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Bubble Formation Resulting from Counterdiffusion Supersaturation: A Possible Explanation for Isobaric Inert Gas 'Urticaria' and Vertigo

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ABSTRACT. In recent simulated diving experiments, subjects have experienced intense itching, confluent maculopapular skin lesions and a severe vestibular derangement with vertigo and nystagmus. These effects have been observed when a gas mixture containing nitrogen or neon was being breathed while a second inert gas, helium, was present in the surrounding environment. Attempts to explain this phenomenon led to a study of counterdiffusion through two-layer composites. When the two layers differ in their relative permeabilities to the two diffusing species, and when the layers are arranged in the proper sequence in a counterdiffusion system, a steady-state supersaturation will result within the two layers. Bubble formation in an oil–water system and continual flow of gas into an intermembrane space in a two-membrane system were demonstrated experimentally: both effects were predicted from diffusion theory. In addition to providing a possible explanation for the itching phenomenon and vestibular derangement, the theory has a wide range of applications to physical and biological processes.

1. Introduction

In recent simulated deep diving experiments in pressure chambers, two unusual and incapacitating conditions have been encountered. In the first, subjects experienced a severe cutaneous itching, and this condition was often followed by raised, opaque white lesions which developed on exposed areas of the skin (Blenkarn, Aquadro, Hills and Saltzman 1971, Lambertsen 1972, Lambertsen, Idicula and Dickson 1973). In the second condition, the subjects developed severe incapacitating vertigo, nausea and nystagmus which persisted even after the nitrogen or neon breathing was terminated (Lambertsen and Sundmaker 1973). Both skin lesions and vertigo have previously been observed in individuals being decompressed after exposure to increased helium or nitrogen pressures. However, in the circumstances described here, and elaborated fully in detailed reports (Lambertsen *et al.* 1973, Lambertsen and Sundmaker 1973), the derangements occurred while the chamber pressure was *constant* and prior to beginning actual decompression. Specifically, the derangements occur when the subjects are in a chamber pressurized with a helium–oxygen mixture and shortly after they begin breathing a nitrogen–oxygen or neon–oxygen mixture at the same pressure through a mask or mouthpiece. The syndrome continues and even worsens as long as the inert gas breathed is different from that to which the exterior of the body is exposed. Areas of the body protected from the chamber environment by rubber suits ventilated with the gas breathed are not detectably affected.

The original observers of the cutaneous phenomenon (Blenkarn, Aquadro, Hills and Saltzman 1971) suggested that transient changes of concentration of an inert gas in tissue fluid generated gas-induced osmotic gradients which in turn created a water flux within the tissues (Kylstra, Longmuir and Grace 1968), and later suggested that such a water movement due to countercurrent fluxes of two gases induce effects encompassing several types of derangements encountered in diving (Hills 1971). The proposed water flux was presumed to be the cause of the itching and skin lesions described. These authors also emphasized that at a fixed ambient pressure, the sum of the tensions of helium and nitrogen in a tissue could not exceed the external hydrostatic pressure at which gases were breathed and therefore that bubble formation in the tissues was impossible under the conditions described. We provide an alternative explanation for the itching and demonstrable skin lesions, which involves actual formation of bubbles at a fixed environmental pressure and show by theory and by experiment that in almost any two-phase system through which counterdiffusion of gases takes place, supersaturation of a liquid with gases is possible (Graves *et al.* 1973). If nuclei are present and if certain other criteria are satisfied, bubbles will necessarily form and grow continuously. This consequence of steady-state counterdiffusion has not been recognized previously, and it has many implications in areas other than hyperbaric and undersea physiology.

2. Counterdiffusion theory

Diffusion is a process which depends on the gradient in chemical potential of the diffusing species, but for the purposes of demonstration, we will assume ideal conditions and express the potential in terms of partial pressure rather than concentration. Although a specific solubility relationship is not required for bubble formation, to simplify further discussion we will assume that these species obey Henry's law. With this restriction, Fick's first law can be written for diffusion of species i in substance j as

$$J_{ij} = -D_{ij} S_{ij} (\mathrm{d}P_{ij}/\mathrm{d}X_j) \tag{1}$$

for constant diffusivity D_{ij} and a linear geometry. J_{ij} is the flux of i through j expressed as volume of i per unit area of j per unit time and S_{ij} is the solubility of the i in j in volumes of i per volume of j per unit pressure. The quotient $\mathrm{d}P_{ij}/\mathrm{d}X_j$ is the partial pressure gradient of i in j. The diffusivity and solubility can be combined as a single permeability factor K_{ij} for convenience and the steady-state flux equation rewritten for a finite thickness slab as

$$J_{ij} = -K_{ij} (\Delta P_{ij}/\Delta X_j) \tag{2}$$

where ΔX_j is the thickness of layer j and ΔP_{ij} the partial pressure difference across j. For a system composed of layers A and B with gases 1 and 2 diffusing in opposite directions, an interesting situation can arise. Let us assume that layer A is in contact with gas 1 and that $K_{1\mathrm{A}} > K_{1\mathrm{B}}$. Likewise layer B is in contact with gas 2 and $K_{2B} > K_{2A}$. The gas reservoirs for 1 and 2 are assumed to be at equal pressures π, well mixed and large in volume. The resulting partial pressure profiles are illustrated in fig. 1. Their sum, shown as a dot and dash line, is greater than the reservoir pressures. This result implies that if a gas phase were present, it would be at chemical equilibrium only at these partial pressures, and that it would therefore tend to expand to reach mechanical equilibrium. Likewise, if a nucleating site were present and if phases A and B were liquid, then a bubble would tend to form. Surface tension at the nucleus-liquid interface, the degree of supersaturation and the size of the nuclei would be the three factors which would ultimately determine whether a bubble formed or not. From previous work, such as that reported by Evans and Walder (1969), there is good evidence that nuclei normally do exist in animal tissues. In our work with artificial model systems, we supplied nuclei when they were required.

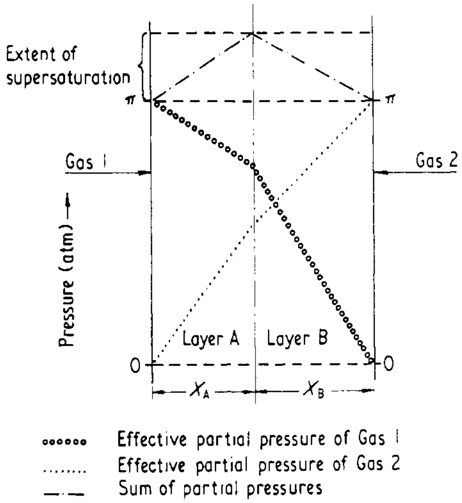

Fig. 1. This schematic representation demonstrates how supersaturation can be achieved in a two-layer system during a countercurrent diffusion experiment. In the real case Gas 1 can be He; Gas 2, N_2; Layer A, H_2O and Layer B, oil. The partial pressure profile of each gas is indicated. Bubbles can form if at least one of the two layers is a liquid.

As fig. 1 indicates, the maximum supersaturation is found at the interface. Through a quantitative analysis of this countercurrent diffusion process with the same limitations of permeabilities which are independent of concentration and equal gas pressures, one can show that

$$\frac{P_i}{\pi} = [\Delta X_B K_{1A}/(\Delta X_B K_{1A} + \Delta X_A K_{1B})] + [\Delta X_A K_{2B}/(\Delta X_A K_{2B} + \Delta X_B K_{2A})] \quad (3)$$

where P_i is the sum of the partial pressures at the interface. This equation implies that for a maximum value of P_i, material A should be a small fraction of the total diffusional resistance for gas 1 and material B a small fraction for gas 2. However, it may be shown that a necessary and sufficient condition for P_i to exceed π is that

$$K_{1A}/K_{2A} > K_{1B}/K_{2B}. \tag{4}$$

In other words, if the permeability ratios for the two materials differ and if the gases diffuse in the proper directions, P_i will always exceed π. It is not necessary that the permeability ratios be opposite for the two materials. If the permeabilities are assumed to be fixed by the choice of materials and gases, one can show from eqn (3) that the value of P_i and thus the probability of bubble formation will be maximized at a certain ratio of $\Delta X_A/\Delta X_B$ given by

$$\Delta X_A/\Delta X_B\,|_{\text{optimum}} = (K_{1A}\,K_{2A}/K_{1B}\,K_{2B})^{\frac{1}{2}}. \tag{5}$$

It is interesting to note that it is the value of this ratio, not the absolute value of the thickness, which determines P_i.

3. Experiments with an oil–water system

Proof that bubbles cause the itching phenomenon has involved many steps including the demonstration that gas bubbles are actually formed in tissue subjected to countertransport (Idicula and Lambertsen 1973, in preparation). We wished to show also that bubbles could form in a simple model system consisting of materials similar to those found in the body and chose a lipid layer (olive oil) and an aqueous layer (water) for this study. Literature data (Lever, Paton and Smith 1971) indicated that water was more than twice as permeable to helium as to nitrogen. Diffusivity data were not available for this oil, but we estimated that it would be slightly more permeable to nitrogen than to helium. The optimum thickness ratio for oil to water was calculated by eqn (5) to be about 2 and the expected supersaturation as high as 30% of ambient pressure with pure gases on the proper sides of this composite system.

We then constructed the cell shown in fig. 2 to see whether bubble formation could be observed during countertransport of helium and nitrogen. It consisted of two polymethylmethacrylate or glass halves with a hydrophobic microporous filter (Aquapel filter, 0·30 μm pore size, Millipore Corp., Bedford, Mass.) clamped between them. Water was layered on the filter support, oil was layered on the water and water-saturated gases were passed through the two sides of the cell. Helium circulated past the filter and nitrogen past the oil, each at atmospheric pressure and at flows too low to stir the oil detectably. Since the filter was not wet by the water, its pores were gas-filled and it contributed virtually no resistance to gas transport. No gas bubbles were seen rising to the oil–water interface from the microporous filter.

We had expected that even at one atmosphere absolute pressure there would be a significant probability of bubble formation. Hills (1967) has found that bubbles form at as little as one-third atmosphere supersaturation during a decompression experiment which is transient rather than steady state. A steady-state supersaturation of the same magnitude would be even more likely to result in bubble formation. Although supersaturation is a function of the

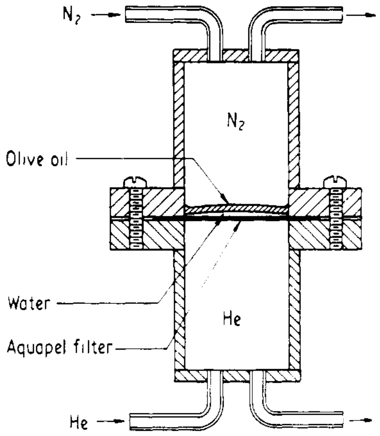

Fig. 2. A two-piece cell of the type illustrated was used in diffusion experiments. For two-membrane experiments, a washer-like ring with a hypodermic needle connection was clamped between the two halves and a membrane was sealed between either face of the washer and a cell half.

ratio of the two layer thicknesses, the time necessary to achieve steady-state conditions is a function of absolute thickness. For this reason we made the layers as thin as practical (total thickness about five millimetres) and estimated that a reasonable approach to steady state could be expected in five to ten hours. Bubbles were seen after about six hours. They formed at the liquid–liquid interface, grew at the interface and eventually broke free and rose to the oil–nitrogen interface. They did not arise at the microporous filter. This was validated at times by placing a sheet of ordinary filter paper on top of the Aquapel to ensure that bubbles were not arising from the latter. The experiment was continued overnight and the next morning no further bubbles were seen. However, when artificial nuclei in the form of crushed glass particles were added, bubble evolution resumed within a few hours. By repeated 'seeding' of the interface as the glass particles lost their effectiveness, continual bubble evolution was possible. Control experiments with the nitrogen and helium entry points reversed, or with the same gas on both sides of the oil–water system, failed (as expected) to produce bubbles. These results were reproduced at least six times. At elevated pressures, the degree of supersaturation and therefore the rate of bubble growth can be expected to be greatly enhanced.

4. Results for a two-membrane system

A liquid–liquid system is not necessary for the counterdiffusion phenomena to occur, nor do the two phases through which diffusion takes place need to be in direct contact. A gas space may be interposed between two solid membrane phases, for example. Since access to this space is relatively easy to obtain, the build-up of pressure or continuous flow of gas into this space can be measured easily. Both effects were demonstrated with a polyethylene membrane about 13 μm thick and a silicone copolymer membrane (General Electric 1969) about

500 μm thick separated by a 3200 μm gap. Permeability data for the membrane materials are shown in table 1. The polyethylene is more permeable to He than to N_2 and the same is true for the silicone copolymer. However the ratio of the permeabilities differs considerably. The optimum thickness ratio for silicone to polyethylene found from eqn (5) for He–N_2 is about 120 rather than the experimentally employed ratio of about 40. Since oxygen was present in the experimental system, the thickness ratio for He–O_2 was also computed and an optimum of about 90 was found in this case.

Table 1. Membrane permeabilities

	He $\times 10^{-10}$	N_2 $\times 10^{-10}$	O_2 $\times 10^{-10}$
Low density polyethylene (Tuwiner 1962)	0·6	0·09	0·3
Silicone rubber (General Electric 1969)	30	25	50

Permeabilities are given as cm^3 of gas at STP per cm^2 of membrane per sec for a pressure gradient of 1 Torr per cm.

Despite the fact that optimum thicknesses were not used, when the polyethylene was exposed to pure helium and the silicone to room air (each at one atmosphere) a steady gas flux of about 0·4 cm^3 h^{-2} (or 0·03 cm^3 of gas at STP per cm^2 of membrane per hour) was measured entering the intermembrane space. This flux was measured by the movement of a fillet of water in a precision bore capillary tube. The gas was allowed to escape to the atmosphere so that pressure did not build up between the two membranes.

The measured flux was a steady state phenomenon since (after an initial transient of higher magnitude) the flow remained constant over the course of a six day experiment. During this time, the total volume of gas entering the space was more than thirteen times the volume of the space itself. Transient fluxes, as typified by the expansion of an air-filled balloon placed in an environment of hydrogen, are well known. They result from unequal permeation rates of two gases through a single membrane, but are quite different from the steady flux described here.

The gas composition in the intermembrane space was not measured, but presumably it would be a helium–nitrogen–oxygen mixture whose composition was determined by the relative permeation rates of the three gases. Next, the exit tube was submerged under water and the gas forced to bubble out under some pressure. The tube was pushed lower and lower every few hours, the intermembrane pressure eventually reaching about one foot of water ($3{\cdot}6 \times 10^3$ N m^{-2}) above atmospheric pressure.

5. Discussion

There are many applications of the two-layer diffusion concept and mechanism. Some of these include new types of gas separation and analysis devices, a new method for study of nucleation processes and a method for recovering as work some of the free energy of mixing of two gases. If chemical activities are considered rather than partial pressures, other implications become evident. For example, reaction rates are generally proportional to the product of concentrations, so that one might find that in counterdiffusion flux of two species, a reaction takes place only in the region between two diffusion barriers. The analyses of three-layer and multi-layer systems and of non-ideal solubility and diffusivity of gases are beyond the scope of this study. New transient phenomena are undoubtedly also possible with a two-layer system under counterdiffusion, and these too remain to be explored.

Animal and human studies will continue to be important in answering questions related to formation of skin lesions. Since the itching phenomenon develops rapidly, the total thickness of the diffusion pathway must be low. On the other hand, the probability that natural biological structures would have the optimal thickness ratio specified by eqn (5) is rather low. A high pressure, therefore, might be necessary to achieve even a moderate degree of supersaturation with helium and nitrogen. Variations in the degree of perfusion, the relative thicknesses and the composition of critical components of the several cutaneous layers might explain why lesions appear first in certain areas and not simultaneously as a generalized rash over all exposed regions of the skin. The complexity of the real situation can best be appreciated by reference to recent work on skin permeability (Scheuplein and Blank 1971).

The skin lesions observed at fixed ambient pressure resembled those of skin 'bends' which occur during actual decompression, and the opaque white appearance of some lesions in addition to subsequent erythematous changes strongly suggested the presence of numerous tiny gas bubbles (Lambertsen 1972, Lambertsen *et al.* 1973). On the basis of the physical experiments described, we have found that bubbles can form in a simple system at fixed ambient pressure and thus can be expected to be the underlying cause of the cutaneous itching and pathological lesions observed in man (Blenkarn *et al.* 1971, Lambertsen *et al.* 1973). Because of the low metabolic rate of skin and fat, the total gas pressure of skin and subcutaneous tissue should be closer to ambient than for tissues with a high metabolic rate. However, even if the sum of gas tensions in skin is lower than ambient as a result of the metabolic use of oxygen, the counterdiffusion mechanism is capable of generating inert gas supersaturation to levels as great as 30% of ambient pressure. The added saturation caused by counterdiffusion can therefore be so great (even at one atmosphere) that the net effect is a supersaturation.

It was the primary intention of this study to examine the physical events associated with inert gas counterdiffusion. Since the results show that an inert gas supersaturation and bubble formation can occur even at fixed ambient pressure, it is necessary to consider that effects of gas counterdiffusion may include not only the cutaneous lesions observed, but also the vestibular derangement described by Lambertsen and Sundmaker (1973). Since gross changes have been induced in one anatomical structure, the skin, changes may also have been produced in other structures or locations. Detailed study in the intact animal should therefore include a search for other possible sites of derangement related to the phenomenon of counterdiffusion supersaturation. The composite clinical expression of any such effects should be designated the 'counterdiffusion syndrome'.

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RÉSUMÉ

Formation des bulles comme le résultat de la sursaturation causée par la diffusion inverse: Une explication possible de 'l'urticaire' et du vertige produits par le gaz inerte

Dans les essais récents relatifs à la plongée simulée, les sujets ont éprouvé un prurit fort, des lésions cutanées maculo-papuleuses confluentes, ainsi qu'un dérèglement vestibulaire avec vertige et nystagmus. On a observé ces effets quand on a respiré un mélange gazeux contenant de l'azote ou du néon, tandis qu'un autre gaz inerte, hélium, était présent dans le milieu environnant. Des efforts visant à l'explication de ce phénomène ont conduit à l'étude de la diffusion inverse à travers des composés consistant en deux couches. Si les deux couches ne s'accordent pas dans leur perméabilités relatives à l'égard de deux gaz diffusants, et si les couches sont arrangées dans la propre succession dans un système de diffusion inverse, on va obtenir une sursaturation stationnaire dans ces deux couches. On a démontré expérimentalement la formation des bulles dans un système huile–eau, ainsi qu'un flux continu du gaz dans l'espace entre les membranes en cas d'une système de deux membranes; chacun de ces deux effects était prédit sur la base de la théorie de diffusion. En plus de fournir une explication possible du phénomène de prurit et de dérèglement vestibulaire, la théorie a une rangée bien large d'applications aux processus physiques et biologiques.

ZUSAMMENFASSUNG

Die aus der Gegendiffusion-Übersättigung sich ergebende Blasenbildung: Eine mögliche Erklärung der Inertgas-'Nesselsucht' und -Schwindel

In den neulich veranstalteten simulierten Tauchexperimenten haben die Subjekte ein intensives Jucken, konfluierende maculös-papulöse Hautläsionen, sowie eine ernste vestibuläre Störung mit Schwindel und Nystagmus erfahren. Die obigen Effekte wurden beobachtet, wenn ein Stickstoff oder Neon enthaltendes Gasgemisch zur Atmung benutzt wurde, wobei ein anderes Inertgas, Helium, in dem Umgebungsmedium vorhanden war. Die zwecks Erklärung dieses Phänomens angestellten Versuche führten zu einer Untersuchung der Gegendiffusion durch aus zwei Schichten zusammengesetzten Körper. Wenn sich die beiden Schichten in bezug auf die relativen Durchlässigkeiten für beide diffundierende Gase unterscheiden, und wenn die Schichten in der richtigen Reihenfolge eines Gegendiffusionssystems angeordnet sind, wird sich eine stationäre Übersättigung innerhalb der beiden Schichten ergeben. Es sind die Blasenbildung in einem Öl–Wasser-System sowie die stetige Strömung des Gases in den Zwischenmembranenraum experimentell gezeigt worden; beide Effekte wurden aus Diffusionstheorie vorhergesagt. Die Theorie liefert nicht nur eine mögliche Erklärung des Juckenphänomens und der vestibulären Störung, sondern besitzt auch vielerlei Anwendungen in den physikalischen und biologischen Prozessen.

Резюме

Образование пузырей, вызываемое противодиффузионным перенасыщением: Возможное объяснение вызываемых инертными газами крапивницы и головокружения

В производимых в последнее время симулированных водолазных экспериментах субъекты испытывали сильный зуд, сливающиеся пятнисто-прыщиковые поражения кожи, а также сильное расстройство преддверника, сопряженное с головокружением и нистагмом. Эти

эффекты наблюдались при дыщании содержащей азот или неон газовой смесью, причем в окружающей среде находился другой инертный газ, гелий. Попытки объяснения этого явления привели к изучению противодиффузии через двухслойные системы. Если оба слоя имеют неодинаковые относительные проницаемости по отношению к обоим диффундирующим газам, и если эти слои расположены в соответственном порядке в противодиффузионной системе, то в этих двух слоях образуется стационарное перенасыщение. Образование пузырей в системе масло-вода и постоянный поток газа в межмембранное пространство двухмембранных систем были показаны экспериментально; оба эффекта были предсказаны на основании теории диффузии. Независимо от возможного объяснения явления зуда и расстройства преддверника эта теория находит большой ряд применений в физических и биологических процессах.

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