15

Isobaric Gas Exchange and Supersaturation by Counterdiffusion

B. G. D'AOUST & C. J. LAMBERTSEN

This chapter recounts some recent developments in deep diving research which have contributed important insights into both diving techniques and their related biophysics. The starting point for much of this recent increase in activity was the demonstration by Hans Keller in 1962 (Keller 1968) that the sequential use of different gases in a particular order, determined by their physical properties, had great potential for extension of time at depth without proportionate increase in decompression obligation. Owing unfortunately to both an attendant accident and the lack of information at that time regarding appropriate ascent criteria, widespread practical application of the principle was delayed for a number of years, even though major laboratories made extensive use of 'gas switching'. During approximately the past ten years investigators have begun to agree at least on the fundamental constraints, if not the most relevant models through which the decompression problem could be consistently approached (Hempleman 1960; Hills 1975; Workman & Bornmann 1975; D'Aoust *et al.* 1977; Hennessey & Hempleman 1977). During this same past decade it has become evident for the first time that gas lesion disease and gas embolism development is not limited to decompression. Each can occur even in stable pressure (isobaric) conditions.

The origin of this recognition came out of laboratory research involving respiration of different inert gases. The initial observation of these phenomena, leading to the identification of a new gas lesion disease distinct from decompression sickness, involved events and experiments at three different laboratories.

INITIAL CLINICAL FINDINGS AND INTERPRETATIONS

When subjects, at 200 ft (61 m) in a helium-filled chamber, were suddenly exposed to changes in composition of breathing gases (neon, nitrogen and helium) (Blenkarn *et al.* 1971), they observed white, raised urticaria not unlike skin bends, but often resembling erythematous allergic hives. Nausea and vertigo were also experienced. The original experience of the group at Duke University is shown in Table 15.1, which summarizes the gas sequences and the results observed. As will become clear, however, interpretation of their experience is complicated by the fact that prior saturation with helium existed in only a few cases and therefore total initial inert gas tensions cannot be computed.

Because Blenkarn *et al.* (1971) were convinced on theoretical grounds that on change from helium to nitrogen or neon breathing '. . . the total tension of nitrogen and helium will show a transient fall and therefore cannot exceed the external hydrostatic pressure . . .', they ruled out formation of bubbles as an aetiological cause of the symptoms in favour of a potential gas osmotic mechanism. There was *in vitro* experimental precedent (Kylstra *et al.* 1968) for this interpretation, albeit using a much more soluble gas. However, because of the low calculated osmotic potential (Hemmingsen 1970) and the improbability of encountering a biological membrane that passes water faster than gas, this explanation did not seem capable of explaining the phenomenon observed. This was further documented by Halsey and Eger (1973).

When repetition by the US Navy Experimental

TABLE 15.1

Order of inert gases breathed during experiment* at 200 ft (61 m) and spirometer temperatures recorded (°C)† (After Blenkarn *et al.* 1971)

Subject F	Nitrogen (31.8)↑	Nitrogen (31.0)↑	Neon (34.2)↑
Subject T	Neon (29.1)	Helium (32.0)	Nitrogen (29.6)↑
Subject W	Nitrogen (27.9)↑	Helium (27.1)↑	Neon (30.5)↑

* Each gas mixture includes 0.21 ATA oxygen.
† Spirometer temperature fluctuations probably do not fully reflect chamber temperature fluctuations, owing to a buffering effect of the spirometer water.
↑ Point where lesions were encountered.

Diving Unit of pressure, ambient gas and respiratory gas exposures used by Blenkarn *et al.* failed to confirm the effects encountered by the Duke Group, the experience was put aside and not specifically investigated.

The discovery that *gas lesions* of serious import do, in fact, occur even *without decompression* evolved from extensive observations of dermal effects in the 200–1200 ft (61–365 m) pressure exposures of the University of Pennsylvania's Predictive Studies III (Lambertsen *et al.* 1977), involving breathing of neon or nitrogen mixtures while surrounded by a helium environment at constant pressure. The time sequencing for these is documented (Lambertsen & Idicula 1975; Harvey & Lambertsen 1979). Hard, raised, white, bloodless skin lesions occurred, as did incapacitating, multiday vestibular derangement with severe nausea and vomiting. Figure 15.1(a), From the University of Pennsylvania studies, shows the nature of one form of the dermal lesions encountered in man; the lesions were accompanied by extreme itching. Investigation in animals showed large accumulations of subcutaneous gas (Fig. 15.1b).

Conceiving that unequal flux of different inert gases between skin capillary and ambient environment could induce a gas supersaturation in cutaneous tissues, the possibility was studied by the Pennsylvania group in physical systems and in animals, with demonstration of continuous bubble formation at constant ambient pressure, *in vitro* and *in vivo*. Because the phenomena occurred (a) without change in ambient pressure, and (b) as a result of mass flux of different gases in opposite directions through tissue fluids, the term 'isobaric counterdiffusion' was coined (Graves *et al.* 1973a, b; Lambertsen & Idicula 1975). It was recognized (Lambertsen & Idicula 1975) that isobaric supersaturation or subsaturation could occur in both a 'Superficial' form (involving continuous counterdiffusion through surface structures) and a 'Deep tissue' form (involving transient counterdiffusion between internal tissues and their capillaries), depending upon the inert gases involved.

The result of these specific observations, experiments and interpretations was (a) the establishment of superficial inert gas counterdiffusion as a continuous, potentially lethal, tissue gas lesion and venous

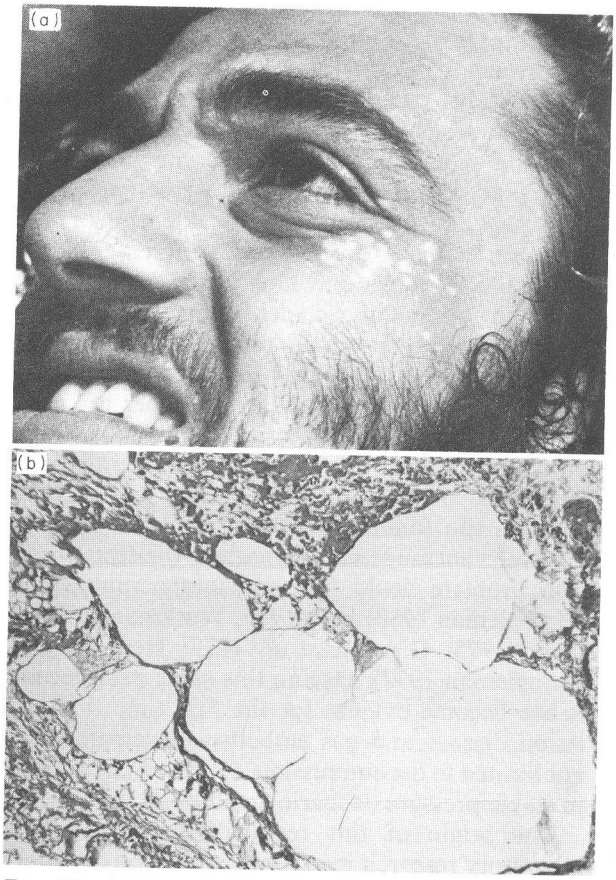

FIG. 15.1. (a) Dermal lesions in subject exposed at 1200 fsw (363 m) to neon/oxygen breathing while surrounded by helium (from Lambertsen & Idicula 1975). (b) Free gas spaces are shown in a section through subcutaneous tissue of pig exposed to superficial isobaric counterdiffusion. Pig breathed 80% N_2O/20% O_2 while surrounded by helium at 1 ATA. Magnification × 100. (From Lambertsen 1979)

gas embolic disease process, and (b) the warning that the deep tissue isobaric supersaturation resulting from sequential breathing of helium after nitrogen or neon must induce deep tissue supersaturation and embolism even at constant ambient pressure (Lambertsen & Idicula 1975; Harvey & Lambertsen 1979). These two different potential gas lesion diseases are now well recognized in commercial diving operations and can be avoided.

A next step in the evolution of information concerning these newly discovered environmental hazards was the determination that the predicted isobaric 'Deep tissue' supersaturation on breathing helium after prolonged nitrogen exposure at high pressure did induce transient venous gas embolization (D'Aoust *et al.* 1977)

Because the circumstances, the sites of origin of gas 'bubbles' and the resulting harm are different in the superficial and the deep tissue situations, consideration must next be given to descriptive terminology. It is important here to recognize that this chapter is intended to derive information from the original definitive sources, and not to establish new terminology.

TERMINOLOGY AND DEFINITIONS

In order to understand the potential importance of the two forms of isobaric gas exchange initially described as pertinent to diving, it is essential to distinguish between differing conceptual, physical and physiological situations, by initially defining two operationally different but consistent definitions. D'Aoust *et al.* (1979), in order not to endorse any particular mechanism, suggested that the term 'isobaric counterequilibration' be used for a transient situation where gases are approaching their equilibrium states, and 'isobaric counterexchange' for those situations involving a steady state. These terms are not here recommended but are to be integrated with others elsewhere. To appreciate the basic difference in these situations, refer to Fig. 15.2. Figure 15.2(a) shows a hypothetical subject *breathing* one inert gas while *surrounded by* another. In this 'Superficial counterdiffusion' (a) there is a gradient of gas 2, which is being breathed, from the subject to the chamber. This gradient would exist chiefly across the skin, and all other body surfaces, since deep parts of the body would eventually become saturated. There is similarly another gradient and transport of gas 1 from the chamber to the lung alveoli of the subject. If it is assumed that

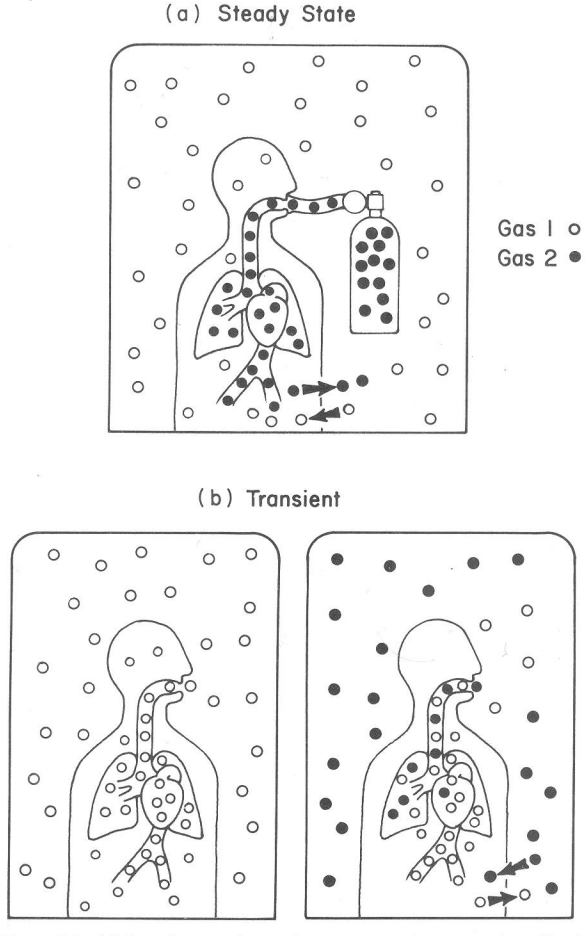

FIG. 15.2. (a) Steady state isobaric counterexchange as described in the text, with the subject breathing gas 2 while surrounded by gas 1. The final standing gradient is seen at the level of the skin. (b) Example of a transient switch when the subject is breathing and saturated on one gas and suddenly breathes another environmental gas which surrounds him. While desaturation of gas 1 and saturation of gas 2 is being achieved, transient supersaturations and gradients exist throughout the body at different parts at different times

the chamber gas is minimally contaminated by the small amount of gas 2 diffusing out of the subject across the skin, the situation initially approximates a steady state where two reciprocal gradients exist, essentially across the skin of the subject.

Ultimately, of course, two things must happen:

1. The superficial tissues of the subject will eventually approach being saturated with gas 2 (•), except at the skin where a gradient sloping to the exterior will exist.

2. The superficial skin will also approach being saturated with gas 1, except for a gradient in gas 1 from the exterior sloping to the interior blood capillaries.

It is now easy to see that supersaturation is inevitable in this situation, because the gas fluxes are in opposite directions. This situation has been conveniently referred to as 'steady state', maintaining 'standing' gradients which are potentially lethal (*c.f.* Fig. 15.4; Lambertsen & Idicula 1975).

In Fig. 15.2(b) a different situation is depicted, cited above, for 'Deep tissue' isobaric gas exchange. This is indicated by the absence of breathing apparatus; the subject is breathing the same gas that surrounds him. The implication is that if the chamber gas is suddenly changed, gas 1 is now being eliminated via the lungs (and initially through the skin and gas 2 is being taken up again via the lungs and through the skin. The schematization represents the fact that somewhere and at some particular time following initiation of this condition, a supersaturation will exist. However, it must be considered as inevitably *transient,* since gas 1 will eventually be eliminated down to a negligible level and gas 2 will eventually saturate the subject at a final pressure no greater than ambient. Thus, one must distinguish between steady state and transient conditions. These have been outlined above, because they cover almost all the experimental work reported thus far (Blenkarn *et al.* 1971; D'Aoust *et al.* 1977, 1979; Lambertsen *et al.* 1978; Cowley & Lambertsen 1979; Cowley *et al.* 1979; Giry *et al.* 1979), and much of the *in vitro* (Graves *et al.* 1973b) and theoretical discussions (Tikuisis & Kuehn 1976; Hills 1977; Karreman & Lambertsen 1977) as well.

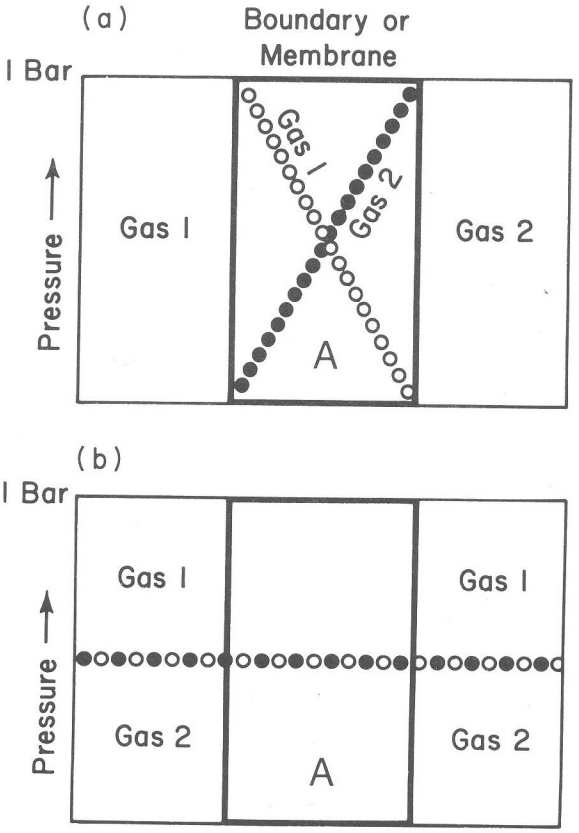

FIG. 15.3. Schematic representation of *homogeneous boundary membrane isobaric counterdiffusion* in (a) a steady state situation; and (b) an equilibrium-approaching situation. In (a) gas 1 and 2 are continuously replenished at a rate far exceeding that of diffusional transfer through the membrane A. In (b) gas 1 and gas 2 are suddenly enclosed and equilibrate against each other until each gas exerts 0.5 bar of pressure

Counterdiffusion

Homogeneous boundary and separating gases. In its simplest form the term is self-explanatory. Figure 15.3 illustrates this schematically. The membrane or boundary, A, has one gas, gas 1, on one side of it and another gas, gas 2, on the other side. If the volumes on either side of the membrane or boundary are isolated, a final composition will be established where each gas exerts 0.5 bar of pressure. If, on the other hand, gases 1 and 2 are continually replenished on either side at a rate well in excess of the diffusion rate of each gas, a symmetrical gradient in the membrane or boundary will eventually be set up. If the permeability of the boundary membrane is different for one gas compared with the other, a transient supersaturation will exist while the system approaches equilibrium. It is important to note here that there is no possibility at the steady state for a total inert gas pressure above one atmosphere. This could only occur as a transient result of the initially unequal diffusion flux of gas 1 or 2, say N_2 or He, due to different diffusion coefficients in homogeneous barrier A.

A form of this situation was experimentally demonstrated by Winsey and Folkman (1967) and can easily be reproduced in the laboratory by fitting one end of a length of small medical grade silastic tubing over the end of a No. 26 blunt needle which is attached to a physiological pressure transducer. By knotting the other end of the silastic tubing and feeding it into a larger i.d. length of plastics tubing, one can now flow any gas over the silastic tubing and can demonstrate a transient pressure change, the magnitude and duration of which depends on the thickness of the tubing, the diffusion coefficient of each gas and the internal volume which must be exchanged.

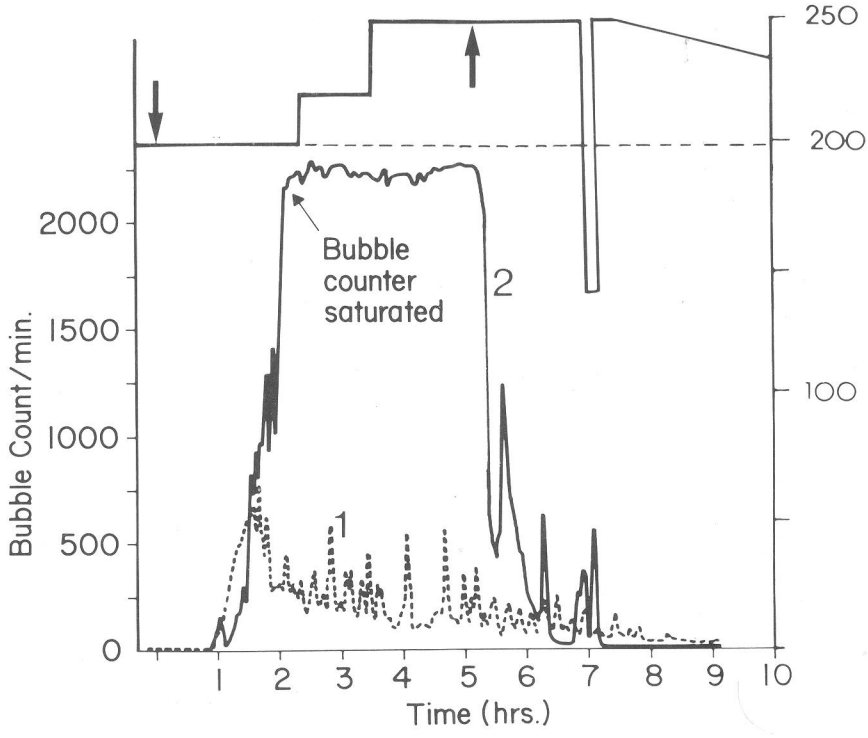

FIG. 15.4. Results of two experiments using Doppler ultrasonic cuffs around the posterior vena cava of an awake goat subjected to (1) transient isobaric counterdiffusion at 7 bar of nitrogen against helium; (2) steady state isobaric counterdiffusion of helium (exterior) against breathing gas of nitrogen. Oxygen in both experiments was at 0.3 bar. Both gas switches were initiated at the left-hand arrow at the top following 17 h of saturation on nitrogen–oxygen. The same animal was used for both experiments. Saturation of the ultrasonic signal indicated far more bubbles than 1500 per minute in experiment 2. Notice the rapid decrease in bubble numbers following an air switch (right-hand top arrow) at aproximately 5 h.

A *physiological* analogue of the transient situation is shown in Fig. 15.4, where central venous Doppler bubble counts are plotted against time (1) after a switch of chamber and breathing gas as depicted in Fig. 15.2(b); (2) following a switch of chamber gas only while breathing nitrogen as depicted in Fig. 15.2(a). In (1) the bubbles eventually disappear with time. In (2) the gradients are permanent and therefore potentially lethal. We consider next the *physical* analogue of this steady state situation.

Bilayer boundary between different gas sources. If, in contrast to the situation shown in Fig. 15.3, the gases 1 and 2 are separated by a bilayer, a very different result is possible. This case is illustrated in Fig. 15.5 (Graves *et al.* 1973a, b). In this situation there is not only a boundary, as in Fig. 15.4, but also a 'complex' membrane composed of at least two different layers. In this configuration the steady state gas gradients have been shown (Graves *et al.* 1973a, b; Karreman & Lambertsen 1977) to produce a permanent supersaturation, i.e. total gas pressure, P_T, which can be directly measured and is greater than ambient gas pressure, B ($P_T > B$). This is the condition of supersaturation where $P_T - B > 0$. They further showed that the steady state supersaturation ratio at the interface of the bilayer,

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

where ΔX_A and ΔX_B are the thicknesses of layers A and B; K_{1A} and K_{2A} are the permeabilities of gases 1 and 2 in layers A; and K_{1B} and K_{2B} are the permeabilities of gases 1 and 2 in layer B.

These experiments, analysis and formulations were prompted by the original observation of the University of Pennsylvania group where subjects at 1200 feet (365 m) saturated on helium–oxygen

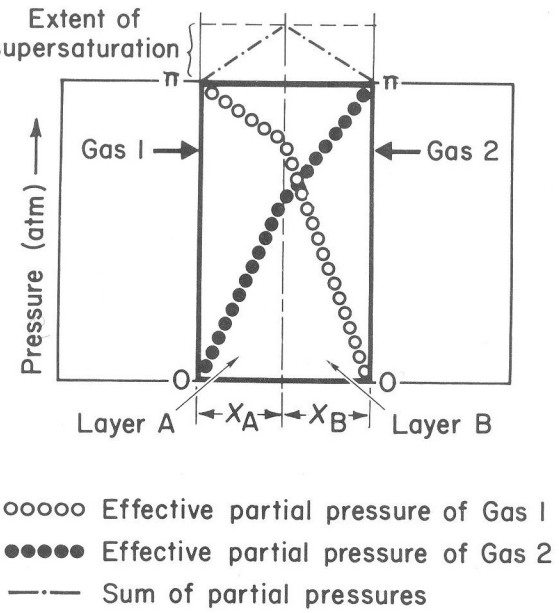

FIG. 15.5. Schematic diagram of *steady state non-homogeneous isobaric counterdiffusion* of gas 1 on the left and gas 2 on the right which are continually replenished on either side of boundary made up of layer A and layer B of distance X_A and distance X_B, respectively. The open circles indicate effective partial pressure of gas 1 at the steady state equilibrium; the closed circles indicate effective partial pressure of gas 2 at the equilibrium; and the dotted line indicates the sum of their partial pressures at any point following the achievement of steady state conditions. (From Graves *et al.* 1973b)

breathed crude neon–oxygen by mask in order to test pulmonary and other functions with gas densities equivalent to helium at 5000 feet (1524 m). The disabling urticaria and vertigo which resulted were a surprise to the investigators, because previous indications of unexplained skin lesions had not been confirmed. While it was proposed that the general mechanism must be at least in part similar to that shown in Fig. 15.5, it was also recognized that the new phenomenon posed many questions concerning numbers of bubble sites; their vascular or extravascular location; the particular vulnerability of different tissues and organs, particularly the inner ear, to this problem; and the relative hazards of different gas sequences (Lambertsen & Idicula 1975; Harvey & Lambertsen 1979).

Although the situation depicted by Fig. 15.5, i.e. steady state isobaric counterdiffusion, is potentially lethal (Lambertsen & Idicula 1975), it need not be considered an inevitable occupational hazard, e.g. welding in inert atmospheres (Peterson *et al.* 1980), since it can be prevented. It is now a hazard to be avoided in operational diving and therapy. On the other hand, it has unique scientific importance as a research tool to answer questions involving bubble growth, numbers of bubble sites per volume of tissue, tissue deformation pressures (Cowley & Lambertsen, 1979; Cowley *et al.* 1979) and critical supersaturation thresholds (D'Aoust & Young 1979).

'Counterperfusion' as a term

A convenient macroscopic conception has been applied to describe the steady state situation by Imbert (1975) and Hills (1977). The term 'counterperfusion supersaturation' was coined by the latter to approximately describe the situation depicted in Fig. 15.2(a), where the arterial blood is saturated with gas 2, and the breathing gas and the venous blood, relatively enriched with gas 1 as well as gas 2, becomes a potential site of supersaturation. This is the same situation as that illustrated in Fig. 15.2(a), where the reciprocal gradients of gases 1 and 2 are imposed chiefly at the level of the skin or other 'diffusion barrier'. In certain respects this approach exposes a conceptual model for the steady state situation first shown to produce skin urticaria and whose microscopic analogue was modelled by Graves *et al.* (1973a, b). As a descriptive term, it is not useful, because it is gas flux, not perfusion of tissue by blood or gas, which is in opposite directions (Lambertsen *et al.* 1981). The potential hazards of this situation have been outlined by Hills (1977) and by Lambertsen (1979), and include the use of inert, oxygen-free atmospheres for welding (Peterson *et al.* 1980).

'Counterequilibration' and 'countertransport' as terms

The above terminology has been offered in the recent literature and is not any more graphic than other conceptions. If any term is confusing, it should be abandoned. The most fundamental distinctions to be made remain functional ones: whether or not the situation will provide a *transient* or a *steady state* over- or undersaturation, and where and when the actual sites of supersaturation or subsaturation exist. Practically speaking, it is obvious that the transient situations are of frequent operational importance; the steady state situations can and should be avoided, but are of great interest to the research community. Some examples of these approaches are presented below.

ISOBARIC GAS EXCHANGE

The above considerations provide a basis for discussing some of the theoretically uncertain issues in current diving decompression theory formulations. In fact, as will be shown, the predictive models used to describe gas exchange critically determine the outcome of some of the hypothetical situations described above. In some cases the results of experiments are consistent with the direction and magnitude of supersaturation produced. In other cases they are not. It is clear that the phenomena of isobaric supersaturation produced by the technique of either steady state or transient isobaric gas exchange can be a powerful research tool which can be used to resolve uncertainties regarding kinetic models, gross time constants of the body and supersaturation thresholds. The effects of either will be very different, according to whether bubbles do or do not exist, as shown by Van Liew (1971) and Hills (1977). This is because of the soluble gas effect (Van Liew 1971), which can have the effect of increasing bubble size, according to the blood–tissue partition coefficients prevailing in the tissue region (Hlastala & Farhi 1973).

Many kinetic models used in diving are based on the original perfusion dependent assumption formulated by Kety (1951) and used in diving tables by Workman (1965), Schreiner and Kelley (1967) and others. Others (for example, Hempleman 1975; Hills 1975) were originally formulated according to a single tissue assumption which was elegantly simple in its conception and surprisingly consistent with some perfusion models, when similar assumptions of supersaturation thresholds were used. Figure 15.6 (D'Aoust 1979) indicates just how similar some of these models can be in spite of radically different mathematics. This suggests that attempts to measure differences empirically in order to resolve such issues may not produce the required precision (Hills 1975; D'Aoust *et al.* 1976; Vorosmarti *et al.* 1978), because of the small differences which would not be detectable and temporal variations in blood flow and diffusion distances.

By contrast, the combined experimental use of ultrasonic Doppler bubble detection and both transient and steady state isobaric gas exchange (Quinn *et al.* 1974; Quinn 1978; Cowley & Lambertsen 1979; Cowley *et al.* 1979; Dueker *et al.* 1979; Lambertsen *et al.* 1978; D'Aoust *et al.* 1980) has already provided extensive information concerning the isobaric supersaturation process, the question of supersaturation thresholds (Cowley *et al.* 1979; D'Aoust & Young 1979; Yount 1979) and

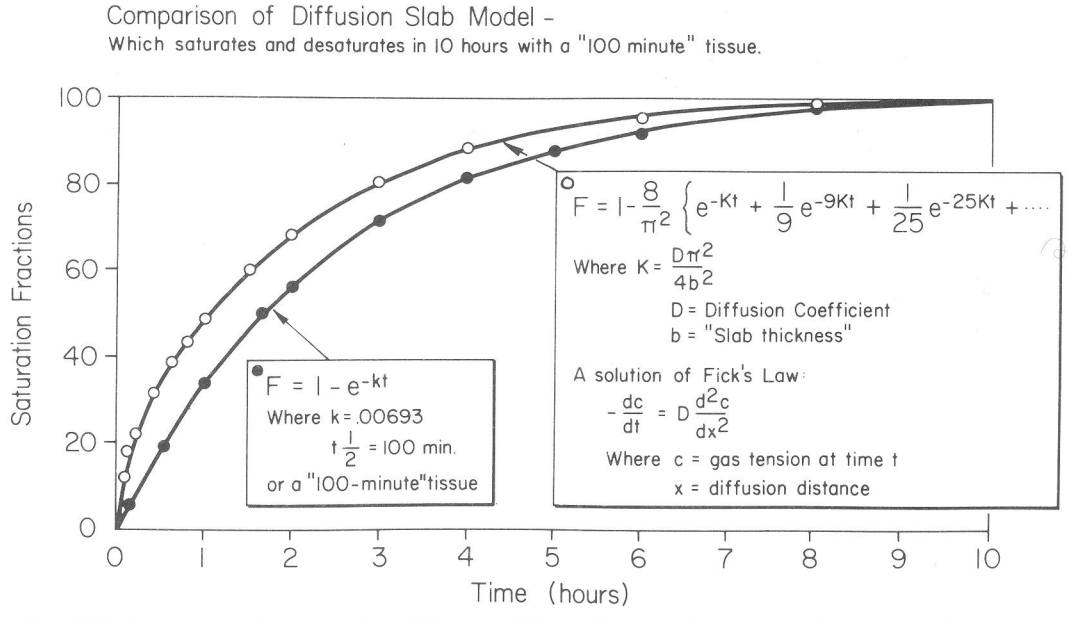

FIG. 15.6. Comparison of a tissue with a 100 min half-time when a perfusion dependent exponential model is compared with a diffusion dependent model reaching equilibrium at the same time. Although obvious differences in kinetics exist, it is also clear that accurate experimental differentiation in awake animals or man would tax the most sensitive available experimental techniques. (After D'Aoust 1979)

gas micronuclei distribution (Yount 1980, 1981).

These advances are best understood with reference to some of the more recent experimental findings regarding inert gas exchange under pressure (Kindwall 1975; D'Aoust *et al.* 1976; Vorosmarti *et al.* 1978).

The assumption of symmetry

It is a fundamental axiom of most early gas exchange models that the kinetics of gas uptake and elimination are symmetrical. That is, the curves describing fractional saturation plotted against time for uptake and elimination are mirror images of each other.

In the case of a simple exponential, this is stated as

$$P_i = P_{io}e^{-kt} \quad (2)$$

for desaturation and

$$P_{it} = P_{i0}\,(1\text{–}e^{-kt}) \quad (3)$$

for saturation following a step change in pressure, where P_{it} is the inert gas pressure at time t, P_{i0} is the inert gas pressure at time 0 and k is the rate constant.

It had been recognized for some time (Hempleman 1975), but not universally acknowledged until recently, that in the case of elimination of inert gas after diving, the symmetry assumption did not hold. This was experimentally demonstrated recently by D'Aoust *et al.* (1976) in awake dogs decompressed from a saturation of 17 h at 2, 3 and 4 ATA of air. A summary of their experimental data appears in Fig. 15.7, which indicates a different curve for venous blood inert gas content during isobaric desaturation as compared with decompression desaturation. These authors argued that their data demonstrated that inert gas remained in the animals following decompression. The kinetics of uptake, on the other hand, did appear to be essentially the mirror image of the isobaric desaturation curve. Other studies by Kindwall (1975) also showed inequalities in fractional inert gas elimination from human subjects, according to whether elimination was occurring at 100 ft, 60 ft or 10 ft (30 m, 18 m or 3 m). However, these experiments were not carried out from saturation, so direct comparisons are not possible. In any case, it is clear that in the absence of symmetry, prediction of gas elimination during decompression remains guesswork, and this means that prediction of supersaturation is no better.

Fortunately, the very questions raised by this development can be approached by the judicious experimental use of isobaric gas sequencing tech-

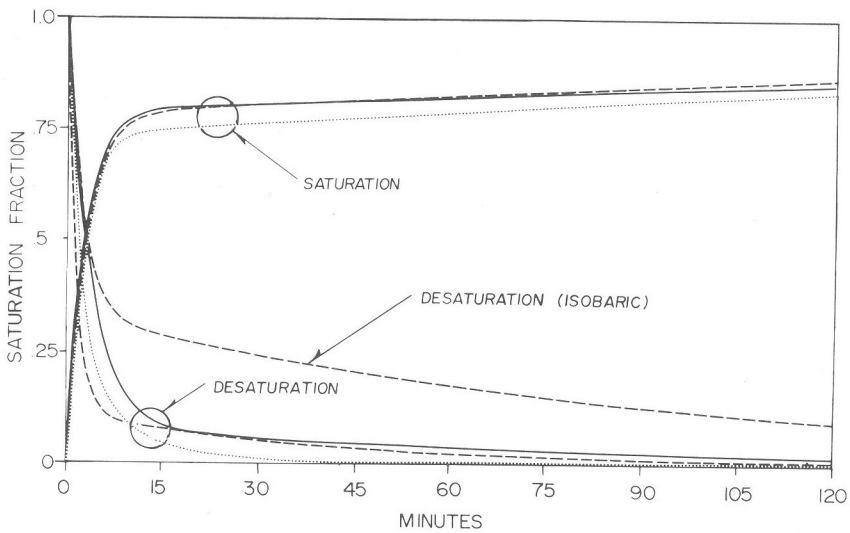

FIG. 15.7. Computer curve fits of actual data obtained from awake dogs subjected to 1, 2 and 3 ATS of compression (saturation) and decompression (desaturation), both compared with isobaric desaturation of animals at 1 ATS. The ordinate is saturation fraction and compares dives of 2, 3 and 4 ATA and decompressions of 1, 2 and 3 ATA. Note that symmetry appears to obtain for saturation and isobaric desaturation but that desaturation following decompression of 1, 2, and 3 ATS implies that the mixed venous blood is rapidly emptied of nitrogen, leaving tissue supersaturation. (After D'Aoust *et al.* 1976)

niques in combination with some other new developments such as ultrasonic Doppler bubble detection (Spencer & Campbell 1968; Evans & Walder 1970; Spencer 1976; D'Aoust *et al.* 1977, 1979).

Theoretical analyses and experimental measurements of isobaric supersaturations

The theoretical analysis by Graves *et al.* (1973a, b) and Karreman and Lambertsen (1977) projects both the degree of supersaturation and the time to reach stable supersaturation levels under conditions of steady state counterdiffusion in hypothetical systems. These projections are shown in Table 15.2, where combinations of nitrogen–neon, nitrogen–helium and neon–helium are considered. The model used is the bilayer model, in which a lipid layer A and an aqueous layer B of varying thicknesses are considered. Both the total pressure of each gas and the supersaturation ratio P_i/π have been calculated, and one can see that in all cases, regardless of whether the lipid or the aqueous layer is the thicker or whether they are equal, a supersaturation at the interface results. Further, while there is a tenfold difference in the degree of supersaturation with different thicknesses of the lipid and aqueous halves, there is rarely a supersaturation greater than 26% of one atmosphere! This seems to be true regardless of the pairs of gases. On the other hand, there is a 10 000-fold difference in the time required to reach such a steady state (meaning a stable supersaturation pressure, P_i, at the membrane interface), depending upon the relative thickness of lipid layer and aqueous layer. It is of particular interest that these authors' analysis revealed that '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'. The analysis is also supported by the experimental results reported by Graves *et al.* (1973a, b). On the other hand, the results of Cowley *et al.* (1979) show that

Table 15.2

Time for development of a stable state in different inert gas counterdiffusion circumstances (After Karreman & Lambertsen 1977)

Gas 1	*Conditions: Thickness of membrane layers (μm)*		*Gas 2*	*Results*		
	Lipid (layer A)	*Aqueous (layer B)*		*Time to reach steady state (s)*	*Last gas to reach steady state*	*P_i/π* at steady state*
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 equations (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 equation (5) from Graves *et al.* (1973b). It must be considered that this 'worst case' will occur somewhere in the body.

in steady state counterdiffusion in the ear of the rabbit (N_2O against He: Fig. 15.8b) the maximum pressures reached in spite of excess gas available were approximately 50 Torr (0.066 bar) or a supersaturation ratio, P_i/π, of 1.066. These are minimum pressures, since periodic decreases were also observed which would be consistent with cleavage of subcutaneous tissue spaces.

Another approach to calculating maximum supersaturation pressures generated during *transient* gas switches was reported by Lambertsen and Idicula (1975) and Harvey and Lambertsen (1979) using ratios of diffusion coefficients as approximations of the ratios of the time constants equilibrating gases. A similar approach was also used by D'Aoust *et al.* (1977) to calculate hypothetical supersaturation curves which were superimposed upon the actual time course of recorded bubble counts following isobaric gas switches from saturated nitrogen to helium. Here again it is of interest that the supersaturation ratios calculated were approximately of the order of 1.26 (see Fig. 15.8a).

The alert reader will perceive here a contradiction in terms, in that an established model which is mathematically rigorous when applied to a perfusion dependent system (i.e. 'a well mixed pot') is being used to rationalize phenomena involving isobaric flux of gases in opposite directions. That more than diffusion was involved was pointed out by D'Aoust *et al.* (1977) when they stated:

> '. . . because the multi-exponential parallel compartment model has been used in our calculation, we have arbitrarily paired helium and nitrogen half times that we must then assume refer to the same actual tissue elements. This assumption itself contradicts part of the rationale supporting use of the multiple parallel compartment model since the latter overcomes the lack of physiological reality by having a spectrum of half times known to span a realistic physiological range of rates. With two gases, however, there is no way to decide which helium half time is best applied to which nitrogen half time. On the other hand, the use of a constant ratio of permeation rates for nitrogen and helium for every half time is obviously an oversimplification because helium diffuses faster, is less soluble, and has a lower fat/water partition coefficient than nitrogen.'

It is therefore inevitable that the perfusion/diffusion controversy (Hills 1975) be revived in order to determine whether one model is better suited than the other to predict supersaturation.

Perfusion dependent vs diffusion dependent estimation of isobaric supersaturation in deep tissues

As stated above, the classical perfusion limited model set out in 1951 by Kety implicitly assumes the importance of tissue-to-blood partition coefficients (Kety 1951; Farhi & Yokoyama 1967; Groom *et al.* 1967). This is easily understood with reference to equations (2) and (3), which describe desaturation and saturation of a one-compartment system according to the time constant (k), which in turn can be shown to be proportional to λ_i, the blood/tissue solubility ratio of inert gas i, α_i, defined as α_{ib}/α_{iT}.

Since the meaning of a time constant is the capacity of any compartment divided by the (perfectly mixed) flow through the compartment, the reciprocal time constant, k, is given by $\dot{Q}\alpha_{ib}/V\alpha_{iT}$, where $\dot{Q}$ equals blood flow and V is the volume through which it flows.

The essential feature of this relationship is that, at constant flow and volume, the time constant is dependent on the tissue-to-blood partition coefficients of the gases, and not their diffusion coefficient, D_i. It follows that predictions of the time course of counterequilibration-produced supersaturations can be conveniently described by the perfusion dependent model briefly outlined above and elsewhere in this volume, which theoretically should be sensitive only to the solubilities of the respective inert gases. The alternative type of kinetics would assume that, in fact, it is the respective diffusion coefficients rather than the solubilities of the different inert gases which are 'to blame' for the differences in uptake and elimination rates which have been observed (Bühlmann 1975).

There are, however, difficulties associated with setting up a diffusion dependent model, and these are related to the need to establish a specific geometry in order to select the relevant mathematical expression. In developing his simple single tissue slab approach, Hempleman justified his approximation of the square root of the time by pointing out that, regardless of geometry, the solution to diffusion equations were all proportional to $\sqrt{t}$ for short intervals of time (see Fig. 15.6). However, such approximations do not lend themselves to calculation of slower time constants.

In spite of this basic mathematical difference, some investigators (D'Aoust *et al.* 1977) have estimated the maximum supersaturations to be expected by a convenient and simple comparison

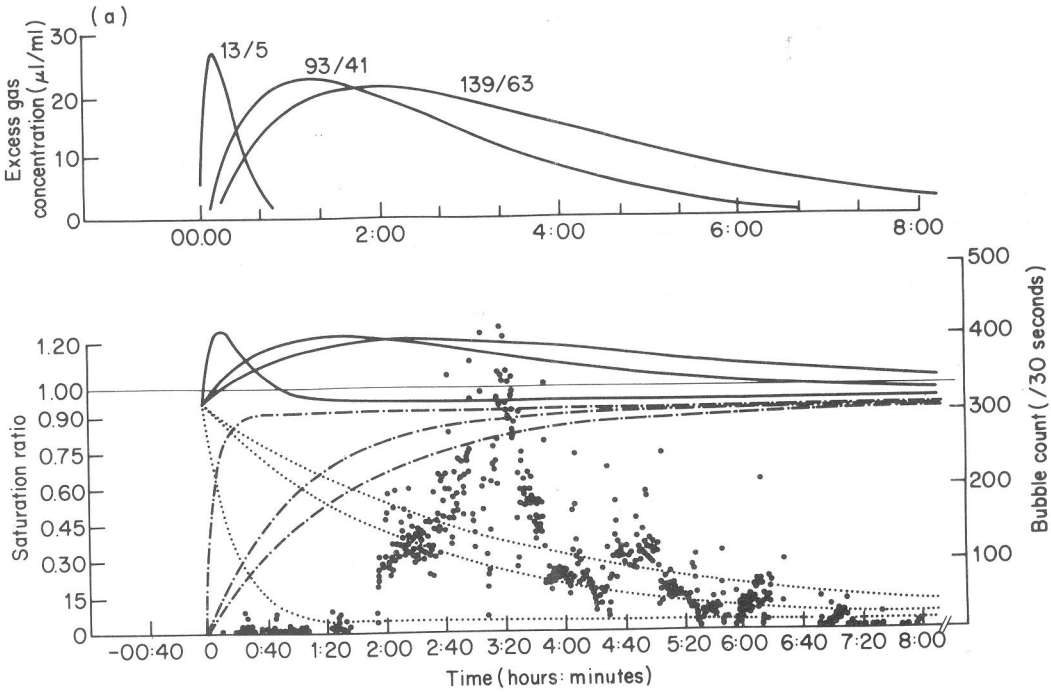

FIG. 15.8. (a) Bubble count with time following an isobaric switch of an awake goat saturated at 198 ft (60 m) for 17 h on nitrogen/oxygen (0.3 ATA O_2) and switching to helium with the same oxygen tension (deep tissue isobaric inert gas exchange). Superimposed on the bubble plot are nitrogen and tissue tension calculations for a number of tissue pairs of 13 and 5, 93 and 41, and 139 and 63 min, respectively, for nitrogen and helium. On the top of the figure are calculations of excess total gas content, which somewhat lags the peak tensions but not to any great degree. (After D'Aoust *et al.* 1977)

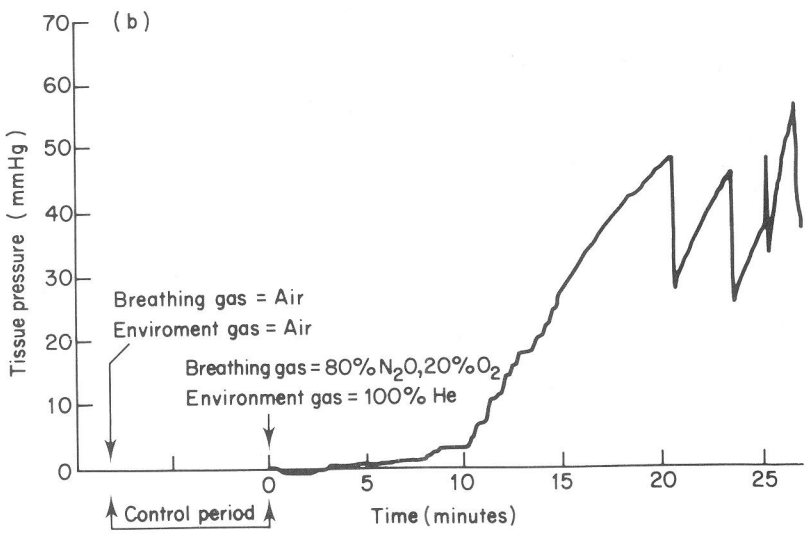

FIG. 15.8. (b) Interstitial pressures of less than 100 Torr measured in rabbit ear subdermal tissue in steady state counterdiffusion of N_2O (breathed) against helium surrounding. Notice the periodic drops in pressure as tissue spaces are dissected by expanding gas. Representative tracing showing subcutaneous tissue pressure during control exposure (breathing gas, air; environment gas, air) and counterdiffusion exposure (breathing gas, 80% N_2O and 20% O_2; environment gas, 100% He). (After Cowley *et al.* 1979)

of different half-times. These authors made no assumption as to mechanism but assumed that the ratios of the half-times of saturating and desaturating gases determined the degree of supersaturation. Harvey and Lambertsen (1979) presented similar results with a similar rationale, and these predictions are summarized in Figs. 15.9(a, b).

These estimates predicted supersaturation ratios of the order of 1.26, P_i/π (D'Aoust *et al.* 1977), when empirically derived half-time ratios for N_2 and He were used, whereas the actual ΔP values used in computing current decompression tables are often much in excess of these values, particularly for the faster tissues. These comparisons are shown

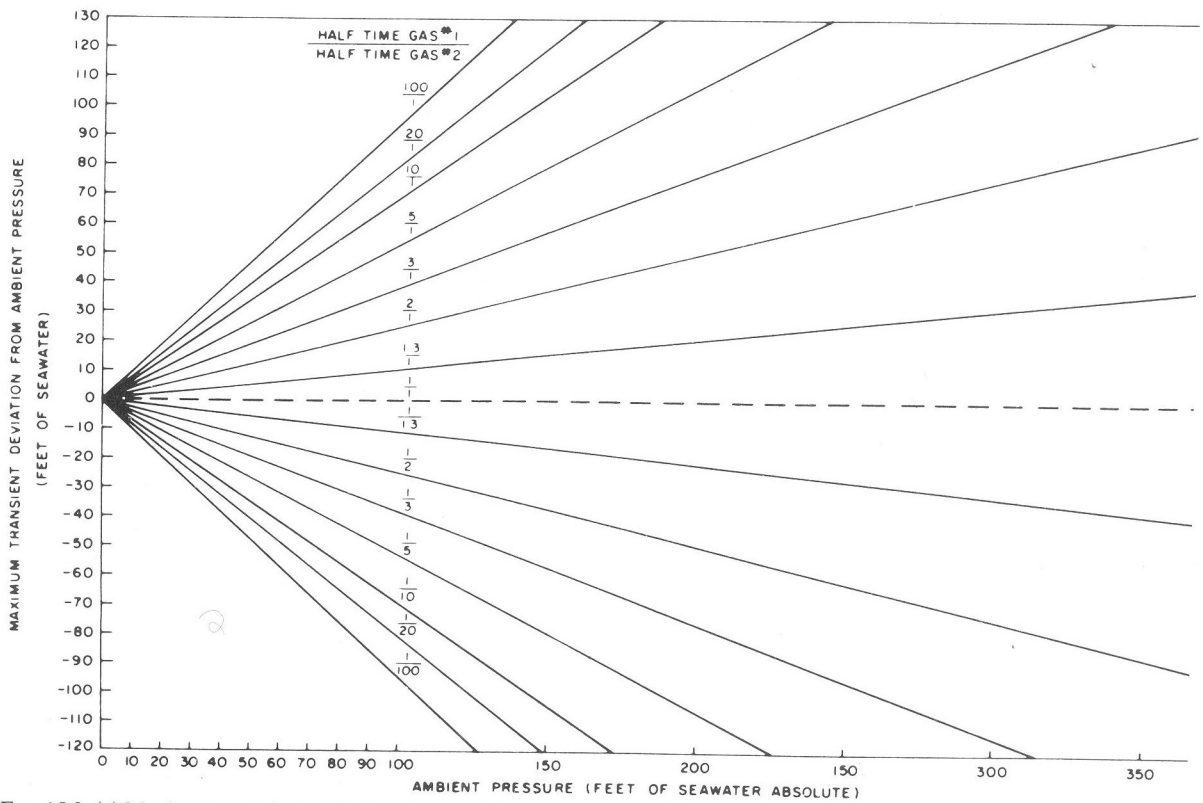

FIG. 15.9. (a) Maximum transient deviation from ambient pressure expressed in feet of seawater (= 0.3 m) for actual transient gas switches in man (deep tissue inert gas exchange) on the basis of the ratios of the half-times of gas 1 (the saturated gas) over gas 2 (the saturating gas). (After Harvey & Lambertsen 1979)

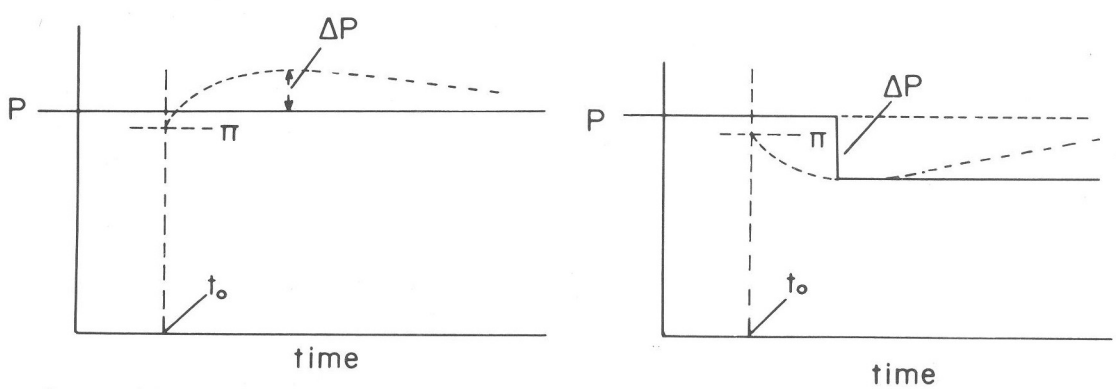

FIG. 15.9. (b) Schematic representation of (left) positive pressure transient when the saturating gas has a shorter half-time than a desaturating gas and negative pressure transient which can be used as an advantage in decompression when the saturating gas is slower than the desaturating gas as in a switch from helium to nitrogen (compare with Fig. 15.16). (After D'Aoust 1979)

TABLE 15.3

Inert gas supersaturations ($\Delta P = P_i - P$) and pressure ratios π/P calculated by equation (2) for total gas switches from saturation on N_2/O_2 (0.3 ATS O_2) to He/O_2 (0.3 ATS O_2) at depths from 66 to 264 ft (20 to 79 m). Gas switches below the dotted line consistently give bubbles. On the right of the vertical dotted line are the empirically derived values of ΔP and π/P for N_2 and He diving used in the USN tables. (After D'Aoust 1979)

Isobaric supersaturation					*Current USN decompression limits*			
Depth, ft (m)	pO_2 *(ATS)*	$\%O_2$	*Calculated*ΔP, ft (m)*	π/P	N_2		He	
					ΔP	π/P	ΔP	π/P
66(20)	0.3	11.1	8(2.4)	1.025	49	1.499	40	1.407
99(30)	0.3	8.1	16(4.9)	1.121	64	1.485	47	1.354
132(40)	0.3	6.4	23(7.0)	1.142	76	1.461	53	1.323
165(50)	0.3	5.0	31(9.4)	1.159	89	1.449	59	1.302
198(59)	0.3	4.3	39(11.9)	1.168	102	1.442	66	1.288
231(69)	0.3	3.8	46(14.0)	1.174	115	1.436	73	1.277
264(79)	0.3	3.3	53(16.1)	1.180	127	1.433	80	1.369

* ΔP values $= P_i - P$ calculated from equation (4) ($P_{ss} = P_i$).

in Table 15.3 (D'Aoust *et al.* 1979) and emphasize the discrepancy between the ΔP values presumed to be safe in decompression and those maximal values calculated to have existed in the isobaric situation and known to have produced bubbles!

There are at least two diverse ways out of this paradox. Either the presumed safe ΔP values which had been used up to the present time were too high and did, in fact, produce bubbles (D'Aoust *et al.* 1976; Spencer 1976), or there were, in fact, other mechanisms which were capable of producing much higher supersaturations than were predicted by the calculations of D'Aoust *et al.* (1977) or Harvey and Lambertsen (1979).

In this connection, the 'chromatographic' model of Tepper *et al.* (1979) is of interest. These authors predicted supersaturation ratios as high as 1.6 times ambient pressure. They used the classical 'Krogh' tissue cylinder model (Krogh 1919) and made the further assumption that axial diffusion could in some instances 'overtake' perfusion and contribute to an increased supersaturation. While they did account for potentially higher supersaturations, no experimental verification could be provided. Further, the maximum ratios which had been produced *in vitro* by Graves *et al.* (1973a, b) were of the order of 1.3. Thus, neither experiment nor theory can be entirely reconciled in this case.

Because of their experimental activity documenting the hazards of isobaric gas sequencing from N_2 to He and the possibility that the Tepper–Lightfoot model could account for greater supersaturations, D'Aoust and Young (1979) began to explore further gas switches with a number of different gases and to reexamine their results in the light of some perfusion dependent vs diffusion dependent macroscopic models (D'Aoust & Young 1979; D'Aoust *et al.* 1980) and a detailed reexamination of Krogh tissue cylinders (Young & D'Aoust 1981).

These investigators not only have shown, by means of both computer models and ultrasonic Doppler bubble detection following transient isobaric gas switches, direct evidence of the hazards and advantages of isobaric gas switches, but also have provided strong support for the perfusion dependent models. At the same time, they have found additional evidence that the vascular bubbles are not generated entirely by a diffusion dependent mechanism.

This is illustrated by results schematized in Figs. 15.10–15.14. Figure 15.10 shows a 'Krogh' cylinder of physiological dimensions. By solving the mass balance diffusion equation for the cylinder at the distal end in the lumen of the vessel, both a geometric and a temporal profile of supersaturation along the cylinder (Fig. 15.11) and at the distal end of the cylinder can be computed for a step-change in gas tension at the arterial end and can be plotted for different blood flows. Figure 15.12 shows the degree of supersaturation plotted against time when the velocity of blood flow is such that the entire volume of the cylinder would have a 3 s 'perfusion' time constant; that is, the blood flow is such that it

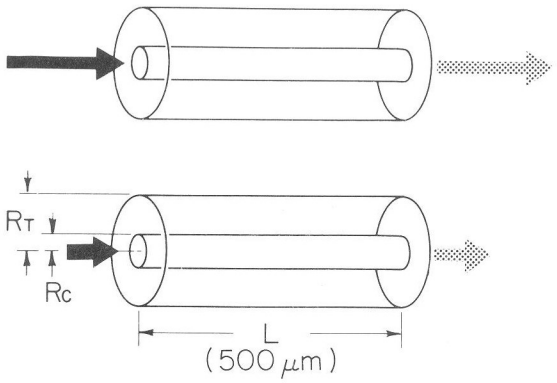

FIG. 15.10. Schematic representation of a Krogh cylinder on which solutions to the diffusion equation were computed by Young (basis for Figs 15.11–15.14). The dense arrow on the left simulates arterialized gas and the stippled arrow on the right indicates the somewhat desaturated venous blood. The velocities are indicated by the length of the arrow. The lower part simulates the same Krogh cylinder but with a lower blood flow. (After D'Aoust & Young 1979)

would replace the entire volume of the cylinder in 3 s. Figure 15.13, on the other hand, shows a similar profile of supersaturation plotted against time at the exit of the cylinder, but for a blood flow remarkably slower, having a perfusion time constant of 600 s, i.e. 10 min. It is very clear that the faster the perfusion, i.e. the smaller the perfusion time constant, the greater the transient supersaturation that can be produced by a step change in pressure at the arterial end when the cylinder is saturated with a different gas. This relationship is exponential, as is shown in Fig. 15.14(a, b).

The analysis (D'Aoust & Young 1979) leads to conclusions which are very critical to this problem. One is that the highest supersaturations could only be possible with prohibitively high blood flows. In fact, a capillary of the dimensions given in Fig. 15.10 with a perfusion time constant of 3 s would require such a high velocity of blood flow that the sheer stresses would actually cause physiological damage. This, then, can be excluded from the realm of possibility. The second point is that the profiled supersaturations are for the blood and not for the tissue cylinder. Thus, even though diffusion dependent bubble formation may be possible in the tissue cylinder, it is unlikely that the forces generated would be sufficient to allow expanding gas to penetrate through the capillary wall. This supports the notion that an entirely vascular origin is likely for the bubbles that these authors are detecting by Doppler ultrasound, and suggests that such bubbles are formed in the intimal layer of the capillary or vessel, since it would seem that considerable pressures would be necessary for them to penetrate the vessel sheath from a tissue space. In this connection, the work of Cowley *et al.* (1979) (Fig. 15.8b) mentioned earlier is of interest. Their observation of periodic decreases in steady state interstitial pressure, which would be consistent with cleavage of subcutaneous tissue spaces, leaves open the possibility that some transport of extravascular bubbles into the vasculature may be possible. However, in the transient experiments of D'Aoust and Young (1979) it is unlikely that enough gas was available to penetrate the vessel wall. Further, intracellular bubbles are extremely unlikely (Hemmingsen & Hemmingsen 1979). Note that the N_2–He gradients are mirror-image.

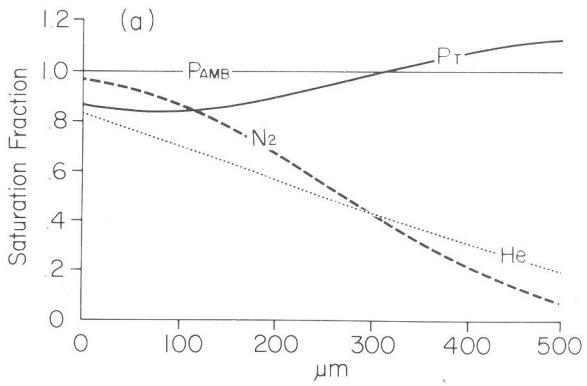

FIG. 15.11. (a) Schematically drawn from Fig. 15.10, indicating the saturation fraction following a switch from nitrogen to helium in a hypothetical capillary. Notice the undersaturation at the proximal end of the capillary leading to supersaturation at the distal end later. The profile is, of course, different for each different time after the switch. The profile shown is for a 600 s perfusion time constant. (After D'Aoust & Young 1979)

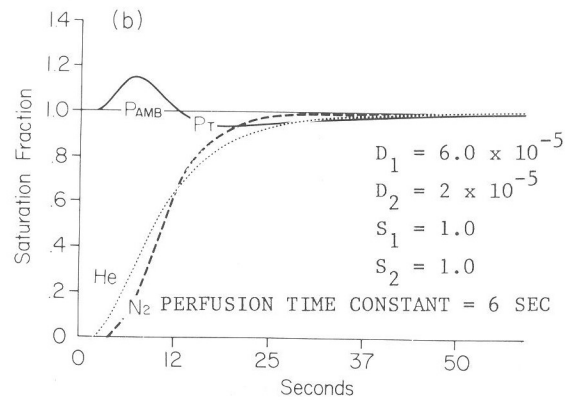

FIG. 15.11. (b) Supersaturation profile at the distal end of the Krogh cylinder shown in Fig. 15.10 computed for time when blood flow gives the cylinder in Fig. 15.10 a perfusion time of 6 s. Only diffusion differences are considered in this model with the partition coefficients of both gases S_1 and S_2 considered to be 1. The perfusion time constant used was 6 s, which indicates an extremely fast blood flow. (After D'Aoust & Young 1979)

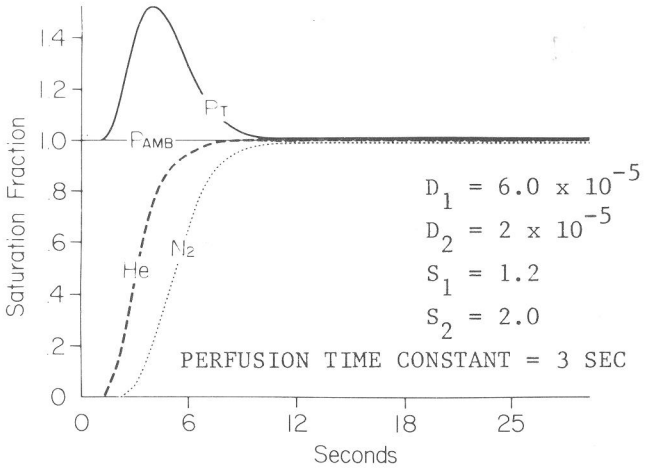

FIG. 15.12. Schematic calculated plot of total supersaturation expressed as a pressure ratio plotted against time for a perfusion time constant of 3 s in the cylinder schematized in Fig. 15.10. In this situation both diffusion and partition coefficients are considered. Notice the high supersaturation of up to 1.5, which is, however, transient and is finished within 12 s.

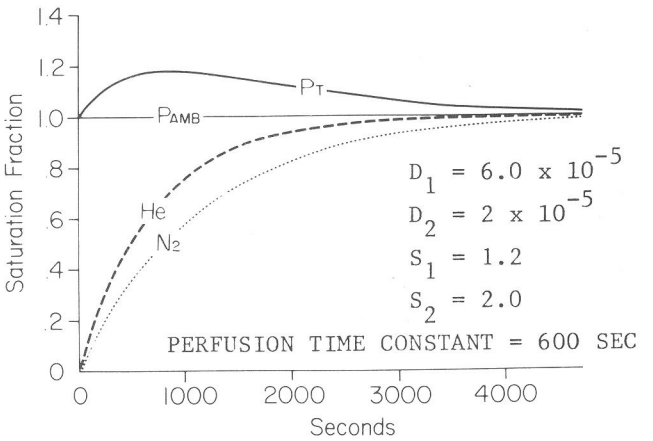

FIG. 15.13. The same plot as in Fig. 15.12 but using a perfusion time constant of 600 s. Notice the much less extreme but longer duration supersaturation time with a ratio of about 1.2. (After D'Aoust & Young 1979)

It is of interest that for those perfusion time constants of more physiological range, e.g. 600 s, the pressure ratio again seems to level out at 1.25. This, however, is coincidence, since it is strictly perfusion related and has nothing to do with the relative ratios of the diffusion constants of the gases in question. An even more persuasive argument in favour of the perfusion dependency of the supersaturations leading to vascular bubbles is provided by experiments (D'Aoust & Young 1979; D'Aoust *et al.* 1980) using a variety of inert gases and Doppler bubble detection in awake goats. This is shown in Table 15.4. In all cases except those dealing with hydrogen, animals were saturated for 17 h at 198 feet (60 m) on 'gas 1' and switched to 'gas 2' rapidly by density stratification. Bubbles were recorded and counted (Belcher 1976; D'Aoust *et al.* 1979) following the gas switch.

According to either perfusion dependent or diffusion dependent approximations, the maximum supersaturations expected were calculated (cf. Fig. 15.9) and are tabulated in Table 15.4. It must be

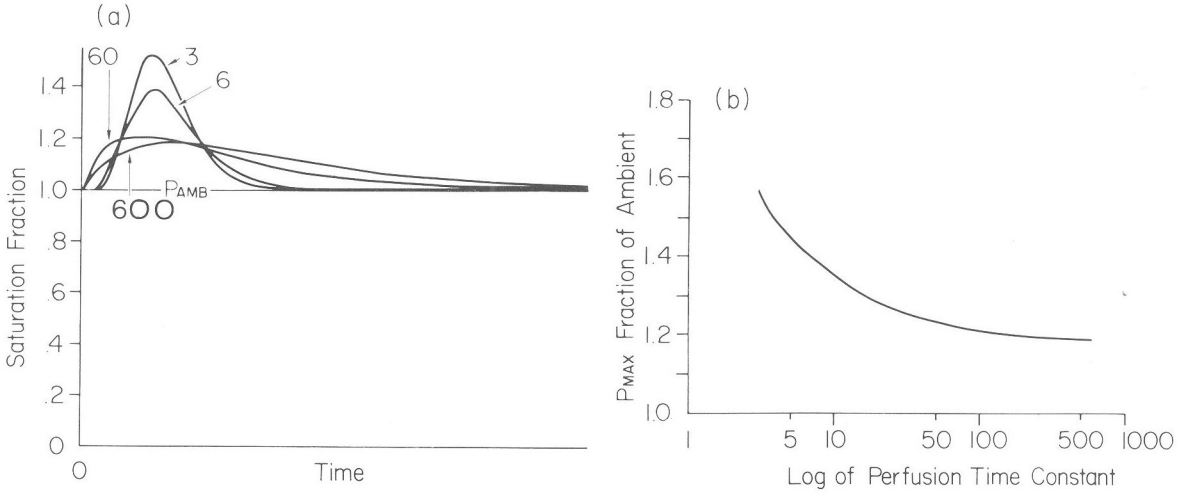

FIG. 15.14. Proportional plot of relative height and duration relative to the perfusion time constant of supersaturation against time for different blood flows in the Krogh tissue cylinder schematized in Fig. 15.10. The most extreme pulse is 3 s, the next 6 s, the next 60 s and the next 600 s time constant. This relationship is shown in Fig. 15.14(b), which indicates a logarithmic relationship of maximum supersaturation plotted against the log of the perfusion time constant. In no case, of course, can the supersaturation ratio be greater than 2, and even this is extremely unlikely.

emphasized that these values are based on solubilities which can be in error; the nature of the arguments, however, is unchanged. The different columns of the table have been calculated in the following manner, in order to demonstrate the hypothetical differences in perfusion dependent vs diffusion dependent supersaturation.

In the perfusion dependent system discussed above, the constant k_i of inert gas i is proportional to the tissue/blood rate partition coefficient, λ_i, of gas i. In a perfusion limited system, and for constant volume and flow, the ratio of the partition coefficients also expresses the ratio of the time constants of two different gases. If the ratio is greater than 1.0, supersaturation occurs; if it is less, undersaturation occurs (cf. Fig. 15.9).

If one assumes an 'average' tissue composition of 15% fat by weight and 85% aqueous, then the new 'average' tissue partition coefficient for helium and nitrogen can be computed as in Table 15.5 and becomes $\lambda_{He} = 1.21$ and $\lambda_{N2} = 1.64$, respectively. Taking the ratio of these two partition coefficients gives

$$\frac{\lambda_{N_2}}{\lambda_{He}} = \frac{1.64}{1.21} = 1.35$$

which we define as γ. This appears in the third column of Table 15.4. By the above reasoning, the

TABLE 15.4

Gas 1	*2*	$\gamma = k_2/k_1$	D_2/D_1	P_T *diffusion*	P_T *perfusion*	*Bubbles*
N_2	He	1.461	3.20	1.405	1.139	Yes
N_2	Ne	1.550	1.40	1.123	1.160	Yes
N_2	H_2	1.231	2.25	1.290	1.076	Very few
Ne	He	0.943	2.33	1.302	0.978	No
H_2	He	1.092	1.40	1.123	1.080	Very few
Ar	H_2	1.280	3.21	1.406	1.091	No
He	N_2	0.6841	0.32	0.60	0.861	No
H_2	N_2	0.075	0.44	0.71	0.890	No
Ar	N_2	1.041	1.429	1.13	1.015	No
Ar	He	1.400	4.5	1.506	1.123	Yes*
Ne	H_2	0.847	1.67	1.187	0.939	No
Ar	Ne	1.485	1.93	1.237	1.145	Yes

* More bubbles than any other combination of gases; near-fatal results.

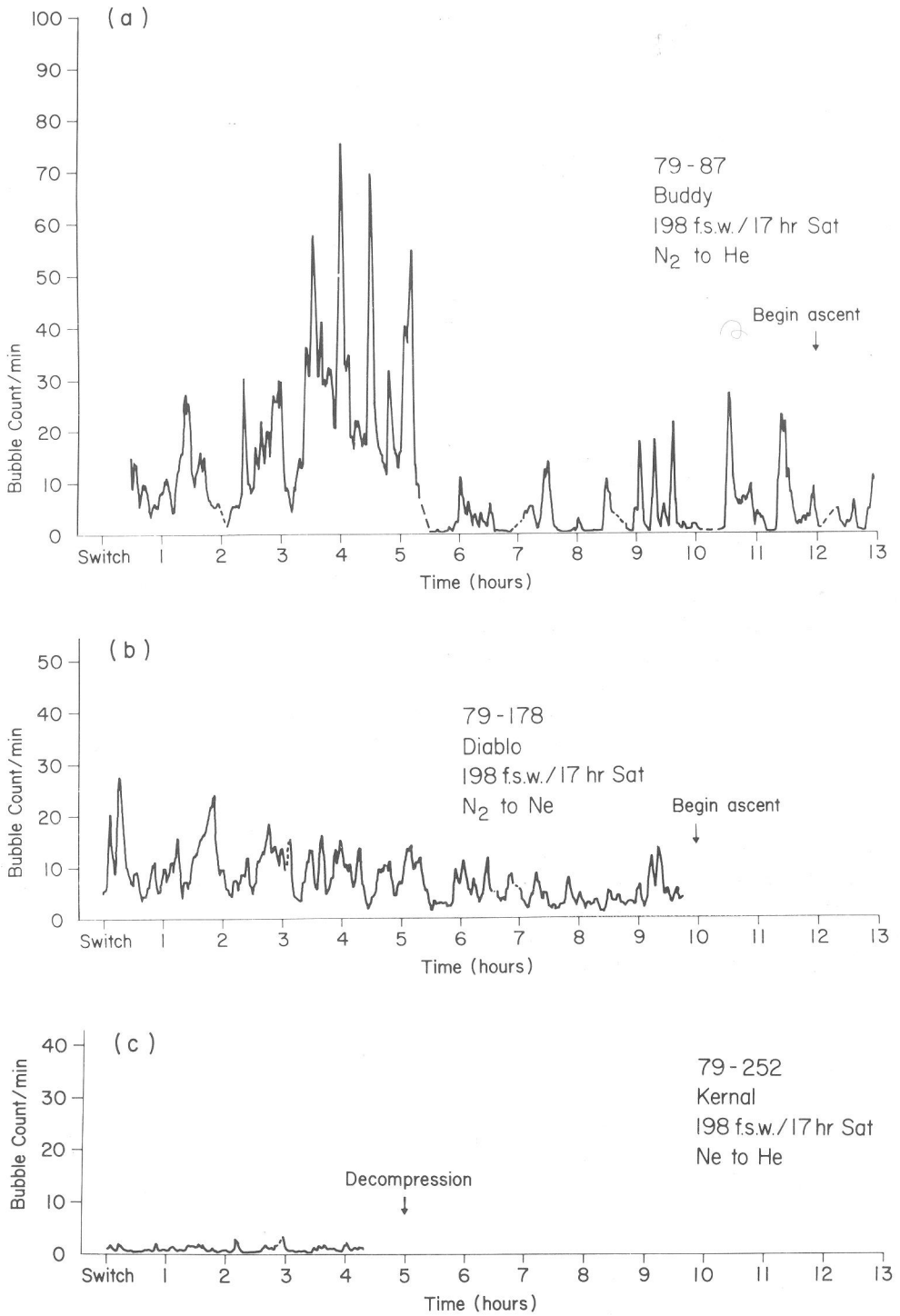

FIG. 15.15. (a) (Top) Bubble count plotted against time following a switch from saturation at 198 ft (60 m) on nitrogen switching to helium with the same oxygen tension (0.3 ATA). Bubbles continue for over 12 h, the entire isobaric period. (b) Results under similar conditions of a switch from saturation on nitrogen to crude neon continued to produce bubbles for 10 h, at which time ascent was begun. (c) Results of a switch from saturation on crude neon to helium. This produced virtually no bubbles, as is shown in Table 15.4. Vascular bubbles are not predicted for this gas switch by equation (4)

nitrogen time constant is of the order of $1\frac{1}{2}$ times as long as the helium time constant, whereas it is common practice in helium diving to assume that helium equilibrates 2–$2\frac{1}{2}$ times faster than nitrogen (Bühlmann 1975).

For the perfusion dependent case, the supersaturation P_{ss} (or subsaturation) expected following a transient isobaric gas switch is given by

$$P_{ss} = P_a e^{-k_1 t} + 1 - e^{-k_2 t} \quad (4)$$

according to the argument developed above (D'Aoust *et al.* 1979). This computation appears in the fifth column of Table 15.4 (P_T perfusion).

On the other hand, if one were to assume that the diffusion coefficients were the main property of the inert gases responsible for their time constants (D'Aoust & Young 1979), calculation of P_{ss} becomes more difficult. For this reason, they made the simplifying assumption that at the capillary level only *one* major diffusion dependent time constant describes the resulting change in total inert gas pressure in any particular region (Young & D'Aoust 1981). It can be shown that for simple geometric situations this is a reasonable assumption and that, moreover, the *direction* of any errors further supports the use of such an approximation.

This gives an equation of the same form as equation (4),

$$P_{ss} = P_a e^{-vD_1 t} + 1 - e^{-vD_2 t} \quad (5)$$

where v is a constant which depends on the geometric arrangement of the tissue, and D_1 and D_2 are the diffusion coefficients of gases 1 and 2 (Hayduck & Laudie 1974). Equation (5) was used to compute the value of P_T in column six of Table 15.4 (P_T diffusion).

This table, therefore, indicates those *unique* gas switches that should be capable of causing bubbles according to equations (4) and (5). In support of these approximate predictions, there is both the theoretical evidence described above and experimental evidence shown in Fig. 5.15. These figures indicate bubble counts plotted against time following isobaric gas switches from nitrogen to helium, nitrogen to neon and neon to helium. Notice that in Table 15.4, the diffusion dependent value of P_T from nitrogen to helium is 1.4 (equation 3) and the perfusion dependent value is 1.139 (equation 2). Both values predict supersaturation and therefore bubbles, and Fig 15.15(a) shows a considerable production of bubbles following a gas switch. In the same manner, for a switch to Ne from N_2, both

TABLE 15.5

Aqueous diffusion coefficients, D, aqueous and fat solubility coefficient, α, and tissue-to-blood partition coefficients, λ, for N_2, He, H_2, Ne and Ar. λ values are calculated assuming an average tissue composition of 15% fat and 85% water

	N_2	*He*	H_2	*Ne*	*Ar*
$D(\times 10^{-5}$ cm^2 s$^{-5})$	2.0	6.3	4.5	2.7	1.4
α, blood*	0.011	0.0063	0.016	0.0099	0.025
α, fat	0.067	0.015	0.050	0.019	0.140
α, tissue†	0.019	0.008	0.021	0.011	0.042
$\lambda = \frac{\alpha, \text{tissue}}{\alpha, \text{blood}}$	1.764	1.207	1.319	1.171	1.69

* Values for goat blood.
† Tissue values based on 15% fat content.

equations predict supersaturation, with 1.123 for equation (5) and 1.16 for equation (4), and this switch also caused bubbles (Fig. 15.15b).

By contrast, switching from neon to helium, which by equation (5) predicts supersaturation), failed to produce significant bubbles, as shown in Fig. 15.15(c) and only the perfusion model (equation 4) predicts undersaturation! This is strong evidence that solubility differences rather than diffusion ratios are the critical parameters determining supersaturation or undersaturation following a gas switch, and strong support for the original classical perfusion dependent model of Kety (1951).

The above results illustrate the nature of the evidence indicating that isobarically produced vascular bubbles originate and grow in the vascular tree, chiefly by a solubility dependent mechanism. While much more extreme supersaturations are undoubtedly generated in the initial moments of an isobaric gas switch which could lead to tissue bubbles, it appears unlikely that such tissue bubbles actually reach the central venous location for several reasons.

One is that, as shown in Fig. 15.12, computations indicate at first a rapid oversaturation and then an undersaturation following a step function change in gas tension at the proximal end of the cylinder. An initial bubble, if formed, would tend to be rapidly reabsorbed. Second, the oversaturation produced appears to be far too transient to allow time for the production and growth of bubbles to a significant size. Third, it seems likely that for bubbles formed in tissue by the relatively low supersaturation ratios shown in Table 15.4, insuf-

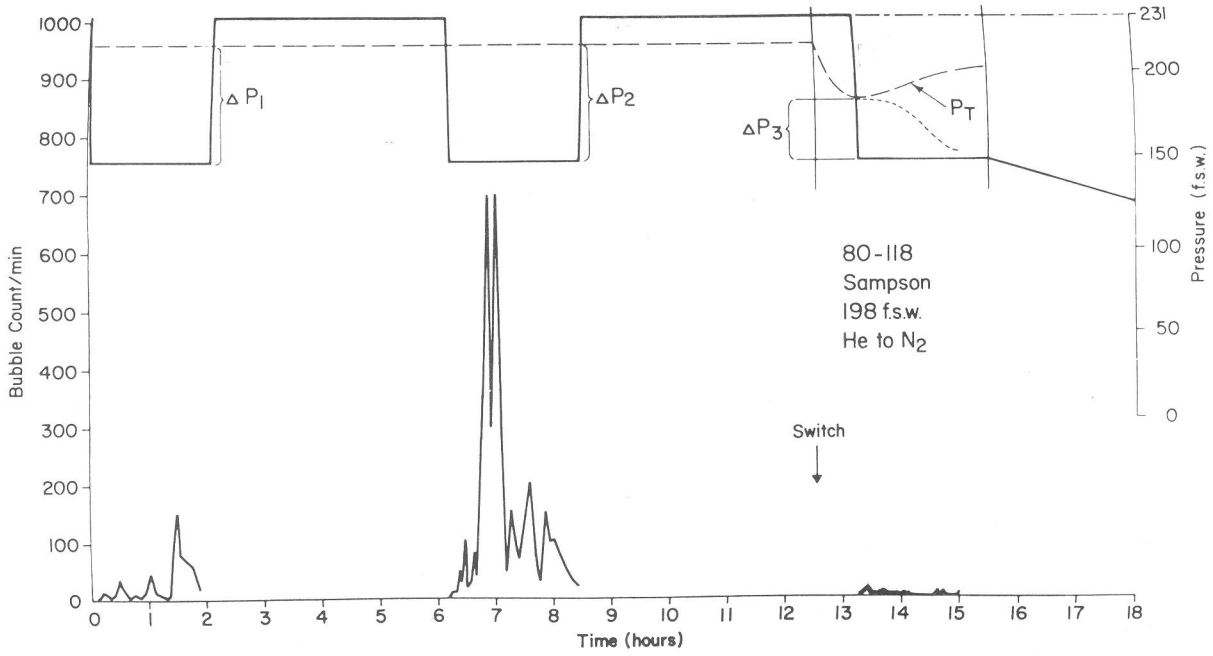

FIG. 15.16. Results of using a reverse switch to provide a decompression advantage. Animals saturated on helium at 198 ft (60 m) were, after saturation of 17 h, subjected to a decompression (ΔP_1) and bubble count followed for 2 h. They were then resaturated at 198 ft (60 m) for 4 h and subjected to another decompression (ΔP_2) of identical degree which resulted in a larger count of bubbles. The animals were then resaturated for 4 h, and, 40 min prior to a third decompression, the animals were switched to nitrogen and 40 min later decompression to the same depth occurred. In this case, however, calculated ΔP_3 was much lower and this was also accompanied by a much lower bubble count. (After D'Aoust *et al.* 1980)

ficient pressure exists to penetrate the capillary wall, since decompressions known to produce much greater supersaturations are by and large free of vascular bubbles (D'Aoust *et al.* 1979). Table 15.4 also shows results of isobaric studies switching from helium to nitrogen which have now demonstrated beyond a doubt the utility of gas sequencing as a potential decompression advantage. A typical experiment is illustrated in Fig. 15.16, which shows an increasing production of bubbles in awake goats after two successive decompressions and then the absence of bubbles following the same decompression where a switch to nitrogen preceded the decompression by 40 min. Forty minutes was chosen as an optimal time because other studies (D'Aoust 1980a, b) indicated that this appears to be a reasonable time constant for saturation with respect to bubble formation demonstrated by the isobaric gas switching technique. Using this time constant and equation (4) above, the time of maximal undersaturation was calculated according to Young and D'Aoust (1981) for a 40 min nitrogen tissue, and this was the time when the gas was switched to helium. The same technique could be used with hydrogen, but with less advantage.

In fact, in some recent isobaric sequencing experiments with nitrogen, hydrogen and helium (D'Aoust & Edel 1980), it has been shown that an isobaric gas switch from saturation on nitrogen–oxygen to hydrogen–oxygen produces very few bubbles as compared with a switch to helium–oxygen (see Table 15.4), indicating that there should be no operational limits on nitrogen bottom time before a switch to hydrogen can be made. A switch from hydrogen to helium also appears safe by this criterion. Further, the validity of the criterion itself is supported by the recent demonstration (D'Aoust *et al.* 1981) that an isobaric switch from argon to helium can be lethal. These results have important practical consequences, since hydrogen lies between helium and nitrogen with respect to decompression but is free of HPNS effects.

These considerations all provide new support for the classical perfusion limited model as applicable to 'deep tissue' isobaric inert gas supersaturation. Adjustments will be possible as more exact measurements of solubility are made available (Gerth & Hemmingsen 1980). They also indicate the utility of isobaric methods for (a) assessing the major time

constants of the body; (b) assessing critical supersaturation thresholds; and (c) assessing the optimal sequence of different inert gases.

Much more investigation remains to be done as basic mechanism and technique have been clarified and should provide excellent means to design optimal gas sequencing schedules for all degrees of saturation.

REFERENCES

BELCHER, E. O. (1976) *Adaptive Detection of Non-Stationary Noise Applied to Detection of Emboli in the Cardiovascular System.* Thesis, University of Washington.

BLENKARN, G. D., AQUARDO, C., HILLS B. A. & SALTZMAN, H.A. (1971) Urticaria following the sequential breathing of various inert gases at a constant ambient pressure of 7 ATA. A possible manifestation of gas-induced osmosis. *Aerospace Med.* **42**, 141–146.

BÜHLMANN, A. A. (1975) The use of multiple inert gases in decompression. In *The Physiology and Medicine of Diving and Compressed Air Work*, 2nd edn. Ed. P. B. Bennett & D. H. Elliott. London: Ballière Tindall.

COWLEY J. R. M., ALLEGRA, C. & LAMBERTSEN, C. J. (1979) Subcutaneous tissue gas space pressure during superficial isobaric counterdiffusion. *J. Appl. Physiol.* **47**, 224–227.

COWLEY, J. R. M. & LAMBERTSEN, C. J. (1979) Isobaric gas counterdiffusion in rabbit eye. *J. Appl. Physiol.* **47**, 220–223.

D'AOUST, B. G. (1979) The significance of transient isobaric countertransport (TIC) to diving medicine. In *Proc. Sixth Int. Congr. Hyperbaric Medicine*, pp. 400–409. Ed. G. Smith. Aberdeen: Aberdeen University Press.

D'AOUST, B. G. (1980a) Critical biophysical perspectives in the etiology of decompression sickness. In *E.U.B.S. Fifth Annual Scientific Meeting, Bergen, Norway*, pp. 95–119. Ed. J. Grimstad. Bethesda, Md: Fedn Am. Socs Exp. Biol.

D'AOUST, B. G. (1980b) ONR Contract No. N00014–78–C–0749. *Investigations of Transient and Steady-State Isobaric Supersaturation by Doppler Bubble Detection.* Virginia Mason Research Center, 1980.

D'AOUST, B. G. & EDEL, P. (1980) *The Significance of Hydrogen Switching Experiments in the Mechanism of Isobaric Supersaturation.* NPC/UMS Meeting (Abstracts, University of Southern California).

D'AOUST, B. G., SMITH, K. H. & SWANSON, H. T. (1976) Decompression induced decrease in nitrogen elimination rate in awake dogs. *J. Appl. Physiol.* **41**, 348–355.

D'AOUST, B. G., SMITH, K. H., SWANSON, H. T., WHITE, R., HARVEY, C., HUNTER, W., NEUMAN, T. & GOAD, R. (1977) Isobaric counterdiffusion; experimental production of venous gas bubbles at 5 atmospheres with diving gases. *Science, N.Y.* **197**, 889.

D'AOUST, B. G., SMITH, K. H., SWANSON, H. T., WHITE, R., STAYTON, L. & MOORE, J. (1979) Prolonged bubble production by transient isobaric counterequilibration of helium against nitrogen. *Undersea Biomed. Res.* **6**, 109–125.

D'AOUST, B. G., WHITE, R. & SEIBOLD, H. (1975) Direct measurement of total dissolved gas pressure. *Undersea Biomed. Res.* **2**, 141–149.

D'AOUST, B. G. & YOUNG, C. A. (1979) Transient isobaric supersaturation: theoretical basis and experimental support. In *USN/UMS Workshop in Isobaric Counterdiffusion.* Ed. R. Bornmann & C. J. Lambertsen. Bethesda, Md: Undersea Medical Society. (in press.)

D'AOUST, B. G., YOUNG, C. A. & EDEL, P. (1981) Switching to hydrogen from saturation on nitrogen is safe. *Undersea Biom. Res.* (Abstract, in press).

D'AOUST, B. G., YOUNG, C. A., WHITE, R. & DUNFORD, R. (1980) The perfusion diffusion dilemma: resolution and clarification by isobaric gas switching. *Undersea Medical Society Meeting.* (Abstract).

DUEKER, C.W., LAMBERTSEN, C. J., RSOWSKI, J. J. & SAUNDERS, J. C. (1979) Middle ear gas exchange in isobaric counterdiffusion. *J. Appl. Physiol.* **47**, 1234–1244.

EVANS, A. & WALDER, D. N. (1970) Detection of circulating bubbles in the intact mammal. *Ultrasonics* **3**, 216–217.

FARHI, L. E. & YOKOYAMA, T. (1967) Effects of ventilation perfusion inequality on elimination of inert gases. *Respir. Physiol.* **3**, 12–20.

GERTH, W. & HEMMINGSEN, E. A. (1980) Heterogeneous nucleation of bubbles at solid surfaces in gas-supersaturated aqueous solutions. *J. Coll. Interface Sci.* **74**, 80–89.

GIRY, P., SERVANTIE, B., MELIET, J. L., BURNET, H., TOURNIER, J. M. & BROUSSOLLE, B. (1979) Tentatives de modelisation de l'evolution des pressions partielles arterielles de gaz inertes en hyperbare. *Med. Aeronaut. Spat. Med. Subaq. Hyp.* **18**, 325–329.

GRAVES, D. J., IDICULA, J., LAMBERTSEN, C. J. & QUINN, J. A. (1973a) Bubble formation in physical and biological systems: a manifestation of counterdiffusion in composite media. *Science, N.Y.* **179**, 583–584.

GRAVES, D. J., IDICULA, J., LAMBERTSEN, C. J. & QUINN, J. A. (1973b) Bubble formation resulting from counterdiffusion supersaturation: a possible explanation for isobaric inert gas 'urticaria' and vertigo. *Phys. Med. Biol.* **18**, 256–263.

GROOM, A. C., MORIN, R. & FARHI, L. E. (1967) Determination of dissolved N_2 in blood and investigation of N_2 washout from the body. *J. Appl. Physiol.* **23**, 706–712.

HALSEY, M. J., & EGER, E. I. II. (1973) Fluid shifts associated with gas induced osmosis. *Science, N. Y.* **179**, 1139–1140.

HARVEY, C. A. & LAMBERTSEN, C. J. (1979) Deep tissue isobaric gas exchange: predictions during normoxic helium, neon, and nitrogen breathing at 1200 f.s.w. In *Underwater Physiology, VI. Proc. Sixth Symp. Underwater Physiology*, pp. 343–357. Ed. C. W. Shilling & M. W. Beckett. Bethesda, Md: Fedn Am. Socs Exp. Biol.

HAYDUCK, W. & LAUDIE, H. (1974) Prediction of diffusion coefficients for non-electrolytes in dilute aqueous solutions. *A.I.Ch.E. Jl* **20**, 611–615.

HEMMINGSEN, E. A. (1970) Supersaturation of gases in water: Absence of cavitation on decompression from high pressures. *Science, N.Y.* **167**, 1493–1494.

HEMMINGSEN, E. A. & HEMMINGSEN, B. B. (1979) Lack of intracellular bubble formation in micro-organisms at very high gas supersaturations. *J. Appl. Physiol.: Resp. Environ. Exercise Physiol.* **47**, 1270–1277.

HEMPLEMAN, H. V. (1960) *The Unequal Rates of Uptake and Elimination of Tissue Nitrogen Gas in Diving Procedures.* Medical Research Council, Royal Naval Personnel Research Committee.

HEMPLEMAN, H. V. (1975) Decompression theory: British practice. In *The Physiology and Medicine of Diving and Compressed Air Work*, 2nd edn, pp. 331–347 Ed. P. B. Bennett & D. H. Elliott. London: Baillière Tindall.

HENNESSY, T. R. (1978) On the role of gas induced countertransport mechanics at high pressure. *Med. Aeronaut. Spat. Med. Subaq. Hyp.* **17**, 122–166.

HENNESSY, T. R. & HEMPLEMAN, H. V. (1977) An examination of the critical released volume concept in decompression sickness. *Proc. R. Soc. B* **197**, 229–313.
HILLS, B. A. (1975) *Decompression Sickness. Volume I. The Biophysical Basis of Prevention and Treatment.* New York: Wiley.
HILLS, B. A. (1977) Supersaturation by counterperfusion and diffusion of gases. *J. Appl. Physiol.* **42**, 758.
HLASTALA, M. P. & FARHI, L. E. (1973) Absorption of gas bubbles in flowing blood. *J. Appl. Physiol.* **35**(3), 311–316.
IDICULA, J., GRAVES, D. J., QUINN, J. A. & LAMBERTSEN, C. J. (1976) Bubble formation resulting from the steady counterdiffusion of two inert gases. In *Underwater Physiology V. Proc. Fifth Symp. Underwater Physiology*, pp. 335–340. Ed. C. J. Lambertsen. Bethesda, Md: Fedn Am. Socs Exp. Biol.
IMBERT, J. P. (1975) *Proposition of a perfusion-limited model for isobaric counterdiffusion.* Report. Institute for Environmental Medicine, University of Pennsylvania, Philadelphia.
KARREMAN, G. & LAMBERTSEN, C. J. (1977) Kinetics of isobaric counterdiffusion. *Bull. Math. Biol.* **39** (5), 587–595.
KELLER, H. (1968) A method of deep diving with fast decompression by alternating different inert gases. *Rev. Physiol. Subaq. Med. Hyp.* **1**, 127–129.
KETY, S. S. (1951) The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharm. Rev.* **3**, 1–41.
KINDWALL, E. P. (1975) Measurement of helium elimination from man during decompression breathing air or oxygen. *Undersea Biomed. Res.* **2**, 277–284.
KROGH, A. (1919) The number and distribution of capilaries in muscles with calculations of the oxygen pressure head necessary for supplying tissue. *J. Physiol. (Lond.)* **52**, 409–415.
KYLSTRA, J. A., LONGMUIR, I. S. & GRACE, M. (1968) Dysbarism: osmosis caused by dissolved gas? *Science, N.Y.* **161**, 289.
LAMBERTSEN, C. J. (1979) Advantages and hazards of gas switching: relation of decompression sickness therapy to deep and superficial isobaric counterdiffusion. In *Proc. Symp. Decompression Sickness and its Therapy*. Ed. C. J. Lambertsen. Allentown, Pa: Air Products and Chemicals inc.
LAMBERTSEN, C. J., COWLEY, R. & CUNNINGTON, J. (1981) *Pathophysiology of Superficial Isobaric Counterdiffusion.* Report 3-81, Institute for Environmental Medicine, University of Pennsylvania, Philadelphia.
LAMBERTSEN, C. J., GELFAND, R. & CLARK, J. M. (Eds) (1978) *Predictive Studies IV. Work Capability and Physiological Effects in He–O_2 Excursions to Pressures of 400, 800, 1200, and 1600 Feet of Sea Water.* Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia.
LAMBERTSEN, C. J., GELFAND, R., PETERSON, R., STRAUSS, R., WRIGHT, W. B., DICKSON, J. G. JR., PUGLIA, C. & HAMILTON, R. W., JR. (1977) Human tolerance to He, Ne and N_2 at respiratory gas densities equivalent to He–O_2 breathing at depths to 1200, 2000, 3000, 4000 and 5000 feet of seawater (Predictive Studies III). *Aviat. Space Environ. Med.* **48**, 843–855.
LAMBERTSEN, C. J. & IDICULA, J. (1974) Cutaneous gas lesions and continuing lethal gas embolisation in animals due to isobaric inert gas counterdiffusion. *Fedn Proc.* **33**, 455.
LAMBERTSEN, C. J. & IDICULA, J. (1975) A new gas lesion syndrome in man induced by isobaric gas counterdiffusion. *J. Appl. Physiol.* **39**, 434–443.
PETERSON, R. E., HAMILTON, R. W. JR. & CURTSELL, I. (1980) Control of counterdiffusion problems in underwater dry welding. In *Association of Diving Contractors Proceedings International Diving Symposium, 1980.* New Orleans: ADC.
QUINN, J. A. (1978) Gas transfer through the skin: a two layer model relating transcutaneous flux to arterial tension. In *Oxygen Transport and Tissue III.* Ed. J. A. Silver, M. Erecinska & H. I. Bircher. New York: Plenum Press.
QUINN, J. A. GRAVES, D. A. & SMACK, R. A. (1974) Bubbles generated in membrane oxygenators: N_2 washout and counterdiffusion supersaturation. *J. Appl. Physiol.* **37**, 479–486.
SCHREINER, H. R. & KELLEY, P. L. (1967) Computation methods for decompression from deep dives. In *Proc. Third Symp. Underwater Physiology*, pp. 277–299. Ed. C. J. Lambertsen. Baltimore: Williams and Wilkins.
SPENCER, M. P. (1976) Decompression units for compressed air determined by ultrasonically detected blood bubbles. *J. Appl. Physiol.* **40**, 229–235.
SPENCER, M. P. & CAMPBELL, S. D. (1968) The development of bubbles in the venous and arterial blood during hyperbaric decompression. *Bull. Mason Clin.* **22**, 26–32.
TEPPER, R. S., LIGHTFOOT, E. N., BAZ, A. & LANPHIER, E. H. (1979) Inert gas transport in the microcirculation: risk of isobaric supersaturation. *J. Appl. Physiol.* **46**(6), 1152–1163.
TIKUISIS, P. & KUEHN, L. (1976) *Optimal Switching of Breathing Gases for Divers.* University of North Dakota, Grand Forks.
VAN LIEW, H. (1971) Dissolved gas washout and bubble absorption. In *Underwater Physiology IV.* Ed. C. J. Lambertsen. New York: Academic Press.
VOROSMARTI, J. JR., BARNARD, E. E. P., WILLIAMS, J. & HANSON, R. G. (1978) Nitrogen elimination during steady state hyperbaric exposures. *Undersea Biomed. Res.* **5**, 243–252.
WINSEY, H. S. & FOLKMAN, J. (1967) Silicone rubber: oxygen, carbon dioxide and nitrous oxide measurement in gas mixtures. *Science, N.Y.* **157**, 203–204.
WORKMAN, R. D. (1965) *Calculation of Decompression Schedules for Nitrogen–Oxygen and Helium–Oxygen Dives.* Res. Report 6-65, US Navy Experimental Diving Unit, Washington, D.C.
WORKMAN, R. D. & BORNMANN, R. C. (1975) Decompression theory: American practice. In *The Physiology and Medicine of Diving and Compressed Air Work*, 2nd edition, pp. 307–330. Ed. P. B. Bennett and D. H. Elliott. London: Baillière Tindall.
YOUNG, C. A. & D'AOUST, B. G. (1981) Factors determining the temporal pattern of isobaric supersaturation. *J. Appl. Physiol.: Resp. Environ. Exercise Physiol.* **51**, 852–857.
YOUNT, D. *UMS Decompression Theory Workshop.* Bethesda. Md: Undersea Medical Society Publ. No. 29WS (DT) 6-25-80.
YOUNT, D. (1979) Multiple inert gas bubble disease: a review of the theory. *USN/UMS Workshop on Isobaric Countercurrent Diffusion Phenomenon.* Bethesda, Md: Undersea Medical Society. (In Press.)