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KINETICS OF ISOBARIC COUNTERDIFFUSION

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Isobaric inert gas counterdiffusion has been demonstrated to produce gas lesions in man (Lambertsen and Idicula, 1975) and lethal gas embolism in animals (Lambertsen, Cunnington and Cowley, 1975). Equations have been derived for the stable-state supersaturation pressures developing at interfaces during inert gas counterdiffusion (Graves *et al.*, 1973). The present analysis is a mathematical treatment of the kinetics of the isobaric counterdiffusion of a pair of gases through a membrane consisting of two layers composed of substances with different diffusion coefficients and solubilities for each of the gases involved. The time to reach the stable supersaturation state due to isobaric counterdiffusion, even when circulatory transport and pulmonary washout times are included, is found to be at least an order of magnitude smaller than the time required for visible bubble formation and tissue distortion.

Introduction. Recently Lambertsen and Idicula (1975) identified a new gas bubble lesion disease in man, occurring at increased ambient pressures during the breathing of nitrogen or neon-oxygen mixtures while the individuals were surrounded with helium. Since no decrease of ambient pressure preceded the development of urticaria and skin lesions, and the circumstances led to dermal gas lesions at a stable ambient pressure, the phenomenon was designated the "isobaric inert gas counterdiffusion syndrome." This phenomenon has been found capable of inducing lethal venous gas embolization (Lambertsen, Cunnington and Cowley, 1975).

Analysis of this phenomenon in its *stable-state* form has been carried out by Graves *et al.* (1973). They substantiated the concept that counterdiffusion of gases through substances or membranes could lead to gas supersaturation, under isobaric conditions, at interfaces between substances having different physicochemical characteristics relating to gas solubility and diffusivity (Graves *et al.*, 1973). It is therefore considered that such supersaturation, in the

presence of gas nuclei, leads to the observed formation and growth of bubbles in tissues, accounts for the gas lesions observed in man and the embolization observed in animals.

Development of the symptoms of urticaria and the actual appearance of cutaneous lesions occur only after a period of sustained counterdiffusion. This period may exceed one hour, even at the ambient pressures of 10 to nearly 40 atm where the phenomena were identified (Lambertsen and Idicula, 1975).

The purpose of this paper is to provide the means to examine mathematically the kinetics of isobaric gas counterdiffusion during transient, *non-stable-state* conditions. The analysis does not pertain to the development of actual lesions in an individual but to development of supersaturation at discrete membranes. The method permits prediction and quantitative comparison of the time courses for the development of supersaturation with gases of varying characteristics and for membranes of specifiable composition.

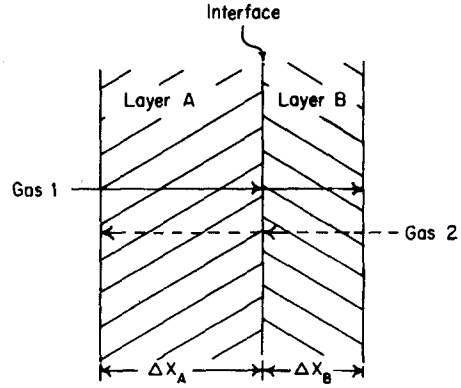

Figure 1. Circumstances of isobaric gas counterdiffusion. The thickness of lipid layer A is ΔX_A, that of aqueous layer B is ΔX_B. At uniform ambient pressure gases diffusing in opposite directions through the layers of the composite membrane develop supersaturated states within the membrane, leading to bubble formation

Approach. The analysis of kinetics for isobaric counterdiffusion extends directly from the stable-state analysis derived by Graves *et al.* (1973). Components of these analyses are illustrated in Figure 1. The example includes:

(1) A lipid-containing membrane having adjacent layers of differing composition, interfacing with gas-permeable structures such as dermis or capillaries. In Figure 1 these adjacent layers are designated Layer A and Layer B.

(2) Two different gases counterdiffusing through this two-layer system. These are designated Gas 1 and Gas 2.

(3) Thicknesses of the layers are designated ΔX_A and ΔX_B.

Characteristics relating the gases to the specific layer substances are identified as follows:

Characteristic		Gas 1	Gas 2
Diffusion coefficient	Layer A	D_{1A}	D_{2A}
	Layer B	D_{1B}	D_{2B}
Solubility	Layer A	S_{1A}	S_{2A}
	Layer B	S_{1B}	S_{2B}
Permeability	Layer A	K_{1A}	K_{2A}
	Layer B	K_{1B}	K_{2B}

Permeability in this special case, is chosen to equal the product of diffusion coefficient and solubility (Graves *et al.*, 1973).

Analysis. The following analysis employs the approximation method of Landahl (1953). It is directed to description of the kinetics of isobaric counterdiffusion at the ultimate sites of counterdiffusion which in *in vitro* experiments may be uniform in character but which *in vivo* must be considered infinitely multiple in number and in composition. Literally billions of discrete sites should have the characteristics of layer proximity, layer composition and layer orientation in relation to the counterdiffusion pathways. Therefore the kinetics of counterdiffusion, as examined here, concern microvolumes of tissue and microdistances, and not gross tissue structures.

Using the same notation as Graves *et al.* (1973) in the description of the stable-state counterdiffusion, the diffusion flux (J) of gas 1 in layer A, prior to reaching the interface, is given by

$$J_{1A} = -K_{1A}\frac{\pi}{r_{1A}(t)}, \tag{1}$$

where $r_{1A}(t)$ is the distance over which the diffusion front of gas 1 has moved at time t, as shown in Figure 2 in which r_{1A} is explicitly shown as a function of time. Pressures for gases 1 and 2 are assumed equal to π. Application of Landahl's approximation method (1953) leads to the equation

$$\int_0^t K_{1A}\frac{\pi}{r_{1A}}\,dt = \frac{1}{2}\pi r_{1A}S_{1A}. \tag{2}$$

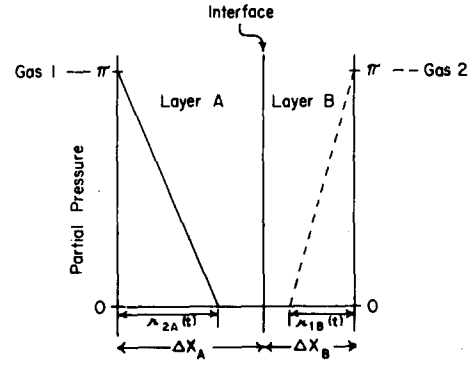

Figure 2. Approximate diffusion profiles of gases 1 and 2 in media A and B respectively at any time t before either gas reaches the interface between the layers. The movement of the diffusion fronts are functions of time as indicated by $r_{1A}(t)$ and $r_{2B}(t)$

Differentiation of both sides of (2) with respect to t yields

$$K_{1A}\frac{1}{r_{1A}(t)}=\frac{1}{2}\frac{dr_{1A}}{dt}S_{1A}. \tag{3}$$

Integration of (3) with the initial condition $r_{1A}(t)=0$ at $t=0$ gives

$$r_{1A}(t)=2\sqrt{D_{1A}t}, \tag{4}$$

in which $D_{1A}=K_{1A}/S_{1A}$ is the diffusion coefficient of the first gas in medium A. The front of the diffusion profile reaches the interface at $t=t^*_{1A}$, i.e., when

$$r_{1A}(t^*_{1A})=\Delta X_A. \tag{5}$$

From (4) and (5) it follows that

$$t^*_{1A}=\frac{(\Delta X_A)^2}{4D_{1A}}. \tag{6}$$

After the diffusion front of gas 1 has reached the interface (i), its pressure at the interface, P_{1i}, starts to increase as a function of time; whereas its front moves now into medium B as shown in Figure 3. The diffusion fluxes of gas 1 in media A and B are equal at the interface so that

$$K_{1A}\frac{\pi-P_{1i}(t)}{\Delta X_A}=K_{1B}\frac{P_{1i}(t)}{r_{1B}(t)}. \tag{7}$$

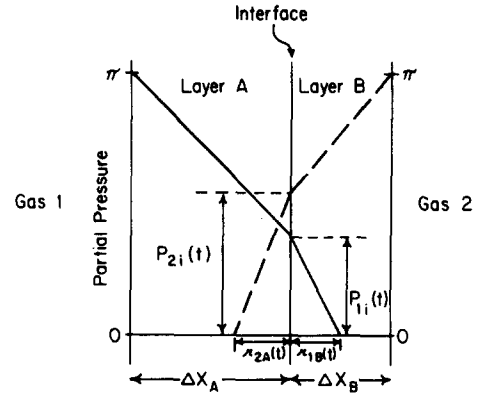

Figure 3. Diffusion profiles of gases 1 and 2 after both gases have diffused through the interface between layers A and B of the membrane but prior to reaching the steady state. $P_{1i}(t)$ and $P_{2i}(t)$ are the pressures of gases 1 and 2 respectively at the interface i as functions of time

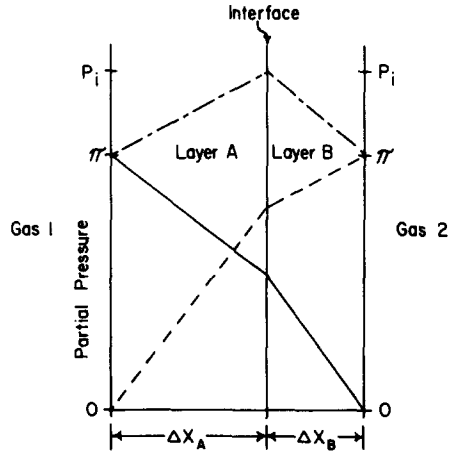

Figure 4. Diffusion profiles of gases 1 and 2 at the steady state when both gases have reached the boundary of the 2nd layer. P_i is the sum of the partial pressures of the two gases at the interface and, in this example, represents supersaturation

Solution of (7) for P_{1i} yields

$$\frac{P_{1i}(t)}{\pi}=\frac{K_{1A}r_{1B}(t)}{K_{1A}r_{1B}(t)+K_{1B}\Delta X_A}. \tag{8}$$

Furthermore, as in (2), application of Landahl's equation to diffusion of gas 1 in layer B leads to

$$\int_{t_{1A}^*}^{t} K_{1B}\frac{P_{1i}}{r_{1B}}\,dt=\frac{1}{2}P_{1i}r_{1B}S_{1B}. \tag{9}$$

Since P_{1i} and r_{1B} are both functions of time t, differentiation of both sides of (9) with respect to t leads to

$$K_{1B}\frac{P_{1i}}{r_{1B}}=\frac{1}{2}S_{1B}\left(\frac{dP_{1i}}{dt}r_{1B}+P_{1i}\frac{dr_{1B}}{dt}\right). \tag{10}$$

Differentiation of both sides of (8) with respect to t gives

$$\frac{1}{\pi}\frac{dP_{1i}}{dt}=\frac{K_{1A}K_{1B}\Delta X_A}{(K_{1A}r_{1B}(t)+K_{1B}\Delta X_A)^2}\frac{dr_{1B}}{dt}. \tag{11}$$

Substitution of (11) into (10), after simplification and separation of variables, yields

$$K_{1B}\,dt=\frac{1}{2}S_{1B}\left(\frac{cr_{1B}}{r_{1B}+c}dr_{1B}+r_{1B}\,dr_{1B}\right), \tag{12}$$

with $c=(K_{1B}/K_{1A})\Delta X_A$; it is seen that c has the dimension of a length. Integration of (12) with the initial condition $r_{1B}=0$ at $t=0$ leads to

$$\tfrac{1}{4}X^2+\tfrac{1}{2}X-\tfrac{1}{2}\log_e(1+X)=\tau \tag{13}$$

containing the non-dimensional variables

$$X=r_{1B}/c,\quad \tau=K_{1B}t/S_{1B}c^2, \tag{14}$$

in which, as in (4), $K_{1B}/S_{1B}=D_{1B}$ or permeability divided by solubility is the diffusion coefficient of gas 1 in medium B.

Integration of (11) for the relative pressure Y, defined as $Y=P_{1i}/\pi$, with $r_{1B}=0$, $P_{1i}=0$ and hence $X=0$ and $Y=0$ *at* $t=0$ leads to

$$Y=X/(1+X). \tag{15}$$

To find the time t^*_{1B} at which the first gas reaches the boundary of layer B so that $r_{1B}=\Delta X_B$, it follows from (12) and (14) that at t^*_{1B}

$$X=\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}. \tag{16}$$

Substitution of (16) into (15) leads to

$$Y=\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A+K_{1A}\Delta X_B} \tag{17}$$

giving the partial pressure P_{1i} of gas 1 at the interface which is the same pressure as that obtained by Graves *et al.* (1973). By substitution of (16) into (13) the time t^*_{1B} to reach this steady state for gas 1 in medium B is obtained

$$t^*_{1B}=\frac{1}{2D_{1B}}\left(\frac{K_{1B}\Delta X_A}{K_{1A}}\right)^2\left\{\frac{1}{2}\left(\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}\right)^2+\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}\right.$$

$$\left.-\log_e\left(1+\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}\right)\right\}. \tag{18}$$

This time, t^*_{1B}, together with the time t^*_{1A} given by (6) gives the total time t_1 to reach the steady state for the first gas, in which its pressure at the boundary of layer B is at its physiological value zero; i.e.,

$$t_1=\frac{(\Delta X_A)^2}{4D_{1A}}+\frac{1}{2D_{1B}}\left(\frac{K_{1B}\Delta X_A}{K_{1A}}\right)^2\left\{\frac{1}{2}\left(\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}\right)^2+\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}\right.$$

$$\left.-\log_e\left(1+\frac{K_{1A}\Delta X_B}{K_{1B}\Delta X_A}\right)\right\}. \tag{19}$$

Similarly, the time t_2 to reach the steady state for the second gas can be obtained. It will be given by the above expression in which subscript 1 is replaced by 2 and the subscripts A and B are interchanged. The time to reach the steady state for both gases is the larger of t_1 and t_2.

Application. Application of this analysis to the gases used in the initial identifications of gas lesions requires assumption of diffusion distances (layer thickness) and substitution of appropriate values for the characteristics of the gases themselves. Table I illustrates the times to equilibrium for helium counterdiffusion with nitrogen or neon and for nitrogen with neon for layer thicknesses (diffusion distances) of 5 and 160 microns. The first may approximate the diameter of a capillary, the last the full diffusion distance from skin capillary through the dermis to the surrounding atmosphere. Values at temperature near 37°C for solubility, diffusion coefficient and permeability of these gases have been given (Lambertsen and Idicula, 1975).

Time to stable-state counterdiffusion in these examples is 0.01 sec at one extreme and 12.4 sec at the other. Each is smaller than the one to two hours

TABLE I

Time for Development of a Stable State in Different Inert Gas Counterdiffusion Circumstances

Conditions				Results		
Gas 1	Thickness of membrane layers (μ)		Gas 2	Time to reach steady state (sec)	Last gas to reach steady state	P_i/π† at steady state
	Lipid (Layer A)	Aqueous (Layer B)				
N_2	5	160	Ne	2.2	N_2	1.035
	160	5		9.1	N_2	1.022
	160	160		12.0	Ne	1.224
	5	5		0.01	Ne	1.224
	10:7.75‡					1.227
N_2	5	160	He	2.2	N_2	1.046
	160	5		9.1	N_2	1.024
	160	160		12.4	N_2	1.261
	5	5		0.01	N_2	1.261
	10:7.11‡					1.268
Ne	5	160	He	2.0	Ne	1.011
	160	5		7.7	Ne	1.002
	160	160		10.9	Ne	1.037
	5	5		0.01	Ne	1.037
	10:4.47‡					1.043

†P_i/π is the relative supersaturation at the given conditions, or the absolute supersaturation P_i divided by the ambient pressure π. P_{1i} and P_{2i} are obtained from (15) and (17). In the example π is atmospheric pressure and $P_i = P_{1i} + P_{2i}$.

‡These values represent the worst possible layer ratio to achieve the maximum value of P_i and thus maximum supersaturation at the tissue interface. Note that P_i/π is a function of the ratio of the tissue thicknesses, not their absolute values. This ratio is calculated using (5) from Graves *et al.* It must be considered that this "worst case" will occur somewhere in the body.

observed to generate symptoms of gas bubble accumulation in man (Lambertsen and Idicula, 1975). Even when circulatory gas transport time (about 10 sec) and pulmonary washout time (half-time about 1.5 min) are added to the time required to reach a stable-state of counterdiffusion, it is evident that the total time in these examples represents only a small fraction of the time required for the full process of bubble formation and tissue distortion. This difference may represent the time for development of supersaturation and gas accumulation in tissue components adjacent to the specific membranes considered in this analysis.

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LITERATURE

Graves, D. J., J. Idicula, C. J. Lambertsen and J. A. Quinn. 1973. "Bubble Formation Resulting from Counterdiffusion Supersaturation: A Possible Explanation for Isobaric Inert Gas 'Urticaria' and Vertigo." *Phys. Med. Biol.*, **18**, 256–264.

Lambertsen, C. J., J. P. W. Cunnington and J. R. M. Cowley. 1975. "The Dynamics and Composition of Spontaneous, Continuous Gas Embolism in the Pig during Isobaric Gas Counterdiffusion." *Fedn Proc.*, **34**, 452.

——— and J. Idicula. 1975. "A New Gas Lesion Syndrome in Man, Induced by 'Isobaric Gas Counterdiffusion'." *J. Appl. Physiol.*, **39**, 434–443.

Landahl, H. D. 1953. "An Approximation Method for the Solution of Diffusion and Related Problems." *Bull. Math. Biophys.*, **15**, 49–61.

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