BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

THE PHYSIOLOGICAL FACTORS WHICH GOVERN INERT GAS EXCHANGE

LT. (J.G.) MANUEL F. MORALES, AND
LT. ROBERT E. SMITH, H(S), USNR*
NAVAL MEDICAL RESEARCH INSTITUTE, NATIONAL NAVAL MEDICAL CENTER,
BETHESDA, MARYLAND

The decay constants (k_j) of the equation of inert gas exchanges are the roots of an algebraic equation of degree $n + 1$, where n is the number of distinct absorbing tissues. The coefficients of this equation can be obtained numerically by certain independent experiments to measure the tissue parameters. Graphical solution of this equation yields theoretical values of the k_j. Combining these constants with the numerical values for the partial derivatives of the k_j then gives the per cent rate of change of the k_j as any one tissue parameter varies by a given fraction of its normal range. A numerical example of these calculations shows good conformity with experiment, and permits a quantitative estimate of variations in the speed of gas exchange from a knowledge of changes in the physiological state.

A central problem in aereo- and submarine physiology is the control of the rate of inert gas exchange in such a way that personnel do not develop the "bends" or "chokes". For either selection or therapeutic purposes it is therefore indispensable to know the factors which govern the exchange and the effectiveness of each. The following is an attempted solution of the problem based on an elementary mathematical analysis which we have presented elsewhere (Smith and Morales, 1944a, 1944b; Morales and Smith, 1944).

Tissue regions (Figure 1), of which the entire body is a distinct parallel arrangement,[1] absorb[2] inert gases in a manner described by the equation:

* The opinions expressed in this article are the private ones of the writers, and are not to be construed as reflecting the policies of the Navy Department or the Naval Service at large.

[1] We have shown elsewhere (Morales and Smith, 1945) that tissues may be arranged in three essentially distinct ways, of which this is one. The other two arrangements predict the loss of two exponentials at a time when the number of distinct absorbing tissues is reduced by one. Under similar circumstances, with a competitive parallel arrangement, only one exponential should be lost. As A. Behnke pointed out in personal communication, the use of helium is practically tantamount to reducing the number of distinct tissues by one, and helium exchange can be described by *one* less exponential than the exchange of nitrogen or krypton. This fact, plus the evidence alluded to later, forms the basis for our choice of arrangement.

[2] Or, with suitable changes in the boundary conditions, desorbs.

$$\phi(t) = \phi(\infty) - Q_0 e^{-k_0 t} - Q_1 e^{-k_1 t} - \cdots - Q_n e^{-k_n t} \qquad (1)$$

where $\phi(t)$ is the amount of gas taken up to time t, and $\phi(\infty)$ is the asymptotic (steady state) amount; n is the number of tissues, and the Q's and the k's are constants depending on the physiological state of the limb and the properties of the gas.

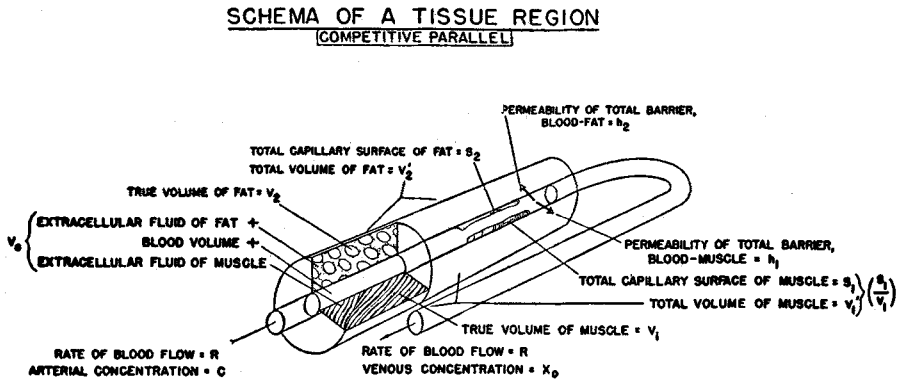

FIGURE 1

We consider that the parameters of the phenomenon are the following quantities:

R[cm^3 sec^{-1}] = rate of blood flow through the limb,
V_0[cm^3] = total amount of fluid outside of cells, including the blood volume,

and for the ith tissue:

α_i = concentration in blood/concentration within cells, at equilibrium.
h_i[cm sec^{-1}] = cell membrane permeability,
V_i[cm^3] = total cellular volume,
$\frac{S_i}{V_i}$ [cm^{-1}] = capillary surface/gross volume of tissue.

It is furthermore convenient to define the function,

$$\pi_i = \alpha_i h_i \frac{S_i}{V_i}.$$

Now it has been shown by several authors (Underwood and Diaz, 1941; Jones, 1941; Smith and Morales, 1944b) that equation (1) taken as a purely empirical fit, describes gas exchange data with remark-

able precision. This is true in particular of measurements of radioactive inert gas exchange by various tissue regions (Lawrence-Jones technique), to which we will turn presently. In such a procedure the decay constants, k_j, can be most conveniently determined by graphical analysis on arith-log paper. The order of magnitude of such constants is therefore well established. On the other hand, the parameters listed above can all be measured or estimated independently of gas absorption experiments (*vide infra*). When the values of these parameters are incorporated into the equations, the *theoretical* values of the k_j may be computed. It is proposed here to demonstrate the theoretical determination of decay constants, to show a favorable comparison with empirically obtained values, and finally to consider the effect of varying the physiological state on the decay constants, hence on the speed of inert gas exchange.

Values of the k_j are determined by [Smith and Morales, 1944a, equation (9)]:

$$V_0 k_j + \sum_{i=1}^{i=n} \frac{h_i S_i k_j}{\pi_i - k_j} - R = 0, \tag{2}$$

the left member of which is a polynomial of degree $n + 1$. In mammalian systems the number (n) of absorbing tissues is practically two, i.e., a tissue region is composed of aqueous tissue, fat, and bone, the last being essentially non-absorbing.

Clearing equation (2) of fractions for the special case, $n = 2$, we obtain

$$k_j^3 - \frac{(\pi_1 + \pi_2) V_0 + \pi_1 \frac{V_1}{\alpha_1} + \pi_2 \frac{V_2}{\alpha_2} + R}{V_0} k_j^2 + \frac{\pi_1 \pi_2 \left(V_0 + \frac{V_1}{\alpha_1} + \frac{V_2}{\alpha_2} \right) + R(\pi_1 + \pi_2)}{V_0} k_j - \frac{R \pi_1 \pi_2}{V_0} = 0, \tag{3}$$

where the subscripts 1 and 2 denote aqueous tissue and fat respectively. On substitution of values for the tissue parameters equation (3) becomes a numerical cubic, which on graphical solution gives three decay constants, k_0, k_1, k_2.

We may now differentiate equation (3) partially and obtain,

$$\begin{aligned}
\frac{1}{k_j}\frac{\partial k_j}{\partial R} &= \frac{\omega_j}{k_j}, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial (h_s S_s)} &= \frac{\omega_j k_j}{(\pi_s - k_j)^2}, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial \alpha_s} &= \omega_j V_s \left(\frac{\pi_s/\alpha_s}{\pi_s - k_j}\right)^2, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial V_0} &= -\omega_j, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial V_s} &= -\frac{\omega_j}{\alpha_s}\left(\frac{\pi_s}{\pi_s - k_j}\right)^2,
\end{aligned} \tag{4}$$

with

$$\omega_j \equiv \frac{1}{V_0 + \sum_{i=1}^{i=n} \frac{V_i}{\alpha_i}\left(\frac{\pi_i}{\pi_i - k_j}\right)^2} > 0$$

corresponding to the per cent changes in the k_j for cgs unit change in a tissue parameter. These derivatives need only be corrected in a physiological sense in order to answer fully the problem we proposed to solve. By this we mean, for example, that a change of 1 cm^3 in volume of muscle is manifestly not the physiological equivalent of a change of 1 cm^3 sec^{-1} in rate of blood flow. We may, however, make these changes comparable by finding the per cent change in the k_j's when tissue paramters vary by, say, 10% of their normal range. Multiplying the differential coefficients by such factors then gives the final desired result.

The methods for obtaining values of the tissue parameters are various, and will be considered in order.

The average rate of blood flow over a three hour period can of course be measured by a water or air plethysmograph.[3]

The total amount of fluid which is outside of the cells is the sum of three contributions: (1) The true *blood volume,* which can be approximated as being equal to the volume change of a limb in passing from a very cold to a warm environment. (2) The *free-space of muscle.* Since Cl^{-1} does not penetrate muscle cells, any "chloride space" method (Fenn, 1936) gives the free space fraction for muscle. This value (18%) can also be checked theoretically, assuming quasi-close packing of cylindrical muscle fibers. The free space fraction

[3] The cgs dimensions for flow are cms^3 sec^{-1}, but in mammalian physiology it is customary to express blood flow in cubic centimeters of blood per 100 cubic centimeters of tissue.

times the total volume then gives the free space. (3) The *free space of fat.* Since the chloride method has not been shown to be applicable to fat tissue for the reason that, unlike the situation in muscle, the Cl^{-1} may be absorbed by the cells, recourse was sought in the value for the theoretical free space fraction of close packed ellipsoids, which can be shown to be 26%.[4] Again, this fraction times the total volume yields total free space.

The partition coefficients can be measured directly (Loomis, 1941).

The ratio of capillary surface/volume of tissue was judged from the work of I. Gersh and M. A. Still (1945), with due allowance for the differences which can be expected to exist in the human hand.

The plasma membrane permeabilities probably involve the greatest error of all of these determinations, since for virtually all systems they are known little more than by the order of magnitude. The computations of H. D. Landahl (1939) show oxygen permeability to be of the order of 10^{-5} cm sec^{-1}. Furthermore, the data of F. M. Müller (1941) and of others (see *International Critical Tables*) show that the permeabilities of oxygen and krypton are probably very similar. Guided by Professor S. C. Brooks' opinion that fat cells may have a higher h for krypton than do muscle cells, we have tentatively assumed 2×10^{-5} and 1×10^{-5} respectively as the krypton plasma membrane permeabilities of fat tissue and muscle.

It will be noted that when dealing with surface, we have spoken about *capillary* surface, while in dealing with permeability we have used *plasma membrane* values. This we feel is justified because the physiological behavior of the gross barrier will be governed by the limiting factors which go to make it up.[5] If such is the case, then certainly the limiting surface is that of the capillaries, and the limiting permeability that of the plasma membrane.

The total volumes were estimated from roentgenographs of hands.

Use of the foregoing techniques can be illustrated by a case of absorption of radioactive krypton by the hand. When measurements

[4] This is based on a simple generalization of the calculation which leads to the same values for close-packed spheres. In histological section, fat cells appear compressed, hence not subject to being treated as rigid ellipsoids; however, a number of observations by Ens. Mary Still and one of us (MFM) were enough to show that surviving fat cells in isotonic solution are truly arranged in the hexagonal lattice of rigid ellipsoids.

[5] This can be easily shown analytically by solving the transfer problem for a double barrier. If the permeability of the first membrane and the surface of the second are assumed to be much greater than the corresponding quantities for the other membrane, then the problem degenerates to one of transfer across a membrane having the lower permeability and the smaller surface.

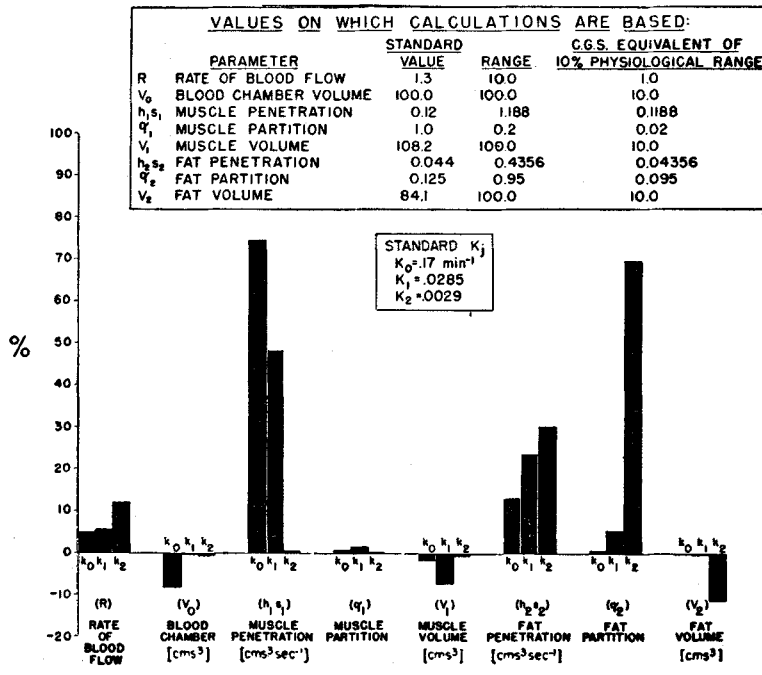

FIGURE 2

of subject C.J.S. (tabulated in Figure 2) are substituted into equation (3), we obtain,

$$k_j^3 - (3.37582 \times 10^{-3})\, k_j^2 + (1.519354 \times 10^{-6})\, k_j - (.06643 \times 10^{-9}) = 0\,,$$

whose graphical solution appears in Figure 3. On the other hand, when we substitute the values into the partial derivatives (4) and

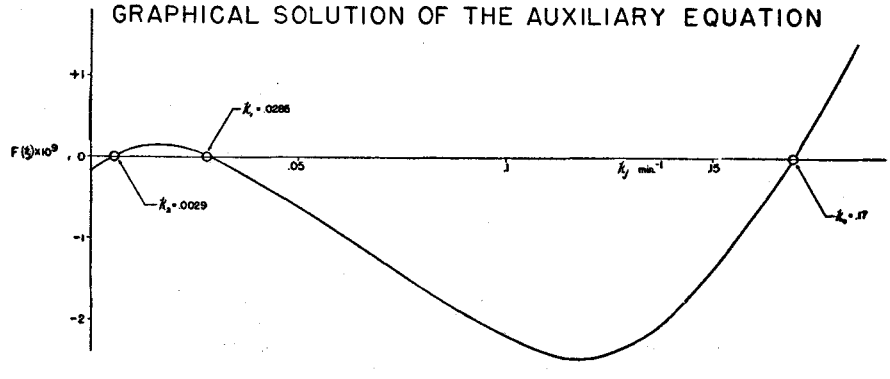

FIGURE 3

correct for range, we obtain the per cent changes (Figure 2) induced in the k_j (hence on the speed of exchange) by changes in the physiological state, *quod erat faciendum.*

Let us now see how justified we are in accepting our results by examining the comparison between experiment and independent prediction.

1. Since in calculating the k_j we have at least on two occasions been obliged to use values which were certain only up to an order of magnitude, we may reasonably require only that the theoretical and empirical decay constants agree up to an order of magnitude. This is certainly the case:[6]

	Empirical	Theoretical
k_0	.11	.17
k_1	.058	.03
k_2	.02	.003

We suppose that it would be improbable indeed that ten reasonable values assumed for ten independent quantities should yield reasonable answers by sheer accident.[7]

2. Not only is the theoretical form (exponential sum) the best fitting empirical expression, but also the predicted number of exponentials ($n + 1 = 2 + 1 = 3$) turns out empirically to be the best number.

3. It will appear below that the size, direction, and nature of the theoretically deduced partial derivatives is in good accord with what one would expect on physiological grounds and/or on the basis of experiment.

The three foregoing observations we have taken to favor the acceptance of our equation (1), and hence to warrant the consideration of the derivatives in Figure 2 as expressing approximately the effectiveness of various influences in governing the speed of inert gas exchange. Study of these derivatives permits the following remarks:

1. The early stages of absorption are governed chiefly by the state of the blood, the intercellular fluid, and the charactertstics of

[6] It has been customary in this field to express decay constants in min^{-1}; we have therefore converted from cgs units.

[7] Where comparison is possible our empirical values are well within the range obtained by others. Since the left member of equation (3) is continuous for $k_j \neq \pi_i$, we can be sure that normal deviations of physiological values from the standards we have assumed will lead to decay constants which themselves remain within the normal range. The interesting ordering relationship between the k_j and π_i has itself important applications (3, 5).

aqueous tissue (e.g., muscle), in the sense that these are the influences to which k_0 is most susceptible.

2. The later stages of absorption are governed chiefly by the interaction of the gas with fatty tissue. Thus the smaller the amount of fat, the greater the fat solubility, or the greater the fat permeability, then the more rapidly will the absorption be terminated, for these are the influences to which k_2 is most susceptible.

3. Both conclusions 1 and 2 can be reached without the untenable concept formerly held that each exponential was determined solely by the constant of one type of tissue.

4. Experimental procedures designed to affect one or another of the physiological parameters could eventually lead to a rather fine control of the absorption curve.

LITERATURE

Fenn, W. O. 1936. "Electrolytes in Muscle." *Physiol. Rev.*, 16, 450-487.

Gersh, L., and M. A. Still. 1935. "Blood Vessels in Fat Tissue. Relation to Problems of Gas Exchange." *Jour. Exp. Med.*, 81, 219-232.

Jones, H. B. 1941. (*unpublished*)

Landahl, H. D. 1939. "Mathematical Biophysics of Cell Respiration: II." *Bull. Math. Biophysics*, 1, 1-17.

Loomis, F. 1941. (*unpublished*)

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.

Morales, M. F., and R. E. Smith. 1945. "A Note on the Physiological Arrangement of Tissue." *Bull. Math. Biophysics*, 7, 47-51.

Müller, F. H. 1941. "The Diffusion of Gases through Highly Polymerized Materials. A Simple Apparatus for Measuring the Diffusion of Gases through Foils." *Physik. Zeits.*, 42, 48-53.

Smith, R. E., and M. F. Morales. 1944a. "On the Theory of Blood-Tissue Exchanges: I. Fundamental Equations." *Bull. Math. Biophysics*, 6, 125-131.

Smith, R. E., and M. F. Morales. 1944b. "On the Theory of Blood-Tissue Exchanges: II. Applications." *Bull. Math. Biophysics*, 6, 133-139.

Underwood, N., and J. T. Diaz. 1941. "A Study of the Gaseous Exchange between the Circulatory System and the Lungs." *Amer. Jour. Physiol.*, 133, 88-95.