scale, or $\lambda \ll 1$. This is effectively assuming the entire extra-vascular space to be fully stirred, which only approaches this condition at large times. This implies that the blood leaves the tissue in equilibrium with the mean tissue inert gas pressure. This latter form was first used by Zuntz (1897) and has since formed the basis of all perfusion theories.

Using this, equation (11) can be considerably simplified to read

$$\frac{dp}{dt} = \frac{\lambda}{1 + \mu}(1 - p) \tag{18}$$

which on integration, using the boundary conditions, we obtain

$$p = 1 - e^{-\lambda t/1+\mu}$$

which may be re-interpreted in terms of dimensional variables to read

$$p = p_a - (p_a - p_0)e^{-kt} \tag{19}$$

where

$$k = \frac{V}{l(1 + \mu)} = \frac{P}{\alpha^2 + (1 - \alpha^2)S_p}$$

where P is the blood perfusion, i.e. the volume of blood entering the tissue per unit volume of tissue per minute. Thus

$$P = \frac{\pi a^2 V}{\pi b^2 l} = \frac{\alpha^2 V}{l}. \tag{20}$$

In the case where $S_p \approx 1$, k reduces to P. Equation (19) is the well-known Haldane equation which gives a tissue half-time T_H

$$T_H = \frac{[\alpha^2 + (1 - \alpha^2)S_p] \log 2}{P} \text{ minutes.} \tag{21}$$

The literature normally quotes $T_H = (\log 2)/P$ where $S_p = 1$ has been assumed. In any case even for lipids, where $S_p \approx 5$, little error is made if α is small. Only in very vascular tissue is there an appreciable difference. Thus the Haldane approach yields two important parameters, the tissue half-time T_H and the blood perfusion P. If the present model is to be contrasted with the perfusion approach, it should relate these two parameters and compare it to the relationship of (21).

It is worthwhile examining in closer detail the meaning of the approximation that the blood leaves the tissue in equilibrium with the average pressure. First of all, as has been noted, this is only likely to be approximately true at large times. The rate of change of the average tissue pressure is given by (11). Compare this with the rate given by (18). It is clear that since $p > p_b(1, t)$ for all t, then the actual rate of increase of the average pressure will always be less than the Haldane rate, becoming closer as the time grows large. This in turn means that the Haldane half-time is in fact an *over-estimate* of the actual tissue half-time, other things being equal (such as perfusion vascularity, diffusion time scale, etc.). This fact can be clearly seen in the numerical solutions.

4. The Diffusion Approach. In contrast to the perfusion theory above, the diffusion approach is based on the assumption that the diffusion time scale is a non-negligible entity in the extra-vascular space. That is, the diffusion coefficient is very much smaller in the cellular space. This of course is an incomplete assumption because the perfusion time scale may also be non-negligible. One must state that $\lambda \gg 1$. Effectively one is assuming that the blood velocity is so fast that the capillary wall is instantly exposed to the full arterial input gas pressure. Proceeding with this assumption, one easily solves the radial diffusion equation into an annular cylinder (Hills, 1966).

This solution is also present in our model, and can be got by simply letting $\lambda \to \infty$ in (14), (15) and (16). The result for $\lambda \to \infty$ is

$$\bar{p}(s) = \left[1 - \frac{2}{\alpha}\frac{S_p}{\sqrt{s}}\frac{f(s,\alpha)}{g(s,\alpha)}\right] \Big/ (1 + \mu)s,$$

which can be inverted by standard methods, and after some labour, yields

$$p(t) = \frac{1}{1+\mu} + \frac{\mu}{1+\mu}\left\{1 - \frac{4}{1-\alpha^2}\sum_{n=1}^{\infty}\frac{e^{-\beta_n^2 t}}{\beta_n^2}\left[\frac{J_0^2(\alpha\beta_n)}{J_1^2(\beta_n)} - 1\right]^{-1}\right\} \tag{22}$$

where β_n are the roots of

$$J_0(\alpha\beta)Y_1(\beta) - Y_0(\alpha\beta)J_1(\beta) = 0. \tag{23}$$

Notice that according to our general definition, the average pressure is that of

the *whole* space, both intra and extra-vascular, whereas Hills definition for the total uptake considers only the extra-vascular space. In other words, he ignores the quantity of gas present in the capillary. Naturally in tissue of small vascularity, this omission is negligible. Thus as $\mu \to \infty$, p approaches the standard result for the average pressure in the annulus. [This is the term in brackets in (22).] This latter term has been used successfully by Hills (1966) as a model of gas uptake in tissue in correlating decompression formats. The value for μ in this model was about 25 and thus a small error of 0.04 is made in the average pressure term.

5. The Perfusion-Diffusion Interaction. Thus it is seen that the present model actually contains as subcases the Haldane perfusion model and the Hills annular diffusion model. In other words, by solving (16), using realistic values of the vascularity α, the diffusion time scale α^2/D_c and the blood perfusion P, the complete interaction may be observed and discussed in the light of the two extreme forms of the model, viz: diffusion versus blood perfusion.

It should be noted that the model proposed by Hennessy (1971b) also attempted to highlight this interaction. In that paper though, the entire extracellular region was assumed to be fully stirred, an assumption which has been avoided here by assuming (i) purely cellular extra-vascular space, and (ii) an axially dependent gas distribution. In addition the present model is more realistic, taking into account radial diffusion from a capillary (as well as axial dependence).

Suppose that the Haldane and Hills curves of half-time are plotted against perfusion on log–log paper. Then by (21), the Haldane curve should be a constant line of slope $-45°$, for $S_p \approx 1$. On the other hand, the Hills half-time is independent of the blood perfusion and the curves will thus be horizontal lines, where the ordinate intercept depends of course on the vascularity α. Clearly there will be zones where the perfusion P is very low, in which case the Haldane half-time $\gg$ Hills half-time, and vice versa for large P.

The numerical solution of (16) may be expected to take up a curve which moves smoothly from the Haldane to the Hills curve as P is increased. The interesting issue is over which range of P is the interaction most predominant. In Section 8, this question will be fully answered, and the main results confirm in a positive manner that neither diffusion nor perfusion may be singled out as the dominant mode of uptake.

6. Large Time Solution. It is of interest to attempt to obtain the large time solution of (16) in the hope that a dominant asymptotic exponential component may be extracted. However, a lengthy analysis and considerable manipulation

of the function $f(r, s)$, $g(r, s)$ for small s proved disappointing. The best that could be done was to show that the average pressure has an exponential behavior at large times, where the time constant k was the same as in the Haldane equation (19). However, the coefficient in front of the exponential could not be evaluated with any certainty (we expect it to be at least greater than the Haldane coefficient of unity). The details are omitted here owing to the inconclusive results. In any case the numerical inversion takes care of this difficulty with apparent ease.

7. Small Time Solution. The next step would be to inspect (16) for large s, i.e. small time. Once again there is considerable labor for the results obtained. The asymptotic expansions for $I_{0,1}$ and $K_{0,1}$ are taken from Abramovitz and Stegun (1965) and a first order approximation is carried out. The result is

$$\bar{p}(s) \sim \frac{\lambda}{s^2(1+\mu)}\left\{1 - e^{-S_p/\lambda\alpha^2}\exp\left[-\left(\frac{s}{\lambda} + \frac{2S_p\sqrt{s}}{\alpha\lambda}\right)\right]\right\}. \tag{24}$$

This function can be inverted analytically without difficulty. On a close examination it will be seen that the expression contains the small time solution when the model is perfusion controlled ($\lambda \ll 1$) and also the small time solution if diffusion dominates ($\lambda \gg 1$). This can be seen by considering the term $e^{-S_p/\lambda\alpha^2}$. For $\lambda \ll 1$, the exponential becomes very small, and the small time solution degenerates to a linear uptake of gas as to be expected. For $\lambda \gg 1$, the exponential approaches unity, and a little manipulation reveals the standard small time solution into the annulus (Carslaw and Jaeger, 1959), plus a correction for the uptake in the capillary itself. For intermediate values ($\lambda \sim 1$), the solution is effectively a balanced combination of the perfusion and diffusion solutions. However, in the numerical calculations, this function was not inverted as a check against the analytical inversion of (24), because the method of inversion was well established and also that the half-time solution was required.

Instead it was found more convenient to compare as a "check" the Haldane half-time and the Hills half-time with the numerical inversion of (16).

8. Numerical Inversion. We wish to invert the function from (14) and (16), viz: the average tissue gas tension:

$$\bar{p}(s) = \frac{\lambda}{s^2(1+\mu)}\left\{1 - \exp\left[-\frac{s}{\lambda} + \frac{2S_p\sqrt{s}}{\lambda\alpha}\frac{f(\alpha, s)}{g(\alpha, s)}\right]\right\}, \tag{25}$$

where

$$\begin{aligned} f(\alpha, s) &= I_1(\alpha\sqrt{s})K_1(\sqrt{s}) - I_1(\sqrt{s})K_1(\alpha\sqrt{s}) \\ g(\alpha, s) &= I_0(\alpha\sqrt{s})K_1(\sqrt{s}) + I_1(\sqrt{s})K_0(\alpha\sqrt{s}). \end{aligned} \tag{26}$$

The numerical method chosen was that of Norden (1961) as modified by Hansson-Mild (1972), owing to the excellent results using this method in a comparative study between the Bellman *et al.* (1966) and Piessens (1972) methods (Hennessy, 1973).

All calculations were carried out in double precision on a Univac 1106 computer of the University of Cape Town. The Bessel functions of (26) were evaluated by Chebyshev polynomials as detailed by Luke (1969) to at least 12 significant figures.

Instead of simply computing the uptake curves of the average tissue tension (which would be useful from a point of view of comparison with likely experimental uptake curves), we compute the half-time of the tissue and plot this against the perfusion P, as being the best method of illustrating the perfusion–diffusion interaction.

The half-time is that time at which the tissue is 50 per cent saturated from its initial to its final tension. In dimensionless units, this simply requires $p(t) = 0.5$, since the initial tension is zero, and final tension unity.

The method of converging to the half-time was considered from several points of view. The final choice was the method of successive bisection. Even though slow, it is extremely stable in our case (since there is only one root $p = 0.5$ in the range $0 < t < \infty$) and once one half-time has been found for a given P, all others follow easily, since there will exist a good guess from the previously found half-time. The algorithm required a little modification since whilst a lower limit to the root always exists ($t = 0$) there is no finite upper limit. Thus each search commenced with a quick check by successive halving or doubling to produce an upper limit to begin the main algorithm. Five-figure accuracy was sought, and so iterating was terminated after 30 steps and an error message printed. However, this never occurred in the numerical experiments.

For each run we select a value for:

(i) the partition coefficient S_p, 1.0 for aqueous, 5.0 for lipid tissue;

(ii) the basic diffusion time scale a^2/D_c, 7.752 min (Hills, 1966), 9.456 min (Hennessy, 1971a, based on $\alpha = \frac{1}{5}$), and two purely aqueous values of 10^{-3}, 10^{-4} min for comparison;

(iii) the vascularity $\alpha(=a/b)$ $\frac{1}{5}$, $\frac{1}{10}$, $\frac{1}{15}$ and $\frac{1}{20}$; the last two were considered a little unrealistic in the sense that the average cell is about 30 μm in diameter, and the radius of capillary about 4–5 μm giving an $\alpha \sim \frac{1}{10}$ as a likely lower limit;

(iv) typical values of the perfusion P, measured in ml blood per ml tissue per minute were taken from Bell *et al.* (1961), where we have $0.01 \leqslant P \leqslant 5.6$ ml/ml/min. Thus P was chosen $10^{-4} \leqslant P \leqslant 10$ on the basis that it

seems possible that very low perfusion rates may occur in cases of partial vasoconstriction, or simply in zones of low vascularity in resting tissue. But it should be recalled that $P \sim 10^{-2}$ ml/ml/min is a common value for muscle tissue.

The actual diffusion time scale/perfusion time scale ratio λ is calculated from the formula $\lambda = a^2/D_c \times P/\alpha^4$, using (20).

The dimensionless half-time is converted to minutes by multiplying it by the factor $(a^2/D_c)/\alpha^2$, where it will be recalled that the dimensionless time was defined by t', $t = (b^2/D_c)t'$.

When P is large, λ is large, and so there is clearly a loss of precision in evaluating (25). Accordingly, the exponential is expanded in a power series for large λ ($\lambda \geqslant 10^3$ was chosen), which allows $\bar{p}(s)$ to be evaluated to its original high precision.

On the same graph we wish to plot the curve for the perfusion or Haldane half-time given by (21):

$$T = [\alpha^2 + (1 - \alpha^2)S_p] \log 2/P \text{ min}, \tag{27}$$

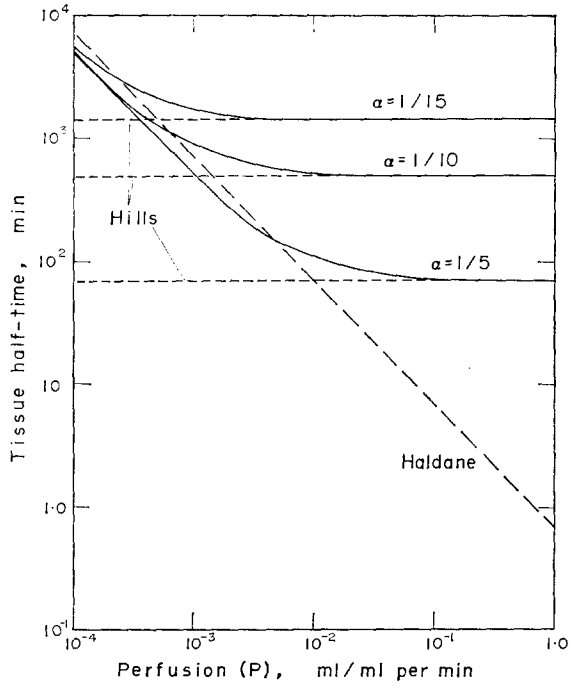

Figure 2. Aqueous tissue half-times plotted against perfusion for various vascularities ($S_p = 1$; $a^2/D_c = 9.456$ min). The equivalent curves of the Haldane (perfusion) and Hills (diffusion) theories are included

and the diffusion half-time, obtained by solving the half-time from (22) and (23) for each α and a^2/D_c. However, this was not done in the latter case directly because the numerical inversion converged to the value in an unmistakable manner. This half-time will be called the Hills half-time even though it is not strictly so [see the note after (23)]. To illustrate these three curves a log–log plot is chosen as already mentioned. In this case the Haldane half-time becomes a straight line inclined at $-45°$, and is unvarying for different α, if $S_p = 1$, an added advantage for comparison. The Hills half-time is independent of the perfusion and is thus a horizontal line. The numerical inversion is shown plotted in Figures 2 and 3 for various vascularities.

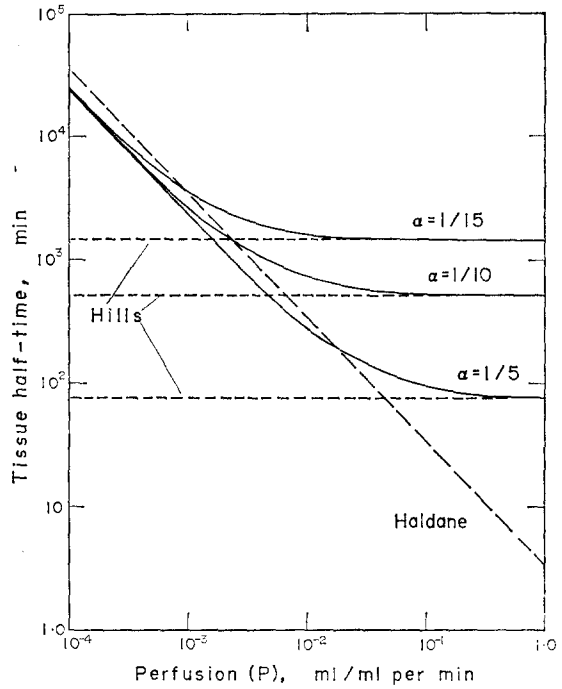

Figure 3. Lipid tissue half-times plotted against perfusion for various vascularities ($S_p = 5, a^2/D_c = 9.456$ min)

Tables II and III show some typical values for an aqueous type tissue ($S_p \sim 1$) and a lipid type tissue $S_p \sim 5$. All the half-times are longer, of course, and there seems to be a general shift towards a diffusion based system.

It will be noticed that for a given perfusion and vascularity, significant differences always exist between the actual and the Haldane half-time, except where the curves cross. On the other hand, the actual half-time merges

TABLE II

Aqueous Tissue Half-Times over a Perfusion Spectrum

($S_p = 1.0$, $a^2/D_c = 9.456$ min)
Hills value is the limit of columns 2, 3 and 4

Perfusion (ml/ml/min)	Tissue Half-Times (min)			
	$\alpha = \frac{1}{5}$	$\alpha = \frac{1}{10}$	$\alpha = \frac{1}{15}$	Haldane
0.0001	4947	5071	5683	6932
0.001	518	887	1788	693
0.01	108	534	1456	69
0.1	73	502	1424	7
1.0	69	499	1421	0.7
10.0	69	498	1421	0.07

TABLE III

Lipid Tissue Half-Times over a Perfusion Spectrum

($S_p = 5$, $a^2/D_c = 9.456$ min)

Perfusion (ml/ml/min)	Tissue Half-Times (min)			
	$\alpha = \frac{1}{5}$	$\alpha = \frac{1}{10}$	$\alpha = \frac{1}{15}$	Haldane
0.0001	23,956	24,541	24,832	33,549
0.001	2397	2671	3439	3355
0.01	279	690	1608	335
0.1	91	522	1446	34
1.0	74	506	1430	3
10.0	73	505	1429	0.3

smoothly with the Hills half-time for large perfusion rates but diverges for small P. The most significant finding is that in the region $P \sim 0.01$ (muscle tissue) and $\alpha \sim \frac{1}{5}$, there is a zone where

(i) all three half-times are a similar order of magnitude,
(ii) the actual half-time is longer than the others.

In other words (i) implies that on a casual analysis it will be very difficult to decide whether perfusion or diffusion is dominant in regions where $P \sim 0.01$ and (ii) implies that in actual fact there is an interaction between perfusion and diffusion to create a longer half-time.

For smaller values of the vascularity, the effect begins to disappear and dif-

fusion dominates as to be expected. On the other hand it can be seen that even for large values of the perfusion, diffusion still controls the uptake half-time. This may at first seem surprising, however, it should be realized that those organs which have a large perfusion require this for metabolic reasons, and this effect has been ignored in this paper. Thus whilst increasing the perfusion by a large amount will not increase the half-time of the tissue for an inert gas, it will of course replenish depleted oxygen tension on high metabolic demand.

Two runs were tried using very low values of the diffusion time scale (0.001, 0.0001 min), and it is confirmed that the actual curve closely follows Haldane's curve as to be expected since this is the basis of the perfusion theory.

It will be noticed that for very low values of the perfusion the Haldane curve and actual curve are parallel. It is of interest to calculate this difference theoretically and compare with the numerical output.

As $P \to 0$, $\lambda \to 0$ and (25) degenerates to

$$\bar{p}(s) \sim \frac{\lambda}{1 + \mu} \frac{1}{s^2}.$$

Thus as $P \to 0$,

$$p(t) \to \frac{\lambda}{1 + \mu} t,$$

a constant rate of increase, as to be expected in cases where V is very low. On the basis of this equation, the actual half-time for very low values of the perfusion approaches

$$T_H = (1 + \mu)/(2\lambda),$$

which in dimensional units, and with $S_p = 1$, is

$$T_H = \tfrac{1}{2}P^{-1}.$$

The log of this term is to be subtracted from the log of the Haldane half-time given by (27) and the result is obviously

$$\log_{10} \log_e 4 = 0.1419,$$

which is in satisfactory agreement with the computed numerical inversion result of 0.1461. (The error is acceptable in that the half-time is very large, where the numerical method starts to yield poor results.)

9. Conclusion. It is seen that the Haldane solution is at best an asymptotically orientated technique which gives too high a half-time over a wide range of small perfusion, and too small a half-time for large P. It is only marginally correct in the interaction zone, which appears to be muscle tissue. On the other hand the Hills type diffusion approach is accurate for large perfusion rates but poor for

small perfusion zones. In general it is to be preferred to the Haldane approach, however.

At first sight, our model may appear to be too complicated to be of practical use (the Hills model likewise).

However, the program used to generate the solutions on a modern computer with adequate library software is quite short. It can thus be seen why the Haldane theory persisted for so many years. It is conceptually straightforward and computationally simple. If it fails to provide a good fit, simply "adjust" the half-time until the data curve gives a reasonable fit. Thus for example, Haldane employed five tissue half-times for his early decompression tables. Over the intervening years more and more half-times had to be invented to fit the facts. Today the U.S. Navy employ up to 14 half-times to provide oxy-helium decompression table predictions based on the Haldane perfusion theory. Clearly with so many parameters virtually *any* theory can be made to fit a data curve. Hills (1966) diffusion theory on the other hand requires only *two* parameters (the vascularity and diffusion time scale) to give a convincing analysis of decompression schedules for exposures to a pressure equivalent to 60 m sea depth.

It is suspected that to carry the validity of decompression calculations to greater depths, the third parameter, the perfusion, must be included as shown in this paper.

LITERATURE

Abramovitz, M. and I. A. Stegun (eds.). 1965. *Handbook of Mathematical Functions.* New York: Dover.

Bassingthwaite, J. B., T. J. Knopp and J. B. Hazelrig. 1970. "A Concurrent Flow Model for Capillary Tissue Exchange." In *Capillary Permeability,* Crone, N. and N. A. Lassen, eds. New York: Academic Press.

Bell, G. H., J. N. Davidson and H. Scarborough. 1961. *Textbook of Physiology and Biochemistry.* London: Livingstone.

Bellman, R., J. A. Jacquez and R. Kalaba. 1960. "Some Mathematical Aspects of Chemotherapy: I. One-Organ Models." *Bull. Math. Biophysics,* **22,** 181–198.

———, R. Kalaba and J.-A. Lockett. 1966. *Numerical Inversion of the Laplace Transform.* New York: American Elsevier.

Blum, J. J. 1960. "Concentration Profiles in and Around Capillaries." *Am. J. Physiol.,* **198,** 991–998.

Boycott, A. E., G. C. C. Damant and J. S. Haldane. 1908. "The Prevention of Compressed Air Illness." *J. Hygiene,* **8,** 342–443.

Carslaw, H. S. and J. C. Jaeger. 1959. *Conduction of Heat in Solids.* London: Oxford University Press.

Gonzalez-Fernandez, J. M. and S. E. Atta. 1968. "Transport and Consumption of Oxygen in Capillary-Tissue Structures." *Math. Bioscience,* **2,** 225–262.

——— and ———. 1972. "Concentration of Oxygen around Capillaries in Polygonal Regions of Supply." *Ibid.,* **13,** 55–69.

Haldane, J. S. See under Boycott, Damant and Haldane (1908).
Hansson-Mild, K. 1972. "Diffusion Exchange between a Membrane-Bounded Sphere and its Surrounding." *Bull. Math. Biophysics*, **34**, 93–102.
Harris, E. J. and G. P. Burn. 1949. "The Transfer of Sodium and Potassium Ions between Muscle and the Surrounding Medium." *Trans. Faraday Soc.*, **45**, 508–528.
Hennessy, T. R. 1971a. "Inert Gas Diffusion in Heterogeneous Tissue: I. Without Perfusion." *Bull. Math. Biophysics*, **33**, 235–248.
———. 1971b. "Inert Gas Diffusion in Heterogeneous Tissue: II. With Perfusion." *Ibid.*, **33**, 249–257.
———. 1973. Ph.D. Thesis, University of Cape Town.
Hills, B. A. 1966. *A Thermodynamic and Kinetic Approach to Decompression Sickness.* Adelaide: Libraries Board of South Australia.
———. 1967. "Diffusion Versus Blood Perfusion in Limiting the Rate of Uptake of Inert Non-Polar Gases by Skeletal Rabbit Muscle." *Clinical Sci.*, **33**, 67–87.
———. 1969. "The Time Course for the Uptake of Inert Gases by the Tissue Type responsible for Marginal Symptoms of Decompression Sickness." *Rev. Subaquat. Physiol.*, **1**, 255–261.
———. 1970a. "An Assessment of the Expression $C = \mathring{Q}[1 - \exp(-PS/\mathring{Q})]$ for Estimating Capillary Permeabilities." *Phys. Med. Biol.*, **15**, 705–713.
———. 1970b. "Vital Issues in Computing Decompression Schedules from Fundamentals: II. Diffusion Versus Blood Perfusion in Controlling Blood-Tissue Exchange." *Int. J. Biometeor.*, **14**, 323–342.
Johnson, J. A. and T. A. Wilson. 1966. "A Model for Capillary Exchange." *Am. J. Physiol.*, **210**, 1299–1303.
Kety, S. S. 1951. "The Theory and Applications of the Exchange of Inert Gas at the Lungs and Tissues." *Pharm. Rev.*, **3**, 1–41.
Krogh, A. 1919a. "The Number and Distribution of Capillaries in Muscles with Calculations of the Oxygen Pressure Head Necessary for Supplying Tissue." *J. Physiol.*, **52**, 409–415.
———. 1919b. "The Supply of Oxygen to the Tissues and the Regulation of the Capillary Circulation." *Ibid.*, **52**, 457–474.
———. 1936. *The Anatomy and Physiology of Capillaries.* New Haven: Yale University Press.
Levitt, D. G. 1971. "Theoretical Model of Capillary Exchange Incorporating Interactions between Capillaries." *Am. J. Physiol.*, **220**, 250–255.
Luke, Y. 1969. *The Special Functions and Their Approximations.* Vols. I and II. New York: Academic Press.
Morales, M. F. and R. E. Smith. 1944. "On the Theory of Blood-Tissue Exchanges: III. Circulation and Inert-Gas Exchanges at the Lung with Special Reference to Saturation." *Bull. Math. Biophysics*, **6**, 141–152.
——— and ———. 1945a. "A Note on the Physiological Arrangement of Tissues." *Ibid.*, **7**, 47–51.
——— and ———. 1945b. "The Physiological Factors which Govern Inert Gas Exchange." *Ibid.*, **7**, 99–106.
——— and ———. 1948. "On the Theory of Blood-Tissue Exchange of Inert gases: VI. Validity of Approximate Uptake Expressions." *Ibid.*, **10**, 191–200.
Norden, H. 1961. "Numerical Inversion of the Laplace Transform." *Acta Acad. Aboensis Math. et Phys.*, **22**, (8), 1–31.
Perl, W. 1962. "Heat and Matter Distribution in Body Tissues and the Determination of Tissue Blood Flow by Local Clearance Methods." *J. Theor. Biology*, **2**, 201–235.
———. 1963. "An Extension of the Diffusion Equation to Include Clearance by Capillary Blood Flow." *Ann. N.Y. Acad. Sci.*, **108**, 92–105.

Perl, W., H. Rackow, E. Salanitre, G. L. Wolf and R. M. Epstein. 1965. "Inter-tissue Diffusion Effect for Inert Fat-soluble Gases." *J. Appl. Physiol.*, **20**, 621–627.

Piessens, R. 1972. "A New Method for the Inversion of the Laplace Transform." *J. Inst. Maths. Applics.*, **10**, 185–192.

Reneau, D. D., D. F. Bruley and M. H. Knisely. 1969. "A Digital Simulation of Transient Oxygen Transport in Capillary Tissue Systems." *A.I.Ch.E. Journal*, **15**, 916–925.

Roughton, F. J. W. 1952. "Diffusion and Chemical Reaction Velocity in Cylindrical and Spherical Systems of Physiological Interest." *Proc. Roy. Soc. B*, **140**, 203–221.

Sangren, W. C. and C. W. Sheppard. 1953. "A Mathematical Derivation of the Exchange of a Labelled Substance between a Liquid Flowing in a Vessel and an External Compartment." *Bull. Math. Biophysics*, **15**, 387–394.

Schmidt, G. W. 1952. "A Mathematical Theory of Capillary Exchange as a Function of Tissue Structure." *Ibid.*, **14**, 229–263.

———. 1953. "The Time Course of Capillary Exchange." *Ibid.*, **15**, 477–488.

Smith, R. E. and M. F. Morales. 1944a. "On the Theory of Blood Tissue Exchanges: I. Fundamental Equations." *Ibid.*, **6**, 125–132.

——— and ———. 1944b. "On the Theory of Blood Tissue Exchanges: II. Applications." *Ibid.*, **6**, 133–139.

Taylor, G. I. 1953. "Dispersion of Soluble Matter in Solvent Flowing slowly through a Tube." *Proc. Roy. Soc. A* **219**, 186–203.

Teorell, T. 1937. "Kinetics of Distribution of Substances Administered to the Body: I. The Extra-Vascular Modes of Administration." *Arch. internat. Pharmacodyn. et Thérap.*, **57**, 205–224.

Thews, G. 1953. "Über Die Mathematische Behandling Physiologischer Diffusion Prozesse in Zylinderförmigen Objekten." *Acta Biotheoretica*, **10**, 105–137.

von Schrotter, H. 1906. "Der Sauerstoff in der Prophylaxe und Therapie der Luft druckerkrankungen." In *Handbuch der Sauerstofftherapie*, Michaelis M., ed., Berlin: Hirschwald. Cited by Kety (1951).

Zuntz, N. 1897. "Zur Pathogenese und Therapie der durch rasche Luftdruckanderungen erzeugten Krankheiten." *Fortschr. d. Med.*, **15**, 632–639. Cited by Kety (1951).

RECEIVED 8-6-73
REVISED 5-8-74