RELATIONS OF ISOBARIC CAS COUNTERDIFFUSION AND DECOMPRESSION CAS LESION DISEASES

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Purpose and Perspective

A personal goal at this Conference is to use the information and concepts of isobaric counterdiffusion to bind together three key elements determining decompression safety. These elements, which cannot sensibly be separate in diving, still tend often to be considered separately. They are the oxvzen effects (1), the several forms of isobaric inert gas exchanges (2) (3) (4) and the forms of decompression-induced inert gas elimination (1).

Oxvzen simultaneously provides: the most predictable physical aid to degassing, a complex of physiologic forces which conceivably modify decompression-relevant de-gassing process, a component of gas spaces or emboli, and variable forms of toxic effect which conceivably can modify decompression-relevant degassing. Only the positive (the physical) role has been specifically demonstrated.

Decompression Gas Elimination would do no harm in the absence of free gas phase growth.

Isobaric Inert Gas Counterdiffusion can aid degassing or it can interfere with degassing during decompression. It can generate stable or transient gas supersaturation, gas lesions and gas emboli at stable ambient pressures, or it can generate transient subsaturation.

The relationships of oxygen, decompression and counterdiffusion are clear on conceiving a decompression or therapy as a series of instantaneous (isobaric) periods in which all ongoing forms of gas exchange and gas affect exist simultaneously (as they do in reality).
A second personal goal is again to urge use of the term "Gas Lesion

Diseases," devised to encompass the several overlapping and impure pathologic stases now obviously related and sometimes concurrent in exposures to unusual pressures and atmospheres (2). The still conventional blanketīng designations of "Decompression Sickness" or "GasEmbolism" are not adequate for present and future diving or hyperbaric medicine, and have led to use of such foolish terminology as "isobaric decompression sickness."

Table 1 indicates the scope of major forms of gas lesion diseases, different in their inducing circumstances or their consequences. The resulting symptoms or objective signs (e.g. neural, vestibular, cutaneous, or local pain may be similar or different, and do not themselves describe or represent the specific disease or fundamental mechanism.

Table 2 emphasizes the clearly obvious fact that the ultimate primary basic for gas phase generation in decompression or in isobaric gas lesion diseases is an excess pressure of gases in peripheral tissues

includins peripheral blood. The complex consequences of bubble growth and bubble-tissue interactions are sequels to the primary event, without which no pathologic effects would occur. The table also emphasizes that the very occurrence of gas lesions and emboli in isobaric states indicates the pre-existence or continuous formation of "nuclei" in normal tissue fluids. Asterisks (*) mark venous gas embolism in four of the forms of gas lesion disease to call attention to the possibility that venous gas embolie process may conceivably lead to arterial gas emboli. While venous gas emboli affect blood and lung, arterial gas embolie phenomena should be considered as having access to all tissues and arterioles. It is therefore here cited as "systemic" embolization.

Table 1.

MAJOR FORMS OF GAS LESION DISEASES	SOURCE or GAS PHASE
Pulmonary Overexpansion	
Sytemic gas embolism (Arterial)	Lung
Pneumothorax	
Subcutaneous/Mediastinal Emphysema	
Istrogenic or Traumatic Gas Embolism	
Venous	
Arterial	Extrinsic
Systemic (Arterial)	
Decompression Sickness (Post Hyperbaric, Hypobaric)	Peripheral Tissus
Cutaneous	
Deep Tissus	
Venous Embolic	
Systemic (Arterial)	
Superficial Isobaric Counterdifusion Sickness (Stable State)	Peripheral Tissus
Cutaneous	
Vestibular	
Venous Embolic	
Systemic (Arterial)	Peripheral Tissus
Superficial Isobaric Counterdifusion Sickness (Transcient)	
Venous Embolic	
Systemic (Arterial)	

Table 2.

GAS PHASE DEVEIOPMFNT IN DIVING DECOMPRESSION AND IS0BARIC COUNTERDIFUSION

Inert gas uptake la not harmful in divinq, Inert gas elimination is not harmful, and decompresion itself is not harmful.

Gas phase development is the pathophysiologic event, whether mlcroscopic or gross. It is itself the result of an elevation of tissue inert gas pressure above ambient.

It is most probable that gas lesion development result from growth of normally present gas nuclei, as indicatad by the isobaric development of gas lesions at one ATA, without prior compression or decompresion.

Gas lesion do not produce detectable symptoms or objective signs at all target sites.

At any site, symptoms and objective signs require time to develop after gas phase development has bagun.

The more conservative the limitation of degree of inert gas excess, the lese severe should be the degree of symptoms or objective signs, of any type at any site.

Localization of gas phase development.

Some effects of early stages of isobaric gas phase development are precisely visible in experiment. Most of those for early stages of decompression sickness are not. Like the counterdiffusion processes, decompression sickness (excluding pulmonary barotrauma) is not a single,"yes or no" event or "threshold" phenomenon. It is potentially a generalized systemic process of gas phase separation and expansion, which may become severe enough in some microanatomical locations to be clinically diagnosed. It can probably simultaneously go unrecognized in many different other locations. Decompression sickness, like the counterdiffusion processes, is surely a diffuse continuum of graded degrees of pathophysiologic event and effect, simultaneously occurring in many scaetered tissue locations, each of which has its own local "stress-effect" consequences. Categorical designations of decompression sickness effects, as for example into Type I and Type II, have been medically and operationally practical. However, they are not descriptors of the fundamental, decompression-induced systemic processes,'or the manner in which they can be expected to be aggravated by forms of isobaric counterdiffusion (1) (2).

Against the license of these "Perspectives" the following review will emphasize empirical observations in experiments with isobaric counterdiffusions

Table 3.

ISOBARIC INERT GAS COUNTERDTFFUSION((Superficiel and Deep Tissue Forms)

Two forms of isobaric counterdiffusion supersaturation can produce gas lesion. or venous gas emboli.

"Superficial" Isobaric counterdiffusion occurs through body surface when air or N2-O2 is breathed and the external environment is helium.

"Deep tissue- Isobaric counterdiffusion occurs when any different inert gases are breathed in sequence.

Each form of isobarie counterdiffusion can lead to inert gas supersaturation of involved tissu.., This supersaturation and gas embolus formation is now entirely preventable, by proper choice of operational gases and sequences.

Each form of isobaric generation of supersaturstions can potentially exaggerate a concurrent decompression supersaturation and related gas lesions.

Each form of isobaric counterdiffusion can lead to inert gas subsaturation of involved tissus.. This result is operationally and therapeutically useful.

"Isobaric" gas exchanges of all types should be considered as able to occur in the course of decompression procedures, as well as at stable pressures.

Hyperoxygenation therapy is rational for isobaric counterdiffusion gas lesions, as it is for gas lesions of decompression sickness.

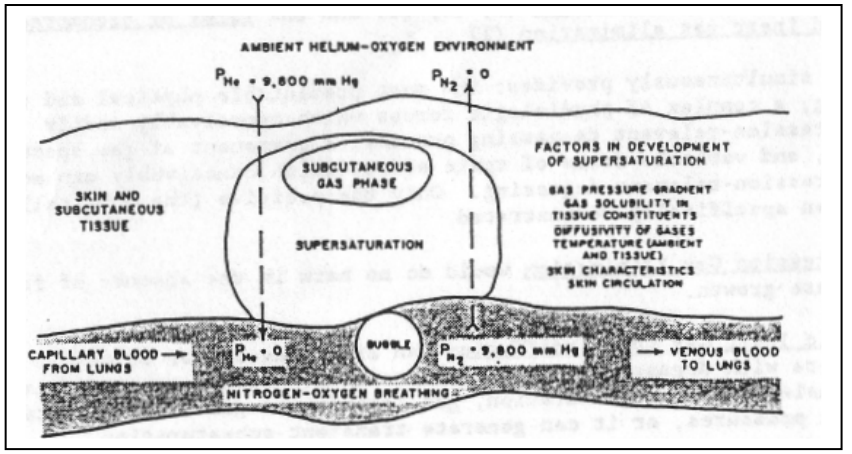


Fig. 1. Dermal Lesion in Superficial Isobaric counterdiffusion.

Schematic of circunstances in gas bubble formation without change in ambient pressure. Encess inert gas saturation develops due to more rapid flux of one gas, e.g. helium, into the tissue and capillary as a less rapidly moving second gas, e.g., nitrogen. diffuses out to the atmosphere (4).

Counterdiffusion was first recognized and named as the cause of gas lesion development in individuels who for a broad physiologic study (3) were saturated in a helium atmosphere at constant pressure and who then breathed neon-oxygen-helium and nitrogen-helium-oxygen mixtures at pressures equivalent to 400, 700, 900, 1200 fsw (3) (4) (5). These individuals developed severe cutaneous itching, the first symptom of a larger problem that was partially solved by encompassing them in a gastight suit into which they exhaled. Only regions of helium-exposèd skin, the scalp, hands, and skin of the face where the mask did not cover, continued to itch (3). Cutaneous symptoms encountered in previous experiments at a lower pressure were discounted as not attributable to gas lesion development (6).

In the human subjects, continued exposure to ambient helium while breathing a slower diffusing inert gas produced hard, raised, white, bloodless, cutaneous lesions. It also produced severe vestibular dysfunction (3) (4). What did the human studies tell us about where bubbles foret? Do they form in the local blood vessels or in tissue spaces (Fig. 1)? The cutaneous lesions looked as though "bubbles" had formed locally in tissue and forced out the blood. When these lesions in man were dissected with a needle et the high chamber pressures, no bleeding occurred. Venous gas embolism was not suspected.

Depth ata	EXPERIMENTAL CONDITIONS breathing gas/chamber gas						
	He/He	N_2/He	Ar/He	N_2O/He	SF_6/He	He/N_2O	He/Ar
1		+	+	+	0	0	0
2		+	+		0		
3		+	+		0		
4	+	+	+		0		
7	+	+	+				
10	+	+	+				

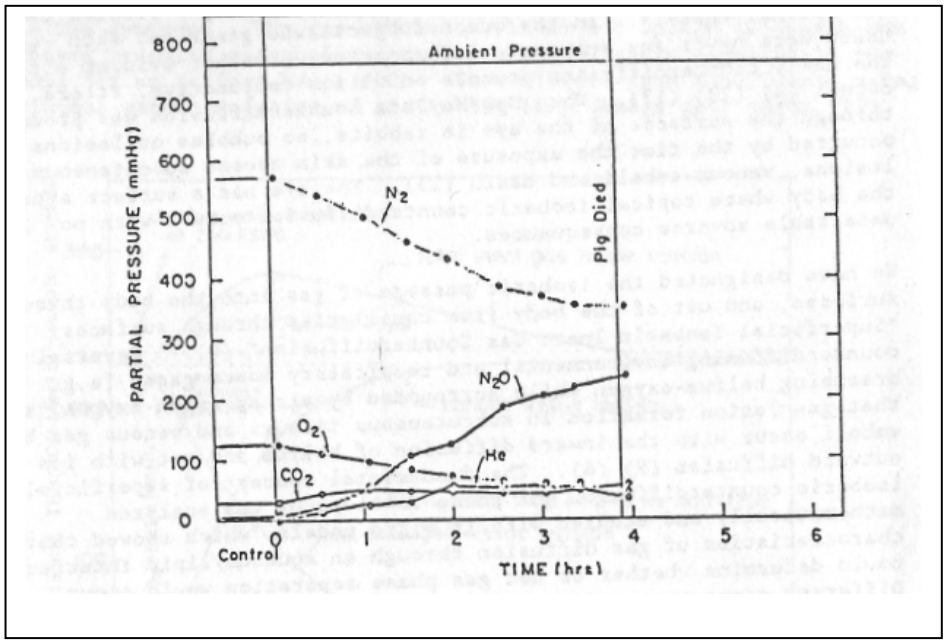
Fig.2 Exposure of pigs to superficial Isobaric Gas Counterdifusion at Ambient Pressure from 1 to 10 ATA.
A (+) indicates that lesions where observed, an open circle (0) that no lesions were seen. The severity of lesions for any given depth and timle was : N2O > Ar > N2 > He (9).

After the observations in human subjects, the cutaneous gas lesions produced in pigs by having helium outside animais which breathed either nitrogen, argon, or neon with oxygen (Fig. 2) (19)?. Cas spaces formed not only in the most superficial layers of the skin, but also formed throughout the skin thickness, and even in subcutaneous tissue spaces. The ptocess also reached blood vessels and caused a continuous venous gas embolism (9) (4) (2). In fact the gas spaces dissect the tissues as gas lesions expand (Fig. 3) (4) (8). The lesions generate after an initial time lag, and the process eventually leads to death from continuous venous gas embolism (2), (9). Postmortem examination shows that the vena cava is filled with gas bubbles (Fig. 4), and vessels of deep tissues such as kidney, heart and retina may unexpectedly also contain free gas (2), (9). Measurement of gas in an artificial subcutaneous depot illustrated the pattern of deep subcutaneous gas environment throughout the lethal process (Fig. 5) (23).

"Superficial Isobaric Inert Cas Counterdiffusion."

The new lethal environmental hazard was christened "Superficial Isobaric Inert Cas Counterdiffusion Cas Lesion Disease." It is easily produced at one atmosphere without ever compressing or decompressing the experimental animal. However, the appropriate gases must be used. An effective combination is nitrous oxide breathing while the animal is surrounded by helium (9).

Other structures besides the skin and venous circulation are involved in isobaric counterdiffusion. Vestibular dysfunction occurred early at a stable pressure equivalent to 1200 feet of ses water in individuals breathing a neon-helium-oxygen mixture while surrounded by helium. In one, nausea, vomiting, and vertigo were so severe that he could not take even fluids by mouth for several days. After about five days, recovery allowed decompression (3).



What mechanism might produce such an unexpected and incapacitating "vestibular" effect at constant ambient pressure? It occurred to us that the round window membrane between the middle Car and inner Car was functionally an external surface of the body, rather than an internal structure, in spite of being located deep, internai to the thin cympanic membrane (4). Helium might therefore at the very large ambient helium partial pressure gradients experienced in 38 ATA experiments (nearly

A specific and basic question is "What is the mechanism of origin of the bubbles in supersaturated tissue and capillary which lead to lethal20,000 mm. Hg.), diffuse through the tympanic membrane, then through the round window while the respired neon gas was escaping more slowly from the endolymph into the middle ear (4). Helium passage through the tympanic membrane of cats was measured, and found to be rapid (10) (11). To learn whether isobaric counterdiffusion would produce bubbles in endolymph we observed the round window by direct microscopy in guinea pigs breathing nitrous oxide et one and at two atmospheres with helium external to the round window (12). No bubbles appeared in the inner ear fluid after several hours of this exposure. The specific cause of this severe and incapacitating isobaric gas'lesion in man therefore still remains an unsettled matter. It may relate to occurrence of as yet undetected arterial gas emboli.

The absence of effects of superficiel isobaric counterdiffusion on the human eye is similarly unexplainable. Post-mortem photographs of the retins, through the lens of the eye after prolonged counterdiffusion of pigs with nitrous oxide and helium at one ATA show gas bubbles deep, in the retinal vessels. In the human subjects who generated skin lesions there were never any symptoms, inflammation, or other evident effects of the early counterdiffusion process on vision conjunctiva, sciera, or cornes (4) (23) (13). When N20/He/2ata counterdiffusion was produced through the surfaces of the eye in rabbits, no bubbles or lesions had occurred by the time the exposure of the skin caused subcutaneous gas lesions, venous emboli and death (13). The eye has a surface area of the body where topical isobaric counterdiffusion occurs with no detectable adverse consequences.

We have designated the isobaric passage of gas into the body through its surfaces, and out of the body from capillaries through surfaces, "Superficial Isobaric Inert Cas Counterdiffusion" (4). Reversai of the counterdiffusing environmental and respiratory inert gases (e.g. breathing helium-oxygen while surrounded by air or argon-oxygen) showed that gas lesion formation in subcutaneous tissues and venous gas bubble emboli occur with the inward diffusion of helium and not with its outward diffusion (9) (4). The fundamental concept of superficial isobaric counterdiffusion gas phase development was analyzed mathematically and studied with in vitro modela, which showed that the characteristics of gas diffusion through an aqueous/lipid interface could determine whether or not gas phase separation would occur. Different gases were made to diffuse in opposite directions through two adjacent but different materials (water and olive cil) (5). Relative diffusion rates for gases are determined by diffusivities and membrane permeabilities, which together determine whether a gas "supersaturation" would be large enough to cause bubbles to grow. Supersaturation was predicted to be maximum when the square root of the product of the diffusivities was equal to the ratio of the thicknesses of the membrane (5).

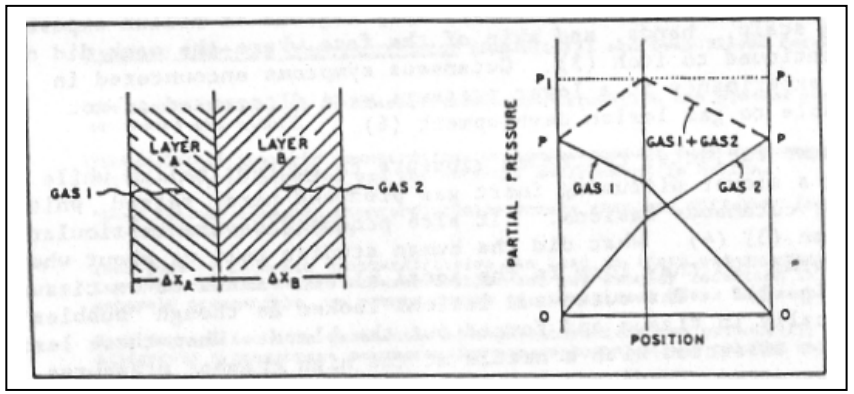


Fig. 6. Cas Partial Pressure Profiles Resulting From Steady Counterdiffusion of Two Inert Cases.

The diagram on the left indicates concept of diffusion of tvo différent gases (1 and 2) across a dual barrier (layera A and B) having différent lipid-water compositions and, hance, different permeabilities. The diagram on the right shows the gradients resulting from this counterdiffusion.

When the gases and barriers are so selected that the resistance to transport is low in the first layer encountered and high in the second, the sum of the gas partial pressures is shown mathematlcally to be above the ambient pressure and is at a maximum at the barrier interface (5).

Such avents may be occurring in many millions of micro-loci during a human exposure.

The potential for development of a very large degree of gas supersaturation in exposed tissues is very great. At 1200 feet of seawater (or 38 ATA where the phenomenon became recognized in man), it should be theoretically possible to generate about 9 atmospheres of supersaturation if the process is allowed to proceed to its maximum extent (4) (5).

A specific and basic question is "What is the mechanism of origin of the bubbles in supersaturated tissue and capillary which lead to lethal venous gas embolism and destructive extravascular lesions at one ATA. Without compression or decompression or even movement?" Without nucleation gas bubble should not form, but bubble do form. A necessary explanation must therefore be that they are. Inevitably and continiously pre-existing gas nuclei in normal tissue in life at one ATA. Whether nuclei persist or randomly form and regress, or both. Such nuclei would appear from the isobaric experiment to be functionally very stable. Since the counterdiffusion syndrome occurs in humans even after compression to 38 ATA. These empirical observations

in animals and man must be kept part of any theoretical discussions of yoles of nucleation in diving and decompression.

The Superficial Isobaric Inert Gas Counterdiffusion phenomenon deserves the designation as one of the "Gas Lesion Diseases" (4). In experiments with pigs at sea level, the process of N20/He/1 ATA superficial counterdiffusion could cause death within an hour and a half when the whole animal body was exposed to helium (9). To slow this rapid process

sufficiently in some experiments for detailed study, only the hind quarters of other pigs were exposed (by enclosing them within a heliumfilled plastic bag). Removing the flow of gas emboli from the vena cava with a bubble trap prevented them from reaching the lungs and extended the life of the animal (14). This bubble trapping enabled measurement of the volume rate at which gas emboli were generated by counterdiffusion through a measured area of skin. It also allowed detailed study of the local lesion development, from initial to severe stages. With the animal breathing nitrous oxide and exposed to helium over the lower body and nitrogen over the upper body, the N20/N2/1 ATA counterdiffusion produced no visible effect, but the N20/He/1 ATA counterdiffusion formed cutaneous gas lesions and venous gas emboli, disrupted skin capillaries, and had a grossly destructive effect on the skin and subcutaneous sites. A very sharp line of visible demarcation existed between the helium exposed region and the nitrogen exposed region.

Venous gas embolism does not appear at once in such experiments (2). There is a delay of approximately one half to one and one half hours before gas emboli begin to accumulate in the bubble trap in the vena cava, after which the rate of gas embolism becomes a stable process (2). During this delay gas lesion development is occurring in the periphery. At two atmospheres pressure, the volume rate of venous gas embolization is the saure as at 1 ATA (about 200m1/hr./sq.m) but the mass rate is twice as great as at one atmosphere (14). The composition of the gas emboli that collect in the vena cava bubble trap is mostly nitrous oxide, some helium, along with a little nitrogen, oxygen, carbon dioxide, and water vapor (2) (14). It is important to recognize that the gas composition of venous emboli can not be considered to reflect the process of counterdiffusion at the skin surface, since the venous blood tomes from many sources, superficial and deep.

This process of N20/He/1 ATA Superficial Counterdiffusion can be used as a controllable experimental tool to study early development of peripheral gas lesions and the progression of any pathophysiologic effects of gas emboli in the venous blood and "bombarding" the lungs.

The magnitude of effects on blood and lung can be experimentally controlled by changing the skin surface area which is subjected to counterdiffusion, or by changing the gas gradients, or by changing ambient pressure. If the area is small enough, there will be no increase in pulmonary artery pressure even though venous bubbles occur. With larger skin areas the gas embolism causes a rise in pulmonary arterial pressure. In pigs which are monitored by venous and arterial Doppler probes, no bubbles appear to cross the lungs despite constant and continuous bombardment over six to eight hours. However, in one animal with a patent septal defect, death occurred early and gas bubbles were present in grossly visible amounts in arterial blood. It was only when normal pigs were near death from severe venous gas embolism that visible arterial emboli were found (17). Undetectable gas emboli could of course pass undetected, as suggested by the present of gas phase in deep tissues in port mortem examinations.

Other pathophysiologic events occur prior to death. Peripheral vascular resistance increases and the blood plasma volume decreases (17). We have assumed these are effects of changes in capillary permeability and injury to peripheral vessels through undefined chemical or physical effects of peripheral gas lesions. No significant change in blood coagulation factors occurred, however, even when the animais were nearly dead. The eventual cause of death was respiratory failure with a shocklike syndrome. The gas bubble emboli do not appear to damage the pulmonary vascular endothelium even when steady state embolism is continuous for up to four hours (20). This differs from experiments using contïnuous venous infusion of air, where lung damage does occur (19).

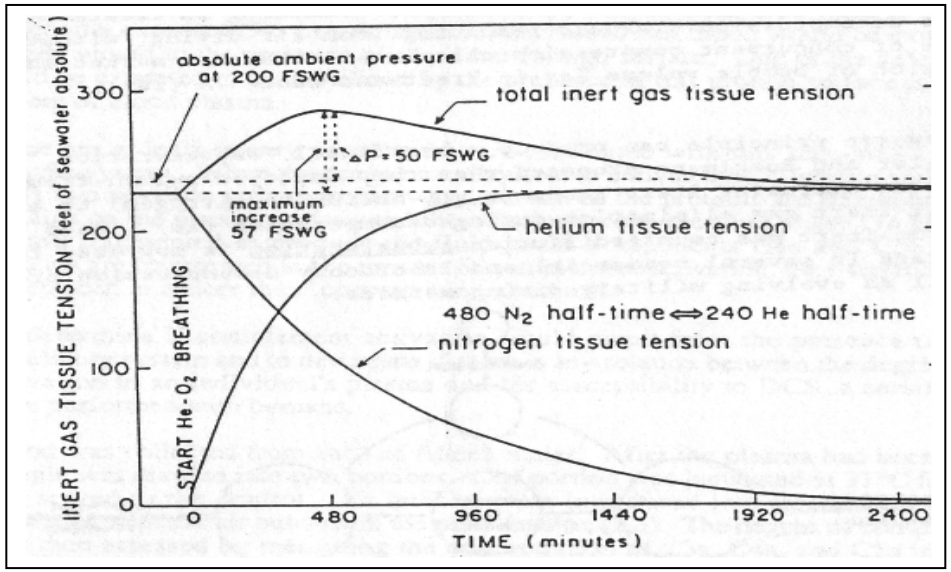


Fig. 7. Diagram of "deep tissue" isobaric supersaturation caused by breathing helium after prolonged exposure to N2-02 mixture. Total inert gas pressure rises, and a composite supersaturation is maintained for many hours in "slow-perfusing" tissues. The opposite affect, an equivalent degree and time course of useful subsaturation, is subsaturation, is expected with breathing N2-02 after prolonged exposure to helium (4).

"Deep Tissue Isobaric Counterdiffusion"

Inert gas counterdiffusion in another form can create supersaturation irn the deep tissues, even when the skin is underwater or not exposed to a different inert gas. "Deep Tissue Isobaric Counterdiffusion" was selected as the narre to designate the supersaturation or subsaturation which occurs when a diver "switches" from breathing one inert gas-oxygenr mixture to a different inert gas carrier for oxygen (4) (15). After such a switch, from a "slower equilibrating" to a "faster equilibrating " gas (e.g. from air to helium-oxygen) a slowly perfused tissue saturated with nitrogen will become transiently supersaturated by entry of the more rapidly exchanging helium. This deep-tissue supersaturation continues for many hours, as predicted (4) and as D'Aoust demonstrated by bubble detection in goats (15). The process has not been widely encountered in man, but has been observed in helium exposures following shallow nitrogen saturation (22). A long transient of venous

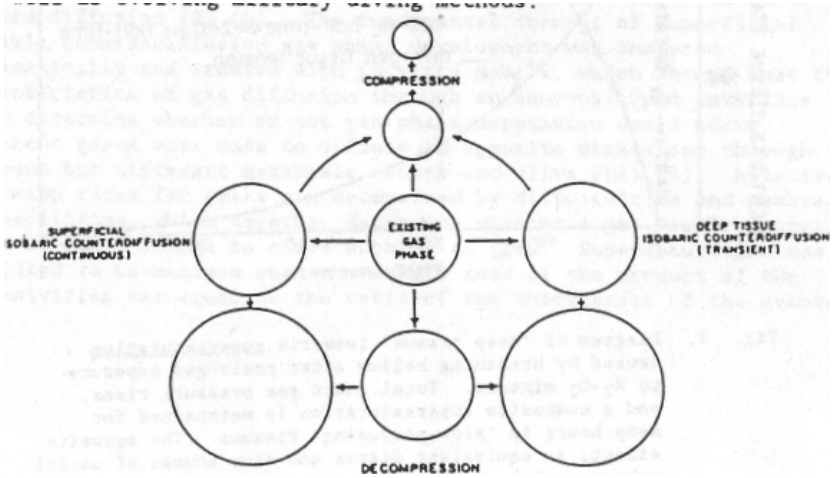


Fig. 8. Interactions among gas phase decompression, compression and isobaric states in several forms of gas lesion (2).

gas emboli can develop (7) (15), and it should for practical purposes of diving safety be assumed until proven otherwise that gas lesions generated by decompression in poorly perfused tissues will be expanded by "deep tissue isobaric counterdiffusion" (2). It is for this reason that helium should not be substituted for air breathing in treatment of severe decompression sickness resulting from air diving, without the degree of concurrent compression calculated to assure marked immediate reduction of bubble volume (as in Treatment Table 7A (18).

The reverse principle can produce a beneficial "subsaturation," however, as Keller and Buehlmann proposed when they employed switch from faster to slower diffusing inert gases (e.g., helium to nitrogen) to accelerate overall inert gas elimination during decompression (16). Deep tissue isobaric inert gas counterdiffusion subsaturation is now used to advantage in several commercial and laboratory decompression procedures, as well as evolving military diving methods.

Interactions of Counterdiffusion Processes. Oxygen and Decompression

The concepts and empirical observations elaborated above illustrate that several types of gas lesion diseases are associated with diving, and can co-exist in two or more forms (1) (2). Decompression must necessarily exaggerate the effects of isobaric gas lesions, and isobaric supersaturations should also be conceived as necessarily exaggerating decompression incidents and the problems of decompression sickness therapy. In ail, the informed use of increased oxygen pressures offers a means of prevention as well as a means of therapy (1). For the counterdiffusion diseases, absolute prevention of each is now possible through proper choice of respiratory and ambient gases or gas sequencing. Practical precautions recommended early to prevent or minimize adverse interactions include (2):

° Avoidance of mask breathing of air or N2-02 while body surface or the ear canais are exposed to helium.

° Avoidance of an abrupt change from air or N2-02 breathing to heliumoxygen at a constant or decreasing pressure.

° When it is clearly desirable during therapy for severe decompression sickness to proceed from air or N2-02 breathing to prolonged exposure at a higher ambient pressure than is sensible for nitrogen, compression on helium is recommended despite the potential hazard of deep-tissue counterdiffusion supersaturation (18). Such change to helium should be accompanied by prompt compression and appropriate oxygen pressure, to counter the tendency for bubble growth or development.

° Switch from prolonged helium breathing to air or N2-02 breathing to achieve deep counterdiffusion subsaturation is a desireable aid to prevention of decompression sickness in helium diving. In a pressure chamber it should occur by a change in ambient atmosphere rather than by mask breathing, to avoid superficiel counterdiffusion. The transition should take place gradually, rather than abruptly, to avoid exaggerated sensations of narcosis which may be confused with vestibular effect.

° Use of increased oxygen in inert gas - oxygen mixtures remains the most effective means to reduce tissue total inert gas pressure in the prevention and therapy of each form of gas lesion disease. In conjunction with deep isobaric counterdiffusion sub-saturation the limitations are those of tolerance to oxygen.