THE THEORY AND APPLICATIONS OF THE EXCHANGE OF INERT GAS AT THE LUNGS AND TISSUES[1]

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The respiratory and circulatory systems of the higher animals constitute a single homeostatic complex whose chief function is the maintenance of an optimal molecular concentration of oxygen and carbon dioxide about each cell. This is accomplished by a highly effective combination of physical diffusion and transport together with reversible chemical reactions. The process of diffusion, which alone is sufficient for the metabolic exchange of unicellular organisms, operates in higher animals only across the microscopic spaces between the blood and pulmonary alveoli or peripheral cells. Between the lungs and the body tissues the molecules of gas are transported by the circulating blood in physical solution and, in the case of oxygen and carbon dioxide, in loose chemical combination with certain blood constituents.

The relative magnitudes and time relationships of these various processes are not obvious in the steady state of metabolic exchange. They become apparent, however, when a new molecular species is introduced into the atmosphere which the organism breathes, and, if the new substance happens to be an inert gas, its behavior in the organism may be explained and predicted on the basis of relatively simple physical laws. For the purpose of this discussion an inert gas will be defined as one which dissolves in the blood and tissues in a manner that can be described by Henry's Law, which suffers no change in chemical identity during its passage through the organism, and which is therefore quantitatively recoverable from the organism at any time (54, 105). This definition would include those volatile anesthetic agents which are not chemically altered in the body even though they produce definite physiological effects.

When an inert gas in abruptly introduced at a constant partial pressure into the inspired air, the tissues of the body do not suddenly acquire the gas at this partial pressure. A number of physical processes intervene, each with its own time rate of change, to delay the eventual saturation of the tissues. First, by means of pulmonary ventilation the gas is inspired, diluted with the functional residual air and distributed to the alveolar membrane. Here diffusion occurs and alveolar gas is equilibrated with pulmonary blood which is then distributed via the peripheral arteries to the individual tissues. A second diffusion step now occurs across the capillary membrane, interstitial fluid and cellular membrane and through the intracellular fluid itself. The venous blood from all the tissues returns to the lungs carrying some fraction of its original gas concentration which is thus contributed to the equilibration process occurring at the alveoli. In this manner the alveolar, arterial, tissue and venous tensions of the inert

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gas in question gradually rise toward eventual equilibrium with the tension inspired. Although this sequence of processes is fairly obvious, no single mathematical theory has hitherto been elaborated which embraces them all.

Study of the manner in which inert gases are taken up and released by the body has important implications in many different fields. Perhaps the earliest interest was aroused by the problem of caisson disease (9, 19, 104, 133) in which it soon became apparent that the cause and treatment of the disease lay in the factors governing the saturation and desaturation of body tissues with atmospheric nitrogen during sudden and severe changes in ambient pressure. Similar problems have more recently been encountered in aviation medicine (5). The advent of scientific anesthesiology soon led to a realization of the importance of the solubilities of anesthetic gases and the relationship of physiological factors to the rates of induction and recovery. Since physiological parameters such as alveolar ventilation, functional residual capacity, cardiac output, and blood flow to different tissues determine various phases of inert gas exchange, analysis of certain of those specific phases may be made to yield quantitative information concerning the physiological constants themselves.

THEORY

The Physiological Parameters

At the outset it is necessary to formalize the anatomical and physiological factors involved in inert gas exchange, so that an aggregation of millions of separate processes occurring at microscopic levels in the lung or in a tissue may be represented by a single average process taking place uniformly and simultaneously throughout that system. A certain amount of this type of simplification is essential if there is to be any hope of mathematical treatment of the processes involved. The usefulness and applicability of the theory finally derived, however, depend inversely upon the number of simplifications introduced.

Previous authors, in their mathematical treatments, have employed different symbols for the various factors; in order to avoid confusion it appears worthwhile to adopt some standard system of symbols for the following discussion, and to express the derivations of previous authors in the same system. The author has chosen the following to conform, wherever possible, to the system adopted by the Committee on the Standardization of Symbols used in Respiratory Physiology. The following primary symbols represent certain generic factors: V, a volume; P, a pressure; C, a concentration; M, a volume flow of gas per minute; F, a volume flow of blood per minute; Q, an amount; λ, a partition coefficient; D, a diffusion constant; R, a ratio; S, a surface. These primary symbols are modified by the following subscripts: A, alveolar; E, expired; I, inspired; D, dead space; T, tidal; s, shunt; i, a particular tissue; a, arterial; v, venous; b, blood; p, pulmonary. Specific combinations of these symbols and their physiological definition are discussed in the immediately succeeding paragraphs.

Ventilation

This process, although it is obviously cyclic, has been treated as a continuous function by most of those who have taken it into consideration. The inaccuracy

thus introduced is hardly of consequence except where the events occurring in a single breath or in time intervals of a few seconds are being treated. Where interest is confined to the ventilatory process itself it is usually more convenient to represent the process as a series of instantaneous breaths. In this discussion wherever ventilation is taken to be a continuous function, the minute rate of alveolar ventilation (ml. of air washed through the total alveolar volume per minute) will be represented by M_A, the ventilation of the respiratory functional dead space by M_D, and the sum of these by M, the total rate of ventilation (ml./min). In conformity with previous practice inspired air is divided into that fraction remaining unchanged in the physiological dead space and that portion which mixes completely with alveolar gas. Where ventilation is treated as a cyclic process V_T will represent the tidal volume (ml), V_D the physiological dead space (ml) and V_T the effective tidal volume ($V_T - V_D$).

Of considerable importance is that volume of gas (V_A) in the lungs within which each functional tidal volume is ultimately distributed. For the cyclic process this is simply the end inspiratory alveolar gas volume and corresponds to the functional residual capacity[2] (41) plus the effective tidal volume. When ventilation is treated as a continuous process the volume of distribution of inspired gas (V_A) can be shown to correspond closely to the functional residual capacity plus one half the effective tidal volume (*i.e.*, the mid-inspiratory alveolar gas volume).

Blood Flow

The inspired inert gas is not only mixed with alveolar gas but is also distributed into the functional pulmonary blood flow (F_p, ml./min). This represents the portion of the cardiac output which is effectively exposed to alveolar gas. The remaining portion (F_s) represents mixed venous blood shunted past the alveoli through intracardiac communications or unventilated portions of the lung. This normally represents an insignificant fraction of the cardiac output (80) but in certain diseases may assume great importance.

The total left ventricular output (F) is now distributed to the various tissues of the body in a system of parallel circuits, blood flow through a particular tissue being represented by F_i. The liver is a notable exception to the parallel circuit description, as Morales and Smith (91) have pointed out, and represents an organ interposed in series between the abdominal viscera and the heart.

The venous outflow from each tissue, which is assumed to be equal to the arterial inflow, is now mingled with that of all the others and returned to the heart as the mixed venous blood. The concentration of any stable substance in mixed venous blood is therefore the average of its respective concentrations in the venous blood from the several tissues, each weighted by a factor $\left(\frac{F_i}{F}\right)$. Since some tissues are closer to the heart than others, the venous bloods from different tissues are represented in the mixed venous blood at the heart with some degree of time staggering (90). Thus blood from the myocardium may complete its

[2] Functional residual capacity is defined as the total gas volume in the lungs and respiratory dead space at the end of a normal expiration.

circuit back to the right atrium perhaps twenty or thirty seconds sooner than blood from the toes. Where the time periods under theoretical consideration are of the order of many minutes or hours such a time difference in arrival is probably not important and has usually been neglected. It assumes greater significance, however, when events at the very onset of inert gas uptake are to be examined. The time interval between the outflow of blood from the lungs and the first appearance of that blood in the mixed venous return to the lung is an important and controversial point in some methods for measuring cardiac output.

Solubility and Partition Coefficients

Since an inert gas will distribute itself in the various phases (air, blood, tissues), at equilibrium, according to its respective solubility in each, such physical constants constitute important parameters in the exchange process. Solubility of gases in liquids has usually been expressed in two alternative manners. The Bunsen solubility coefficient (α) represents the amount of a particular gas, expressed as ml. reduced to standard temperature and pressure (0°, 760 mm Hg), which is dissolved at complete equilibrium in 1 ml. of a particular liquid when equilibrium has occurred at a specified temperature and a partial pressure for the particular gas of 760 mm Hg. Henry's Law has been shown to apply to the blood solubility of several of the inert gases (50, 61, 109) and probably applies to all (*i.e.*, concentration of gas in liquid is proportional to its partial pressure). The Bunsen coefficient, therefore, yields directly the amount of gas dissolved by 1 ml. of liquid after equilibration at any partial pressure (P) as $\frac{\alpha P}{760}$. The Ostwald solubility coefficient (λ) (sometimes designated α') is similar to the Bunsen coefficient except that the volume of gas dissolved in 1 ml. of liquid is not converted to standard temperature. Thus λ is also the partition coefficient of the gas between the liquid and gas phase after equilibration at any pressure, *i.e.*, λ represents the ratio of the equilibrium concentration of the inert gas in the liquid (expressed in any units) to its concentration in the gas phase (expressed in the same units). It is easily shown that when a quantity of an inert gas Q_x dispersed in another gas is equilibrated with a volume (V_b) of a liquid, the final concentration of x in the liquid will be $\frac{\lambda Q_x}{\lambda V_b + V_a}$ and in the gas phase $\frac{Q_x}{\lambda V_b + V_a}$ where V_a is the final volume of the gas phase and λ the particular partition coefficient. This concept is important in describing inert gas exchange at the lungs. Since both α and λ for a particular gas:liquid system vary with temperature, the particular temperature must be stated; throughout this discussion, unless otherwise noted, values for these coefficients are at 37° C. These two coefficients are related to each other at any temperature (t) as follows:

$$\alpha_t = \lambda_t \left(\frac{273}{t + 273} \right) \tag{1}$$

Another partition coefficient describes the ratio at equilibrium between the concentration of a particular gas in a certain tissue and its concentration in the blood. Throughout this discussion, unless otherwise noted, λ will refer to the blood:gas partition and λ_i to a tissue:blood partition. Values for these coefficients for the different gases have been obtained by numerous investigators and are summarized in Table I. The values for blood:gas partition in general

TABLE I

*Values for partition coefficients at 37°–38° C. of some inert gases**

GAS	WATER / GAS	BLOOD / GAS	TISSUE / BLOOD	OIL / WATER
Hydrogen	0.018 (79)			3.1 (79)
Helium	0.0097 (79)	0.0098 (61)		1.7 (79)
Nitrogen	0.0144 (125)	0.0147 (125)	brain 1.1 (24) liver 1.1 (24) fat 5.2 (21)	5.2 (123)
Argon	0.0295 (79)			5.3 (79)
Neon	0.011 (79)			
Krypton	0.051 (79)			9.6 (79)
Xenon	0.097 (79)			20.0 (79)
Radon	0.17 (79)			125 (79)
Ethylene	0.089 (50)	0.140 (50)	brain 1.2 (60) heart 1.0 (60)	14.4 (98)
Nitrous Oxide	0.440 (109)	0.466 (71) 0.473 (97) 0.474 (109)	brain 1.0 (71) heart 1.0 (38)	3.2 (98)
Cyclopropane	0.204 (98)	0.457 (98)		35.0 (98)
Acetylene	0.850 (50)	0.795 (119) 0.842 (50)		
Divinyl ether	1.32 (103)			41.3 (103)
Chloroform	4.6 (89a)	7.3 (89a)	brain 1.0 (94, 122) liver 0.9 (94)	110 (87)
Ethyl ether	15.5 (53)	15.0 (53) 14.9 (107) 14.4 (65)	brain 1.14 (56)	3.2 (98)
Acetone		333 (130)		

* Parenthetical figures are references to the literature.

agree well with those for water:gas. This is largely fortuitous and results from the fact that the solubility of most gases is higher in the erythrocyte and lower in plasma (13, 87, 96, 109, 125), the solubility in water lying between the two. For this reason some investigators have found the blood:gas partition to vary with the percentage of red cells in the blood (71, 125). There are comparatively few values for the solubility of gases in tissues probably because of the technical difficulties involved in their determination. Those which are tabulated have been obtained *in vivo* after equilibration of the whole animal or *in vitro* by the use of finely divided tissue. It is interesting to note that except for adipose tissues the tissue:blood partition coefficients are close to unity.

Diffusion Processes and Diffusion Coefficients

The diffusion process has been assigned roles of varying importance in the exchange of foreign substances, from a practically exclusive one (120) to one of insignificance (64). For an exhaustive discussion of diffusion processes in biological systems the reader is referred to the excellent review by Jacobs (63). Stated in mathematical terms, Fick's law of diffusion in its most general sense is,

$$dQ = -DS \frac{\partial C}{\partial x} dt \tag{2}$$

where dQ represents the amount of a substance diffusing in time dt across a plane of area S under an instantaneous concentration gradient $\frac{\partial C}{\partial x}$ and D is the diffusion coefficient for the substance at a definite temperature in a definite medium; its units are cm^2 per unit of time.

This general equation may be solved to yield useful values for specific geometrical systems or boundary conditions. Since the solution itself depends to a great extent upon the boundary conditions assumed for the system under examination, these particular assumptions become of great importance.

Perhaps the simplest assumption which can be made for the lung or the tissues is to consider diffusion as occurring in parallel streams across a membrane where the concentrations on each side of the membrane, though different and variable with time are uniform at any instant. Such a treatment would apply to the situation in which two aqueous compartments, whose contents were continuously and perfectly stirred, were separated by a watery membrane. In such a situation the diffusion process would take place only within the membrane itself and if the membrane were sufficiently thin (of the order of 10 μ) a steady state of diffusion would almost instantly (Jacobs, p. 63) ensue which would be described by the following particular solution of Fick's equation:

$$\frac{dQ_1}{dt} = -\frac{DS}{H}(C_1 - C_2) \tag{3}$$

that is, the rate of loss of the diffusing substance from the compartment of higher concentration (C_1) would be equal to the specific diffusion coefficient for the substance in the material of the membrane multiplied by the ratio of the area to the thickness (H) of the membrane and multiplied by the concentration difference between the compartments.

This situation is somewhat more complicated where the two compartments may contain different solvents, and the membrane substance itself may constitute still a third phase. Consider first the most complicated system where the two compartments contain different solvents and where the solubility of the gas in question is different in each of the two solvents and in the membrane. Since diffusion occurs only within the membrane the values for concentration in equation 3 refer to the concentration in the membrane and not in the com-

partments. Now in the face of the membrane exposed to compartment 1 the concentration is $\lambda_1 C_1$ where λ_1 represents the $\frac{\text{membrane}}{\text{solvent 1}}$ partition coefficient for the gas. Similarly the concentration of gas in the face of the membrane exposed to compartment 2 is $\lambda_2 C_2$ where λ_2 is the $\frac{\text{membrane}}{\text{solvent 2}}$ partition coefficient. Equation 3 then becomes,

$$\frac{dQ_1}{dt} = -\frac{DS}{H}(\lambda_1 C_1 - \lambda_2 C_2) \tag{4}$$

In some cases it is more convenient to think in terms of gradients of partial pressure rather than concentration, especially where different phases are involved. Here if P_1 and P_2 be the partial pressure of inert gas on either side of the membrane, then immediately adjacent to compartment 1 the membrane will have a concentration $\frac{\alpha P_1}{760}$ and adjacent to compartment 2 the membrane concentration will be $\frac{\alpha P_2}{760}$, α being the Bunsen solubility coefficient for the gas in the membrane. Equation 3 then becomes,

$$\frac{dQ_1}{dt} = -\frac{DS}{H}\left(\frac{\alpha P_1}{760} - \frac{\alpha P_2}{760}\right) = -\frac{DS\alpha}{H\,760}(P_1 - P_2) \tag{5}$$

Thus from equation 5 the diffusion rate of a gas from the gaseous state through a membrane is directly proportional to its solubility in the membrane. Therefore carbon dioxide, although its diffusion coefficient is lower, diffuses much more rapidly than does oxygen through the pulmonary membrane since its solubility in the membrane solvent (presumably water) is nearly twenty-five times as great.

Values of D in dilute aqueous solutions have been determined for many gases (62); these diffusion coefficients for hydrogen, nitrogen, oxygen and carbon dioxide at temperatures near 20° C are, respectively, 5.2, 2.0, 1.98 and 1.77 $\times$ 10^{-5} cm^2 per second. Krogh (73) found that diffusion coefficients increased approximately by 1% per degree in the region from 0° to 36° C. The coefficients for diffusion through some body tissues have been determined in the case of a few gases (73) (132); they were found to be one third to two thirds their values in water. Recently a beginning has been made in determining coefficients of other gases in living tissues (111); there is need for further work along such lines.

In the treatment of diffusion in the tissues as occurring across a membrane, usually assumed to be that of the capillary, the surface area of this membrane becomes of great importance. This area has been estimated in various tissues from data obtained by several investigators employing injection technics (29, 34, 45, 74, 75, 76, 110, 126). Such studies give quite accurately the number of capillaries open during the injection; the functional surface, however, must be

inferred by means of an assumption as to capillary diameters during life. Table II summarizes some of these findings and deductions.

The treatment of diffusion at the tissues as if it occurred only across the capillary membrane into a tissue chamber of spatially uniform concentration has the advantage of simplicity if not verisimilitude. It is perfectly apparent that concentration gradients must exist within the tissue itself during inert gas exchange and it is only by taking them temporarily, at least, into consideration that their importance in the diffusion process may be realized. But in order to take them into consideration one must decide upon some geometrical model of

TABLE II

Capillary density, capillary surface, and maximum diffusion distance in various tissues, from the data of different investigators

TISSUE	SPECIES	REF.	CAPILLARY DENSITY no. per mm²	CAPILLARY SURFACE cm²/cm³	MAXIMUM DIFFUSION DISTANCE μ
Muscle	frog	76	400	190	28
Muscle	horse	76	1400	240	15
Muscle	dog	76	2600	590	11
L. ventricle	human	126	5730	1090	8
R. ventricle	human	126	5680	1080	8
Vent. septum	human	126	4450	850	8
Papillary muscle	human	126	5220	990	8
Heart muscle	mouse	110	5300	1000	8
Cerebral cortex	human	29	1000	190	18
Cerebral cortex	mouse	110	1250	240	16
Cefebellum	mouse	110	1700	330	14
White matter	human	29	300	57	33
Adipose:					
Fat-rich	rat	45	274	52	34
Fat-poor	rat	45	1000	222	18
Liver	mouse	110	4200	800	9
Duodenum	mouse	110	2400	460	11
Pancreas	g. pig	110	1900	360	13
Renal cortex	mouse	110	4500	850	8
Renal medulla	mouse	110	7400	1400	7

the relationship of capillaries to tissue. One possibility is to consign to each capillary a cylinder of tissue equal in length to that of the capillary and with a volume equal to that of the tissue divided by the number of capillaries (12, 74). On the basis of such a model, governing equations and boundary conditions may be set up (93) and solutions eventually achieved. Such a model might be satisfactory if all the capillaries were disposed in parallel and oriented so that all the arterial ends were on one side. Where the arrangement is more or less random with the arterial end of one cylinder adjacent to the venous end of another there would be gradients not only within but also between the cylinders, introducing almost hopeless complexity into an attempt at mathematical treatment. A relatively simple first approximation may be to consider diffusion as occurring

radially from the capillary in only two dimensions and to calculate the length of time for the attainment of a specified degree of equilibrium between the average concentration in the tissue and an assumed constant concentration in the capillary (31). Such a treatment is much closer to the truth than the theory of linear diffusion across a membrane since it assumes radial diffusion and includes the tissue in the diffusion process. Copperman (31) has obtained a series of solutions for the general diffusion equation on this basis and in terms of available tissue parameters. This was accomplished by solving the radial diffusion equation,

$$\frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} = \frac{1}{D}\frac{\partial C}{\partial t} \tag{6}$$

with initial conditions: $r = a, C = C_0, a < r \leq R, C = 0$, and with boundary conditions: $r = R, \frac{\delta C}{\delta r} = 0$. For a mean tissue concentration 95% of the final value the exact expression for the time t becomes,

$$\frac{4}{R^2 - a^2} \sum_k \frac{1 - e^{-Dk^2 t}}{k^2 \left\{ \left[\frac{R}{a} \frac{V_0(kR)}{V_0'(ka)} \right]^2 - 1 \right\}} = 0.95 \tag{7}$$

where $V_0(k r) = Y_0(k a) J_0(k r) - J_0(k a) Y_0(k r)$ and where k is given by $V_0'(k R) = 0$. J_0 and Y_0 are the zero order Bessel functions of the first and second kind, respectively. Only the first term in the series is needed for calculation of t. In Table III are presented values for the time in seconds necessary to achieve 95% equilibrium throughout a tissue region of radius R from a capillary of radius $a (= 2.5\ \mu)$ for substances of different diffusion coefficients. Solubility is assumed to be uniform throughout the system. From an examination of the maximum diffusion distances in the various tissues presented in Table II it is apparent that for most tissues and most inert gases, blood:tissue equilibrium, according to this theory, would be nearly complete in about one second.

THE THEORETICAL APPROACH

Since interest was first aroused in this problem there have been only a few mathematical treatments proposed for the description of inert gas behavior in the body. Some of these are highly theoretical, but a large number are frankly empirical, represent merely a formula which best fits the data obtained and have little theoretical justification. The reviewer will attempt to point out in each case the assumptions made, the mathematical results, and their general applicability.

A.) Zuntz (1897), von Schrötter (1906). This theory was apparently first developed by Zuntz (133) and later amplified by von Schrötter (104) to explain the uptake of nitrogen by the body when exposed to an increase in ambient pressure. These authors made the following assumptions. (i) The inspired concentration of nitrogen is immediately transmitted to the alveoli; they therefore

neglected the phase of lung washout. In this special case of exposure to increased ambient pressure, such an assumption is perfectly permissible since the alveolar gas is also compressed and increases in nitrogen concentration along with the inspired air. (ii) The alveolar and arterial nitrogen concentrations remain constant following their instantaneous arrival at the new level. In this they neglected the continuous removal of some alveolar nitrogen by the pulmonary blood flow, which, because of the low solubility of nitrogen in blood, introduces little appreciable error. (iii) The circulation was visualized as a somewhat discontinuous function in which the entire blood volume is equilibrated instantaneously in the lung at the new nitrogen tension, then instantaneously equilibrated with all the body tissues simultaneously. The nitrogen-poor venous blood, representing the mean nitrogen tension of the whole body, is now re-equilibrated at the ambient nitrogen tension in the lungs and the process is repeated until the tissues approximate this tension. Thus, if the blood volume, as they assumed, were 1/11th of

TABLE III

Approximate time in seconds for 95% equilibrium between tissue region of radius R and capillary of radius 2.5 μ for a substance of diffusion coefficient through the tissue of D

$D \times 10^5$	$R = 15\ \mu$	$R = 30\ \mu$	$R = 50\ \mu$
1.0	0.4	2.3	8.3
1.5	0.2	1.5	5.5
2.0	0.2	1.2	4.2
2.5	0.1	0.9	3.8
3.0	0.1	0.7	2.8

the nitrogen capacity (tissues + blood) of the body, then in each circulation the tissues would go 1/11th of the way remaining toward complete saturation, and thus describe a logarithmic function. A serious compromise, however, lies in the treatment of the whole body as a single tissue phase equilibrated uniformly with arterial blood so that at all times the nitrogen concentration is uniform throughout all tissues. In reality, as Boycott, Damant and Haldane (19) have pointed out, each tissue has access only to a particular quota of arterial blood and increases in nitrogen concentration at a rate which may be quite at variance with that of another tissue with a different blood flow. This fact does not alter the exponential form of the solution which still remains as the fundamental basis of modern theories; it is necessary, however, to increase the number of terms to embrace these differences among tissues. (iv) No difference in the solubility of nitrogen in blood or in tissues was assumed; this can readily be adjusted by the inclusion of an appropriate partition coefficient. (v) The assumption that complete equilibrium is reached almost instantaneously between a tissue and its blood so that the tension of nitrogen in the tissue is equal to that in its venous blood implies that diffusion is not a limiting factor in this process and also that all the blood flow through a tissue partakes in the equilibration (that is, that there are no arteriovenous shunts). Although the latter assumption

may be justified by considering only effective blood flow, no evidence was offered to indicate that diffusion at the tissue is indeed a process rapid enough to be considered instantaneous. A similar assumption has been made by subsequent authors (55, 64) and evidence is being accumulated which may eventually justify it (31, 64).

von Schrötter's actual equation is not nearly so useful as the concepts which Zuntz had previously elaborated. On the basis of these fundamental assumptions, plus the Fick principle (40), it is possible to derive a more generally applicable expression for inert gas uptake by a single tissue. For an inert gas the Fick principle may be stated as follows—the amount of inert gas taken up by the tissue per unit of time is equal to the quantity brought to the tissue by the arterial blood minus the quantity carried away in the venous blood, *i.e.*,

$$\frac{dQ_i}{dt} = F_i(C_a - C_v) \tag{8}$$

assuming that arterial inflow = venous outflow = F_i, and defining a tissue to include its contained blood which constitutes only a few per cent of its total volume (V_i).

Also,

$$\frac{dC_i}{dt} = \frac{1}{V_i}\frac{dQ_i}{dt} = \frac{F_i}{V_i}(C_a - C_v) \tag{9}$$

Now from Zuntz' basic assumption that venous blood from a tissue is in equilibrium with the tissue itself with respect to inert gas, then at all times,

$$C_i = \lambda_i C_v \tag{10}$$

λ_i being a specific partition coefficient for the inert gas in question between tissue (including its contained blood) and blood. From equations 9 and 10 is obtained,

$$\frac{dC_i}{dt} = -\frac{F_i}{\lambda_i V_i}(C_i - \lambda_i C_a) \tag{11}$$

which, if C_a, and therefore $\lambda_i C_a$, are constant, has the following solution for the saturation process:

$$C_i = \lambda_i C_a(1 - e^{-kt}) \quad \text{where} \quad k = \frac{F_i}{\lambda_i V_i} \tag{12}$$

and for the desaturation process:

$$C_i = C_{i_0} e^{-kt} \tag{13}$$

where C_{i_0} is the concentration at the onset of desaturation. From equation 10 similar expressions for C_v are obtained:

$$C_v = C_a(1 - e^{-kt}), \quad \text{for saturation} \tag{14}$$

$$C_v = C_{v_0} e^{-kt}, \quad \text{for desaturation} \tag{15}$$

Thus, on the basis of instantaneous diffusion equilibrium between blood and tissue and with a constant arterial concentration of an inert gas, the concentration in a particular tissue will rise toward its equilibrium value as a single exponential function, with a time constant equal to the blood flow through the tissue divided by the relative capacity of that tissue for the inert gas. Since in reality the body consists of n tissues each with an uptake implicit in equation 11:

$$Q_i = V_i C_i = V_i \lambda_i C_a (1 - e^{-k_i t}) \tag{16}$$

the total amount in the body as a whole (Q) for the saturation process is given by:

$$Q = C_a[V_1\lambda_1(1 - e^{-k_1 t}) + V_2\lambda_2(1 - e^{-k_2 t}) + \cdots + V_n\lambda_n(1 - e^{-k_n t})]$$

$$= Q_{\infty 1}(1 - e^{-k_1 t}) + Q_{\infty 2}(1 - e^{-k_2 t}) + \cdots + Q_{\infty n}(1 - e^{-k_n t}) \tag{17}$$

(where the $Q_{\infty i}$ are the quantities of the inert gas in each tissue at complete saturation $= C_a V_i \lambda_i$)
and for the desaturation process, by,

$$Q = Q_1^0 e^{-k_1 t} + Q_2^0 e^{-k_2 t} + \cdots + Q_n^0 e^{-k_n t} \tag{18}$$

where the Q_i^0 are the quantities of the inert gas in each tissue at the onset of desaturation. Since the total quantity eliminated (Q_E) from the body up to any time t must equal the difference between the total quantity present at zero time and the total quantity present at time t,

$$Q_E = Q_0 - Q_t = (Q_1^0 + Q_2^0 + \cdots + Q_n^0) - (Q_1^0 e^{-k_1 t} + Q_2^0 e^{-k_2 t} + \cdots + Q_n^0 e^{-k_n t})$$

$$= Q_1^0(1 - e^{-k_1 t}) + Q_2^0(1 - e^{-k_2 t}) + \cdots + Q_n^0(1 - e^{-k_n t}) \tag{19}$$

B.) Widmark (1919). The Zuntz-von Schrötter assumptions and the above expressions which the reviewer has derived from them are rigorously applicable only to a state in which the alveolar and arterial concentrations of an inert gas are constant throughout the duration of saturation or desaturation, that is, to a gas of infinitesimal solubility in blood introduced abruptly and at its final concentration into the alveolar spaces. Such a treatment is, therefore, of only limited value in the general problem of inert gas exchange. Widmark (130), on the other hand, derived a relatively simple expression for the elimination (and therefore also the uptake) of inert gases by the body, which is applicable only to gases of extremely great solubility in blood. This author concerned himself especially with the elimination of acetone, the blood:air partition coefficient of which he reported as 333. Because of this preponderant solubility in blood, Widmark could reasonably assume in the case of this gas that in one passage through the lungs the blood loses so little acetone that the concentration in arterial blood is practically identical with that in mixed venous blood. He also assumed that the elimination was sufficiently slow so that the tension of acetone in the blood was always equal to that in the tissues. On the basis of these two assumptions, plus the concept that at the lungs the alveolar air was

brought into equilibrium with pulmonary blood, he set up the following differential equation for the elimination of acetone at the lungs:

$$\frac{dQ_x}{dt} = -\frac{M_A C_b}{\lambda} = -\frac{M_A Q_x}{\lambda V_x} \tag{20}$$

where M_A represents alveolar ventilation rate; Q_x, the total quantity of acetone in the body; C_b, the blood concentration; and V_x, the acetone space or the volume of distribution of acetone in the body. Equation 20 may be solved to yield:

$$Q_x(t) = Q_{x_0}e^{-kt} \quad \text{or} \quad C_b(t) = C_{b_0}e^{-kt} \tag{21}$$

where $k = \frac{M_A}{\lambda V_x}$

Similarly for saturation at a constant inspired concentration C_I:

$$C_b(t) = \lambda C_I(1 - e^{-kt}) \tag{22}$$

Widmark determined blood acetone concentration during the desaturation process in man and animals and demonstrated a single exponential decay for acetone. He also found, however, that even in the case of a soluble gas like ether ($\lambda = 14.9$), the resulting curve could not be described in terms of a single exponential. Thus Widmark's treatment is of very limited usefulness and is valid only for gases of inordinately high solubility in blood.

C.) Haggard (1924). This theory was elaborated to explain the uptake and elimination of ethyl ether by the body (55). It embraces three of the Zuntz-von Schrötter assumptions (i) that there is a single body tissue mass with a uniform blood flow; (ii) that λ_i is unity; for this particular assumption Haggard obtained empirical data (total quantity absorbed, total weight of the animal, and blood concentration of ether) which appeared to substantiate an average λ_i near unity (54), but possible differences among tissues were neglected; (iii) that there is complete equilibrium between blood and tissue and also between blood and alveolar gas.

In addition, Haggard introduced an important new concept into his theory, one which appears to have been neglected by most subsequent authors. Dealing with a highly soluble gas, he realized that its alveolar concentration would not immediately equal the concentration inspired, but would rise slowly toward that asymptote as the body tissues and venous blood became saturated. Zuntz, who confined his attention to nitrogen could neglect that important fact without making his theory wholly inapplicable; but any mathematical treatment designed to explain the behavior of all inert gases must include this important concept of Haggard.

Haggard treated the ventilation as continuous and recognized and corrected for the respiratory dead space. He then proceeded in a manner reminiscent of Zuntz to treat the phenomena in a discontinuous manner. In the first minute

of inhalation of ether at a constant inspired concentration (C_I), the arterial concentration of ether is given by,

$$C_a = \frac{M_A C_I \lambda}{\lambda F + M_A} \tag{23}$$

(In this he neglected dilution of C_I by the functional residual air and assumed that all the cardiac output (F) is equilibrated with alveolar gas.) The quantity of ether absorbed in one minute (Q_1') is,

$$Q_{1'} = FC_a = \frac{FM_A C_I \lambda}{\lambda F + M_A} \tag{24}$$

The quantity of ether exhaled in the first minute ($Q_{E_1'}$) is,

$$Q_{E_1'} = M_A C_I - Q_{1'} = \frac{M_A^2 C_I}{\lambda F + M_A} \tag{25}$$

Assuming that there is a time of one circulation, it would be V_b/F minutes; therefore the quantity of ether absorbed in the first circulation (Q_1) is obtained from equation 24:

$$Q_1 = V_b C_a = \frac{V_b M_A C_I \lambda}{\lambda F + M_A} \tag{26}$$

This quantity is now, after the manner of von Schrötter, equilibrated with all the tissues of the body ($V_n + V_b$); therefore the amount remaining in the blood and brought back to the lungs at the end of the first circulation (Q_{v_1}) is,

$$Q_{v_1} = \left(\frac{M_A C_I \lambda V_b}{\lambda F + M_A}\right)\left(\frac{V_b}{V_n + V_b}\right) = \frac{M_A C_I \lambda V_b^2}{(\lambda F + M_A)(V_n + V_b)} \tag{27}$$

Now in the second circulation, the quantity of ether carried away from the lungs (Q_2) equals the quantity inhaled plus the recirculated quantity (Q_{v1}) distributed between the total blood and air and multiplied by the outflow of blood:

$$Q_2 = \left[\frac{M_A C_I V_b}{F} + \frac{M_A C_I \lambda V_b^2}{(\lambda F + M_A)(V_n + V_b)}\right]\frac{\lambda F}{\lambda F + M_A} \tag{28}$$

This concluded Haggard's formal analysis. He then stated that this process repeated indefinitely is one in which the body, in equal intervals of time, goes a constant fraction of the way toward full saturation. This is the form of a single exponential rise so that Haggard's conclusion is the same as von Schrötter's: $Q = Q_\infty(1 - e^{-kt})$.

Haggard's derivation, although fairly adequate for ether, contains an important oversimplification which precludes its general applicability to any inert gas. Equation 28 neglects the quantity of ether remaining in the lungs at the end of the first circulation and therefore treats the lungs as collapsing com-

pletely at each expiration. In the case of a gas as soluble in blood as is ether, little indeed remains in the residual air and this neglect of the pulmonary dilution phase of inert gas exchange introduces only a slight error. This error becomes increasingly great, however, as the inert gas in question decreases in solubility. Even on the assumption of a single tissue phase made by both Zuntz and Haggard, rigorous treatment must yield an expression containing at least two exponential terms determined by tissue *and* lung dilution. It is interesting to note that each of these authors obtained a single exponential by neglecting lung dilution for reasons quite different, and, in each specific and quite limited application, almost justifiable.

Haggard's derivation, however, permitted him to draw the following important conclusions regarding the uptake of ether and other inert gases: (i) The shape of the curve of saturation vs. time for the body is independent of C_I. (ii) From equation 24 he demonstrated that rate of uptake is proportional to $\frac{M_A}{\lambda F + M_A}$ if M_A alone changes, and therefore for very soluble gases (λ large) the rate of absorption is practically proportional to ventilation. For relatively insoluble gases, he pointed out, this dependence on ventilation decreases. (iii) From the same equation he concluded that rate of uptake is proportional to $\frac{\lambda F}{\lambda F + M_A}$ if F alone changes, and, therefore for very soluble gases the rate of uptake is relatively independent of F, becoming increasingly dependent as λ decreases.

D.) Teorell (1937). This author developed a mathematical theory to describe the kinetics of distribution of substances injected into the body (120, 121). He was not directly concerned with the distribution of inhaled gases and none of his derivations is directly applicable to this problem. His point of view, however, must be taken into consideration since it stands in direct antithesis to that of Zuntz. Whereas the latter neglected the diffusion process as a limiting factor in blood:tissue exchange, attributing the rate entirely to circulation, Teorell considered diffusion to be the sole determinant in this exchange and did not include circulation in his derivation. His differential equation for transfer from tissue depot to blood has the form,

$$\frac{dQ_i}{dt} = -k'\left(\frac{Q_i}{V_i} - C_b\right) = -\frac{k'}{V_i}Q_i = -kQ_i \qquad (29)$$

with the assumption that C_b can be neglected. k' represents a permeability coefficient including the diffusion constant for the substance as well as membrane surface and thickness, so that the solution : $Q_i = Q_0 e^{-kt}$ is independent of blood flow. Teorell offered no empirical justification for excluding this important parameter and it is difficult to reconcile his concept with the observation (67) that removal of Na^{24} from an injection site is quite sensitive to local circulation and with the even more cogent results of Jones (64) who found identical values for k of two gases of widely differing diffusion constants.

E.) Morales and Smith (1944–48). These authors have made the most ex-

haustive analysis to this date of the theory of inert gas exchange. In a series of papers (90, 91, 92, 93, 112, 113) they have treated practically all aspects of the problem by a fairly complete mathematical analysis. Their basic approach is perhaps best illustrated by their most recent publication (93) which treats the exchange problem at a single homogenous tissue. With few simplifying assumptions they have set up the following differential equations for the quantities of gas (Q_b) in the blood compartment of a tissue and in the tissue volume itself (Q_i):

$$\frac{dQ_b}{dt} = V_b \frac{dC_b}{dt} = F_i(C_a - C_v) - D_iS_i(C_b - C_i/\lambda_i) \tag{30}$$

$$\frac{dQ_i}{dt} = V_i \frac{dC_i}{dt} = D_iS_i(C_b - C_i/\lambda_i) \tag{31}$$

where D_i is a permeability coefficient for the particular gas and the particular membrane and S_i is the area of the diffusion interface. This treats diffusion as occurring across a definite membrane into a tissue space of uniform concentration C_i.

To evaluate C_b, the mean concentration in tissue capillary blood, they have assumed that it is some constant fraction between C_a and C_v, *i.e.*, $C_a - C_b = r(C_a - C_v)$, and substitute appropriately in equation 30 to get,

$$V_b \frac{dC_b}{dt} = \frac{F_i}{r}(C_a - C_b) - D_iS_i(C_b - C_i/\lambda_i) \tag{32}$$

Equations 31 and 32 are simultaneous differential equations in C_b and C_i and may be solved for each. In order to do this conveniently they have assumed a constant arterial concentration. The solution for C_i is especially pertinent:

$$C_i = \frac{Q_i}{V_i} = \lambda_i C_a(1 + A_1 e^{k_1 t} - A_2 e^{k_2 t}) \tag{33}$$

where $A_1 = \dfrac{k_2}{k_1 - k_2}$ $\qquad$ $A_2 = \dfrac{k_1}{k_1 - k_2}$

and k_1 and k_2 =

$$-\frac{1}{2}\left[\frac{F_i}{V_b r} + \frac{D_iS_i}{V_b}\left(1 + \frac{V_b}{\lambda_i V_i}\right)\right] \pm \frac{1}{2}\left\{\left[\frac{F_i}{V_b r} + \frac{D_iS_i}{V_b}\left(1 + \frac{V_b}{\lambda_i V_i}\right)\right]^2 - \frac{4F_iD_iS_i}{\lambda_i V_b V_i r}\right\}^{\frac{1}{2}} \tag{34}$$

Thus Morales and Smith, by taking into consideration both blood flow and diffusion in a homogenous tissue, have arrived at an expression for inert gas uptake which contains two exponential terms instead of the single exponential of Zuntz-von Schrötter or Teorell. In an effort to determine whether one of their exponential terms is physically negligible they have reviewed some of the data

of others, seeking reasonable values for the physiological parameters in particular tissues (93) and concluding that "whereas in certain cases the von Schrötter approximation might be quantitatively justifiable, in others it would be very poor indeed". They have justifiably insisted upon their more rigorous treatment of the blood:tissue exchange, at least until better evidence is obtained for its simplification.

In another paper (91) Morales and Smith have shown that, where the tissues of the body can be assumed to exist as a distinct parallel arrangement each with its own blood supply, the content of inert gas in the body as a whole at any time t during saturation may then be given by the expression,

$$Q = Q_\infty - \sum_{i=1}^{i=n} (A_{i,1}\, e^{-k_{i,1}t} + A_{i,2}\, e^{-k_{i,2}t}) \tag{35}$$

where, as is to be expected from equation 33, there are two exponential terms for each tissue and the A's and k's are determined solely by the physiological parameters of that tissue. In the same communication they have derived an expression for inert gas uptake for tissues in series in which the venous blood from one tissue supplies a succeeding tissue with blood. This also leads to a sum of exponentials where the number of exponential terms is twice the number of tissues, where the decay constants are peculiar to the individual tissue, but where the coefficients are determined by the parameters of all the tissues in series:

$$Q = Q_\infty - \sum_{s=1}^{s=n} (A_{s,1}\, e^{-k_{s,1}t} + A_{s,2}\, e^{-k_{s,2}t}) \tag{36}$$

This type of arrangement is seen to an important extent only in the portal circulation through the liver.

In the first paper of the series (112), Smith and Morales derived an expression for inert gas uptake for a limb on the assumption that there is in the limb a single blood chamber supplying all the tissues which remove the inert gas in a competitive manner. It is not unexpected, perhaps, that this assumption leads to a solution in the form of a series of exponential terms of one more than the number of tissues, all of the coefficients and decay constants being determined by the parameters of all the tissues:

$$Q = Q_\infty - \sum_{j=0}^{j=n} A_j\, e^{-k_j t} \tag{37}$$

It is the opinion of this reviewer that this treatment is needlessly cumbersome and no closer to physiological reality than the distinct parallel system, since individual tissues do in general have their own capillary network and any slight admixture of tissues (*e.g.*, fat cells among muscle fibers) may be taken into account reasonably well in mean parameters for the tissue as a whole.

Morales and Smith have also attempted a mathematical analysis of inert gas exchange at the lung (90). Starting with the drastically limiting assumption that at the instant of the first breath the alveolar concentration is suddenly

increased to its final constant value, they derived a set of expressions for four stages of the pulmonary exchange process. Stage (a) persists only for as long a time as the blood spends in the lungs and during this time the partial pressure of the inert gas in the blood is rising exponentially toward that in the alveoli. Stage (b) extends from the end of stage (a) to stage (c), the onset of which is marked by the first return of venous blood containing the inert gas to the lung. Stage (d) begins when the region with the longest roundtrip circulation time just begins to contribute to the venous return to the lung and continues through the remainder of the saturation process. Since this treatment neglects the phase of dilution of inspired air with residual air, and all the ventilatory parameters as well, and neglects the depletion of alveolar gas by carriage of inert gas from the lung in the pulmonary venous blood and the consequent rise of alveolar and arterial blood concentrations as a function of mixed venous concentration, it is applicable only to the special case treated by Zuntz of an insoluble inert gas (N_2) forced into the lung by a sudden increase in ambient pressure or to the special case in which the inspired concentration can be made to vary in order to keep the alveolar concentration constant. It is apparent that the limiting assumptions of this treatment are such as to prevent its applicability generally to the pulmonary exchange of many inert gases.

F.) Kety (1949). This reviewer has had occasion to resort to inert gas exchange theory in the past several years in an effort to comprehend the physiological factors involved in the uptake of nitrous oxide by the arterial blood. Several hundred such curves had been obtained over the early periods of saturation for quite a different purpose (66). It was, however, apparent that the arterial curve varied with important physiological parameters and it seemed desirable to obtain an expression which would demonstrate this relationship. Since all the existing theories save Haggard's assumed a constant arterial concentration and Haggard's treatment was incomplete, it was necessary to develop a theory (70) which comprehended inert gas exchange at the lung.

If the inhaled concentration of an inert gas (C_I, mg./ml.) is held constant and alveolar ventilation is treated as a continuous process represented by M_A (ml./min.), then in a short time (dt), $M'\ dt\ C_I$ mg. of gas are delivered to the alveoli and $M'\ dt\ C_A$ mg. are removed from the alveoli by ventilation. By means of the pulmonary blood flow (F_p ml./min.), $F_p\ dt\ C_v$ mg. of inert gas are delivered during the same time to the alveoli in the mixed venous blood and $F_p\ dt\ C_p$ mg. are removed in the pulmonary venous blood (C_v and C_p representing concentrations of inert gas in mg./ml. in mixed venous and pulmonary venous blood, respectively) thus,

$$\frac{dQ_A}{dt} = V_A\frac{dC_A}{dt} = M_A(C_I - C_A) + F_p(C_v - C_p) \tag{38}$$

This equation neglects the quantity of gas which dissolves in the tissue and blood of the alveolus unless one defines V_A to include not only the alveolar air but also the blood and tissue present in the alveolus with an appropriate partition

coefficient correction (*i.e.*, $V_A = V_{air} + \lambda V_{tissue + blood}$). Recent work indicates that for CO_2 this "phantom" residual air is equivalent to an average of 0.7 l. of blood (37).

If one assumes diffusion equilibrium between alveolar gas and pulmonary venous blood then $C_p = \lambda C_A$, where λ is an appropriate partition coefficient. If one is not willing to make such an assumption, another relationship can be obtained by employing a derivation similar to that of Bohr (14): Let C_b represent the variable blood concentration of inert gas along a pulmonary capillary of length L, and x a variable distance along the capillary. Further, let s' and v' represent the diffusion surface and the capillary blood volume, both per unit length of capillary, f the average linear velocity of blood in the capillary, and D' the diffusion coefficient per unit area for the gas across the alveolar membrane. Now assume that the concentration in the gas phase (C_A) is uniform from one end of the capillary to the other.

As an element of blood moves in the capillary from x through dx, it takes up a quantity of gas according to the law of diffusion through a membrane:

$$dQ_b = D's'dx(\lambda C_A - C_b)dt \tag{39}$$

which is also equal to the gain in concentration in the blood (dC_b) multiplied by the volume of blood under consideration ($v'dx$). But $dx = fdt$, whence,

$$dC_b v'fdt = - D's'dx(C_b - \lambda C_A)dt$$

and,

$$\frac{dC_b}{dx} = - \frac{D's'}{v'f}(C_b - \lambda C_A) \tag{40}$$

whence

$$(C_b - \lambda C_A)_x = (C_b - \lambda C_A)_0 e^{-(D's'/v'f)x} \tag{41}$$

At $x = o$, $C_b = C_v$; at $x = L$, $C_b = C_p$, therefore,

$$C_p - \lambda C_A = (C_v - \lambda C_A)e^{-(D's'/v'f)L} = (C_v - \lambda C_A)e^{-(D'S/F)} \tag{42}$$

where $\frac{S}{F}$ is the ratio of diffusion surface to volume flow of blood for the capillary or the lung as a whole. From equation 42 it is readily shown that

$$C_v - C_p = \theta(C_v - \lambda C_A) \tag{43}$$

where $\theta = 1 - e^{-\frac{D'S}{F}}$ and is probably close to 1 under most circumstances.

The value of $(C_v - C_p)$ obtained in equation 43 may now be substituted in equation 38 to yield:

$$\frac{dC_A}{dt} = \frac{M_A}{V_A}C_I - \frac{M_A + F_p\theta\lambda}{V_A}C_A + \frac{F_p\theta}{V_A}C_v \tag{44}$$

For the case of saturation with an inert gas where at $t = o$, $C_A = C_v = o$, the following solution is obtained,

$$C_A = A_1 C_I(1 - e^{-kt}) + A_2 e^{-kt} \int C_v e^{kt}\, dt \quad . \tag{45}$$

where $A_1 = \dfrac{M_A}{M_A + F_p\theta\lambda}$ $\qquad A_2 = \dfrac{F_p\theta}{V_A}$ $\qquad k = \dfrac{M_A + F_p\theta\lambda}{V_A}$

Equation 45 represents only a partial solution for the alveolar concentration in terms of physiological parameters since the mixed venous concentration (C_v) remains undefined. It is useful, however, in explaining the differences among the uptake curves of different gases (69) and in assigning appropriate weights to the pulmonary parameters, and it has a certain heuristic value in suggesting means for determining some of the constants involved.

In order to define the arterial concentration (C_a) with close adherence to physiological reality, it is necessary to consider the possibility of venous to arterial shunts by-passing the alveoli. If the ratio of effective pulmonary blood flow (F_p) to total cardiac output (F) be designated as R_p then it is apparent that

$$C_a = R_p C_p + (1 - R_p) C_v \tag{46}$$

which, combined with equation 37 yields,

$$C_a = R_p\theta\lambda C_A + (1 - R_p\theta) C_v \tag{47}$$

When extra alveolar shunts and diffusion limitation become negligible, equation 47 reduces to $C_a = \lambda C_A$ which should be subject to experimental demonstration. It is interesting that in the case of a single inert gas (as opposed to oxygen (80)) the effect of an extra alveolar shunt would be indistinguishable from that of a diffusion barrier, although the two could be differentiated by employing two gases with markedly different diffusion coefficients. In such a case θ would be different but R_p the same for the two.

Since mixed venous concentration (C_v) in equation 45 remains undefined and since it obviously represents the weighted sum of the venous concentrations from all the separate tissues, it is important now to discuss blood:tissue exchange. A special case of this exchange (the clearance of injected sodium ion from a tissue depot) has previously been published (67); a more general derivation, however, is desirable. The Fick principle, applied to a particular tissue (i), yields as before (equation 8) the equation,

$$\frac{dQ_i}{dt} = V_i \frac{dC_i}{dt} = F_i(C_a - C_{v_i})$$

On Zuntz' assumption that diffusion equilibrium is instantaneous, it has been shown that this reduces to a single exponential expression for C_i. It is now proposed to take the diffusion process into consideration in the manner previ-

ously employed at the lung. The assumption is now made that there is some mean tissue concentration of inert gas (C_i) which remains constant during the passage of blood from the arterial to the venous end of the capillary. Since the capillary volume represents less than 5% of the volume of most tissues, marked changes in the blood concentration along the capillary would be reflected in only a slight change in mean tissue concentration. In a manner exactly analogous to that used at the lung the following relationship can be shown to exist for $C_a - C_{v_i}$:

$$C_a - C_{v_i} = m_i(C_a - C_i/\lambda_i) \qquad \text{where } m_i = 1 - e^{-(D_i' S_i/F_i)} \tag{48}$$

which substituted into equation (8) yields,

$$\frac{dC_i}{dt} = \frac{m_i F_i}{V_i \lambda_i}(\lambda_i C_a - C_i) \tag{49}$$

which has the following special solutions:
If C_a is constant and positive (saturation process),

$$C_i = \lambda_i C_a(1 - e^{-k_i t}) \tag{50}$$

If C_a is constant and zero (desaturation process),

$$C_i = C_{i_0} e^{-k_i t} \qquad \text{where } k_i = \frac{m_i F_i}{V_i \lambda_i} \tag{51}$$

These solutions are the same as those derived previously (equations 12 and 13) for similar cases from Zuntz' assumptions except that the k_i now includes a diffusion dependent factor (m_i). This result is to be contrasted with the two term exponential of equation 33 obtained by Morales and Smith by means of a more rigorous derivation. The loss of one exponential term resulted from the assumption that changes in mean tissue inert gas concentration, during the time of passage of an element of blood through the tissue, were negligible in comparison with the concentration change occurring in the blood itself. Although less exact than the expression of Morales and Smith, equations 44 or 45 may be more useful if this assumption can be justified for any particular tissue. Experimental data obtained in two tissues at least (muscle and liver) appear to fit the single exponential form (67, 127), and it is suggested that this less rigorous treatment may be adequate. Where the arterial concentration is variable with time, which unfortunately is often the case, the respective solutions for equation 49 are somewhat more complicated:
For saturation,

$$C_i = \frac{m_i F_i}{V_i} e^{-k_i t} \int C_a e^{k_i t}\, dt \tag{52}$$

For desaturation

$$C_i = C_{i_0} e^{-k_i t} + \frac{m_i F_i}{V_i} e^{-k_i t} \int C_a e^{k_i t}\, dt$$

In a manner similar to that employed at the lung it is possible to set up expressions for C_v assuming the presence of some degree of arterial to venous shunting of blood. Let R_i represent the ratio of effective capillary flow through the tissue to the total capillary plus shunt flow and $C_{v'}$, the resultant venous concentration, then clearly,

$$C_{v_i}' = R_i C_{v_i} + (1 - R_i)C_a$$

whence, from equation 48,

$$C_{v_i}' = R_i \frac{m_i}{\lambda_i} C_i + (1 - R_i m_i)C_a \tag{53}$$

which, in the absence of tissue arteriovenous shunts and with instantaneous diffusion ($R_i = 1 = m_i$) resolves to $C_{v_i} = C_i/\lambda_i$.

Now it is apparent that mixed venous blood entering the lung is a weighted average of the venous blood from the several tissues, so that, neglecting the time stagger mentioned previously,

$$C_v = \frac{F_1}{F} C_{v_1}' + \frac{F_2}{F} C_{v_2}' + \cdots + \frac{F_n}{F} C_{v_n}' \tag{54}$$

so that by means of equations 52 and 53 mixed venous blood has been defined in terms of tissue parameters and arterial blood and by equations 45 and 47 arterial blood has been defined in terms of cardiorespiratory parameters and mixed venous blood. If it were possible to eliminate the blood concentration variables common to both expressions it should be possible to arrive at an expression for the complete lung:blood:tissue exchange of an inert gas entirely in terms of physiological parameters. It is possible to do this to a degree of verisimilitude and, unfortunately, of complexity which is dependent only on the number of assumptions made. The simplest solution is achieved by assuming, with Zuntz, that all the body tissues comprise a single homogeneous tissue mass (V_T) regarding blood flow and gas solubility, and further that equilibrium between alveolar gas and arterial blood and between blood and tissue is complete and, finally, that the blood:tissue partition for the inert gas in question is unity. On the basis of these assumptions m_i and λ_i drop out of equation 49, $C_i = C_v$ and $F_i = F = F_p$. The simultaneous differential equations 38 and 49 now give the following solution for the saturation process:

$$C_A = C_I(1 - A_1 e^{-k_1 t} - A_2 e^{-k_2 t}) \tag{55}$$

where,

$$k_1 \text{ and } k_2 = \frac{1}{2}\left\{\frac{M_A + \lambda F}{V_A} + \frac{F}{V_T} \pm \left[\left(\frac{M + \lambda F}{V_A} + \frac{F}{V_T}\right)^2 - \frac{4M_A F}{V_A V_T}\right]^{\frac{1}{2}}\right\}$$

$$A_1 = \frac{M_A/V_A - k_2}{k_1 - k_2} \qquad A_2 = 1 - A_1$$

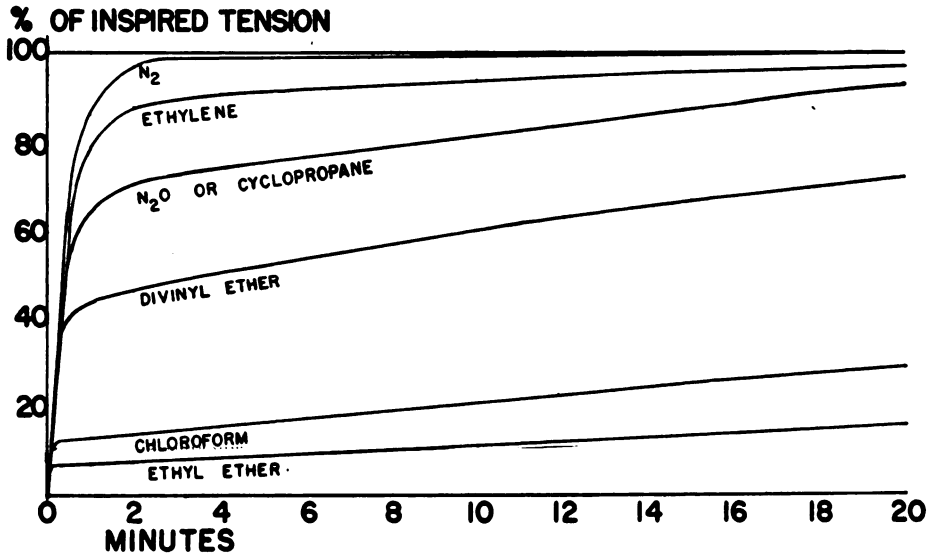

FIG. 1. Alveolar or arterial tensions of several inert gases (expressed as percent of a constant inspired tension) at various times as calculated from equation 55 using values for λ given in Table I. The physiological parameters are assumed to remain constant and to have the following respective values: $M_A = 6$ l./min., $F = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

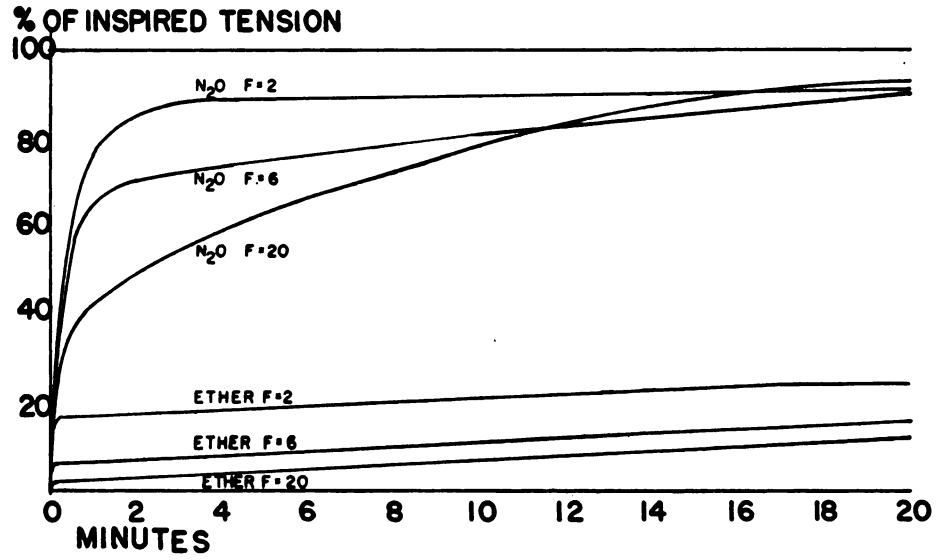

FIG. 2. The effect of variations in cardiac output on the alveolar or arterial tensions of two inert gases as calculated from equation 55 with other physiological parameters remaining constant: $M_A = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

Equation 55, although inexact, is nevertheless more complete and general than any previous treatment of this problem. It is applicable to any inert gas regardless of its solubility in blood and in fact can be used to describe the uptake

of gases of different solubility (Fig. 1) which it does rather faithfully especially in the early phases of saturation. It is also useful in predicting the effect of changes in some of the important physiological parameters on the uptake of any specific inert gas (Figs. 2, 3).

Equation 55 neglects the different blood flows to the various tissues and treats the body as a single tissue mass with a blood flow equal to the cardiac output. It neglects possible differences in gas solubility in the several tissues and treats diffusion as an instantaneous phenomenon. It therefore represents a special case of a more exact and general equation which can be derived and which is given in the following section.

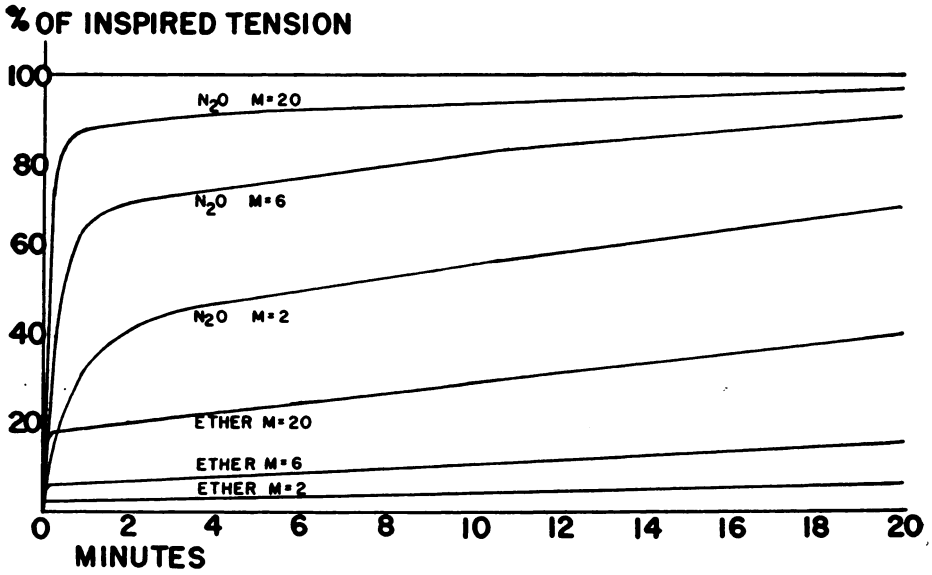

FIG. 3. The effect of variations in alveolar ventilation on the alveolar or arterial tensions of two inert gases as calculated from equation 55 with other physiological parameters remaining constant: $F = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

G.) Copperman (1950). Starting with the respiratory and tissue exchange equations derived above, Copperman (31) has combined them and obtained for the first time a general equation entirely in terms of physiological parameters and based on a minimum of simplifying assumptions. Its only restriction is that the inspired concentration of inert gas be held constant, but the alveolar, arterial and venous concentrations are permitted to vary as they will. In the expression derived here he has chosen to neglect the presence of shunts at the lung and tissues ($R_p = 1 = R_i$) and to assume instantaneous diffusion at the lung ($\theta = 1$) but retaining the diffusion process at the tissues. He obtains therefore from equation 8,

$$\frac{dC_i}{dt} = \frac{F_i}{V_i}(\lambda C_A - C_{v_i}) \tag{56}$$

and from a Bohr derivation as in equation 42,

$$\frac{\lambda_i \lambda C_A - C_i}{\lambda_i C_{v_i} - C_i} = e^{D_i' S_i / F_i} = \psi_i \qquad \psi > 1 \tag{57}$$

Copperman has also treated blood-tissue diffusion in a somewhat more rigorous fashion (Table III) than that employed here and suggests that in reality diffusion at the tissues is practically an instantaneous process for most gases.

From equations 56 and 57, C_i is eliminated to yield,

$$\frac{dC_{v_i}}{dt} + r_i C_{v_i} = \frac{\lambda}{\psi_i}\frac{dC_A}{dt} + \lambda r_i C_A \tag{58}$$

$$\text{where } r_i = \frac{F_i(\psi_i - 1)}{V_i \lambda_i \psi_i} > 0$$

The $(n - 1)$ tissue venous concentrations are related to the mixed venous concentration as before by,

$$\sum_{i=1}^{n-1} F_i C_{v_i} = F C_v \tag{59}$$

Finally C_v and C_A are related by the equation for respiratory exchange (equation 38):

$$\frac{dC_A}{dt} = \frac{M_A}{V_A}(C_I - C_A) + \frac{F}{V_A}(C_v - \lambda C_A) \tag{60}$$

Simultaneous solution of equations 58, 59 and 60 yields a solution of the form,

$$C_A = A_0 + \sum_{j=1}^{n} A_j e^{k_j t} \tag{61}$$

where A_0 can be shown to equal C_I and the k_j's are the n roots of the following equation,

$$\lambda \sum_{i=1}^{n-1} \frac{F_i}{\psi_i}\frac{k_j + \psi_i r_i}{k_j + r_i} = M_A + \lambda F + V_A k_j \tag{62}$$

where it can be shown that each k_j is negative and real.

The n arbitrary coefficients A_j are determined from initial conditions: For the saturation process, at $t = o$, $C_A = C_{v_1} = C_{v_2} = \cdots C_{v_{n-1}} = 0$ and the following definition is achieved,

$$A_j = -\frac{\prod_{i=1}^{n-1}\left(1 + \frac{k_j}{r_i}\right)}{\prod_{\substack{i=1 \\ i \neq j}}^{n}\left(1 - \frac{k_j}{k_i}\right)} C_I \tag{63}$$

The A_j's are shown to be real and, in every particular case examined, to be negative, although a rigorous proof that they are always negative has not been obtained. The alveolar concentration of an inert gas inhaled at a constant

concentration has therefore the form:

$$C_A = C_I(1 - A_1e^{-k_1t} - A_2e^{-k_2t} - \cdots - A_ne^{-k_nt}) \quad (64)$$

where the coefficients A_1 to A_n and the decay constants k_1 to k_n are related in an obvious manner to corresponding coefficients and decay constants defined by equations 62 and 63 entirely in terms of physiological parameters. It is immediately apparent that these A's and k's are not specifically referable each to a particular tissue, but that all are determined by all the parameters. It may be possible by appropriate assumptions to simplify these expressions so that each coefficient and decay constant refers to a particular tissue. It will always be necessary, however, to justify such assumptions by experimental proof.

THE EMPIRICAL APPROACH

A wealth of experimental data pertinent to the problem of inert gas exchange has been accumulated since the earliest interest in the role of nitrogen in decompression sickness. In reporting their results most investigators made use of some mathematical expression which they or others had previously derived or which they found by trial from their data. With one notable exception (117) these expressions have assumed the exponential form, as indeed, have all the theoretically derived equations.

Inert Gas Exchange in the Body as a Whole

Campbell and Hill (21) in 1931 reported measurements on the elimination of nitrogen by the lungs effected by the breathing of practically pure oxygen. They distinguished between the nitrogen present in the residual air at the beginning of oxygen inhalation and that subsequently eliminated from the body tissues via the pulmonary circulation by means of an initial flushing of the lung during one minute of hyperventilation, and measured the residual volume of the lung in this manner. Although they did not attempt a mathematical analysis of the nitrogen elimination process they report that its rate decreased with time and suggested that the slower rates represented regions with poor blood supply and therefore slower diffusion. They also observed that after exposure to several atmospheres of nitrogen the quantity of that gas eliminated in the denitrogenation process was proportional to original saturation pressure, *i.e.*, the conditions of Henry's law were satisfied for the uptake of nitrogen by the body.

In the United States much of the early and fundamental work on the exchange of nitrogen and other inert gases was done by Behnke and his associates (4, 6, 7, 108). By means of considerably improved technics they studied the elimination of nitrogen during oxygen breathing of several hours duration (6). Total nitrogen elimination beginning after an initial 5-minute period for lung washout was found to fit the expression,

$$Q_E = A_1(1 - e^{-k_1t}) + A_2(1 - e^{-k_2t}).$$

The following values for the constants were obtained in one experiment: $A_1 = 458$ ml., $k_1 = 0.098$ min.$^{-1}$, $A_2 = 382$ ml., $k_2 = 0.0085$ min.$^{-1}$. These investigators have refrained from suggesting an interpretation of the k's in terms of physiological parameters. Their original interpretation of the A's as represent-

ing the quantities of nitrogen initially in the water and fat components of the body, although supported by the reasonable values thus obtained for these components, was a rough approximation. More recent analysis of Behnke's nitrogen elimination data by Smith and Morales (4) has yielded a three term exponential expression:

$$Q_E = 172(1 - e^{-0.13t}) + 353(1 - e^{-0.028t}) + 255(1 - e^{-0.0079t})$$

Underwood and Diaz (124) have reported an interesting series of experiments in which a solution of radon was injected intravenously in dogs and the quantity exhaled over the next several minutes measured by means of a Geiger counter. The elimination was found to fit an exponential decay curve ($k = 0.66$ min^{-1}). They suggest that the elimination curve is actually a series of exponentially decaying functions, without attempting what might have been a fairly taxing theoretical analysis.

A unique expression for the quantity of nitrogen eliminated during breathing of oxygen has been obtained by Stevens and his collaborators (117). In 85 carefully performed experiments on 37 individuals they found that after an initial period of lung washout, the total nitrogen eliminated (Q_E) in time t from 1 to 20 minutes and in some cases up to several hours could be expressed as $Q_E = a\,t^b$, a and b being arbitrary constants. Although this frankly empirical expression enables one to report cumbersome nitrogen elimination data in terms of only two numbers, that is probably its greatest value, since there does not appear to be a theoretical basis for the expression used in terms of physiological mechanisms.

Jones has recently summarized the results of extensive experiments performed over the past several years (64); these have included studies with many different gases and of the uptake and elimination by the body as a whole as well as that confined to local regions. In his studies of inert gas exchange for the body as a whole, Jones has assumed expressions for the total quantity exhaled or absorbed up to time t, or in differential form, the time rate of these processes at any instant:

$$Q_E = A_1(1 - e^{-k_1 t}) + A_2(1 - e^{-k_2 t}) + \cdots + A_n(1 - e^{-k_n t})$$
$$dQ_E/dt = k_1 A_1 e^{-k_1 t} + k_2 A_2 e^{-k_2 t} + \cdots + k_n A_n e^{-k_n t}$$

His data fit such expressions to a satisfactory degree. For example, one of the best resolved curves yielded for nitrogen (exclusive of initial lung nitrogen) the following values in units of ml. for the A's and min.$^{-1}$ for the k's: $A_1 = 111$, $k_1 = 0.462$; $A_2 = 193$; $k_2 = 0.087$; $A_3 = 428$, $k_3 = 0.024$; $A_4 = 95$, $k_4 = 0.008$; $A_5 = 600$, $k_5 = 0.0025$.

Jones was able to derive physiological quantities from these empirical constants by assuming first, that each pair of constants is representative of a single tissue or group of tissues having similar perfusion characteristics, and second, that the constants themselves are related quite simply to these physiological parameters. A_i was then taken to denote the total quantity of the inert gas in question in a particular tissue or group of tissues after full saturation at the partial pressure in question, that is $A_i = C_I \lambda \lambda_i V_i$ where C_I is the concentration in inspired air during the saturation process. Similarly k_i was considered to

represent the perfusion rate of the tissue in terms of blood flow and tissue capacity for the inert gas, $k_i = F_i/V_i\lambda_i$. Although he presented no theoretical justification for these simplifications, Jones offered in evidence (i) the fact that among the gases nitrogen, krypton, helium, and xenon no appreciable differences were found in the respective k's obtained and (ii) that the total amounts of inert gas exchanging could be predicted from their solubility in body tissues. Such data are quite pertinent and the number of such experiments could with profit be extended. However, direct and conclusive proof is still to be obtained that the empirical constants (k) of Jones are in fact simply tissue perfusion rates.

The equations 62 and 63 of Copperman indicate that none of the A's and k's of an expression like that of Jones is in general defined exclusively by the parameters of a single tissue or group of tissues. It is probable, however, that Jones, by a combination of relatively insoluble gases and an initial period of hyperventilation, succeeded in achieving arterial concentrations of the inert gases which were practically constant over most of the experimental period. Under such special circumstances the general equation could be approximated by one in which each of the j terms could be referred to a single tissue or group of tissues. It is important to point out, however, that such an approximation is not generally permissible and would not be valid in the case of more soluble gases, *e.g.*, the anesthetic gases.

Inert Gas Exchange in the Individual Tissues or Organs

Early studies on this phenomenon as it occurs within the living body were few in number and confined to experiments in animals which could be sacrificed at intervals during the gas exchange process and the tissues in question analyzed for their content of the inert gas (24). The difficulties of handling and analyzing tissues without loss of these volatile constituents are obvious, and results must often be interpreted with caution.

The recent availability of radioactive isotopes of the elements has made possible a means for studying exchange phenomena in living tissues with a minimum of disturbance to the phenomena themselves. By means of suitably placed and properly shielded detecting instruments, the time course of the uptake or removal of a radioactive substance in particular parts of the body may be obtained if the emanations are sufficiently penetrating (64, 67, 113, 123, 127). Such technics, although admirably suited to the problems of local inert gas exchange, are not entirely free from objections. The problem of shielding the detecting device from radiation arising elsewhere than the region of interest is often a difficult one, and safety requirements place a definite limit on the dosages permissible in man. In addition, conversion from radiation intensity in the detecting instrument to concentrations or quantities in the tissues involve complicated calculations, assumptions, or the preparation of satisfactory models. Most investigators have not attempted to calculate absolute quantities involved, since, fortunately, the time constant of an exponential function is independent of the units in which the function is measured.

Inert gas exchange in the *brain* has been studied by both technics (24, 64, 71). Campbell and Hill (24) reported a very slow rate for the uptake of nitrogen by the brains of goats exposed to 4, 5, and 6 atmospheres of pressure, observing only 50% saturation in that organ at the end of an exposure lasting 3 to 5 hours (24). Kety, Harmel, Broomell and Rhode (71), employing a similar but perhaps more precise technic, obtained data indicating, on the contrary, practically complete equilibrium with the inspired tension of nitrous oxide within ten minutes. They were also able to demonstrate a very rapid loss of this gas from the exposed brain unless certain precautions were taken and thus probably to explain the low nitrogen contents found by Campbell and Hill. By means of radioactive krypton, Jones (64) has demonstrated a very rapid uptake of this gas by the human brain which yields two time constants of 1.4 and 0.35 $min.^{-1}$, respectively. On that basis one would expect a saturation of better than 98% at the end of 10 minutes, a prediction in good agreement with the results above obtained for nitrous oxide in dogs. This reviewer has made mathematical analyses of arterial and cerebral venous curves of nitrous oxide which confirm Jones' finding of a system of two components, possibly gray and white matter.

Campbell and Hill (24) also obtained results which suggest a slow uptake of nitrogen by the *livers* of goats exposed to increased ambient pressures. Their results are not in accord with expectation on the basis of the known rapid blood flow through the human liver (20) and the rapid clearance rate (0.4 $min.^{-1}$) of radioactive sodium from this organ obtained by Wechsler and associates (127).

The radioactive isotope of krypton ($Kr^{79,81}$) has been used to study the dynamics of inert gas exchange in the *extremities* of man (64, 113, 123) and animals (30). In studies on the normal human hand, Tobias and coworkers (123) found a three component uptake curve with average k's of 0.16, 0.021 and 0.0037 $min.^{-1}$ in a series of 9 cases. In one case Morales and Smith (92) obtained k's of 0.11, 0.058 and 0.02 $min.^{-1}$ for the hand. They calculated theoretical magnitudes for these constants on the basis of known and assumed reasonable values for the physiological parameters and obtained 0.17, 0.03 and 0.003 $min.^{-1}$. Although these theoretical constants agree only within an order of magnitude with the empirical values found by Morales and Smith it is interesting to note that they are in almost perfect agreement with the values found by Tobias. In a series of 7 studies at the popliteal region Tobias found two components with k's of 0.013 and 0.0018 $min.^{-1}$, respectively.

Three important tissues are included in these studies upon the extremities of man: muscle, fat and skin, not to mention bone and bone marrow. Some authors have attempted to relate the k's to these tissue components; in general, however, there are practically no studies on the uptake or removal of inert gases by pure tissues. Whitely and McElroy (128, 129) have reported denitrogenation curves on samples of blood draining *muscle* or *fat*. Although they have not attempted mathematical analyses of their curves there appear to be two exponential components in each, one of which is extremely slow. It is difficult to exclude the possibility of a continuous diffusion of nitrogen from the surrounding air into the tissues as an explanation of this slow component, since apparently

little precaution was taken to exclude it, and since others (4) have demonstrated that this phenomenon may occur in the presence of open wounds. Kety (67) has demonstrated an average clearance rate of 0.05 $min.^{-1}$ for Na^{24} ion injected into the human gastrocnemius muscle, but the relationship between this and the exchange rate of an inert gas has not yet been investigated.

The rate of inert gas exchange through the intact human *skin* was investigated by Behnke and Willmon (8) by means of an ingenious technic. They found, at room temperature and under a gradient of close to one atmosphere, that some 50 ml. of helium were able to diffuse through practically the entire cutaneous surface per hour. Nitrogen diffused through the skin approximately one half as rapidly as helium under similar circumstances. The cutaneous diffusion of these gases was quite sensitive to temperatures above 29° C. and increased rapidly so that at a temperature of 35° C. the total diffusion of helium was 160 ml./hr. By means of their data and the Fick principle these authors calculated a total cutaneous blood flow of 333 ml./min. at 35° C. This is probably an underestimate of the true value since they assumed complete diffusion equilibrium between the ambient helium tension and that in cutaneous venous blood, which is not likely to have occurred through the fairly gross distances involved. Several other gases have also been shown to diffuse through the intact skin (99).

Campbell and Hill (22) studied the uptake of nitrogen by the *bone marrow* and found it to be quite slow (25% of full saturation in one hour). Jones (64) has compared these results with his own obtained by a different method.

The uptake of radioactive krypton from the *stomach* and *intestinal tract* was qualitatively demonstrated by Tobias and his associates (123). This was found to occur fairly rapidly when the gas was introduced into the duodenum, but at a much slower rate from the stomach or colon.

Ferris, Molle and Ryder (39) have recorded several interesting examples of the time course of nitrogen concentration in blood from various sites in man during denitrogenation. These include analyses of arterial, internal jugular and antecubital venous blood and ascitic, cerebrospinal and synovial fluid. The nitrogen concentration in arterial and internal jugular venous blood fell rapidly while the clearance from cerebrospinal fluid was quite slow.

The accumulation and removal of some anesthetic gases from artificial subcutaneous and peritoneal pockets have been examined by one group (105). Cyclopropane was found to appear in and disappear from these pockets at a rate approximately twice that of ethylene. Since the ratio of exposed surface to volume in this situation is extremely small, this would be expected to be a diffusion limited process and as such the respective solubilities of the two gases in water should be the determining factor in the rate of exchange (equation 5). The results found are entirely in accord with the fact that this solubility for cyclopropane is twice that for ethylene (Table I).

The Effects of Changes in the Physiological Parameters on Inert Gas Exchange

Haggard (58) has reported the results of experiments designed to test the effects of varying certain cardiorespiratory factors on the uptake and elimination

of ethyl ether by the body. He showed that pulmonary ventilation was a factor of prime importance in the case of this very soluble gas. Underwood and Diaz (124) also showed that hyperventilation increases considerably the rate of elimination of radon, another soluble gas, while Stevens (117) demonstrated that the elimination of relatively insoluble nitrogen from the body, excluding the initial quantity present in the alveoli (43), was little affected by prolonged hyperventilation. All these findings are compatible with equation 45, the general expression for gas exchange at the lungs.

Exercise has been shown by Behnke and Willmon (7) to increase the rate of nitrogen elimination via the lungs, but largely during the first thirty minutes of the denitrogenation curve. This may probably be explained on the basis that nitrogen, being slightly soluble in blood, achieves a constant and low arterial concentration fairly early so that the subsequent elimination is a function largely of tissue parameters. Furthermore, muscular exercise probably does not increase the exchange processes in adipose tissue which constitute the bulk of the slower components and thus the latter part of the denitrogenation process is not accelerated. Locally, muscular exercise has been shown to increase the rate of gas exchange in the limbs (30) and the clearance of nitrogen (128) or Na^{24} (67) from the active muscles.

The local rate of exchange of inert gas or of sodium can be increased by warming the region (30, 39), by reactive hypermia (67), or by vasodilating drugs (30). Cooling the extremity or the administration of vasoconstrictors (30) has been shown to decrease these rates of exchange. These results may be explained by changes in effective blood flow through the tissue or by changes in the number of functioning capillaries with consequent effects on capillary surface and mean diffusion distance. It is quite difficult to differentiate among those effects which probably occur simultaneously and affect the exchange rate in the same direction.

There remains a wide gap at the present time between the theory of inert gas exchange at the lungs and tissues and empirical data with which to substantiate the numerous assumptions or to test the predictions of theory. Although it is apparent that the exchange processes are everywhere dependent on physiological and physical parameters, much remains to be done in relating those factors rigorously to the phenomena which may be observed in the expired air, the arterial or venous blood, or directly in the various tissues.

THE APPLICATIONS OF INERT GAS EXCHANGE TO MEDICAL PROBLEMS

The earliest interest in this general problem was stimulated by the astute demonstration of the remarkable physiologist, Paul Bert (9), that decompression illness was probably due to the release of dissolved gases from the tissues. The mass of theory and data which has been acquired since that time and which has amply substantiated that observation is well summarized in a number of recent excellent reviews (5, 25, 64).

The practical implications of these phenomena, however, have not been confined to decompression sickness. Their obvious dependence on physiological

factors soon led to numerous attempts to measure these factors by study of various aspects of inert gas exchange as a result of which a number of clinically useful methods have been developed for measurement of pulmonary ventilation, cardiac output, and blood flow through various organs.

A.) *Pulmonary Ventilation*

Examination of the general pulmonary exchange equation developed earlier (equation 45) reveals that for the special case of gases with very low solubility in blood the term containing C_v becomes negligible and

$$C_A = C_I(1 - e^{-(M_A/V_A)t}) \qquad \begin{matrix} \lambda << 1 \\ C_v << C_A \end{matrix} \tag{65}$$

In other words under such circumstances the lungs are acting like bellows, continuously diluting the inspired gas with the mid-inspiratory lung volume. This equation may readily be converted to one which treats ventilation as a discontinuous process (1a, 36, 44). After n breaths of nitrogen-free oxygen, the concentrations of nitrogen in alveolar and expired air would be as follows:

$$C_{A_n} = C_0\left(\frac{V_R}{V_R + V_T}\right)^n \tag{66}$$

$$C_{E_n} = \left(\frac{V_T}{V_T + V_D}\right) C_0\left(\frac{V_R}{V_R + V_T}\right)^n \tag{67}$$

where $C_I = O$, C_0 = initial nitrogen concentration, V_T, V_D, V_R are, respectively, effective tidal, physiological dead space, and functional residual volumes.

Darling, Cournand and Richards (36) include a correction for the small contribution of nitrogen to the alveolar gas from the mixed venous blood. This rate of nitrogen elimination is assumed to remain constant; it was determined empirically and found to vary with surface area of the body, averaging about 200 ml. in seven minutes for a normal adult (33, 35). Measurement of lung volume has been accomplished with the use of hydrogen (11, 88), nitrogen (15, 21, 28, 33, 35, 36, 44, 81) or helium (46, 89, 131) in one or several breaths.

It was soon realized that some unevenness existed even in normal pulmonary ventilation (11, 42) and that this became quite marked in patients with emphysema. Individual measurement of these ventilatory components from analysis of expired air has been accomplished independently by Robertson, Siri and Jones (101a) and by Fowler (44).

B.) *Cardiac Output*

Bornstein (16) was apparently the first to apply the principles of inert gas exchange to measurement of pulmonary blood flow. Starting with Zuntz' concept of gas exchange (133), he reasoned that the quantity of nitrogen eliminated in unit time during oxygen breathing should be proportional to the tissue—alveolar nitrogen gradient and to the pulmonary blood flow or cardiac output. He

devised a technic for measuring the nitrogen eliminated and the mean alveolar nitrogen tension by oxygen rebreathing from a rubber bag and calculating relative values for cardiac output in the same individual under different conditions compared to the resting state.

Krogh and Lindhard (77) soon pointed out that if Bornstein's determination were to be done within a time short enough to prevent the recirculation of blood through the lungs, it would then be possible to obtain an absolute value for pulmonary blood flow. They devised a technic for making measurements within a period of about 15 seconds and in this way hoped to avoid recirculation. Their method employed 10–25% nitrous oxide as the inert gas and consisted essentially in measuring the loss of this gas from the alveoli during an accurately determined period of breath-holding following its introduction into the alveoli by means of one or several deep breaths. By simultaneous measurement of oxygen loss from the alveolar gas they found an increase in oxygen consumption during the determination which they attributed to an increased pulmonary blood flow induced by the procedure itself. On the assumption that only pulmonary blood flow and not the mixed venous oxygen content was altered by the short procedure, they reduced the experimentally determined values for pulmonary blood flow to corrected values by the use of a factor which was the ratio of the experimental to the pre-experimental oxygen consumption. The latter was determined in the usual manner immediately before the nitrous oxide inhalation. Most of the resting values for pulmonary blood flow thus obtained were within 4 to 5 l./min. and showed approximately a four-fold increase during exercise. Krogh and Lindhard's method was followed by a great surge of methods and modifications, all of which utilized the principle of inert gas exchange (17, 18, 27, 78, 76, 82, 83, 84, 85, 86, 114, 116).

After an elaborate evaluation and modification of Bornstein's method (86), Marshall and Grollman developed a technic using ethylene (85), which Grollman subsequently modified by substituting acetylene (49, 51). This method is essentially that of Krogh and Lindhard except that the technic for determining the quantity of inert gas absorbed was improved by introducing a procedure of rapid rebreathing from a rubber bag. Thus the alveolar gas and the gas in the bag were in essential equilibrium throughout the procedure, permitting the calculation of gas removed from the alveolar-bag system to be made from samples taken at 15 seconds and 8 seconds later. The acetylene technic also incorporates the ingenious oxygen correction which Krogh and Lindhard introduced for minimizing the effect of the procedure *per se* on pulmonary blood flow. In 50 young adults, Grollman (51) obtained mean values of 3.87 l./min. for cardiac output (pulmonary blood flow) and 2.21 l./min./m.^{2} for cardiac index.

All the technics above are subject to certain errors and difficulties. The errors associated with analytical methods, correction for change in gas volume during absorption, etc. simply require their recognition and sufficient patience for satisfactory solution. The problem of obtaining representative samples of alveolar air is a real one although it is likely that by the technic of Marshall and Grollman satisfactory uniformity could be achieved in normal subjects. In patients with

pulmonary disease and uneven ventilation even this method might be open to some question. The problems of the uptake of the inert gas by the lung tissue itself and by its contained blood volume (as distinct from its blood flow) and the possibility of loss by diffusion into the other thoracic structures were all considered by Krogh and Lindhard but often overlooked by subsequent investigators. Even the former pair of workers, however, achieved only a partial solution to the problem by a short preliminary period of equilibration.

An important difficulty in these methods and the one which has been largely responsible for their disrepute up to the present time has been the fact that venous blood carrying some of the inert gas in question returns to the lungs before a single determination has been completed. Although most of the proponents of these methods have insisted that significant recirculation does not occur during their determination others have emphasized the extreme rapidity with which some venous blood returns to the heart. In the dog (59, 115) significant recirculation has been shown to occur in 15 seconds. Baumann and Grollman (2), by direct cardiac puncture in man, found the mixed venous blood concentration of acetylene to be almost 6% of the arterial in samples taken from 12 to 20 seconds after the first inhalation of that gas. In 25 to 30 seconds this had reached 12% and in 33 to 37 seconds, 18% of the arterial level. By less direct procedures Gladstone (47) and Adams and Sandiford (1) have found evidence for recirculation of blood containing acetylene in 10 and 20 seconds, respectively, and quite recently mixed venous blood samples obtained by cardiac catheterization (26) indicated that recirculation begins at about 8 seconds. These investigators (26), in an excellent critical evaluation of the Grollman method, have discovered a number of factors which together explain the discrepancy between that method and the direct Fick determination. They suggest several corrections which may permit the indirect method to yield valid results. Methods have been described recently (1, 48) in which more serious consideration has been given to this problem of recirculation. By means of one such method, Gladstone (48) found in seven individuals a mean cardiac output of 5.4 l./min. which is higher than the values found by Grollman and almost exactly the normal mean of 5.5 l./min. obtained by Cournand (32) by direct cardiac catheterization. With this latter technic for direct comparison and with newer and possibly more precise technics for gas analysis now available the near future will probably see further developments in the estimation of cardiac output and pulmonary blood flow by study of inert gas exchange at the lungs.

C.) *Measurement of Blood Flow to Organs and Tissues*

A technic for the determination of cerebral blood flow in man has recently been developed (64, 72) which makes use of the principles of inert gas (nitrous oxide) exchange at a tissue. The equation for the Fick principle applied to a single organ (equation 8) may be integrated to yield an expression for the mean concentration of inert gas in the organ at any time, u, measured from the beginning of inhalation of the inert gas:

$$(C_i)_u = \frac{F_i}{V_i}\int_0^u (C_a - C_{v_i})\, dt \qquad (68)$$

so that if C_i can be determined at any time and also the integrated values for concentration of the inert gas in arterial and venous blood from the organ, then the blood flow per unit volume of organ can be calculated. Without assuming instantaneous or even rapid diffusion equilibrium, it is nevertheless true, that if the time (u) over which the determination is made is sufficiently long, then, $(C_i)_u = \lambda_i(C_{v_i})_u$. At that time, then,

$$\frac{F_i}{V_i} = \frac{\lambda_i(C_{v_i})_u}{\int_0^u (C_a - C_{v_i})\,dt} \tag{69}$$

This principle can be applied to any organ for which it can be shown (i) that venous samples representative of all the venous drainage from that organ are obtainable, (ii) that there is negligible contribution to the venous blood sampled of drainage from other regions or organs than that under study, and (iii) that the experimental time period (u) is sufficiently long so that the inert gas tension in the venous blood sampled is representative of the mean tension in the organ itself. Evidence has been obtained (71, 72) that these conditions can be met in the case of the human brain. It is apparently also necessary (64) to point out that this principle does not require a constant arterial concentration and all the factors which go into that variable are conveniently eliminated by the simple expedient of measuring the arterial concentration throughout the determination and using the function so obtained in the calculation.

This technic has found successful application not only to measurement of human cerebral circulation (68) but also to the determination of coronary blood flow in dog (38) and man (10). Its application to other regions such as the extremities or the splanchnic area is beset with the difficulty that in such regions extremely slow components (resting muscle, fat) make the time of venous equilibrium impractically long.

In contrast to the technic above which yields a value for blood flow to an organ independently of diffusion factors are the methods which measure the time constants of uptake or clearance of inert gas (64) or other diffusible substances (67) in the various regions of the body. These depend first upon the assumption of constant arterial concentration of the substance in question, a condition which can be approximated by use of poorly soluble gases and hyperventilation (64) or local deposition of the tracer substance (67). In addition, however, in order to employ these time constants as quantitative measures of blood flow per unit volume of tissue it is necessary to assume instantaneous diffusion and the absence of arteriovenous shunts. Although such assumptions have been made and partially substantiated by Jones (64) who uses these constants synonymously with blood flow, it is not really necessary to take so bold a point of view. These uptake or clearance constants of diffusible substances measure a very important homeostatic function—the ability of the local circulatory and diffusion processes to supply substances to and remove them from the tissue cells. From the point of view of the local economy these overall constants are much more important than the quantity of blood flowing through the vessels.

D.) *Application in Anesthesiology*

Since the volatile anesthetics behave like inert gases in the body, the principles of this exchange both at the lungs and the tissues are of fundamental importance to this clinical specialty (3, 52, 69, 118). Whatever the mechanism whereby an anesthetic gas produces its effects, there is little doubt that the intensity of those effects is directly dependent upon the concentration of the anesthetic in the tissues of the brain. Haggard (56) has demonstrated an excellent correlation between anesthetic level and brain concentration of ether as reflected in the concentration in internal jugular blood. A rigorous test of any theory of inert gas exchange in the body is its ability to explain the known differences in rate of induction and recovery among the anesthetics and the observed effects of changes in the various physiological parameters.

In an earlier part of this review, an expression (equation 52) was derived for the concentration of an inert gas in a tissue in terms of the factors which determine it. Thus cerebral concentration is dependent on cerebral blood flow per volume of brain, on factors of diffusion and solubility, and upon the past history of the arterial concentration of that gas. On the basis of recent experience (64, 66, 71), it may be stated that the factors of flow and diffusion in this organ are normally such as to introduce a time lag of the order of 10 minutes for the achievement of complete equilibrium between all parts of the brain and a certain arterial concentration of inert gas. It may be concluded, therefore, that the arterial concentration of anesthetic is the important determinant of rate of induction or recovery where this rate is slow (as in the case of ether); but where induction or recovery is rapid (as with ethylene), cerebral blood flow assumes considerable importance in addition to arterial concentration. Obviously, also, if the cerebral parameters are kept reasonably constant, as they would tend to be in a normal patient in the care of a competent anesthetist, the rise in brain concentration will depend almost entirely upon the shape of the arterial concentration curve.

In the section on theory, an expression was derived (equation 55) which described the alveolar concentration of a foreign gas as a function of time. Since one may assume, without serious error in the case of a normal individual, that the arterial inert gas tension is equal to that in the alveoli, this same equation also describes the shape of the curve of inert gas tension in arterial blood. It is seen that the alveolar curve appears as the sum of two terms, the first representing the process of lung washout, or the initial dilution of the inert gas by the residual gas and the pulmonary blood flow, the second representing the contribution of gas by the recirculating mixed venous blood. Since k_1 is quite large (never less than $\frac{M_A}{V_A}$ and therefore at least 1), this term represents an initial rapid rise toward some fraction of the inspired partial pressure. The remainder of the rise toward the inspired tension of inert gas in governed by the mixed venous blood tension and is a much slower process depending on blood flow, diffusion, inert gas solubility, and volumes of all the tissues of the body.

Thus the alveolar and arterial tension curves for any inert gas inspired at a constant partial pressure have three distinct phases (69): (i) an initial rapid rise occupying 3 minutes or less, (ii) a sharp inflection and (iii) a progressive slow rise reaching the inspired tension only after a period of hours. The rapidity of induction or recovery peculiar to each anesthetic is determined by the fraction of complete saturation or desaturation achieved in the initial rapid rise or fall of the arterial curves and this is given by the coefficient A_1 in equation 55. It is apparent that A_1 is quite sensitive to the solubility of the gas in blood and varies inversely with it. From the known values for λ, assuming normal values for M_A and F_p of 6 l./min. each, and neglecting diffusion lag across the pulmonary membrane, it is possible to estimate the fraction of complete saturation of arterial blood with inspired gas achieved within the first few minutes for each anesthetic, as follows (in order of decreasing value): ethylene 87%, nitrous oxide 67%, cyclopropane 68%, divinyl ether 42%, chloroform 12%, and ethyl ether 6%. This order is also one of decreasing rapidity of induction or recovery with each of the anesthetics named. Data have been reported for ether (56, 102), cyclopropane (100, 101), nitrous oxide (66), divinyl ether (103) and ethylene (95) which qualitatively confirm these predictions from the theoretical equation. There is need, however, for more such data obtained with a constant inspired tension, for all the anesthetics.

It is also possible to predict from equation 55 the effect of variations in the physiological factors concerned on the shape of the arterial curve. Increased respiratory minute volume will increase the height of the initial rise (A_1), especially where pulmonary blood flow or blood solubility is large, and will increase the rate of the whole arterial curve (k), especially where blood flow or solubility are low. This in general confirms the predictions and observations of Haggard (55, 58). Increased pulmonary blood flow will decrease the initial rise especially for soluble gases but will speed the rate of rise of the whole curve and thus shorten the time necessary for complete saturation or desaturation. Increased adiposity will slow the latter portions of the arterial curve especially for the highly fat soluble gases but will not significantly affect the initial phase of induction or recovery. For the effect of some of these variables see Figures 1, 2, 3.

In general, although theory seems capable of explaining many clinically observable facts, the applications of the principles of inert gas exchange to anesthesiology manifest the same tendency which is seen throughout all aspects of the inert gas exchange problem—a tendency for theory to advance far beyond empirically obtainable evidence. It is to be hoped that with the great number of physical technics now available some advance may be made in our comprehension of these phenomena, for intimately associated with them are the basic functions of the circulatory and respiratory systems.

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