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THE TWENTY-SECOND UNDERSEA MEDICAL SOCIETY WORKSHOP

ISOBARIC INERT GAS COUNTERDIFFUSION

PHILADELPHIA, PENNSYLVANIA
13-14 NOVEMBER 1979

CO-CHAIRMEN

CHRISTIAN J. LAMBERTSEN
ROBERT C. BORNMANN

EDITOR

MARTHE BECKETT KENT

UNDERSEA MEDICAL SOCIETY, INC.
9650 ROCKVILLE PIKE
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N O T E

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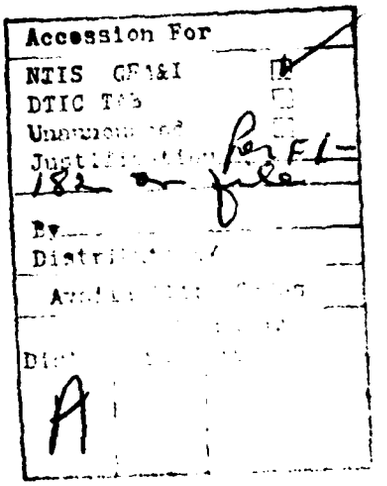
Inquiries concerning the Final Report should be directed to Christian J. Lambertsen, M.D., or Capt. Robert C. Bornmann, MC,USN, co-Chairmen of the Workshop.



ISOBARIC INERT GAS COUNTERDIFFUSION

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INTRODUCTORY REMARKS

Capt. Robert C. Bornmann, MC, USN

Welcome to the twenty-second workshop of the Underseas Medical Society. These workshops, which began in 1973, are intended to serve several special purposes. First, they are forums where workers in rapidly expanding or developing research areas can discuss experimental results and assimilate recent information. Second, these workshops provide an opportunity to encourage research and to direct it into promising channels. And finally, these meetings deliberately mix persons who have backgrounds in a variety of scientific disciplines, to promote a stimulating and provocative exchange of technical information.

This particular workshop will concentrate on the countercurrent diffusion phenomenon. We will review the experimental data, examine the explanatory hypotheses, and attempt to integrate the available information on countercurrent diffusion into a general scientific context. We are also interested in relating this phenomenon to the practicalities of modern diving in general and of Navy diving in particular. For example, will countercurrent diffusion present difficulties in future diving operations? If so, how can we avoid them? Does this phenomenon explain hitherto inexplicable occurrences? Has it perhaps obscured our understanding of inert gas behavior?

It will be interesting to investigate whether some of the things that have occurred in Navy diving in the past can be attributed to countercurrent diffusion, or whether Navy and commercial divers have in fact been dealing adequately with this phenomenon all along, even though they may have had no idea what they were actually contending with. I

recently was looking through the old Navy diving manual I used in diving school in 1960. The normal procedure in deep-sea helium diving with heavy dress was to dive breathing a helium-oxygen mixture in semi-closed-circuit flow, and then to switch to oxygen at 50 feet. At this point the suit was flushed for a time with a large volume of oxygen, to eliminate the helium. There was an alternate procedure for continuing to the surface on helium-oxygen if it was not possible to switch to oxygen. There was also a third alternative in case at any time the diver lost his helium-oxygen supply and had to switch to air. The schedule for coming to the surface was an old Navy treatment table based on the idea that the diver would be completely saturated and would have to be returned to the surface at the ascent rate for an air saturation exposure. However, there was also a caution in the diving manual that said, if the third of these situations occurs and the diver is switched to air, do NOT follow the normal procedure, which is to ventilate the suit with a large volume of gas to remove any residual helium. In this situation, continue with a semi-closed breathing gas circulation. The new gas, air, should simply be injected into the suit, and this should continue all the way to the surface so that the diver is gradually switched from helium-oxygen to a mixture of helium-oxygen and air; and then to air. The manual noted that experience had shown that if this procedure wasn't followed, the diver would become ill. I am not certain, but it is possible that the diver's discomfort in this situation would be caused by isobaric counterdiffusion, although other factors may also have contributed.

The progra of this w rkshop follows a planned sequence. The first session will cove esea.ch observations and experiments, and the second

session today will focus on theories and hypotheses which have been advanced to explain what has been observed. The first discussion on the second day of the workshop will deal with the terminology used to discuss the countercurrent diffusion phenomenon. Currently, different researchers use different terms to refer to the same event.

The final workshop session will feature a panel discussion on the implications of countercurrent diffusion for open-sea and chamber diving operations, and for decompression and decompression sickness therapy.

It is the hope of the organization sponsoring this workshop, the U.S. Navy, that we will all leave this meeting with a better understanding of isobaric inert gas counterdiffusion and its implications.

Session I. Experiments and Observations

Chairman: Capt. R. C. Bornmann

HISTORICAL REVIEW, DEMONSTRATED FORMS OF THE COUNTERDIFFUSION SUPERSATURATION PROCESS, AND PATHOLOGY AND EXPERIMENTAL PATHWAYS

C. J. Lambertsen, M.D.

Historical review

My task is to review the historical development of counterdiffusion generally, rather than to present a specific set of experiments or a particular point of view. The countercurrent diffusion story goes back quite a long way, touches many people in many different places in the world, and describes some of the events that happen in animals or humans exposed to isobaric counterdiffusion processes. After this historical review, the emphasis in this morning's session will be on measurement, while the afternoon session will attempt to relate theory to measurement.

First, with countercurrent diffusion we are dealing with a phenomenon that is very old; everyone here remembers that, whether the term isobaric counterdiffusion was used or not, individuals thought in terms of counterdiffusion with no change in pressure, and mention of this occurs occasionally in the literature. At the first underwater physiology symposium (Washington, D.C., 1955), the concept of facilitating inert gas transfer by alternating inert gases was introduced. Before that, facilitating the transfer of inert gas had been thought about but not thoroughly discussed. Keller and Buehlmann first used these concepts, even

though they didn't think in terms of the isobaric no-pressure chain but rather in terms of subsaturation and desaturating more rapidly by alternating the gases breathed during decompression.

Things might have remained there, except that the group at Duke was studying the respiratory effects of various inert gases at a pressure of 200 fsw, by administering nitrogen or neon in a chamber filled with helium. In the course of one such experiment, a situation developed which no one at the time understood: the subject developed skin lesions. They looked like skin bends to the team at Duke, but they had developed in an individual who had not decompressed and who had been kept at a relatively constant pressure of about 200 fsw for a long time during the experiments. Dr. Aquadro, who was a member of the Duke team, called me to discuss what to do. The individual should have been subsaturated because he had been given nitrogen or neon after having breathed helium, so it didn't seem reasonable that he should have skin bends. A decision was made to treat the subject as though he had skin bends, and the lesions disappeared during treatment. Later, the Duke research group developed the concept of osmotic changes caused by inert gas dissolving in body tissues to explain what had occurred. The Experimental Diving Unit repeated the Duke studies under the same conditions and found nothing, after which many of us put the whole issue aside, although we didn't quite forget about it.

Even before the Duke experiments, however, we began a series of experiments at the Institute for Environmental Medicine called

"Predictive Studies." One of them, in 1970, involved saturating individuals on nitrogen for a few weeks to study nitrogen effects at four atmospheres and to investigate respiration and respiratory reactivity by administering other gases. One of these gases was helium, which was given to nitrogen-saturated individuals for an hour, during which different amounts of carbon dioxide were administered. Before this study was initiated, the laboratory undertook an intensive self-appraisal, because it looked as though the planned experiment would create a peculiar supersaturation that might be hazardous. Such a supersaturation would have been almost opposite to the subsaturation sought by Keller and Buehlmann. We recognized this potential hazard even before isobaric supersaturations of any significant degree were being considered. Ultimately, we decided that the experiment would not be hazardous because the increase in total inert gas pressure under experimental conditions would not be greater than had been experienced in true saturation decompression studies in the past, and so we proceeded with the study. No symptoms were generated when nitrogen-saturated subjects at 100 fsw were given helium.

There were, then, two conflicting pieces of evidence. On the one hand, symptoms did not occur when helium was given sequentially to individuals saturated with nitrogen. On the other hand, there was the confusing situation uncovered at Duke (which had not been confirmed by Navy studies), in which, under saturation conditions, subjects exposed to helium and administered another breathing gas had developed symptoms. It was in this situation that we planned

our third predictive study, which was designed to compare helium, neon, and nitrogen effects and would therefore require giving gases in series. Once more, there was the possibility that sequencing might cause subsaturations of major degrees in some situations and significant supersaturations in others, because the alternating was to take place at many different pressures, ranging from 100 to 300, and 400 to 1200 feet of seawater. Again, we evaluated the potential hazard in advance and, because no adverse effects of supersaturation at high pressure had ever been demonstrated, we proceeded with the experiment.

What did in fact happen, beginning at about 200 fsw, was a situation very much like the one at Duke: the subjects developed skin lesions and severe itching. Only these two symptoms occurred; there were no central nervous system effects, no signs of vestibular derangement. And by severe, I mean intolerable: violent cutaneous itching. Despite the itching, however, there were initially no lesions such as had been observed at Duke. This marked the first in a series of a dozen or more observations of symptoms in various subjects surrounded by helium, breathing different gases, at a variety of pressures. It was not until a pressure of 1200 fsw was reached that true gas lesions -- visible, prominent, and capable of being photographed -- and severe vestibular derangement, incapacitating for as long as five days -- developed. At 1200 fsw, three of our four subjects had vestibular symptoms; two were incapacitated, unable to move their heads without nausea, vomiting, and violent dizziness. Since it is always easier to interpret events in terms

of known causes than to develop a theory to explain events, we thoroughly explored the possibility of viral infection before concluding that a process involving subsaturation of deep tissues must underlie both the dermal and vestibular effects experienced by our divers.

We made an instinctive judgment that the process was related to gas movement through the skin; at this stage, no theory was involved -- only judgment. The approach we used to test this judgment involved enclosing the subject almost entirely in a gas-tight suit and allowing the same gas that the subject was breathing to pass through the suit. Except on those areas of the skin, such as the face and hands, that continued to be exposed externally to helium, all the dermal lesions disappeared during this procedure, confirming our feeling that gas movement in two directions, between the capillaries and the environment, was involved.

The phenomena we have discussed so far today are not unitary but complex. . . .

They involve different events: in one case, different gases are administered sequentially, and in the other, one gas is breathed while another gas surrounds the subject. Both the order of the sequence and the relation of the external environment to the internal are important. With this general background in mind, I will now discuss the circumstances in which these phenomena occur and illustrate their effects.

Forms of the counterdiffusion supersaturation process

Figure 1 conceptualizes nitrogen saturation at high pressure

and the administration of helium, which comes in at a faster rate than nitrogen is thrown off. This is not a new concept, but some of its implications are only beginning to be understood. One of the more important may be the effect of the duration of the probable excess saturation. As the figure shows, the times are long, providing many hours during which bubble formation can occur.

Fig. 1 here

The next figure shows the subject's dermal lesions (Fig. 2). These lesions were not vesicles; they were bloodless lesions. They were not gas lesions, and no gas could be sampled from them. They were hard and raised, and something had squeezed the blood out of them so that they did not bleed when they were opened. Although the figure doesn't show them, there were many lesions on the scalp, where the itching was extreme. There were no lesions under the diver's suit, and there were also no lesions on the mucous membranes. Since the eye, like the skin, was exposed, the question whether bubbles occurred in the conjunctiva of the eye has been raised. No human exposures have caused bubbles in the eye, the mouth, the nose, or the mucosae.

Fig. 2 here

The next figure (Fig. 3) is a diagram of a capillary, showing how the nitrogen breathed diffuses out into the environment from the capillaries, while the helium in the environment diffuses into the capillary and continues to move from there. This diagram was drawn in the chamber at 300 fsw to explain that a process

involving two moving gases might be causing the symptoms, and that a subcutaneous gas phase might be involved.

Fig. 3 here

Figure 4 shows a semi-cartoon, semi-serious experimental plan for exposing subjects in a bathtub in a high-pressure chamber to one breathing gas while surrounding them with water, which might even permit the escaping gas bubbles to be seen as they left the body. We did not perform this experiment because of the seriousness of the vestibular effects caused by exposing the entire body. Instead, the experiment we conducted involved the diver keeping an arm under water while breathing helium, and no bubbles were seen coming through the skin. We will later talk about why no bubbles occurred in this situation.

Fig. 4 here

We also talked to people in the Chemical Engineering Department, to get a better understanding of gas transfer from the engineering perspective. We made a cell, put a membrane on top of it that would hold water, and put water and then oil on top of the membrane. By simply filling one part of the cell with nitrogen and the other with helium, it was possible to see bubbles being generated at the oil-water interface. The bubble-making process could be accelerated by seeding at the interface. Here, then, was an example of bubbles forming in an isobaric, steady-state situation, without pressure on either side of the membrane. Both "isobaric" and "counterdiffusion" were obvious terms to choose to describe this <u>in vitro</u> situation.

Next, we extrapolated from this environmental situation to the high-pressure chamber exposure that had produced the lesions and the vestibular derangement. Theoretically, the ratio of maximum generatable excess supersaturation in relation to ambient pressure is about 0.3 atmospheres. At 100 fsw, that would be about one atmosphere, and at 37 atm, the pressure at which our symptomatic episodes occurred, the steady-state supersaturation would be about 9 atmospheres. This seemed unreasonable; even if such a supersaturation was theoretically feasible, gradients would be established and gases would diffuse in all directions from many tiny foci, causing excess saturations of lesser degree in adjacent tissues.

Our next step in the process of trying to measure what was happening involved exposing animals to various isobaric inert gas counterdiffusion circumstances. Figure 5 shows lesions in a pig, similar to those that developed in human subjects, and Table 1 displays the results of a series of experiments undertaken by Joe Idicula in animals to follow what had been observed in man. In this series, different breathing gases — neon, nitrogen, argon, nitrous oxide, and sulfur hexafluoride — were administered at different pressures ranging from 66 to 300 fsw to animals surrounded by helium in a chamber. The internal-external relation of the gases was also reversed, with helium given as the breathing gas and the other gases used as the environmental gas. The plus-marks on the table indicate the experimental situations that caused lesions in the pigs, who were anesthetized and otherwise without

symptoms.

Fig. 5 here

Table 1 here

After these experiments, our work at the laboratory involved tissues, synthetic membranes, biological membranes, and whole animals; Fig. 6 shows an animal in a box with its head in a hood, which permits it to be exposed to one atmospheric gas while breathing another one. This experimental arrangement also allowed us to put the box inside a pressure chamber, if necessary. The Idicula group's experiments had shown that nitrous oxide breathed at one atmosphere by animals surrounded by helium generated bubbles in the bloodstream in addition to severe isobaric skin lesions. This finding caused us to use nitrous oxide at sea level for many of our investigations.

Fig. 6 here

In a pig in this experimental set-up, one of the most obvious effects is the expansion of the gut, which is not related to the environment but to nitrous oxide entering that gas space via the lungs and circulation. Bubbles do form in the blood, and are visible post mortem in the cut kidney, the atrium, and the vessels of the eye, which means they also occur in the brain. The seriousness of the problem is shown by the fact that animals exposed to nitrous oxide breathing while surrounded by helium die in about 1-1/2 hours after the beginning of the experiment. The rapidity of this lethal process handicapped this type of experiment, so we began to investigate where bubbles were going from the pulmonary

artery. They began to appear in the blood after about 26 minutes of nitrous oxide breathing, and at about 45 minutes, there was massive bubbling in the venous blood coming to the lung. Almost from the beginning, bubbles seemed to have been breaking through the lungs; the lungs did not filter the bubbles out effectively. It is important that we not continue to believe that they do filter all the bubbles out.

Another group at our laboratory, which included Dr. Cowley, wanted to study counterdiffusion using a rabbit's ear, in which the circulation is visible. Figure 7 shows the experimental set-up, with the rabbit breathing one gas through a mask while its ear is surrounded with a different gas. A group of rabbits exposed in this way at a pressure of 11 atmospheres died within 2 hours just from breathing air while surrounded by helium, with no other stresses. Nitrous oxide kills at sea level in a counterdiffusion situation, and air kills at 10 or more atmospheres of pressure. However, rabbits breathing normoxic nitrogen at 11 atmospheres who are not surrounded by a helium environment do not die, so it is clear that we are dealing with an inert gas phenomenon. Moreover, many of the diving studies done at several laboratories have involved pressures, gases, and times very similar to those of the experiments we have just described, so we have often been very close to exposing human subjects to these conditions.

Fig. 7 here

The next experimental problem was how to keep the animal alive long enough to study the counterdiffusion process. We

decided to counterdiffuse only a part of the animal, such as the ear, leg, or hindquarters, and to insert a trap in the vena cava to catch the bubbles coming from the counterdiffused region. This procedure is shown in Fig. 8. Since the trap catches the emboli before they can kill the animal, the heart, lungs, and brain continue to operate properly, although the counterdiffused region, in this case the pig's hindquarters, is clearly in bad shape. As Fig. 8 shows, after 4 to 6 hours of counterdiffusion, the process, though superficial, is intense. Several significant changes have occurred: there is a marked derangement of the cutaneous circulation. Bubbles have accumulated in the capillaries, causing an almost complete cessation of circulation and extravasation from the capillaries into the tissues. The line of demarcation between the counterdiffused region and the rest of the skin is very sharp, as can be seen in the photograph (Fig. 8). This preparation permits the animal to continue to live, and it is sometimes necessary to kill it after 8 hours or so.

Fig. 8 here

The next step in our investigation was to measure the volume and composition of the bubbles coming from the pig's hindquarters. Figure 9 shows a plot of the volume of bubbles in the trap. The same gas is measured cumulatively as it increases in volume; eventually, the rate of gas bubble formation peaks and stabilizes, regardless of the duration of the exposure. A major problem with this technique is that no measurements can be taken until the bubbles begin to form, which takes about 1-1/2 hours. The time

Fig. 9 here

of greatest experimental interest, the beginning of the counter-diffusion process, cannot therefore be observed with this preparation. The volume of gas that comes through the trap (in partial pressures) is shown in Fig. 10. About 200 milliliters of gas per hour per square meter of surface area were generated in the pig's hindquarters at a pressure of one atmosphere and in a nitrous oxide/helium counterdiffusion environment. The same amount, proportionately, seems to be liberated in experiments involving the rabbit's ear, which Dr. Cowley will discuss later.

Fig. 10 here

Pathology and experimental pathways

It is also possible to determine the composition of the vena caval blood in the trap, and to deduce certain pathways for gas exchange. Helium is found in the blood at a level of 16%. The composition of the arterial blood is known, as is that of the venous blood. Some blood does not go through the skin but is shunted back into the venous blood, but other blood does go through the skin and is affected. These two streams then merge. The chart shown in Fig. 10 reflects our estimate of what happens in the skin during counterdiffusion, and shows the percentage of each gas in the trapped bubbles.

Next, we conducted a study designed to measure the rates at which different gases -- helium, neon, methane, ethane, carbon dioxide, nitrous oxide -- move through the skin, i.e., the flux of various gases. Temperature has an influence on the flux of

helium through the skin. Simple diffusion of helium at temperatures in the 37 to 41° C range accounts for 60 ml/hr/m^2/atm. Using these figures, it is possible to imagine the amount of helium movement that would occur at 40 atm (1200 fsw) in a diver suddenly starting to breathe a neon-oxygen mixture in a helium environment; the amount entering the diver's body through the skin might be as great as 5000 ml per hour.

The final point of this review is to see that we are dealing with more than one topic, and with different aspects of these topics. We know that helium diffuses through the skin and other surfaces, and we know that dermal lesions occur. These lesions should be thought of as warnings of incipient embolization, whether or not the emboli have broken out. We know that continuous embolization occurs, and that this can break through the lungs and is one of the mechanisms that may be involved in vestibular functional effects.

We are looking at events occurring at the surface and away from the surface, at events that are both transient and continuous. Where a gas phase is involved, many different elements are pertinent: decompression, compression, deep gas exchange, and superficial gas exchange. These events must all be tied together, and it is essential that we avoid becoming compartmentalized to the extent that we miss the interconnections between them.

Discussion

Q. Has the rate of embolization been measured under other counterdiffusion situations, for example, during N_2O breathing in a helium environment? Have different pressures been used?

A. We have conducted N_2O studies at 2 atm, and the rate-of-formation curve was essentially identical to the one at 1 atm. The same volume of gas was produced per square meter, but there were twice as many molecules because the pressure was 2 atm. In experiments with pigs at 1200 fsw, using Ne and N_2, we have seen skin lesions but no emboli over periods of time at least equivalent to those of the human studies.

Q. Have experiments been conducted to observe the onset of the process or the effect on the process of varying the inert gases to look at the rate of change?

A. In experiments designed to measure gas flows, gas volumes, and gas composition, we have not tried to alter the process. In studies of gas exchange in the ear, we have administered oxygen, to observe the change in gas volume caused by the experimental equivalent of therapy.

Q. Have you observed whether reverting to the original gas causes the embolization to stop, or whether, once started, the process proceeds inevitably?

A. We have not as yet conducted a systematic effort to determine that.

Q. Why were experimental gases such as N_2O and SF_6 used?

A. N_2O was used because it was convenient and could be worked with at sea level; SF_6 was part of an attempt to study all the inert gases that had been used as breathing gases and to look at respiratory function when dense gases were being breathed.

Q. Since a venous bubble must be more or less equilibrated by the time it gets into the major flow, would it be possible to measure the time it takes for the gas to go from the skin to the bubble trap by adding a fast isotope to the gas diffusing in?

A. We were not able to find a rapidly diffusing radioactive isotopic gas to use in such studies.

Q. Is the gas in the bubble trap equilibrated with the gas in the venous blood so that it in fact represents the partial pressure of the gas?

A. Any tonometer that equilibrates a gas phase with a liquid phase has to have the ability to reach an equilibrium pressure. The venous blood is at a subatmospheric pressure, which means there cannot be true equilibrium between any gas phase in contact with that blood. We have estimated partial pressures at atmospheric pressure of the gases in the gas phase of the bubble trap. These values do not precisely equal the gas tensions in the blood because there is no true equilibrium, but there is a close near-equilibrium between them.

Q. What is known about the location of bubble formation?

A. Initially, we believed that gas spaces were being formed subcutaneously in millions of tiny locations, and later we decided they could form in the capillaries in addition to the gas spaces. Now we believe they form in the gas spaces, and there are gas spaces where there are no capillaries.

Q. Was there any fluid at all in the skin lesions? Were they gas-filled?

A. In the divers, they were hard, raised, bloodless lumps, in which something had pressed on the capillaries and squeezed the blood out. When scratched open, no blood or fluid came out. Without microscopic sections, which we didn't do on the human subjects because it is impossible to do histology properly at pressure, it was difficult to tell what was inside the lesions. In the pigs, however, the microscopic sections showed the gas spaces you saw on the histological slides.

Q. Is there any danger that a long surgical procedure in a nitrogen environment could cause differentials great enough to cause bubble formation?

A. It might occur with nitrous oxide at high partial pressure, but not with halothane or with other anesthetics, which are used at low concentrations.

Q. Did the divers with the vestibular problems have any auditory symptoms such as tinnitus, hearing loss, ear pain, or a feeling of ear fullness?

A. The divers who had the vestibular problem had no hearing loss afterwards, even on audiometric tests, and they showed no signs of hearing loss during the episode. They had no auditory or visual symptoms; severe vertigo and nausea were

the only symptoms. It is important to remember, however, that the vestibular derangement associated with gas switching is distinct from the other type of vestibular problem related to changing from nitrogen to helium during decompression. There should not be any blurring of the distinctions between these two phenomena.

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THEORETICAL BASES OF TRANSIENT ISOBARIC SUPERSATURATION: EXPERIMENTAL SUPPORT

Brian G. D'Aoust and Christopher Young

There are three important reasons for this workshop: 1) to assemble and organize theoretical vs. experimental information on isobaric counterdiffusion more clearly; 2) to eliminate current confusion in terminology; and 3) to assess both the present risk and potential advantage in gas switching or steady-state differential situations such as those that occur when switching back to air by mask after heliox exposures or when breathing heliox during welding in an argon atmosphere. At Virginia Mason, we entered into this research area about four years after the phenomenon was described by Dr. Lambertsen's group. At that time the discovery was a surprise to us, mired as we were in a program to clarify the basic aspects of bubble formation on the one hand and gas transport on the other. It soon became clear that counterdiffusion might be an effective research tool; we believe we can increase our understanding of these basic questions by using countertransport, counterequilibration, or counterdiffusion as a research tool.

I had lunch with Dr. Per Scholander the other day, and he repeated something that has always impressed me: "I have never talked about anything I understood." With that as an introduction, I hope I can press on confident of some sympathy on your part.

We became very interested in Drs. Lightfoot and Tepper's ideas on counterdiffusion supersaturation when we were initially studying this phenomenon, which we were trying to fit into the concept of what makes a bubble? What is the relationship of ΔP and the pressure ratio?

Our contribution to this workshop will have two parts. First, we will present some results of an analysis by Dr. Young of a standard Krogh cylinder model with wash-in and wash-out of helium and nitrogen, respectively, as well as a number of other gases. This analysis will be based on two extremes and one compromise. The two extremes occur when time constants of the equilibrating gases are controlled or determined by either the solubility of the counterequilibrating gases, or by the diffusion coefficients. The compromise involves both diffusion differences and various values of tissue-to-blood partition coefficients, i.e., solubility ratios. The results of these analyses demonstrate not only the improbability of a strictly diffusion-related time constant but also suggest, in concert with our experimental evidence, that the perfusion (solubility)-related time constant is even more controlling than we have previously thought, at least as concerns the bubbles observed by Doppler at the central venous location after isobaric supersaturation.

Second, we will present a summary of our experimental work, which approximately delineates the time constants important for whole body supersaturation in the awake goat and also supports a perfusion-limited model.

Synopsis

We know that the isobaric countertransport of two gases produces supersaturation, and must now decide which of a number of transport processes in combination with which particular properties of the gases produces these supersaturations. To avoid semantic problems, I prefer the following terms for the various operational situations. When a sudden switch of environmental gas which is also breathed occurs in the vertebrate body, the situation can clearly be termed a transient isobaric counterequilibration. If only the breathing gas is changed, counterequilibration approaching a steady state in which one can conceive of stable decreasing gradients between the skin and the lungs of the surrounding gas on the one hand and the lungs and the outside of the skin on the other is involved.

This latter situation I prefer to describe as steady-state isobaric countertransport rather than "counterdiffusion," since it is not yet clear whether the perfusion vs. diffusion ratios are the most critical in determining the degrees of supersaturation measured. As we shall show, there is increasing evidence that it is indeed the perfusion-limited situation or model that best describes our experimental results with transient switches, i.e., bubble formation in the vascular beds (Hills 1977; Kety 1951).

The model of Graves, Idicula, Lambertsen and Quinn (1973), for which a physical analogy has been constructed and supersaturation pressures directly measured, has only two limitations: size and the difficulty of experimenting with capillary dimensions. This model is of greater conceptual value in demonstrating a mechanism at the steady state. In a situation involving transient switches, Fig. 1 shows transient excess pressure across silicon rubber, and provides a useful conceptual analogy for the transient situation.

This physical observation was actually first reported in 1967 by Winsey and Folkman, who suggested exploiting it as a simple gas fraction analyzing method. This is feasible and both inexpensive and simple and, as reported by Graves and his co-workers (1973), has now resulted in a commercial product (see paper by Graves, this workshop). This phenomenon can be considered a pure example of isobaric counterdiffusion.

In an earlier paper (D'Aoust, Smith, Swanson, White, Harvey, Hunter, Neuman and Goad 1977), we alluded to the difficulty in deciding upon the mechanisms of isobaric supersaturation. This is readily understandable when it is accepted that helium saturates the body faster than nitrogen (Behnke and Willmon 1941; Buehlmann 1975); however, the reason that these time constants differ has never been clearly explained. In the case of helium, solubility and diffusivity could be involved. The time constants or half-times of these gases are empirically derived

and expressed in the multiple exponential parallel compartment model. Because such a model is so common in diving calculations, it is worth re-emphasizing how the phenomenon of isobaric supersaturation confounds such a model and forces us to consider the actual tissue or vascular location of bubbles (Lambertsen and Idicula 1975).

Part of the rationale supporting a multiple parallel compartment model is that it allows for a spectrum of half-times in the body, for which there is much evidence (there being nothing said about how much gas is dissolved in which tissues of which half-times). However, once the phenomenon of isobaric bubble formation was demonstrated, it became necessary to consider where the bubbles were forming and what specific half-times applied in these regions.

Thus, with the two gases, 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 half-times for helium and nitrogen (Buehlmann 1975) is obviously an oversimplification because helium diffuses faster, is less soluble, and has a lower fat/water partition coefficient than nitrogen. For this reason, in our original analysis we arbitrarily used a pairing scheme (Fig. 3) which provided for a different helium/nitrogen half-time ratio according to the supposed basis for the nitrogen half-time. Thus, for a very fast tissue (which was assumed to be aqueous), a ratio of 2½:1 ($T\frac{1}{2}N_2$:$T\frac{1}{2}He$) was used; whereas for the long tissues (which were assumed to be more fat controlled) a lower ratio was used. This is still arbitrary; however, it seemed a more reasonable approximation to known facts than using a constant ratio. In fact, it may have been even less justified than we imagined, as we shall show in this presentation.

It was natural as a next step to try to calculate the different degrees of supersaturation that would be encountered if the ratio of the time constants was, on the one hand, chiefly due to a diffusion ratio difference or, on the other, to a solubility or perfusion-limited ratio difference. This gave rise to the following analysis, performed by Dr. Young.

In the perfusion-limited situation, the time constant k_i of the compartment i is $\frac{\dot{Q}}{V}\cdot\lambda_i$ where $\dot{Q}$ is the blood flow into the compartment, V is the volume of the compartment, and λ_i = the tissue-to-blood partition coefficient of gas i. Thus, if αB_i is the solubility of gas i in the blood and αT_i is the solubility of gas i in the tissue, then the time constant of gas i is

$$k_i = \frac{\dot{Q}}{V}\ \frac{\alpha B_i}{\alpha T_i}$$

In other words, at given flow ($\dot{Q}$) and volume (V), the time constant k_i is equal to the blood tissue ratio of solubilities for gas i.

Now suppose gas 1 and 2 are counterequilibrating. If gas 1 is washing out while gas 2 is washed in, then the total pressure at any

Fig. 1

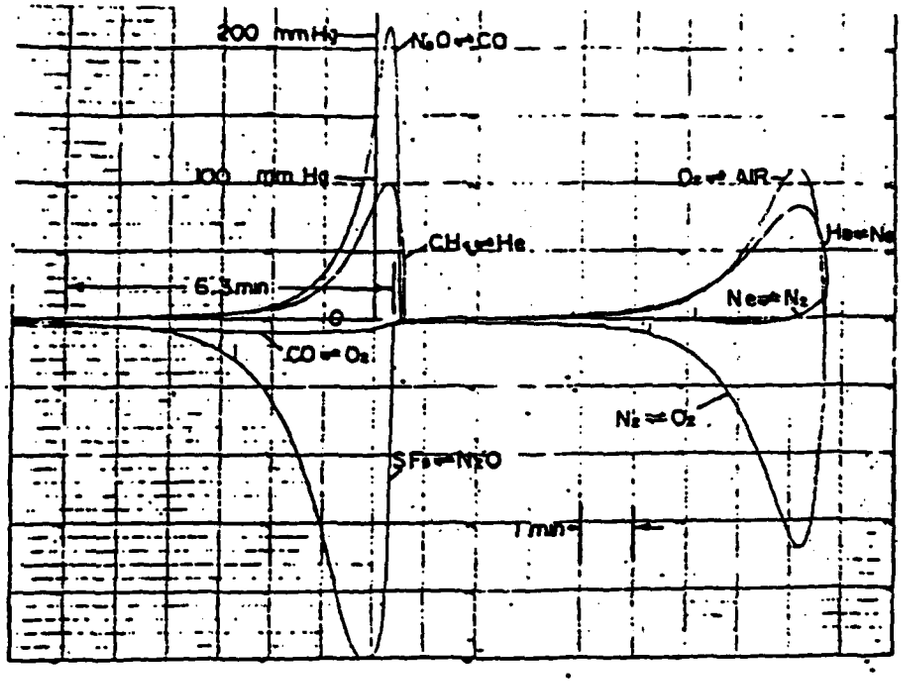
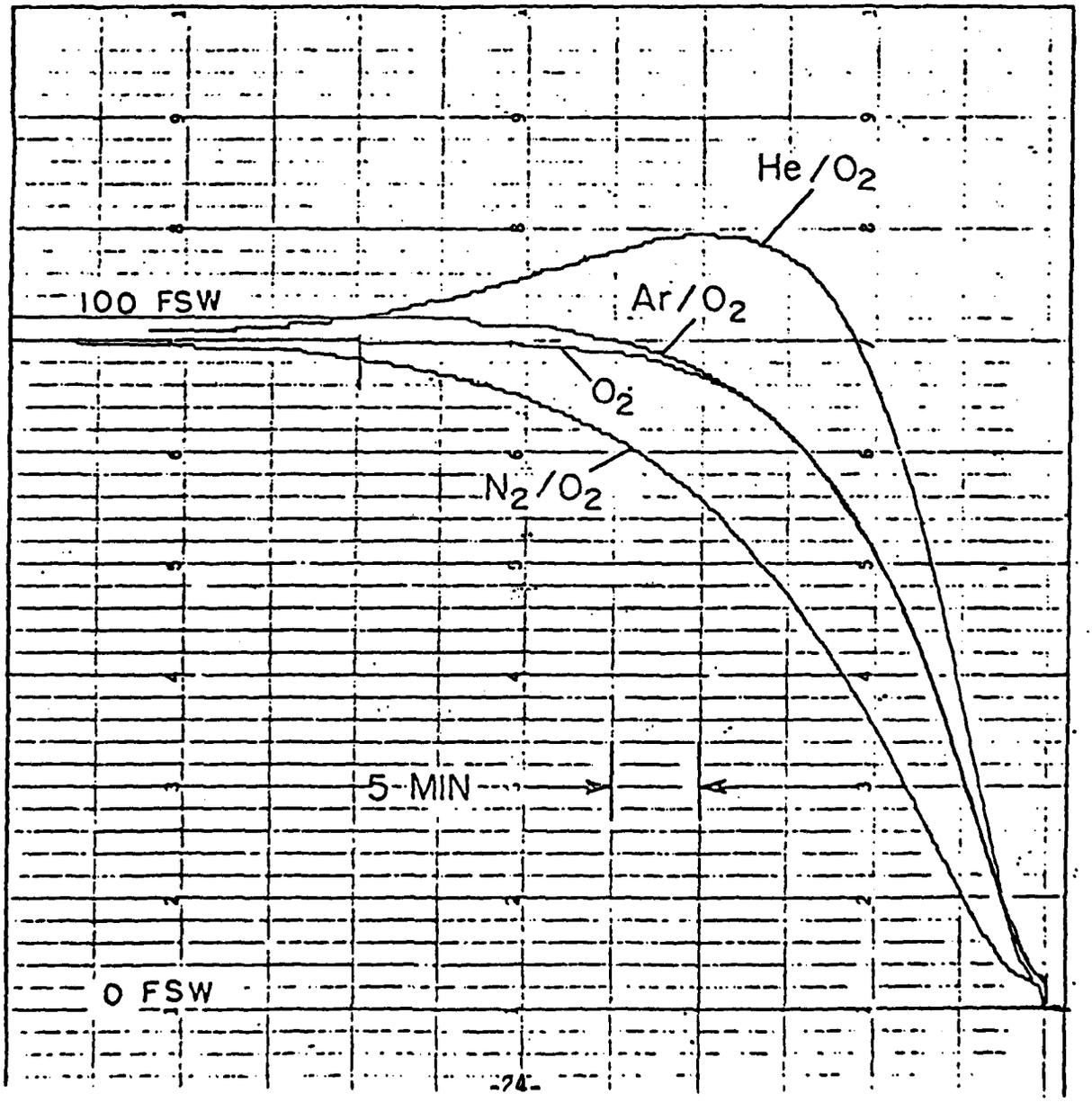

200 mm Hg
$N_2O \rightleftharpoons CO$
100 mm Hg
$O_2 \rightleftharpoons AIR$
$CH_4 \rightleftharpoons He$
$He \rightleftharpoons N_2$
6.3 min
0
$Ne \rightleftharpoons N_2$
$CO \rightleftharpoons O_2$
$N_2 \rightleftharpoons O_2$
$SF_6 \rightleftharpoons N_2O$
1 min

Fig. 2


He/O_2
100 FSW
Ar/O_2
O_2
N_2/O_2
5-MIN
0 FSW

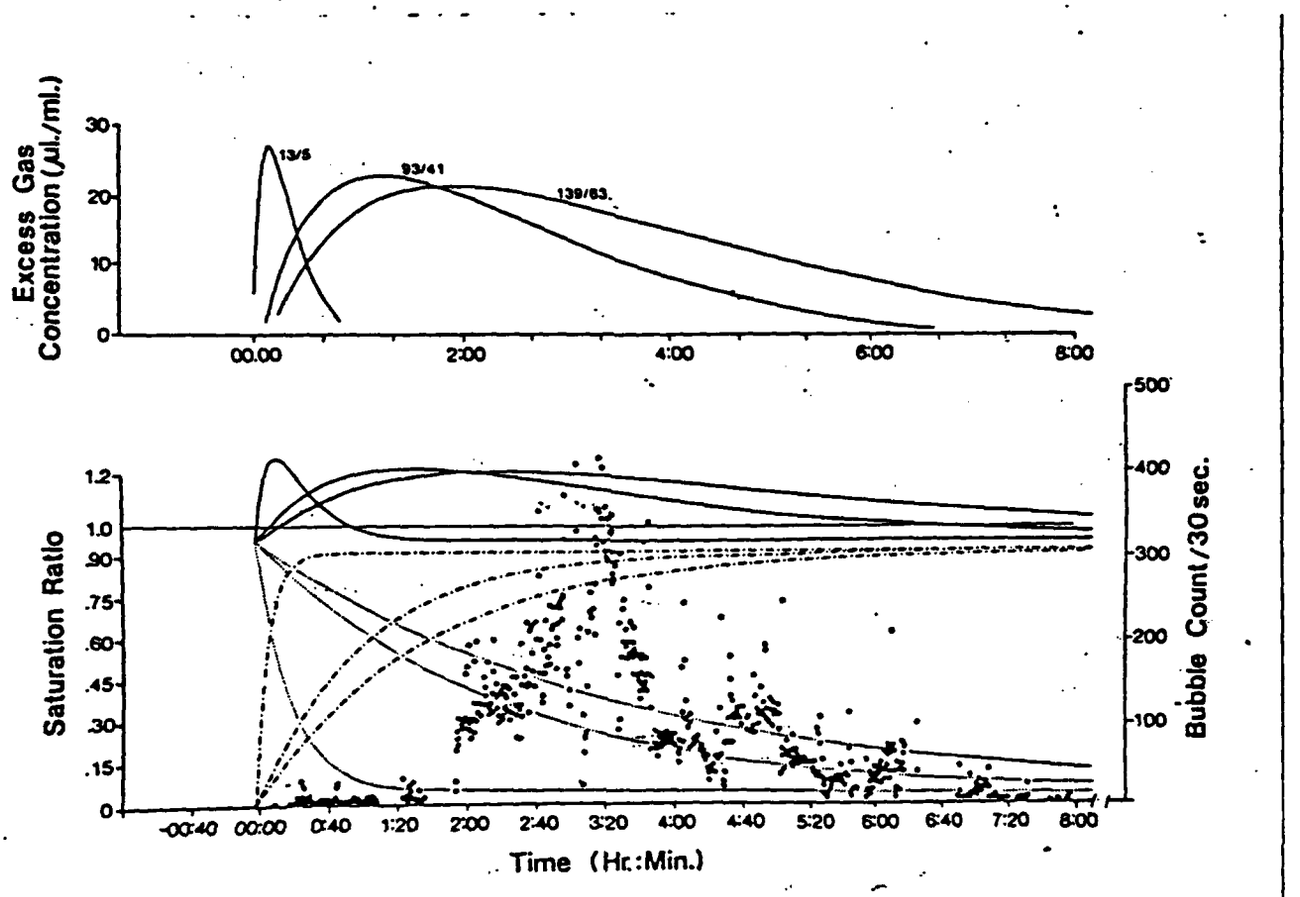


Fig. 3. (Lower panel) Bubble counts (right-hand ordinate) plotted against time with calculated gas saturation and total supersaturation plotted on same time scale. Only inert gases He and N_2 have been included in the computation; thus the initial fractional saturation is less than 1.0 (0.956) at time zero because of the O_2. Values for N_2 (.....), He (-.-.-.), and total gas tension (———) are plotted for 13 + 5, 93 + 41, and 139 + 63 N_2 + He pairs of half-times. At every point in time, total gas tension is sum of He and N_2 fractional saturations. (Upper panel) Excess gas concentration, excess volume of gas (standard temperature and pressure) dissolved in tissue as a result of supersaturation. Maximum gas concentration precedes maximum supersaturation by approximately 30 min in 93 + 41 tissue pair; similar results were seen for the other tissue pairs. Although time frame of transients in total excess gas concentration as opposed to pressure P_T is similar to transient in P_T, distinction is important when considering the relative supply of excess gas to provide bubbles shown in Figs. 15 through 20.

time

$$P_T = P_a \cdot [e^{-k_1 t} + 1 - e^{-\gamma k_1 t}]$$

where gamma (γ) equals the ratio $\frac{k_2}{k_1}$. Further, by differentiating P_T with respect to time, the maximum (or minimum, in the case of a reverse switch) pressure will occur when

$$T = \frac{\ln(\gamma)}{k_1(\gamma - 1)}$$

We now can express the maximum pressure in terms of γ, the ratio of the time constants according to the formula $\frac{P_T}{P_a}$ (assuming $P_a = 1$) equals

$$[e^{-\ln(\gamma)/\gamma - 1} + 1 - e^{-\gamma \ln(\gamma)/\gamma - 1}]$$

Thus, this maximum supersaturation is independent of the time constant of the tissue and only dependent upon the ratio of the time constants of the gases. In other words, in this case

$$\gamma = \frac{\alpha B_2 \cdot \alpha T_1}{\alpha B_1 \cdot \alpha T_2}$$

This approach has been used to estimate the maximum supersaturations, P_T, according to a perfusion-limited system, which are shown in Table 1.

In the extreme opposite case of diffusion, the concentration, C, of gas $_i$ at any time must satisfy the diffusion equation

$$\frac{\partial C_i}{\partial t} = D_i \nabla^2 C$$

where D_i is the diffusion constant of the gas, and ∇^2 is the Laplace operator.

Deriving a useful solution to this equation requires separation of X and T variables and adoption of some assumptions. These assumptions involve both geometric models and boundary conditions, and all have limitations. If a geometrically regular model is chosen, one is immediately faced with accommodating the tortuous vascularity of most capillary beds. On the other hand, if one uses the conclusions of Krogh and Roughton, that radial diffusion is essentially immediate, one is led to a predominately perfusion-limited model. However, because of our interest in the chromatographic model of Tepper, Li[illegible]foot, Baz, and Lanphier (1979), and the more extreme supersaturations that it can apparently predict, we wished to compare perfusion-dependent vs. diffusion-dependent supersaturation mechanisms.

Our original paper (D'Aoust, Smith, Swanson, White, Harvey, Hunter, Newman, and Goad 1977) emphasized that these isobaric bubbles were

occurring at a P much lower than P-values used in current decompression calculations. In the present analysis, it has been assumed that one time constant only applies such that the result is the same equation in the example above but with only the diffusion coefficients in the exponent for gases 1 and 2. In my view, the validity of this assumption as a working hypothesis depends less on mathematical rigor than on the magnitude of the errors involved. An estimate of these errors shows that they are in the direction of even shorter times than those calculated — of the order of seconds — which therefore justifies this approach, since, experimentally, bubbles take a much longer time to appear.

This approximation results in an equation in which the pressure ratios are uniquely related to the ratio of the diffusion coefficients. Using the same argument as in the perfusion-limited situation, the maximum pressure is again a function only of the ratio of the time constants, which in the diffusion-limited case is approximated by the ratio of the diffusion coefficients. The results of this analysis are also summarized in Table 1, which shows the gas switches, the ratios of the diffusion coefficients, the ratios of the perfusion time constants, and the maximum pressures, P_T, expressed as a pressure ratio to be expected in the diffusion-limited vs. perfusion-limited case. The first three combinations of gas switches are those which have now been completed experimentally in this laboratory.

To clarify the significance of these experiments, I will outline the results of Dr. Young's analysis of a typical Krogh cylinder model along the lines suggested by Tepper and his co-workers (1979) in relation to counterdiffusion. These were classically described by Krogh (1919), Morales and Smith (1948), and Roughton (1952). We include these results here to demonstrate their apparent incompatibility with many of our experimental observations.

Figure 4 shows orientation and concepts used in the model. Assumptions similar to those used by Tepper and his research group (1979) were made — in which only axial diffusion was taken into account — it being assumed that radial diffusion was instantaneous. This assumption is made on experimental grounds because we are dealing with bubbles in the venous blood and we assume they form in or near the intima of the vasculature. As Fig. 5 and 6 show, if we consider just a diffusion limitation — that is, we allow no differences in solubility (i.e., $\gamma=1$) — the model predicts that there would be first an undersaturation, then an oversaturation with one direction of the gas switch, and an oversaturation followed by an undersaturation with the other direction (Fig. 6). This result is interesting but not easy to test. However, it is developed with conventional diffusion equations applied to this quite conventional model and it suggests that we should be cautious in predicting decompression advantages from gas switching.

For comparison, Fig. 6 shows the supersaturation of helium and nitrogen when He replaces N_2 (plotted as if both gases are washing in rather than one washing out and another washing in). It is clear that in a switch of nitrogen saturation to helium in the Krogh cylinder

Table 1. Maximum possible pressures after switches from saturation on gas 1 to saturation on gas 2, expressed as ratio of total inert gas pressure to ambient hydrostatic pressure.

	GAS 1		GAS 2	$\gamma = \frac{k_2}{k_1}$	$\frac{D_1}{D_2}$	P_T Diffusion Limited	P_T Perfusion Limited	BUBBLES
COMPLETED EXPERIMENTS	N_2	⇄	He	1.82	3.15	1.40	1.22	Yes
	N_2	⇄	Ne	2.13	1.35	1.11	1.28	Yes
	Ne	⇄	He	.85	2.33	1.30	.94*	No
	Ar	⇄	N_2	1.22	1.43	1.13	1.07	---
	Ar	⇄	He	2.22	4.5	1.5	1.28	---
	Ar	⇄	Ne	2.61	1.71	1.19	1.31	---
	H_2	⇄	He	1.25	1.40	1.12	1.08	---
	Ne	⇄	H_2	.68	1.67	1.19	.86*	---
	N_2	⇄	H_2	1.45	2.25	1.29	1.14	---

Gamma = ratio of time constants, whether diffusion or perfusion limited. Gas switches below dotted line have not yet been performed.

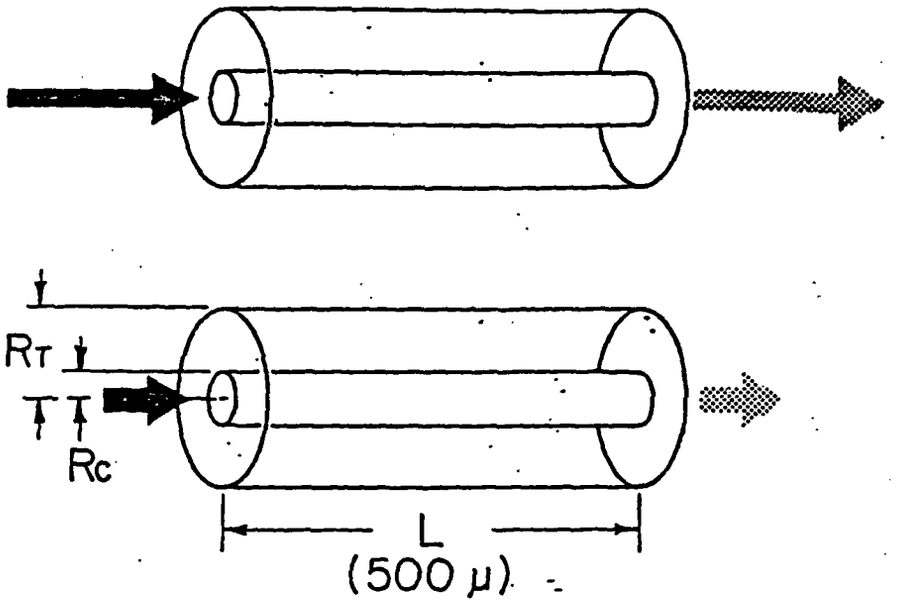
model, total gas pressure along the entire cylinder (in the blood and tissue) (Fig. 5) is first undersaturated and then becomes oversaturated. Also, with time (Fig. 6) there is an initial oversaturation and then an undersaturation which, if a bubble was initially formed, might tend to redissolve the bubble. One might gain the impression here that depending on the model one chooses or its geometry and boundary conditions, gas switches can be predicted to have completely opposite results. An important consideration in this example, however, is that the required perfusion time constant of the entire cylinder is on the order of 12 seconds. Remember that radial diffusion is considered instantaneous in this situation and we are only modelling axial diffusion. According to the analysis, the tube behaves as if a "front" of supersaturation moves down the tube. The particular profile shown occurs 6 seconds after initiation of conditions. This is obviously a very short time compared with the time it takes to visualize bubbles at the central venous location after such a gas switch, and the relationship (if any) between these concepts and our results is not yet clear. The chief advantage of this analysis, however, is that it apparently allows us to exclude certain theoretical mechanisms from consideration. This is shown by the next series of figures, Figs. 7 through 14, which show results of the analysis with a variety of solubilities, diffusivities and flows. We are on the one hand considering only solubility differences (Fig. 8) and on the other considering both solubility and diffusion differences (Fig. 7). Note that there is very little difference among these figures (Figs. 7-14) when they are compared on the basis of similar perfusion time constants of more than 60 seconds. This points to the conclusion that taking the effects of solubility into account tends to dampen the extremes arrived at in the strictly diffusion-limited case.

For example, Fig. 7 and Fig. 8 show the plot of the supersaturation (P_T) with time in the venous end of the model in Fig. 4 with (Fig. 7), and without (Fig. 8), diffusion differences taken into account. The values S_1 and S_2 are the tissue-to-blood partition coefficients and, it will be noticed, are extreme values related more to fat/water partition coefficients than actual tissue-to-blood partition coefficients. Note, however, the very slight difference in P_T max in both figures (Figs. 7 and 8). It is clear that in this model diffusion differences can have significant effects only for short time constants of a few minutes at most. This is the important point to remember when comparing this analysis to our results (Figs. 15 through 19).

This is illustrated more clearly in Figs. 9 through 12, which show the same results for different flow rates (i.e., perfusion time constants = volume ÷ flow). These range over 3, 6, 60, and 600 seconds and take into account both diffusion and solubility differences, and are more physiologically reasonable time constants than the ones used in Figs. 7 and 8.

Notice that for very short perfusion time constants -- in fact unphysiologically fast blood flow (Fig. 9) -- the maximum P_T occurs, and that this decreases as the perfusion time constant becomes more "physiologic" (Figs. 10, 11, and 12) to the point at which the P_T is approximately 1.2 x ambient for a 600-second tissue cylinder, i.e., a

FIGURE 4


RT
Rc
L
(500 μ)

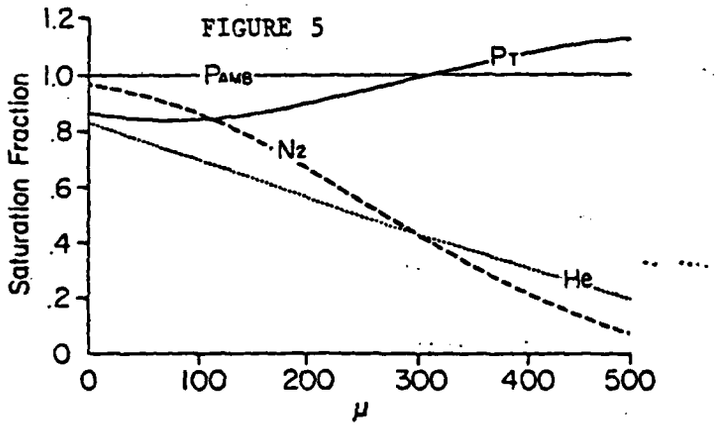


FIGURE 5
Saturation Fraction
PAMB
PT
N2
He
μ

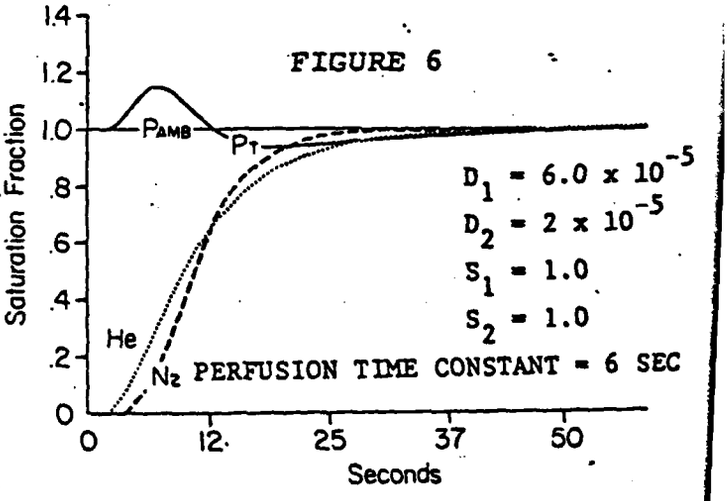


FIGURE 6
Saturation Fraction
PAMB
PT
He
N2
D1 = 6.0 x 10-5
D2 = 2 x 10-5
S1 = 1.0
S2 = 1.0
PERFUSION TIME CONSTANT = 6 SEC
Seconds

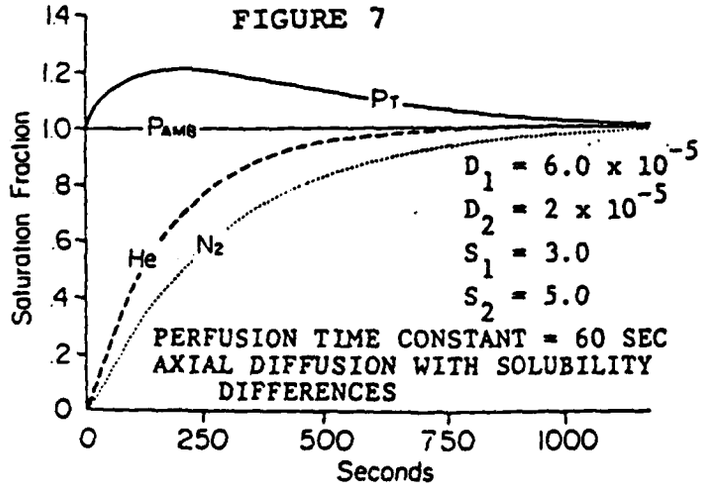


FIGURE 7
Saturation Fraction
PAMB
PT
He
N2
D1 = 6.0 x 10-5
D2 = 2 x 10-5
S1 = 3.0
S2 = 5.0
PERFUSION TIME CONSTANT = 60 SEC
AXIAL DIFFUSION WITH SOLUBILITY DIFFERENCES
Seconds

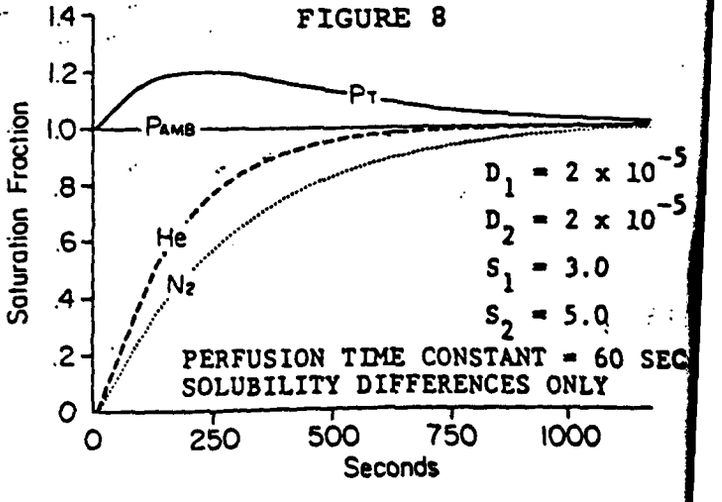


FIGURE 8
Saturation Fraction
PAMB
PT
He
N2
D1 = 2 x 10-5
D2 = 2 x 10-5
S1 = 3.0
S2 = 5.0
PERFUSION TIME CONSTANT = 60 SEC
SOLUBILITY DIFFERENCES ONLY
Seconds

Fig. 4. Schematic of two Krogh cylinders, the top indicating a high velocity of flow relative to the bottom. Arrow entering indicates a concentration of dissolved gas of 1, and arrow leaving is shaded according to degree of transport to tissue in transit through the inner tube. On lower diagram, a slower flow (indicated by a shorter arrow) on the left is accordingly more depleted of gas as it exits on the right.

Fig. 5. Supersaturation in model shown in Fig. 4 when only diffusion differences are considered, that is, solubility partition coefficients are similar for each gas. Abscissa is length of Krogh cylinder, and ordinate is saturation fraction. Notice that when switching from nitrogen saturation to helium there is an initial undersaturation and then an oversaturation along the length of the tissue cylinder. By the same token, the reverse switch should provide first an oversaturation, then an undersaturation of a similar degree. The helium concentration line is a flatter slope along length of the tissue cylinder because of its more rapid diffusion.

Fig. 6. Time plot of situation shown in Fig. 5. Initial lag in both supersaturation and apparent increase in concentration in blood leaving the cylinder is due to the diffusion effect coupled with a very short perfusion time constant. The physiological relevance of this model is questionable.

Fig. 7. Same flow model as in Fig. 8; however, diffusion is taken into account in this situation. Very little difference is shown because solubility differences are sufficiently extreme (modelled after fat/water solubilities) to be responsible for most of the supersaturation, whereas despite a three-fold difference in diffusion coefficient, little effect is seen because of relatively long perfusion time constant of 60 secs.

Fig. 8. Same Krogh tissue cylinder shown in Fig. 4 modelled according to solubility differences only where diffusion constants of each gas are considered similar. Flow is set to give a 60-sec perfusion time constant and plot is in the time domain. Notice degree of supersaturation due only to solubility differences, not to diffusion.

10-minute time constant. Notice also the relatively slight difference in P_T between a 60-second and 600-second time constant, with the 10-minute time constant producing a proportionately greater duration of supersaturation.

This is important relative to experimental information we have accumulated. Figure 13 conveniently summarizes this relationship with a composite plot of P_T for 3, 6, 60, and 600 second tissues. It shows the proportionately shorter duration of supersaturation relative to perfusion time constant for faster flows. Figure 14 plots P_{max} as a function of perfusion time constant on a log scale to illustrate this point. This indicates a decreasing exponential relationship between maximum supersaturation and the perfusion time constant. In other words, only the very well-perfused tissues can produce the highest supersaturations.

It is clear that taking into account some reasonable values for the blood tissue partition coefficients of helium and nitrogen, that is, 1.2 for helium and 2 for nitrogen, also tends to prolong the period of supersaturation. These values of N_2 solubility are taken from estimates of an approximate nitrogen capacity in the body of 20-22 ml/kg (Groom 1967).

Notice particularly that the very high supersaturations require almost ridiculously short perfusion time constants for the Krogh cylinder; this raises the question as to their physiological reality and provides an argument against the importance of diffusion-dependent time constants in producing isobaric supersaturation in the microcirculation. Further and more important support comes from our experimental results.

Figures 15 through 18 show results illustrating bubble production after gas switches from nitrogen saturation to helium at 66, 100, 132, 165, and 198 fsw and saturation times of 2, 4, 8, and 17 hours. Note that these are all transient effects and cannot necessarily be compared to the original observations of Blenkarn, Aquadro, Hills, and Saltzman (1971) and Idicula (1975).

In addition, the results of two gas switches from nitrogen to crude neon on the one hand and crude neon to helium on the other are also shown (Fig. 19). These are of particular value and interest in relation to the predictions in Table 1. One notices in these results a high degree of variability in bubble count and time; however, it is quite clear that when exposure time is reduced to 2 hours, the number of bubbles decreases markedly, suggesting that the major time constants of the body (which are involved in the bubbles we detect) are saturated at less than four hours and involve half-times of approximately 40-60 minutes.

Figures 15 and 16 show linear plots of bubble counts against time after gas switches at 66-99, 132, 165, and 198 fsw. It is clear that reliably large numbers of bubbles do not occur until 165 fsw and 198 fsw, though again variability is considerable.

FIGURE 9

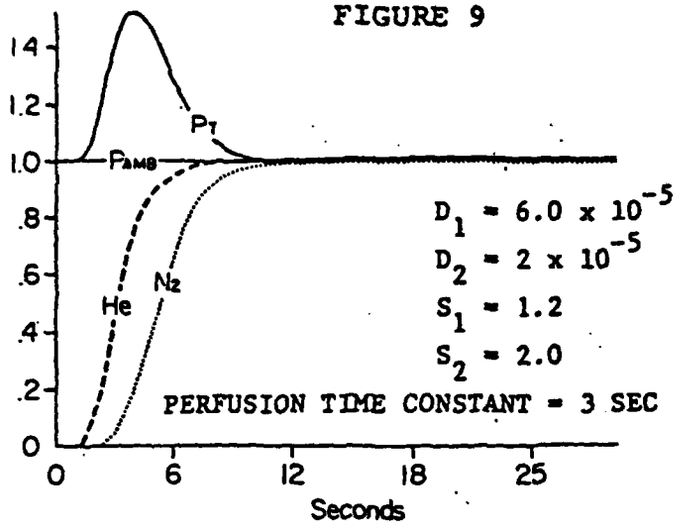


FIGURE 10

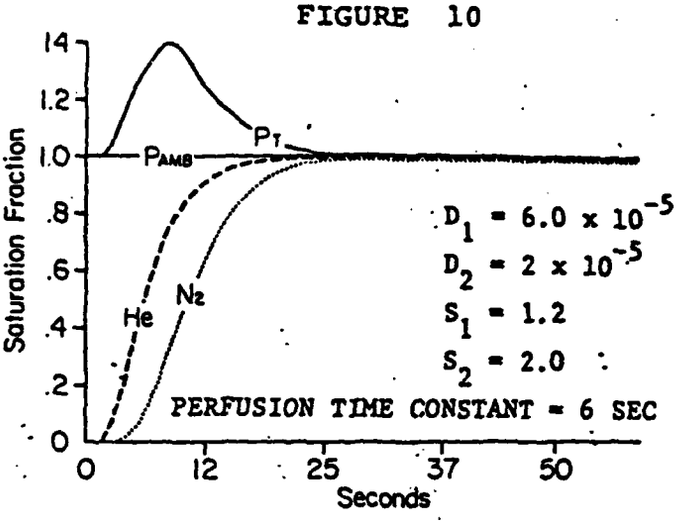


FIGURE 11

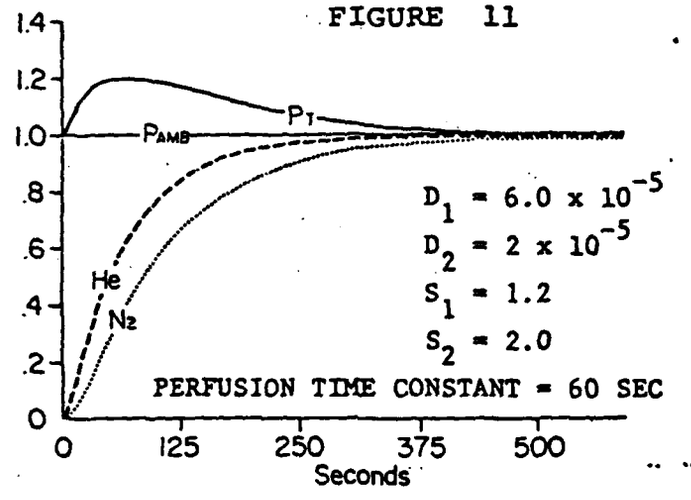


FIGURE 12

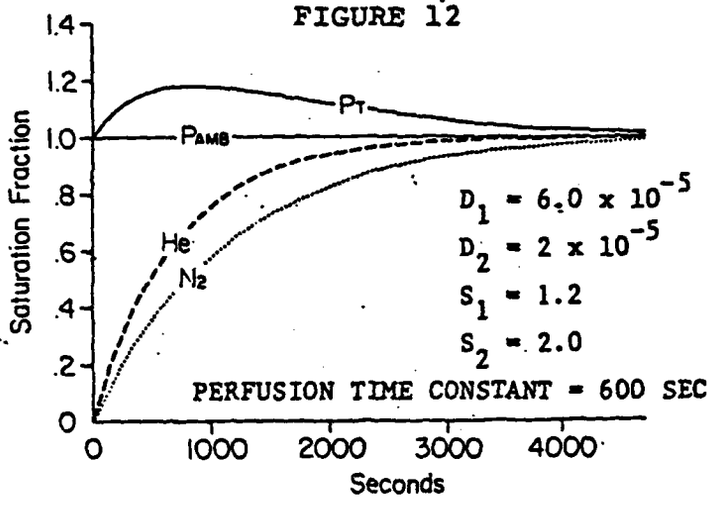


FIGURE 13

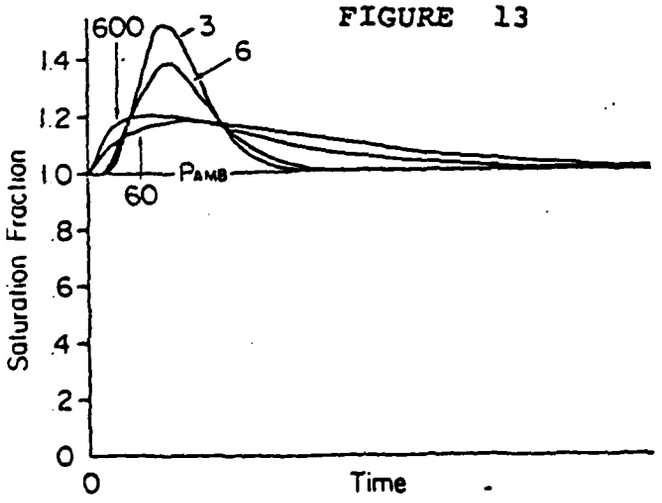


FIGURE 14

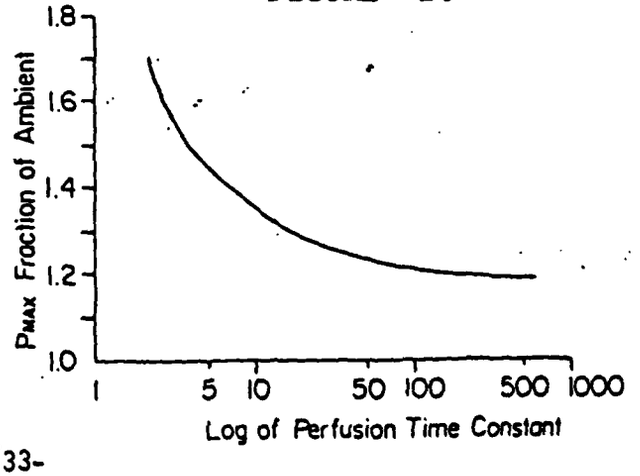


Fig. 9. Very fast perfusion time constant modelled according to diffusion differences and more physiologic solubility ratios of 1.2 for helium and 2 for nitrogen, that is, the tissue to blood solubility ratio for each gas. Notice maximum supersaturation pressure of 1.567 x ambient pressure together with considerable lag in helium/nitrogen kinetics.

Fig. 10. Slightly slower perfusion time constant of 6 sec showing a still elevated P_T and a still considerable lag before P_T rises.

Fig. 11. A perfusion time constant of 60 sec with same parameters as in Fig. 10. Notice much less extreme supersaturation pressure as well as much shorter lag relative to perfusion time constant.

Fig. 12. Same conditions as in previous three figures, with a 600-sec perfusion time constant. Notice again a not much decreased supersaturation pressure relative to a 60-sec time constant but a rather more protracted supersaturation time relative to perfusion time constant of 60 sec, i.e., 10 minutes.

Fig. 13. Composite plot of previous 4 figures showing supersaturation pressure only relative to fractional superposition of time constant (abscissa). Notice, for the diffusion-related extreme supersaturations, both an increased lag relative to the time constant and a shorter duration relative to the time constant, compared with a longer perfusion time constant tissue of 60 and 600 seconds.

Fig. 14. Plot of data in Fig. 13, with P_{max} fraction of ambient plotted against log of perfusion time constant, showing how maximum supersaturation pressure asymptotes as perfusion time constant increases.

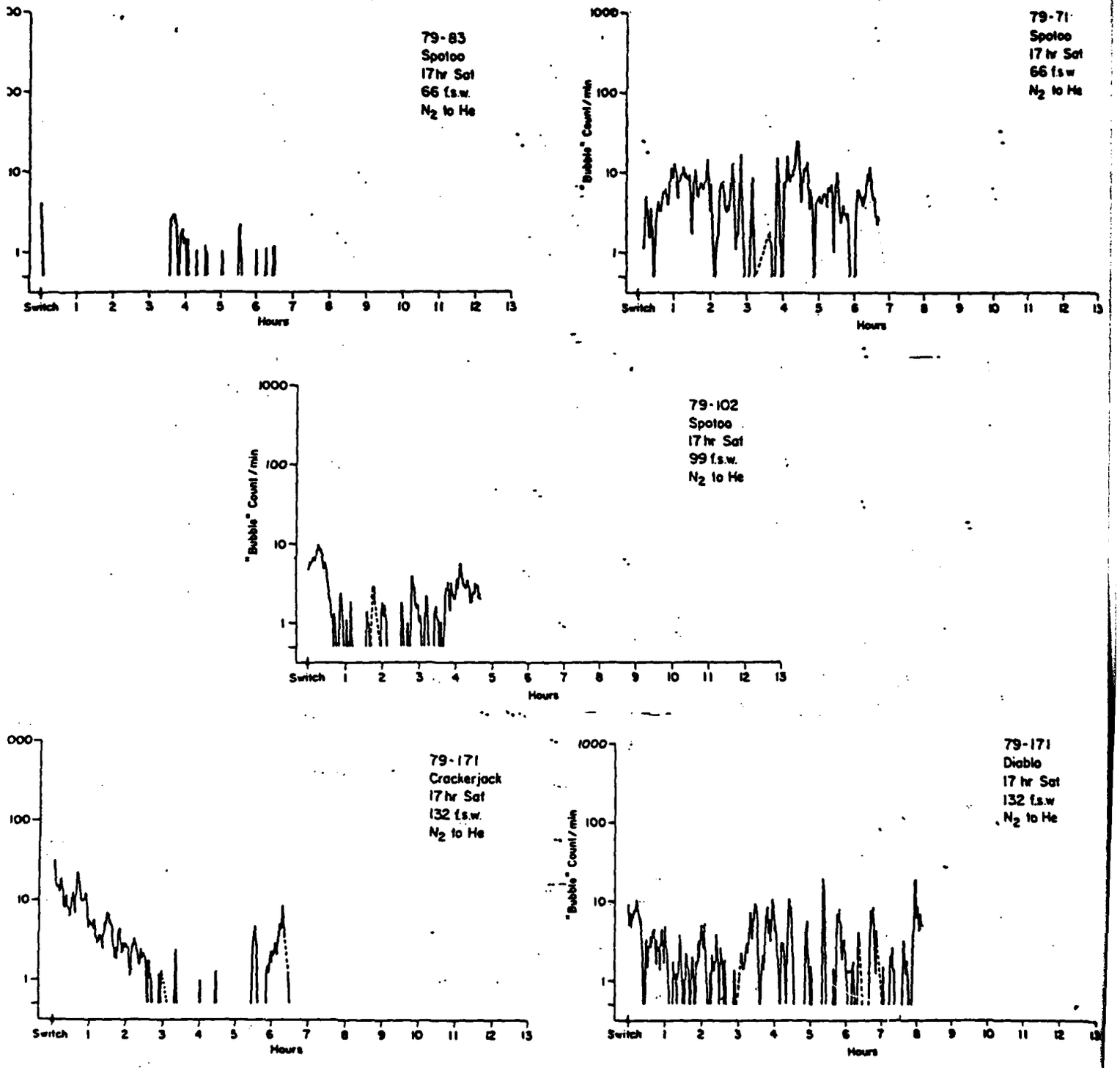


Fig. 15. Bubble counts with time after gas switches from saturation on nitrogen (0.3 atm O_2) to helium at 66, 99, and 132 fsw. Audible bubbles are heard but level fluctuates and rarely gets above 10 per min in the 132 fsw switch.

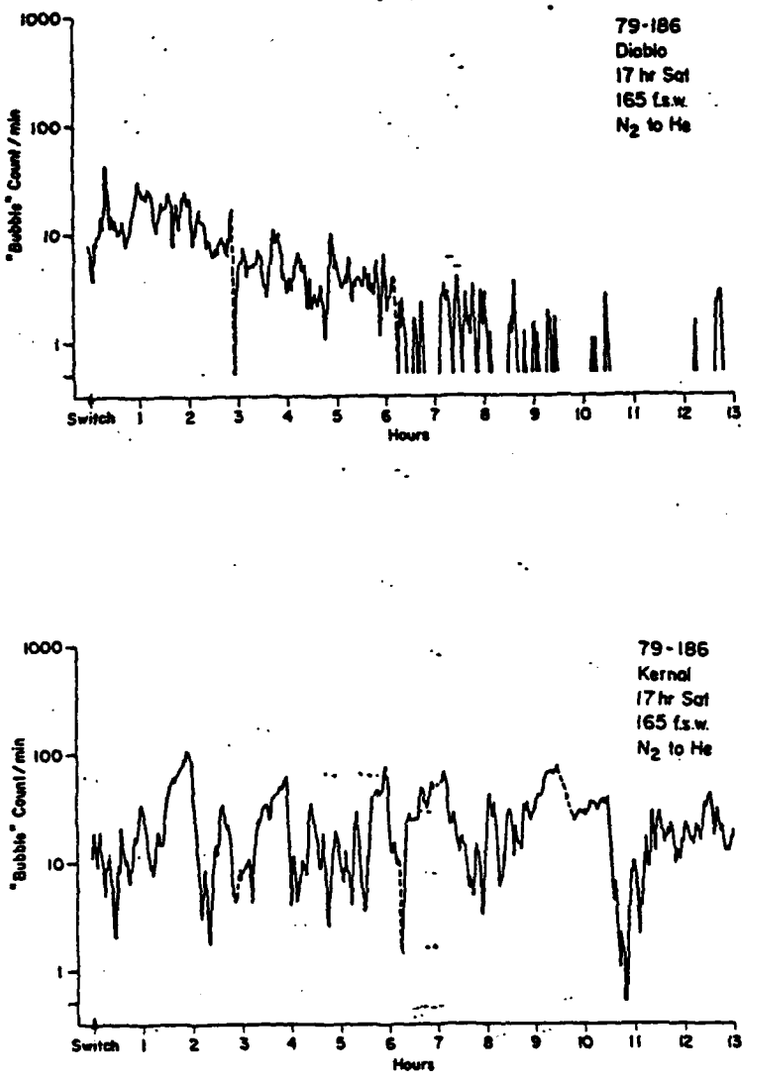


Fig. 16. Bubble counts with time plotted for a gas switch at 165 fsw. Notice level frequently rises above 100 bubbles per minute.

This depth was then chosen to "titrate" saturation time prior to the switch. Although a matrix approach would be preferable, time and funding limits preclude using such an approach. These results are shown in Fig. 17, in which saturation times of 8, 4, and 2 hours are compared at a depth of 165 fsw. A 4-hour saturation time appears to be indistinguishable from an 8-hour saturation time, whereas a 2-hour saturation gives markedly fewer bubbles. However, these data obviously possess only limited accuracy for comparison. More statistically complete experiments are necessary.

A word about our bubble counting procedures is necessary. The bubble counter used has been previously described (Haugen and Belcher 1976). The output from the counter is monitored by a Wang computer and recorded and stored on tape, which is then used to plot the average bubble counts per minute against time on an X-Y plotter. A running mean-smoothing program is used to damp the oscillations observed. Figure 18 compares a direct minute-by-minute plot with the smoothing program, which averages over seven consecutive counts and plots the mean at the time of the middle count to show the degree of smoothing which can arbitrarily be accomplished. The small error (±5 minutes) in time which this allows is unimportant relative to the time frames of the record.

By far the most interesting results of this work are the three gas switches shown at the top of Table 1. Both nitrogen to neon and neon to helium switches (Fig. 19) were carried out at 198 fsw. It is very interesting that the maximum pressure ratios predicted by the diffusion-limited scheme (see the table in Table 1) are 1.1 (14 fsw) for nitrogen to neon and 1.3 (56 fsw) for neon to helium. By contrast the perfusion-limited situation predicts 1.28 (52 fsw) for the nitrogen to neon and 0.94, i.e., undersaturation, for neon to helium. Remember these are based on best estimates of λ, the tissue/blood partition coefficient. It is therefore extremely interesting that on the neon to helium switch, almost no bubbles were heard (Fig. 19), suggesting that the perfusion-dependent model is by far the most important one in predicting the bubbles we see. Up until the present time, we have perhaps been subconsciously assuming that diffusion differences are the major factor in determining bubble formation. Thus, it is more probably the solubility ratios or more properly the ratio of the solubility-dependent partition coefficients of gases 1 and 2 which in the transient situation are important in producing the bubbles we detect by Doppler, and probably are also the major mechanism in the steady-state situation as well. We intend to continue these switching combinations according to the switches outlined in Table 1. Particular attention will be paid to the neon to hydrogen switch, which also indicates an undersaturation, and which Peter Edel and I hope to carry out next year.

The full significance of these experiments cannot yet be estimated and requires finer analysis of a number of different combinations of gases before some choices can be made between the importance of the diffusion vs. perfusion-related time constant. However, Fig. 20 presents some past experiments relevant in this regard. Two transient gas switch experiments with a pig are presented, and it is apparent

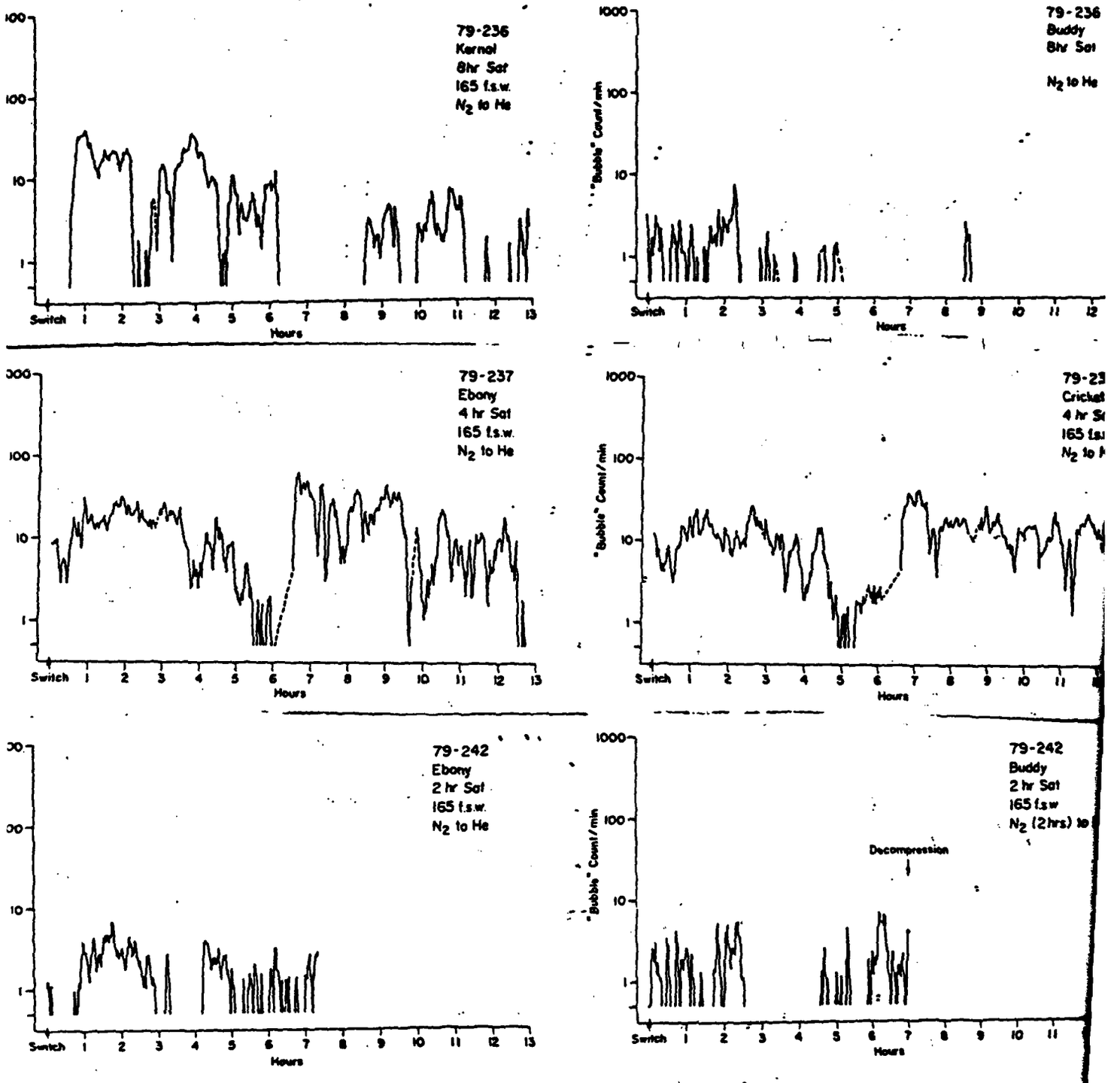


Fig. 17. Bubble counts with time plotted for "titrations" in which saturation time is varied for same gas switch as in Fig. 16 and times of saturation are 2, 4, and 8 hrs. Largest difference occurs between 4 hrs and 2 hrs.

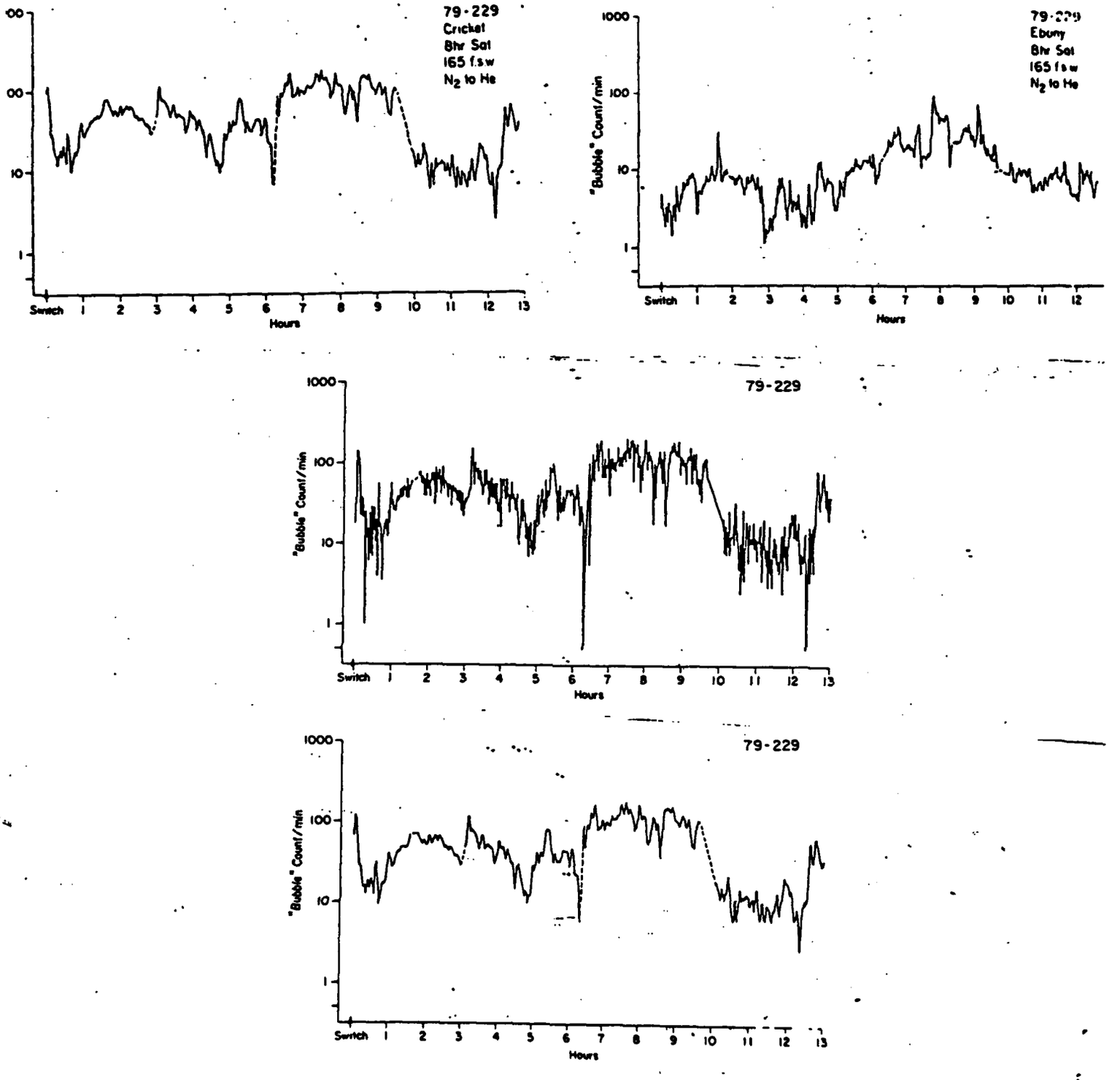


Fig. 18. Difference in variability when plotted on an individual basis minute by minute compared to a running mean of seven consecutive samples with time of the middle plotted. Considerable smoothing results when plotted in this way, whether or not the seven samples are weighted or even, top and bottom, respectively.

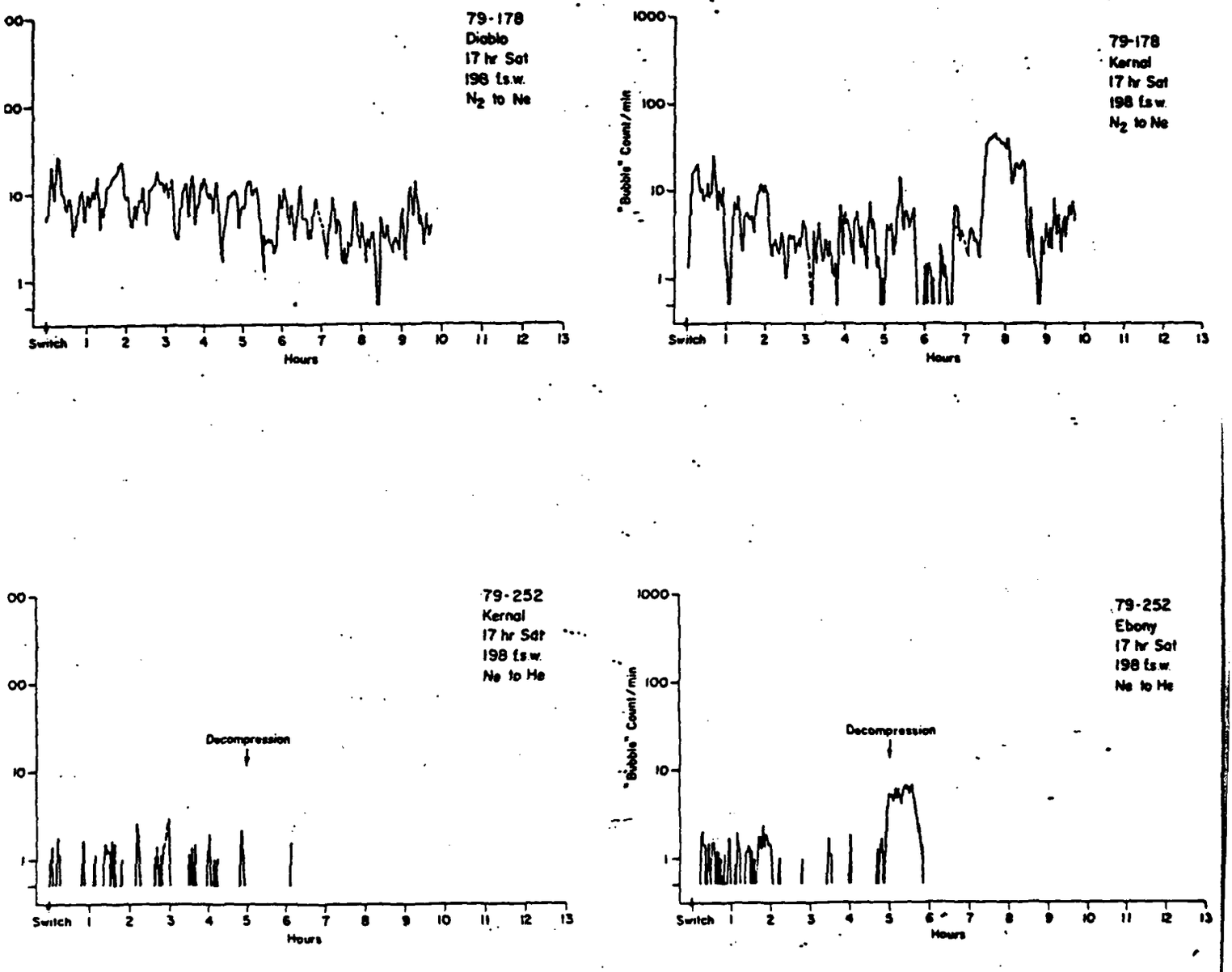


Fig. 19. Comparison of two switches; top, N_2 to Ne, which caused a considerable number of bubbles in both animals; bottom, Ne to He, which caused no bubbles compared to number shown in top switch. Also note that these gas switches were carried out at 198 fsw. Decompression revealed few bubbles, so that one cannot conclude that none were present after the switch.

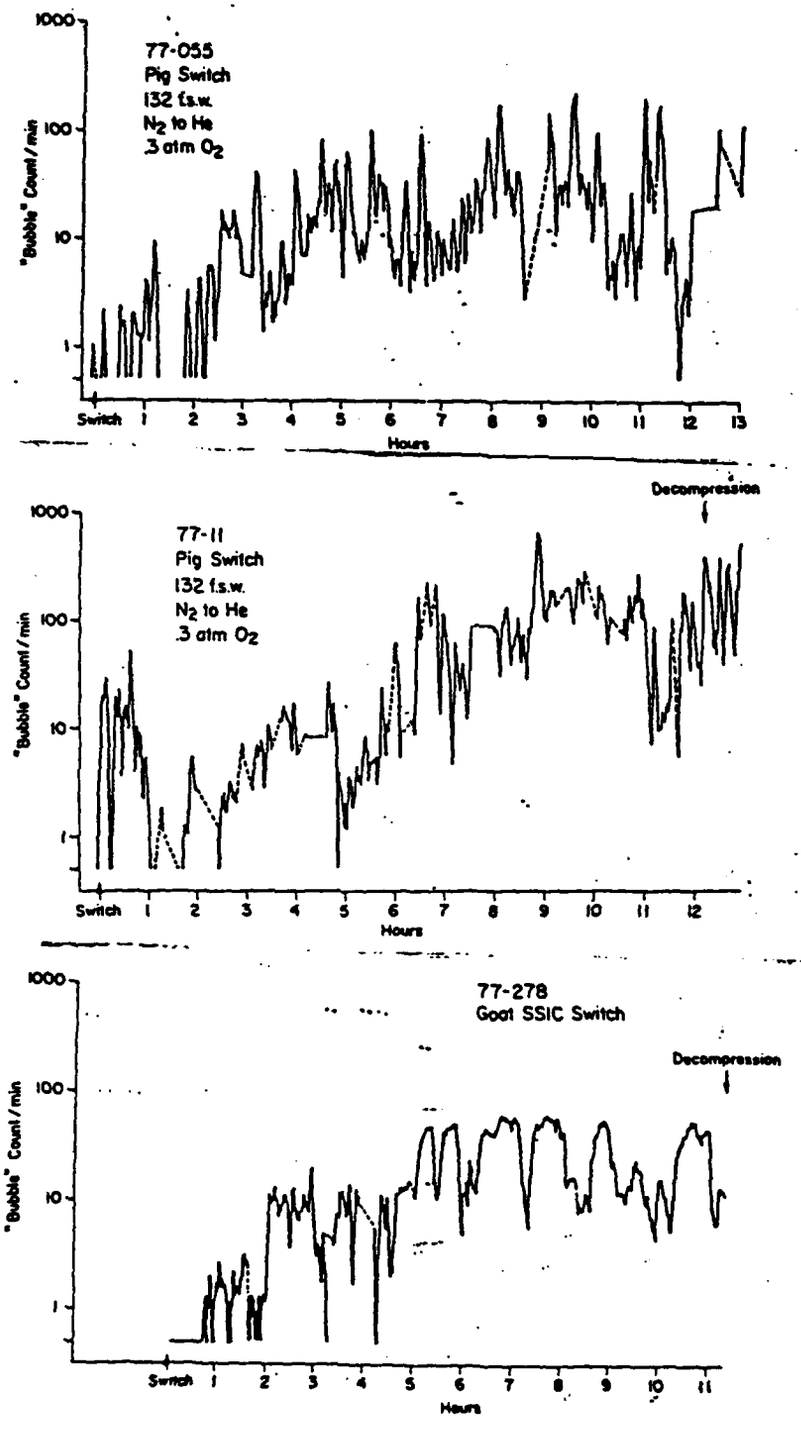


Fig. 20. Comparison of three gas switches, two on a pig with a central venous Doppler bubble detector after a transient gas switch at 132 fsw and one on a goat where only the breathing gas was changed. Note variability in pig experiments, which highly resembles the initial part of the goat experiment. On the other hand, the later part of goat experiment shows much more regular patterns, with an apparent hourly period.

that the duration and number of bubbles are greatly increased over those which have been seen in the goat. In view of the additional fat content in the pig and its greater gas content, this result fits very well. Not only could there be some tissues where the actual reservoir of gas is greater than in the goat but these same tissues might also be likely to exhibit a much higher value for the tissue-to-blood partition coefficients.

It is also noteworthy that the variability in bubble count with time in both pig gas switches resembles the initial part of the plot in the goat experiment; however, in the goat this was a breathing gas switch only, which was therefore approaching the steady state. Equally interesting is the fact that the latter part of the goat experiment showed a different quality of bubble count with time, characterized by a high sustained count for approximately 50 minutes and then decreasing sharply for a shorter period. This may reflect vascular "programming," which was able to clear out skin-related bubbles.

What then is the mechanism of bubble formation in the experiments we have done so far? Both the theoretical analysis and the results presented allow the conclusion that the mechanism of supersaturation responsible for the bubbles we observe by Doppler ultrasound at the central venous location depends primarily on the blood partition ratios of the saturating and desaturating gases. This is additional support, but support of a new and different nature, for the classical perfusion-dependent model (Kety 1951) used in diving, and it provides no support at all for a diffusion-dependent mechanism. This conclusion is consistent both with the analysis presented initially, in which it was shown that the effects of diffusion which are accessible to the capillary can only be exerted for very fast perfusion time constants and with the estimates of P_T presented in Table 1, which indicate undersaturation with the neon to helium gas switch. Further, both the magnitude and direction of the error involved in our approximation of the diffusion-dependent time constant strengthen rather than weaken this argument.

Finally, the critical supersaturations for bubbles formed in the microcirculation would appear to be over 25 but under 52 fsw, or very, very near the original ΔP suggested empirically by Haldane. This has now been supported even further by results of our studies of decompression in salmonids (Beyer, D'Aoust, Smith, and Casillas 1978; D'Aoust, Smith, Swanson, White, Stayton, and Moore 1979). However, at high pressures, other factors may have to be considered, since empirically critical ΔP values have been demonstrated to change with depth (Hennessy and Hempleman, 1977; Hennessy, 1978).

Acknowledgments

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Q. Does the upper curve in Figs. 15-20 represent the difference between the two lower curves?

A. No, the sum. These switches are nitrogen desaturating and helium washing in, but they have been plotted as if both are washing in, which permits comparison of the time course of each gas. To get the total, they should be added at the same time. For looking at the time constants of the gases, this method of plotting is much more convenient.

Let me run through a series of these quickly now (Figs. 15-20). Remember, these are extreme solubility ratios that almost certainly do not apply in vivo, so this is an extreme case, but it does show the difference (remember we have a different time scale now) in the time form of this supersaturation and the effect which the solubility differences would have upon it. With diffusion limitations, it is very brief compared to the time here.

We looked at a number of these, to make diffusion limiting, and optimized the maximum supersaturation. We are looking at a maximum supersaturation of 0.57 times ambient. The perfusion time constant you need for that is 3 seconds. The flows are so extreme that we would be stripping intimal cells off the capillary. Notice (Fig.) what happens when you allow for a slower perfusion time constant, and also notice these are more reasonable tissue-to-blood partition coefficients now. We have the same relative coefficients for helium and nitrogen, but different solubility ratios. And again at 6 seconds, total pressure comes down a bit. Sixty-second perfusion time constant; that means the Krogh cylinder's ratio of capacity to flow gives you that time to exchange the total volume of it. Notice we are getting protracted but lower supersaturations and this protraction increases more. However, it requires a more reasonable physiological time constant. Don't ask me to tell you what tissue this is.

Q. Kidney?

A. And perhaps some muscle, heart muscle (which is bad analogy). Now here (Fig.) the time constants are overlaid -- 3 seconds, 6, 60, 600. And this shows the effect on the time of maximum supersaturation pressure relative to the perfusion time constant. This indicates that if you really want to go for high supersaturation pressure, you have to get impossibly fast perfusion time constants, in this particular model.

Where does that leave us? I wanted most to talk about the real world and our experiments. These figures (Figs. 15-20) show the kind of saturation we have been allowing. We are making overly sure the animal is saturated. At 66 fsw we can say there are virtually no bubbles. By overemphasizing the noisy part of the trace, we are

being conservative, which means when we get a high count it is more reliable relative to the signal-to-noise ratio, which is still a problem. Anybody who has used Doppler realizes that. We are taking steps to get more reliable counting but we do not have it yet.

So let's go through this quickly. At 66 fsw apparently there is not sufficient delta P (ΔP) there, somewhat under an atmosphere. Perhaps occupationally this could be said to be a safe switch at saturation with these two gases. One-hundred fsw gives a similar picture. We have done more dives than you see here at each level. At 132 fsw, we are starting to get levels higher than you can count with your ear, but we still have periods when there are no bubbles. Notice how long this continues: this is a transient switch, so ultimately the bubbles have to go away. There are plots that do not continue so long, to subject the goats to the same regime. Most of these switches have the bubbles cleared out by 12 hours.

Q. Let me be sure I understand these figures (Figs. 15-20). You've got the animal saturated on nitrogen?

A. Yes, and it is 0.3 atmospheres of oxygen.

Q. At 132 fsw. And all of a sudden you can put the entire animal into helium?

A. Yes, we layered the helium on top. It takes about 5 minutes at the most. We end up with a residual concentration of N_2 of the order of 1-2% of nitrogen.

Q. Then you leave the goat there the whole time?

A. The isobaric period is all the second gas, that's right.

Q. So the rest of the dive or experiment is on this helium atmosphere?

A. That's correct.

Q. Why just bubble numbers?

A. These are bubble counts per minute. I used to plot single counts and they showed the same thing. We have left a little "token" zero point here (Figs. -) because, in fact, there are periods when the bubble counter does not count any bubbles and when you do not hear bubbles. I think it gives a better impression of what is physiologically happening. It is very easy to tidy this up, but I think it allows you too many liberties with the meaning of these data.

I will go on with the next pressure, 132 fsw. We have a suspicion there is a tremendous amount of difference in these animals. We have the impression also that these bubbles (Fig.) are forming at the inner surface of a vessel or capillaries and are being collected by perhaps a critical flow, or sheer, and are therefore

collected according to the perfusion of that compartment, which varies. There is a pattern that seems to suggest that anxiety on the part of the animal makes a lot of difference to what we see. We are getting ready now to try to take some through-the-chamber samples with the catheter to determine what different catecholamine levels can do to this. At 165 fsw we get a much higher rate of bubbles. One-hundred ninety-eight fsw is the deepest we have gone, and we have shown a lot of data on that.

These are now plots (Figs. -) of minute-by-minute bubble counts smoothed by a computer program that simply takes every 7 and computes the middle one as the mean time and smoothes according to the mean 7 counts and weights according to a normal distribution. If you do not do that you get a far more noisy looking plot. The next thing we wanted to do was titrate the time.

Q. The 165 fsw experiment interests me because this is the natural depth point at which many tables change to air from helium, and the solution to the problem arising at the switch was to make the change much more slowly. You say you took 5 minutes; have you ever done an experiment with 15 or 20 minutes to make the change?

A. That is another form of titration and, of course, adding any variable geometrically increases the matrix of experiments and it just takes time. We have not done that yet. What we are trying to do is to evaluate an optimal depth and this seems to be it, so this is the one we have started to titrate the time at.

Q. "Optimal" means you make the most bubbles?

A. Yes, reliably. But I think we will make more bubbles if we just keep going deeper. I would not want to go where we got a reliably level plot or even something like the 198-fsw experiments, because I think we would be missing aspects of variability that often can give us a clue that will shorten this process, which is very time consuming. For example, this point about catecholamines; when we first did this switching technique, we found about as many bubbles at 132 fsw of the switch with these same kinds of animals -- they are different individuals but I have no reason to think they are basically different. We got the same number of bubbles at 132 fsw then as we do at 198 fsw now with this technique of layering, which is much less noisy, more gentle, and just as efficient. We have every reason to believe from looking at the animals that are awake that they were much more anxious with the noise. Our accountants upstairs got upset with it, so you can imagine what the animals felt like. I have been in there during one switch, and it was very noisy the old way.

Q. Do the animals move around, kick?

A. They are restrained. They can move their feet, they can move up and down.

Q. Do they move when you make the switch?

A. No, not now. They used to. Now they are very quiet. You can see the gas discontinuity come down. They sometimes shake their heads which makes you suspect there are some middle ear or vestibular happenings. But that's very brief and we have never had any indication that an animal was bent. (Though how you tell that I wish I knew.)

Let me go on with the titration of time. This is 17 hours (Fig.). We regard this kind of plot as not too different from this, although subjectively, when you listen to it, it is quite different. We simply do not have the automatic counting technique optimized yet, so I cannot say that if we took Spencer's "bubble grade" and had a sheet with time on it and had an observer listening and grading 1, 2, 3, 4, we would have a much cleaner plot. But I have confidence that we are improving this technique and we can always go over these tapes and redo them when we get a better logarithm. You will see a tantalizing periodicity here that may or may not mean something. The other picture (Fig.) of that type of response we have from a steady-state situation with this animal, the only one we have done where the animal was surrounded by one gas and breathing another. So at 8 hours we see what we must regard as essentially the same picture, or at lease we cannot statistically tell it is different from listening to the bubble count. And at 4 hours, a similar picture. We have obviously been wasting a lot of time on this one. And at 2 hours, we definitely see things change, i.e., decrease. So I do assume that what we are seeing is the major time constant, by which I mean bulk of gas. I think we are seeing the major time constant saturated at around 3 to 4 hours. That makes it around 40 minutes, which if you look at a goat and a man is probably not too unreasonable. I do not know if anybody has accurately measured skeletal muscle time constants at exercise, but I am sure that is what we are looking at. Here is another 2-hour saturation. I think we have pretty well established that 2 hours is too short. Four hours might be adequate if we can find one exposure and one depth to work with for these other types of experiments that Dr. Bennett suggested and which we would like to do. At the present time there is so much variability we are not sure. This is just an illustration of what happens if we plot a moment-by-moment count as compared to a smoothing procedure.

Q. You're talking about a transient phenomenon. On the other hand, since your data are going out to 12 hours, that does not seem like a transient phenomenon. Conceivably is it possible that you have got a mixed effect of some sort here?

A. I think it is possible but unlikely. The fact that we have 1% nitrogen or 2% residual means there could not be any steady state. I think there are probably several things going on here, different mechanisms of bubble formation, as we showed with the diffusion model. You ought to get some bubbles right away, fast, but where they are going to be and whether you are going to see them, I do not know. And since in our analysis the supersaturation went down and then up, that logically must be interpreted to mean that the

reverse switch would also make bubbles or make supersaturation.

Q. Have you done the reverse experiment?

A. Not yet, but we shall.

Q. Did you follow this out far enough to see if it went down to zero?

A. In many cases the bubbles stop by 12 hours.

Q. I mean it is transient in the sense that eventually the bubbles must go away.

A. Eventually they have to stop, and as some of you heard me report before, when we first did two pigs that were awake and rather large (about 300 lbs.), after the goat-work, they just kept bubbling after the 12 hours. We thought we should wait to see how long they would last. The longest time was 48 hours. They did start to wane, and we rationalized that since a pig has a lot of fat and a lot more gas in it and was a bigger animal, the bubbles lasted longer. We also wondered whether we were looking at bubbles. We thought we might be looking at some dots or thrombi, which led to experiments in which we medicated the goats with antiplatelet drugs, and that turned up something else new. So we came back and regrouped, trying to concentrate on first things first, which is the biophysical side of it, the time constant and the degree of supersaturation. We have shown that the time constant we are thinking about is around 40 minutes. A 4-hour saturation is necessary and at least 130 to 132 fsw. We now realize, however, that the collection process is rather protracted.

Q. Aren't you actually mixing two phenomena, since you are switching the entire chamber?

A. No, this has got to be transient.

Q. The animals are both inspiring and being externally exposed.

A. And nitrogen will eventually be completely eliminated down to whatever ambient level in the chamber. So how can we be mixing two phenomena?

Q. You are getting a transient, which is your deep tissue.

A. Logically it is one switch. In terms of the actual mechanisms going on (this is what I tried to allude to) there are several different ones. Initially there is going to be a skin effect, but it is initial only in contrast to Dr. Lambertsen's steady-state situation, where it is the chronic situation.

Q. True, but I don't see how you can separate the two because you have a superficial initial isobaric effect, and I do not know how you can distinguish which one was the transient.

A. Well, I am looking at the goat as a "blob" of tissue per se, and some of everything we collect comes from the skin initially, although I think that's rather minor because the gas level comes down rapidly and is biphasic, according to Dr. Young's analysis. The gradient there would be a gradient of nitrogen out from the skin and some bubbles that perhaps may never get collected. Basically, I agree with you.

Q. Transient experiments leave helium diffusing against nitrogen superfically, and the same effect is caused by the respired gas, and I do not think you can tell which is producing the bubbles.

A. Transient is the key word. The gradients are transient, whatever their direction. That is the difference. Yes, we are probably mixing a number of phenomena, but the way I prefer to look at it is transient vs. a steady state. Now the steady-state situation mixes a transient with a steady state, but it builds up to an equilibrium or a constant situation.

Q. But you do not know that the so-called 40 minute time constant is not the 40 minute time constant it would take until somebody started itching?

A. No, I do not, but I believe that is contrary to clinical experience. I believe your itching is rather soon, is it not? 15 minutes? Up to 40? Well, I cannot argue with the point now except to say that eventually those gradients have to dissipate, and that is the real logical difference in this case.

Q. I think it comes down to the question: where are bubbles generated and which are you at risk from?

A. I would be happy if it came down to just that question. I think we have said you are not at risk from a switch at less than 60 or 100 fsw. I think the bubbles we are seeing come from everywhere.

Q. Is there any reason why you cannot just change the inspired gas or the surroundings so that you could at least say which?

A. That is coming. We have done one experiment of that sort. We are just beginning to do the next half of this project, which was to compare the steady state vs. the transient situation.

Q. Did you ever notice any dermal lesions, or in the experiments that were done at New London with humans, was itching noticed in that case?

A. Yes, Claude Harvey noticed itching. I think it was at the 100 fsw. They did not wait to find out if the itching was transient. Also one subject reported something that looked like a knee bend, although it was somewhat vague. They compressed one more atmosphere to treat the knee bend and the itching became worse, even though they compressed on helium. This suggests that whatever was causing the

itching perhaps had not reached equilibrium by that time and the added pressure still added more gas to the bubbles than it reduced them in volume.

Q. Saturated on nitrogen and then switched to helium?

A. Yes. The divers were all in gas-tight exposure suits in nitrogen. First they were in the chamber overnight. Then they wore the suits, the helium was brought into the chamber, and they just stepped out of the suits. So they accomplished the same thing that we do, only probably faster. That was a fairly fast gas switch. But the logical distinction I am making is the situation where gradients must dissipate vs. the situation where they reach a steady state.

Q. I noticed that your dramatic changes occurred in 2 hours. There was an interruption. Now I wonder if that has anything to do with other bubble formation mechanisms like nucleation, for instance. You also mentioned that later on you used platelet anticoagulants. Have you ever considered coagulants or anticoagulants? Hageman factor is a contact factor, and Newton Harvey showed that it was dependent on lipids in glass tubes, etc. So what do you think of the effect of nucleation as another mechanism?

A. You mean actual nuclei that are in the blood? Or stationary? I think something like that has to be the explanation of the bubbles we see. The long, protracted appearance of these bubbles gives you the idea of looking at a beer glass. It is constantly bubbling from one point. If it was nuclei, we have to keep regenerating them somehow because the nucleus is gone. So this is why the model we chose theoretically does not distinguish between the inside of the capillary and the tissue.

Q. I think it is a mistake to say you have to keep regenerating nuclei to keep regenerating bubbles. As soon as you form a macroscopic bubble, it will probably produce rosaries, etc., the kind of thing that Albano has talked about. You may have a gas phase trapped in the tissue. The tissue deformation pressure prevents it from expanding in that place, but gas keeps leaking out of that region and diffusing into that region from the tissue. In other words, bubbles once formed can produce lots of bubbles.

A. That is the mechanism I think we have in order to get a physical analog, because I think that is what is troubling us all. I do not think that is a viable explanation for this. But if it was just extravascular or extracapillary, is there a mechanism? You have to bud off a bubble that is bigger to get a lower pressure. If you do one smaller, you require a higher pressure. And how do you get it when you have already passed the peak of supersaturation?

Q. In these sections that Albano has made he sees strings of bubbles, which apparently originate at a site which is an original. In other words, nucleation theory is relevant to the formation of that primary bubble. Once you have those primary bubbles, then you can

bubble continuously until all the supersaturation is relieved. Way back in the 30's, Becker and Douring and other investigators -- even Vulgarea -- studied the formation of primary nucleation. Now the probability of bubble formation generated spontaneously is very low, as I think Placid and other people have shown. But there is still the possibility that other substances like dirt started it off.

A. I agree with that completely. I think it is facetious to call a platelet dirt or an intimal cell dirt, but physically, I think this is reasonable. Let me answer one query you had. We did do an experiment where we medicated the animal with antiplatelet drugs -- anturane, persantine, and aspirin, and we wanted to follow this up, but not until we had a clearer idea of the time constants that we are generally dealing with. The remarkable thing about that was the kind of plot we got after a switch at 198 fsw -- the goats stopped eating when we switched to helium, perhaps because they did not smell because of the helium. I think they lost their appetite. So we can assume they had only a 3-hour dose of the drugs. But what we got here was the clearest phasic increase in bubble count with the least variability we had ever seen. I got very excited about this. I wanted to pursue it, but there are some biophysical factors we have to look at first because we are studying the transients involved and we need to get at these basic limits. But this was very, very clear and rather immediate. It was as if this picture is clouded by some sort of stickiness. The bubbles hang up in capillaries, perhaps. There is perhaps a mechanism to hold them there and with those drugs everything seemed to slide along a little better and so we got the kind of peak we thought we should get. So that kind of medication may be a tool to try to get at the time constants.

Q. Have you tried aspirin instead of persantine?

A. We tried all three at once to be most sure of an effect, anturane, persantine, and aspirin. We have done only two experiments. They both turned out similarly, but again, with different levels and we have not done anything more.

Q. I think regarding regeneration of nuclei there is fairly strong evidence for thinking that this occurs. For example, Newton Harvey years ago squashed bubbles out of existance and found it very difficult to generate free gas. More recently, Walder took some shrimps and squashed any potential nuclei out and found it very difficult to give them decompression sickness. But he did an important further step, which was to wait four hours or thereabouts and they returned to normal. In other words, you can decompress them and they will fizz. It would seem, therefore, there are gas spaces floating around in the tissues.

A. That's the key. In the tissues, and we have to get a mechanism -- perhaps what Dr. Yount suggested -- to get that gas into the bloodstream. Because that is all we are seeing or can see with this method.

Q. Most people would agree you could not conceivably move the heart at the rate it is moving and past structures like that without some form of embolization occurring. Once you have got nuclei present a lot of these explanations are not necessary.

A. I agree, once you have the nuclei.

Q. There is a certain attractiveness in assuming there are bubbles already there, maybe attached to walls.

A. We do not hear them. They are stationary.

Q. Harvey attached them to walls of vessels. It is the wrong part of the program, but I was hoping to say there is good evidence for this.

A. I think that is almost universally accepted. I do not see that what I am saying here contradicts that in any way. Maybe my conception of what is important is off. But we are dealing with a phenomenon. We are looking at bubbles that are collected. It is some fraction, we hope most, of the total amount of gas embolization. I want to ask a question. You remember that table I put up (Table 1). Now I want everybody to tell me: we have done two extra switches that are not nitrogen and helium. One was nitrogen to neon and the other was neon to helium. Which one do you think gave bubbles? We had saturation on nitrogen and we switched to neon. Neon's diffusion coefficient is about 2.7 to 3 cm^2 $sec,^{-5}$ depending on where you look it up. The other switch was neon to helium, and all of this is at 0.3 atmospheres of oxygen and 198 fsw. Which one bubbled? The solubility values for neon are just over those for helium, at 37°C about .009 ml/L/atm. That's a Bunsen solubility coefficient. Helium is 0.006 and nitrogen is about 0.012.

Q. Are those lipid solubilities?

A. Those are aqueous. Here is the N_2 into helium switch. We got a lot of bubbles on this. We got no bubbles with the neon to helium. This is the supersaturation predicted on a strictly perfusion-limited or solubility-limited system. And this is the situation predicted with the diffusion-limited system. The switch from neon to helium involves a higher diffusion coefficient, according to this ratio. Yet we got no bubbles on that switch.

This figure (Fig.), unfortunately, is mislabeled. This is actually nitrogen to neon, and this is nitrogen to neon on the other animal. Something that has made me think about the two situations is this sometimes different bubble counting pattern which occurs after a while. In any case, it could have something to do with "vascular programming."

Now, here is the neon to helium story (Fig.). I think I heard what I would call one or two bubbles over 5 or 6 hours. But there were a few during decompression. There must have been some

bubbles there because as soon as decompression was instituted, we heard some bubbles. I should say on these switches when we decompress, which is according to a U.S. Navy saturation approach, we hear bubbles that do not increase in number at all; in other words, they are indistinguishable from the isobaric periods. So we feel we are not blowing them up or making any more.

Here then (Fig.) was the difference in a pig switch which kept on bubbling in this case to 12 hours because that is when we terminated the experiment. What I am trying to show here is that in our Krogh cylinder what happens in the tissue may or may not be reflected in what we see with the Doppler.

Q. What is that thing going through the wall of the vessel? Is that a gas bubble?

A. That is what I am supposing and, if you like, rhetorically asking. If all we are seeing is something that starts here -- that is one way to interpret it -- there is much more tissue than there is volume of vasculature in action and we have to provide for some mechanism to get this gas into the circulation. Maybe there is some damage associated with this and perhaps it is minor. I am not sure.

Let me continue with this last pig experiment. This isobaric period went on for 48 hours. It increased and it leveled off and maintained itself. This next figure (Fig.) shows our only steady-state experiment. But it was done by a tracheostomy, which for a goat has a number of problems. The operation changes brain blood flow. It changes temperature response. Equilibrium temperature in the chamber is abnormal because of helium. I do not think it is a normal environment at all. So we have changed our approach and are simply trying to either baffle the head or use a mask. This is the only steady-state study we have done. Notice we have a plot that looks much like the other transient switches and then up here we have this kind of periodicity. I wonder if this is something that just reflects vascular programming to some tissue bed? We do not know if it is significant, but we see it quite often. And of course, once again you have to take my word for it that the bubbles stopped, although it makes sense to assume they would stop. One of these days we will do a longer experiment to satisfy the skeptics: we will simply camp there until the bubbles stop.

CONTRASTS OF SUPERFICIAL COUNTERDIFFUSION IN SKIN AND EYE

J. R. M. Cowley

Two recent papers of mine, which appeared in the Journal of Applied Physiology (47:224-227, 1979; 47:220-223, 1979), cover attempts to study isobaric counterdiffusion in the eye of the rabbit and attempts to measure increases in tissue pressure in the ear during the process. In my presentation today, I will discuss the information in those papers and expand upon them briefly.

As has already been noted, in the human counterdiffusion exposures there were no obvious visual disturbances, nor was there any itching at the conjunctiva. We decided to investigate this further in animals. However, even under the most severe counterdiffusion stress, which for the rabbits turned out to be nitrous oxide breathing while surrounded with helium at sea level, we were unable to produce measurable gas bubble formation in either he cornea or the conjunctiva. We were interested in conducting this type of experiment at higher pressures, but we couldn't take the rabbits to more than two atmospheres because they die of nitrous oxide toxicity at greater pressures. Also, at higher pressures the pulmonary effects in rabbits are much greater than the counterdiffusion effects.

In the JAP paper on the eye, I included a mathematical model of counterdiffusion that combines both perfusion-limited and diffusion-limited models across a slab of tissue. Using this model, we explained why we didn't see bubbles. We assumed that bubbles were the normal

state of affairs, and tried to explain their absence.

The model assumes the tissue has a moving slab of blood behind it, a surface area, a diffusion distance, and a diffusion rate. This model uses a block instead of a cylinder, but is otherwise very similar to a Krogh cylinder.

Fig. 1 here -- slab model

The dynamics of the rabbit's eye are well documented in terms of thickness and perfusion with aqueous fluid, and for simplicity we assumed that everything in the eye was aqueous rather than fat. We didn't worry about solubility coefficients, either -- if they play a part, it will only be to make bubbles come more easily. Theoretically, then, there would be a supersaturation at the base of the cornea at the corneal-aqueous fluid surface, which would be less than the intraocular pressure at sea level using nitrous oxide and helium. Exposing the animal to 5 atmospheres or so would cause the intraocular pressure to fall to an insignificant level, at which point it would be possible to generate gas. It would take about 48 hours to generate one milliliter of gas. At the same time, any small bubbles that were generated would be carried away in the aqueous drainage. We believe this explains why we didn't see any bubbles in the eye. On the surface of the eye there would not be any overpressure -- since the conjunctiva itself has no perfusion, the pressures would be much lower.

In the skin, the same model would predict that counterdiffusion would generate a supersaturation and bubbles. We had attempted to measure this supersaturation by gas analysis several times, without success, so we decided to measure it directly. We chose the rabbit's ear because there wouldn't be any question of muscle artifacts, and

because the ear could be isolated and experimented on without killing the animal. We simply inserted a very small multi-hole needle into the subcutaneous tissue, counterdiffused the animal, and measured the tissue pressure. Within 5 minutes of switching from air breathing in an air environment to nitrous oxide breathing with the ear surrounded by helium, we obtained pressures in excess of 100 mmHg above ambient pressure. The median increase in this interval was about 40 mmHg. The precise increase in pressure apparently depends on the architecture of the particular rabbit's ear and the location of the needle.

Many of the tracings (Fig. 2) show periodicity. The air breathing-

Fig. 2 here - pressure tracing

air environment portion of the experiment, which appears on the tracing as a flat line, reflects in effect a control condition. Within two minutes of the switch in gases, there is a rapid response in the form of a pressure increase. After reaching a maximum pressure, there is a tendency for sudden drops and increases, shown on the tracing by this sawtooth pattern. We felt that this was adiabatic expansion, with an initial bubble nucleus transmitting pressure hydrostatically through the tissue fluid.

At the point at which the tissue cleaved, there is a drop in pressure and a larger gas space, and then the pressure builds up again in the larger space. We have been able to simulate this by injecting gas into the rabbit's ear via the same set-up, and have produced the same pressure tracing pattern. We think this is hydrostatically transmitted pressure caused by an increase in pressure in a microbubble, small bubbles, or bubble fluid.

We have for the first time been able to show an actual increase in tissue pressure of up to 50 mmHg during counterdiffusion. It has been suggested that the bubble, or gas phase, may have been introduced by the needle rather than caused by the supersaturation, but since we have not medicated the animal and have only disrupted it to the extent of inserting a fluid-filled needle into its ear, we feel that is unlikely. Also, the pressure in the ear tissue of the several rabbits we injected built up to about 20 mmHg before the first drop in pressure. But this cleavage pressure varied a great deal depending on where on the rabbit's skin surface we injected the needle. It was greatest at the nose and the tips of the ears, where it reached about 200 mmHg. On rabbits, these are the only points at which the skin is attached closely. It appears that where the skin is tight, the gas phase is very small — there is a correspondence between the size of the gas phase and the tissue deformation pressure or cleavage pressure. The time interval between the peaks would range from about 1 to 2 minutes.

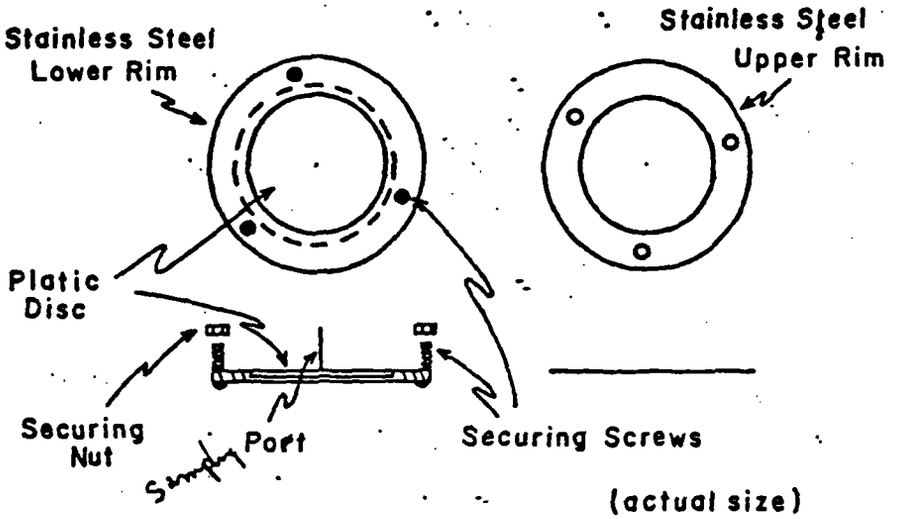
To verify some of our findings, we created an ear window in the rabbit by removing the cartilage on one side of the skin and leaving the other side of the skin intact, with its blood supply. Then we counterdiffused the animal. Rabbits have an interesting characteristic: they regulate

Fig. 3 here - window set-up

thermally via two mechanisms, panting and changing the blood flow to their ears. There is a linear correlation between these two phenomena, as shown in Fig. 4. Despite the physiology textbooks, rabbits do not

Fig. 4 here - temp/resp. rate graph

breathe at 50 breaths a minute. They breathe at a higher rate, but if


Stainless Steel
Lower Rim
Stainless Steel
Upper Rim
Platic
Disc
Securing
Nut
Sampling Port
Securing Screws
(actual size)

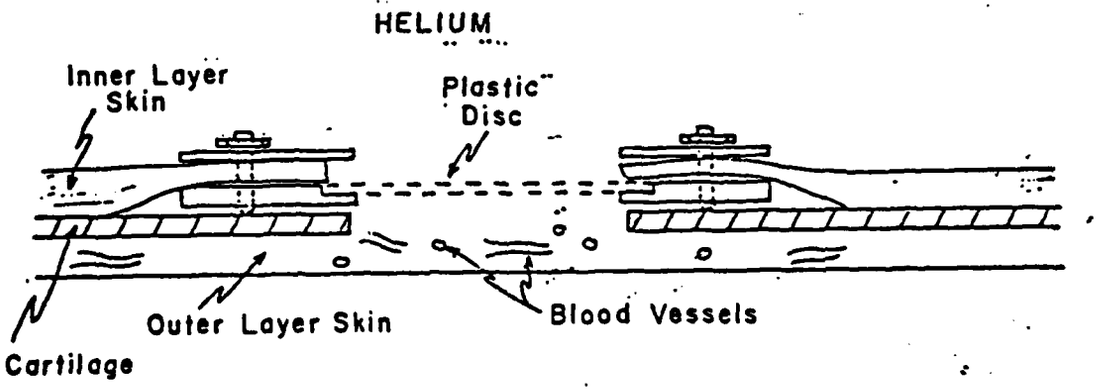

HELIUM
Inner Layer
Skin
Plastic
Disc
Outer Layer Skin
Blood Vessels
Cartilage
HELIUM

Figure 3

Richard Cowley
Paper, Tues 13th

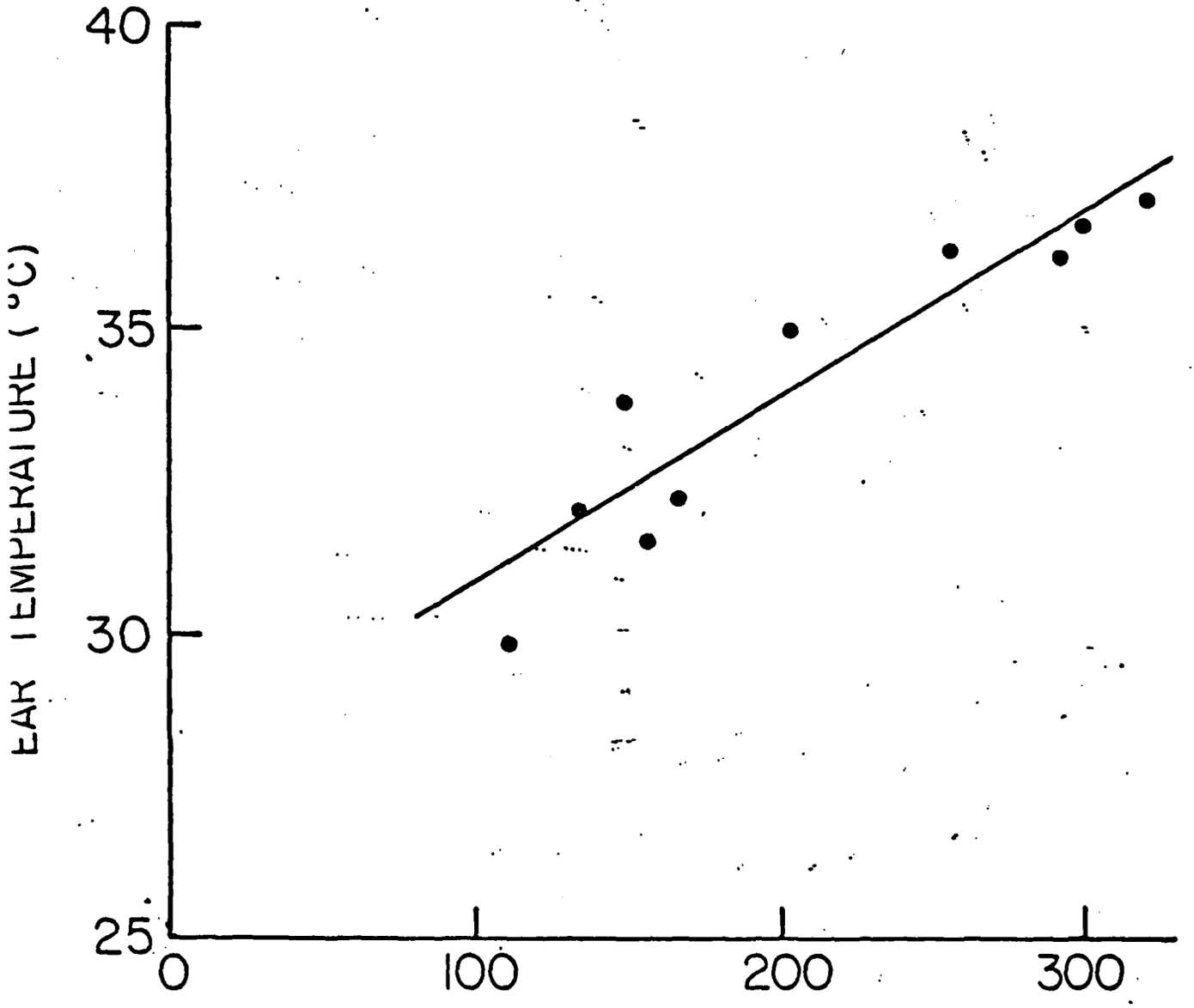


Fig. 4.

you give them barbiturates the rate drops to 50 per minute. We tried in these experiments to use respiratory frequency as an index of the perfusion of the ear. We counterdiffused 5 rabbits, and their respiratory frequencies, which vary naturally, gave us 5 different perfusion rates. We then measured the volume of gas released or generated in the 7-cm^2 ear window area, using a gas-tight syringe, and then we measured the gas composition of a sample of this gas to obtain the nitrous oxide to helium ratio (Fig. 5).

Fig. 5 here - expt. results N_2O/He

Table 1 shows the data for these experiments. The correlation is

Table 1 here - summary table

between breathing rate and rate of gas evolution. We used at least 7 volume measurements to calculate the rate of gas evolution per minute. These data confirm the rates per square meter of skin surface seen in the pigs; the order of magnitude is the same for rabbits and pigs.

Our mathematical model would predict, breathing 80% nitrous oxide while surrounded by helium, a nearly linear relation between the ratio of nitrous oxide to helium and the perfusion (Fig. 6). If the experi-

Fig. 6 here - math predictions

mental data (Fig. 5) are compared to the model's predictions, they show a similarly shaped hump-backed curve for the gas evolution rate, and an almost linear relation between the nitrous-oxide/helium ratio and the respiratory rate.

This series of experiments was interesting because, without doing any gas analysis, we were able to confirm directly that counterdiffusion produces an increase in tissue pressure.

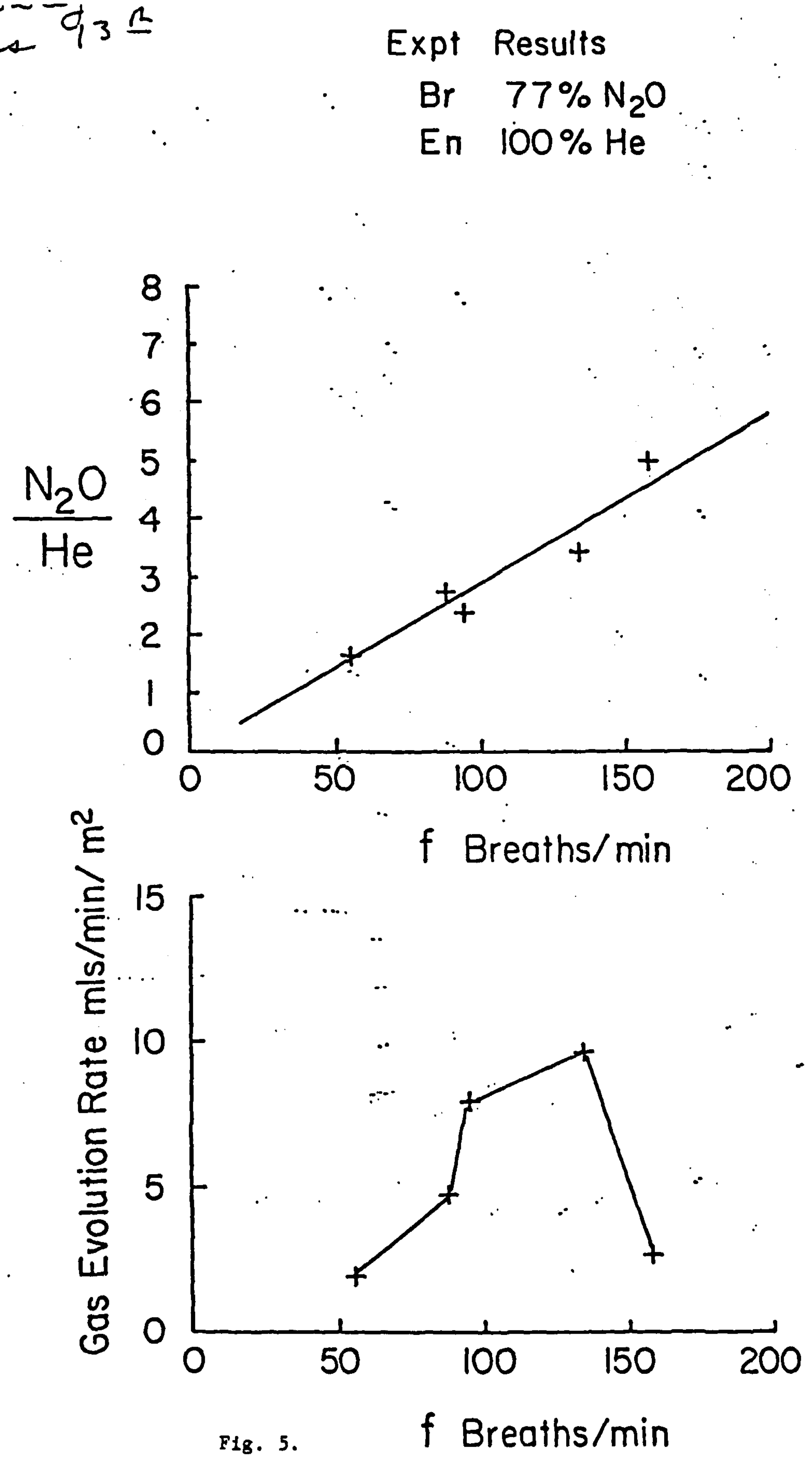

Expt Results
Br 77% N_2O
En 100% He
N_2O / He
0
1
2
3
4
5
6
7
8
0
50
100
150
200
f Breaths/min
Gas Evolution Rate mls/min/ m^2
0
5
10
15
0
50
100
150
200
f Breaths/min

Fig. 5.

R Cowley
piper 013 Δ

Mathematical Predictions

Br 80% N_2O

En 100% He

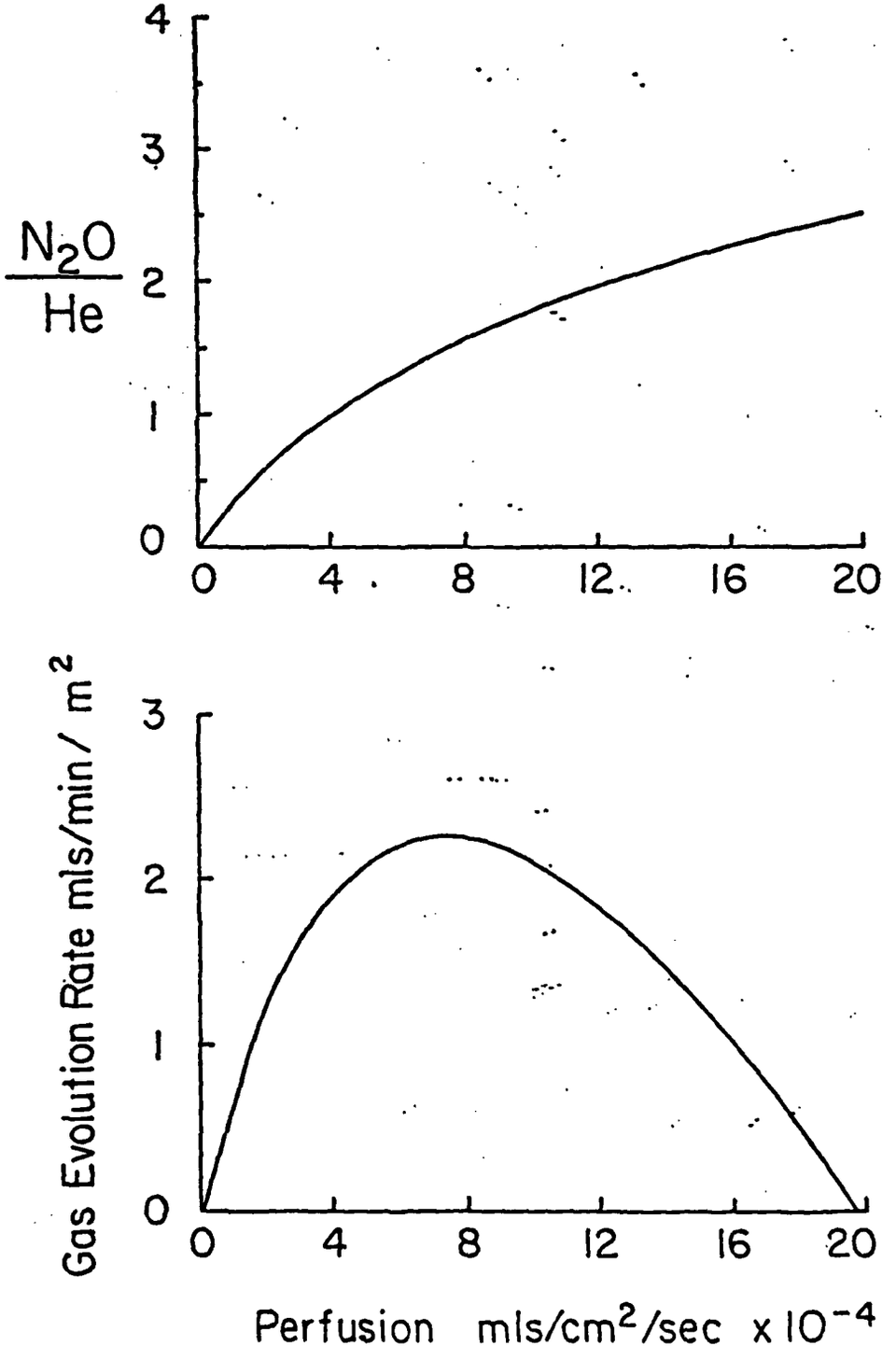


Figure 6

K. Lowes
paper, 15th

SUMMARY TABLE 1

	F BREATHS/MIN	SEM	N_2O:He MLS/ML	SEM	EVOLUTION RATE MLS/MIN/M^2	CORRELATION
1	158	±26	5.00 ± 0.30		2.7	.94
2	55	± 2	1.63 ± 0.20		2.0	.96
3	135	± 7	3.46 ± 0.13		9.7	.99
4	88	± 2	2.76 ± 0.14		4.7	.96
5	94	± 4	2.40 ± 0.19		6.8	.98

Discussion

Q. Have you attempted to measure the cleavage pressure after injecting fluid instead of gas?

A. We have not done that experiment yet.

Q. Is this bubble formation self-contained, i.e., limited to the skin, or does the gas get injected into the capillaries? If it does get into the capillary, you would expect to see, after a long experiment, some hematological evidence of endothelial damage.

A. It may be that the hemorrhagic skin lesions seen in the pig counterdiffusion experiments correspond to that sort of damage.

Q. Did you see any evidence of bubbles at the central venous location before gas formation occurs in the skin?

A. You see bubbles building up in the tissue which are palpable. If you follow the lymphatics you can dissect them. Rabbits have lymphatic emboli but no venous emboli. They only occur in the venous system below the point in the vena cava where the lymphatic system dumps.

INERT GAS EXCHANGE IN THE MIDDLE EAR*

A. Ranade

I will briefly go over the data for middle ear gas exchange, because I would like later to present an hypothesis about how that gas exchange is related to vestibular problems.

The gases in the middle ear provide an external environment for counterdiffusion to the round window, and so our first studies investigated whether the gases in the external canal and the gases in the blood would provide a sufficient exchange to sustain the required gradient. We considered a model whose parameters were: geometry of the surface area of the tympanic membrane; thickness of the tympanic membrane; surface area of the affected mucosal lining of the ear; the effect of Eustachian tube function; the blood flow through the tympanic membrane; and thickness across the mucosal lining. We used the ideal gas laws and made the following assumptions: 1) the volume of the middle ear cavity remains constant (any changes due to the effects of positive and negative pressure would be so small it was safe to ignore them); 2) the partial pressure inside the tympanic membrane remained uniform -- no local differences needed to be considered; 3) the Eustachian tube functions as an ideal pressure regulator -- as soon as the pressure in the middle ear rises, the tube will open to vent the pressure, so that the pressure within the cavity remains constant. Using these assumptions, and parameter values from the literature, we looked at how the model behaved and how its results compared with experimental data.

* This paper is incomplete.

One of our early experiments involved a tracheostomized cat breathing nitrous oxide while it was surrounded by air. The gases in the middle ear were sampled by a gas sampling syringe. As Fig. 1 shows, the gas uptake curve is not exponential, which would indicate

Fig. 1 here - N_2O uptake x middle ear P

a continuous exchange of nitrous oxide from the middle ear to the outside through the tympanic membrane. This experiment strongly suggested that the membrane was significantly permeable to nitrous oxide, since the nitrous oxide was added to the respiratory tract below the level of the nasal pharynx and had diffused into the middle ear through the blood flow in the mucosal lining and perhaps in the tympanic membrane.

We then did three types of experiments. One type was designed to study the effect of the gases coming from the mucosal lining by plugging the tympanic membrane with a dense plug of epoxy to prevent diffusion across the membrane. To study the membrane effect only, we would then fill the middle ear cavity with sulfur hexafluoride and put helium and nitrous oxide or helium and neon in the breathing gas and determine their uptake into the middle ear cavity. In the early part of these experiments when the gas build-up was so small that the gradient was not affected, we could observe diffusion across the tympanic membrane. (We ignored the effect on the mucosal lining in these experiments.)

Dr. Vann: During the discussion today, diffusion between compartments has been neglected. From the time of Haldane on, people have assumed that the body is made up of tissues and organs that have different perfusion rates, different exchange rates. These organs are occasionally next to each other, and when a concentration difference occurs between adjacent tissues, there is going to be diffusion between them, and concentration differences and perhaps supersaturation will be introduced into the system.

Dr. Tepper: An experimental example of the situation you've just described occurs when one is trying to wash out and measure renal blood flow with an inert gas that is very fat soluble. The gas will saturate the perirenal fat, which will diffuse in and be measured as part of the washout, skewing the data significantly.

There are also real differences between the chromatographic and a totally perfusion-limited model; the predictions about supersaturation made with the two models are completely different. In the chromatographic model, theoretically, inert gas switches can produce supersaturations in aqueous tissues, which cannot be done in the perfusion-limited model.

Jumping from phenomenology to a model again, if we can invent a diffusion mechanism, a chromatographic mechanism, to increase supersaturations over those we'd predict with a perfusion-limited model, how do we account for the time delay we see when the bubbles get back to the central venous location?

We must either assume that those bubbles were waiting to be picked up, or were formed relatively recently. How does this supersaturation have the supreme leisure to wait around for 8 hours before becoming manifest?

Discussant: Perhaps the opening and closing of pre-capillary sphincter valves, which accounts for the stop-start rather than continuous flow of blood through the capillaries, plays a role in the supersaturation time lag. Vascular tone, and active vascular reactions, might explain a lot of the variation we see.

Discussant: Yes; for example, the helium may come in and occupy what was previously a nitrogen bubble, slightly expanding it. When the circulation opens up again and the nitrogen comes back in, the helium would of course diffuse out while the nitrogen diffuses in. This might initially appear to be simply a back-and-forth situation, but in fact when the nitrogen diffuses back in, it is greeted by a larger surface area in which to diffuse. So there is a continuous sort of rectified diffusion occurring, with the bubble getting bigger and bigger. At some point, presumably, it will block the circulation, at which time it will have nitrogen at the blood end and helium at the other end. It is a highly unstable situation; it just continues to expand until the partial pressures in the bubble are equal to the partial pressures of the gases diffusing in, which can never happen. Therefore the bubble just bleeps out through the venous end.

Dr. Karreman: Another concept that will become more important as time goes on, I think, is that of cooperative phenomena, such as those that operate in blood coagulation.

Discussant: Are there data on the time lags involved in Dr. Cowley's experiments?

Dr. Cowley: Yes; for the intact, undrugged animals I showed you, there was a mean time lag to the beginning of generating a steady-state gas phase of 50 minutes, plus or minus a standard error of 20 minutes. A second group of animals pretreated with 10 milligrams of valium, intramuscularly, showed a time lag of 248 minutes with an SE of 24 minutes. We were thus able to exert the beginning of pharmacological control over the process. In rabbits, the drug apparently interfered with temperature control; in fact, it dropped the perfusion rate in the rabbit's ears. If we could lower the perfusion rate of the skin it might be possible to remove divers from the range of embolization. It might be easy to do by just cooling them.

Dr. D'Aoust: It is important to remember that solubility is temperature dependent.

Dr. Flynn: Wasn't the combination of valium and nitrous oxide inhalation a potent cardiovascular depressant?

Dr. Cowley: No; the rabbits were still walking around and kicking, even though their ear temperatures had dropped by 7 degrees C.

Dr. Flynn: What kind of rabbits were these?

Dr. Cowley: New Zealand Whites.

Discussant: Dr. D'Aoust, what would you predict if you saturated your goats with helium and then switched them to nitrogen?

Dr. D'Aoust: I would predict an undersaturation, and Keller and Buehlmann's work demonstrates it. I would now predict it on the basis of the ratio of blood-tissue solubilities rather than on the diffusion coefficients' ratio, which we used in earlier publications. Peter Edel has shown that contrary to expectations, hydrogen is between helium and nitrogen with respect to decompression. We will be doing a hydrogen switch to confirm this.

Discussant: Dr. D'Aoust, what happened when you went from helium saturation, with goats, to a nitrogen or neon atmosphere?

Dr. D'Aoust: No isobaric phenomena happened, because we changed both the breathing and the environmental gas at the same time, in the middle of the decompression.

Dr. Lambertsen: Here at the Institute, we had several different kinds of isobaric phenomena occurring either sequentially or simultaneously. For example, our subjects were saturated with nitrogen at the beginning of the experiment, and then were switched to helium. Then they were saturated with helium and changed to neon; later, they were breathing neon while surrounded by helium, which means there were three different isobaric phenomena in one set of experiments. This needs to be looked at in relation to the earlier discussion that saturation on helium followed by a switch to nitrogen causes vestibular problems.

Discussant: Perhaps we ought to stop switching gases toward the later stages of decompression, since we have seen such a high

percentage of cases of inner ear decompression sickness after the switch. However, these inner ear cases might still be counterdiffusion phenomena, because there is a fluid reservoir in the inner ear that is saturated with helium, and the diver then goes to a nitrogen environment. The diver's skin is surrounded by nitrogen, and he is breathing nitrogen, but in the inner ear compartment, the blood carrying nitrogen is coming into this helium reservoir.

Dr. Lambertsen: There is definitely the potential for a counterdiffusion episode in these vestibular cases, but it still might be a form of decompression sickness. We have at least ruled out one factor: a decrease in pressure. These divers were either at 1200 fsw or in decompression. But it's difficult to pinpoint where the counterdiffusion lesion is: in the vasculature of the inner ear, the fluid compartments of the inner ear, or whether it is caused by endolymphatic hydrops. It is also difficult to relate these occurrences to Dr. D'Aoust's experiments.

Dr. Flynn: Also, there were no vestibular problems on the nitrogen exposures down to 400 fsw, but after a helium dive, there were vestibular problems at 150 fsw. Further, even after a day of exposure to helium at 400 fsw and a sudden switch to nitrogen breathing, the only problems were cutaneous ones.

Dr. Lambertsen: True, and once the divers were at 1200 fsw and exposed to a denser gas, they did have vestibular problems in 3 out of 4 cases.

Discussant: Didn't that only occur in neon, or on an exposure right after a neon interval?

Dr. Lambertsen: To our knowledge, this is the only episode of its type that has occurred with no change in pressure.

Discussant: There was a similar event involving xenon as an anesthetic, which was followed postoperatively by vestibular derangement. That was also an isobaric situation.

Dr. Hempleman: I noticed in one of your examples that using SF_6 as the breathing gas caused no bubbling at all in the circumstances you've experimented with.

Dr. Lambertsen: We expected to see a problem with SF_6, but we didn't; perhaps the situation was hidden, or masked, or perhaps the symptoms were just too insignificant to be noticeable.

Dr. Yount: If there is anything to Cowley's results with the eye, and the prediction of the volume of gas released, the overpressure with SF_6 should be high. The total volume of gas produced, because SF_6 has such a low solubility, would be similar to that for nitrogen, rather than a high volume as with nitrous oxide, which would be consistent with a low solubility in water.

Discussant: Yes, but the fat solubility of SF_6 is very large; however, the fact that it has low solubility in water fits with the superficial situation.

Discussant: How do we explain the situation in which the diver with decompression sickness is recompressed on air and complains that the pressure is making his pain worse?

Discussant: Oxygen is an inert gas until it is metabolized; in some

situations where there is a near-zero level of metabolism in the tissues involved, we would expect oxygen to act that way. Examples are fluids that have no circulation: the aqueous humor of the eye, and perhaps the inner ear fluid. Oxygen may behave as an inert gas in the inner ear fluid.

Discussant: To what extent do you think that the rate of embolization of nitrous oxide might have been artificially high due to emboli coming up the vena cava and picking up nitrous oxide?

Dr. Bennett: That's difficult to answer because the time required for a bubble to grow and reach near-equilibrium with the blood is not very long; with very tiny bubbles, the time may be only seconds. We have tried to measure the rate of equilibration with tonometers by injecting a bubble and then serially analyzing it, and it is simply impossible to catch it before equilibrium has essentially been reached. I would guess that whatever the bubbles are like when they reach the vena cava is what they're like further down in the circulation. However, they might coalesce on the way up, after coming from different capillaries. But I don't think the individual gas partial pressure changes.

Discussant: I wonder whether this venous gas embolization is going to be clinically significant -- for example, in the presence of cutaneous lesions?

Dr. Lambertsen: I don't think there is anything to worry about unless there is itching, because there have never been vestibular problems without severe skin lesions or lesions without severe

itching. But I do worry about the interactions among these several phenomena, where, for example, one phenomenon reinforces another and makes it serious. These are the things that have practical implications for diving practice.

Dr. Lanphier: I am generally skeptical about modelling, and I think it's important to remember that in the case of bubbling and decompression sickness, no one has ever tied them together sufficiently to relate them usefully. It has been said that capillaries open and close; what happens to the Roughten cylinder when the capillaries close down? Maybe Roughten intended his tube as a schematic, in which the capillary is assumed to be in the middle of this very regular tube. But what if the capillaries *are* scattered about and shift over time, so that *mathematically* the summation is the same as if you had a central capillary inside a cylinder? Expressed differently, if there was a big slab of tissue with capillaries all over, opening and closing so that the shear was decreasing and enlarging in diameter and moving from place to place throughout the larger slab, the effect in any one position with the overlapping of these discs would be, over a period of time, that they would all equalize out and could be summated in a simple mathematical form. Is it possible, perhaps, that the bubble of decompression sickness is somewhere in an area that has somehow been left out of this shifting geometrical pattern?

Discussant: The problems you raise can be handled either by assuming that the capillaries are random, or by assigning them a definite probability distribution. That way, you could figure out what the equivalent capillary would be, in the random case. However, I agree with Dr. Tepper that capillary position is not random, but scattered with a purpose. In the second case you mentioned, once you have the probability distribution it is relatively simple to solve the problem. If, as you suggested, the capillaries are moving, that can be handled mathematically either by a stochastic approach or something else.

Dr. Lanphier: It's important to remember that the capillaries are opening and closing to change the CO_2 and PO_2, not to relieve inert gas. Also, even if the process is random and the exit concentration is uniform, the local effects are different. You are probably hitting a boundary region when a capillary doesn't open; diffusion probably affects it. It doesn't really matter if there is an interaction between perfusion and diffusion if it's an axial or a radial grade in, because the same phenomenon could occur radially, too. Any geometric relationship that causes perfusion and diffusion to interact, whether axially, radially, or square, can produce the same type of effect. If there was a counterdiffusion system with the endolymph and the perilymph, it would slow helium washout. As the nitrogen went around in the perilymph, it would make a hairpin curve.

Dr. Farmer: The perilymph and endolymph really don't flow like that. The cochlea is richly supplied with blood vessels all the way around its turn, so that what is happening in one section is very similar to what's happening in another. It does not depend on how the perilymph and endolymph flow in relation to each other.

Dr. D'Aoust: In response to Capt. Bornmann, the evidence obtained by watching the concentration of venous blood change after decompression is, as you say, that the decompression per se alters the rate of nitrogen elimination, probably by affecting the vascular programming; whatever it is, it's apparently related to oxygen demand. If you compute two curves, you get a mixed venous blood desaturation. Assuming that one curve reflects a normal body desaturation (the one I am talking about would be just switching to oxygen and watching the nitrogen come out isobarically), you watch the nitrogen come out after decompression and plot that to the same fractional scale. You have to accept the conclusion that a lot of nitrogen is left in the system. If you compute that nitrogen, on the average, again, and thinking of the body as one compartment, you will get enormous supersaturations. Since we know that bubbles form at supersaturations well below these, we are forced to assume that these bubbles do affect the capillary flow, and probably whole groups of capillaries, and probably whole organ parts. That is consistent with the data one gets looking at mixed venous blood. You will get about 10 microliters of

nitrogen per cubic centimeter of blood; if you breathe oxygen suddenly, that figure will drop to 1 or 2 cubic centimeters, and if you decompress to 60 fsw, in goat and dog data that will drop almost to the ambient level or to 10% of capacity. It is as if you are recirculating blood without picking up any tissue nitrogen. This fits in with earlier comments that decompression is a real stress on this normal vascular programming, whatever controls it.

Dr. Hempleman: We tend to lose sight of the fact that in liquids and in blood, nothing will happen unless there is a nucleus. It is therefore profitless to pursue mechanisms that will produce supersaturations of negligible proportions anyway, compared with the atmospheres necessary to break liquids. It is the nuclei that are important (and they only seem to occur in blood). In endless experiments, the first bubbles seen are vascular. Most of us believe, I think, that the bubbles in both decompression sickness and counterdiffusion are vascular.

Dr. Flynn: If you assume that there is a certain distribution of radii of these gas nuclei in order to recruit any significant number, it might be necessary to have a certain supersaturation before you could begin to expand any of them. But according to Dr. Yount's model, it would need to be a relatively large nucleus that would expand with the minimal amount of supersaturation.

Dr. Hempleman: In 1972, when the first pictures of the counterdiffused pig were shown, Keith Miller said to me: one thing that this shows is that there are plenty of nuclei about and they're

very easily provoked. I think he was totally correct.

Dr. Yount: I agree with that statement. About models, although I'm a model builder myself -- the idea is to find a problem to model that is simple enough so it can be solved. The real world of capillary beds is too complicated to solve. Also, model builders only extract the most important features of the real situation to model; they disregard the details.

What I am interested in about supersaturation mechanisms is that: 1) supersaturation is feasible; 2) the amount of supersaturation that is feasible is about 30 or 40 percent; and 3) it usually takes about 20, 30, or 40 minutes to get a supersaturation, but it can also be quite quick. With this information, I know what I need to know from the model builders; I am now ready to make tables or whatever else.

In response to Dr. Hempleman, I believe there are nuclei in aqueous media of all types; in the bones or in anything that has water in it, it is almost impossible to get rid of a nucleus. I would therefore expect to see bubble formation in the vitreous humor, in the skin, almost anywhere, in fact. I also believe that most bubble formation occurs in the tissue, and I invoke the concept of tissue deformation pressure to account for what is seen. A bubble growing in tissue will only grow to a limited degree, maybe to 5 or 10 microns, at which point its growth will stop because of deformation pressure. It may then serve as a site for secondary bubble formation; Dr. Corley's talk showed that the bubbles stop

growing at around 15 microns. Thereafter, it sends out one bubble at a time, which then gets into the bloodstream, where it can grow indefinitely. There is no tissue deformation pressure in the blood, and these bubbles, of perhaps 100 microns or larger, can be detected by Doppler or even be seen — but not in the tissue, because they are too small there to be detected.

SESSION II: ISOBARIC INERT GAS COUNTERDIFFUSION:

Hypotheses and Theory

INITIAL CONCEPTS

D. Graves

When Dr. Idicula of the Institute staff originally contacted me about the problems with the skin lesions, Dr. Quinn, who was also in the Chemical Engineering Department, and I came up with the following idea. We proposed a model with two layers of material -- not necessarily physically distinct layers, but something that offers resistance to the transfer of material -- called for convenience layer A and layer B.

Fig. 1 - schematic of model

One gas is diffusing in one direction and another gas in the opposite direction. In a physiological situation, gas 2 is dissolved in the blood and is diffusing outward through the skin, and gas 1 in the surrounding atmosphere is diffusing in and being carried away by the blood. In the simplest conceptual terms, if we assume that the gas contacts first the layer that has the least resistance, the drop in partial pressure of gas 2 will be less steep in this layer than it is in the outer layer and, conversely, for the other gas the drop is less in the outer layer than in the inner. If you add the partial pressures of the two, the sum will exceed the ambient pressure P, which is assumed to be the same on both sides, and will be at a maximum between these two layers.

In this model, which isn't new, the pressure can be described by an equation in which the thicknesses of the layers are represented by Δx_b and Δx_a, and there are four constants: the permeability for gas 1 through layer A and through layer B, and the permeability for gas 2 through layer B and through layer A. Solving this equation will tell you what the partial pressure at the interface between the two layers

will be. This model makes a number of simplifying assumptions: that there are pure gases on the inner side of the layers and that there are equal pressures; that the permeabilities are constant; and that the flux of gas is a simple linear relationship given by: flux equals a constant times the partial pressure difference, divided by the thickness.

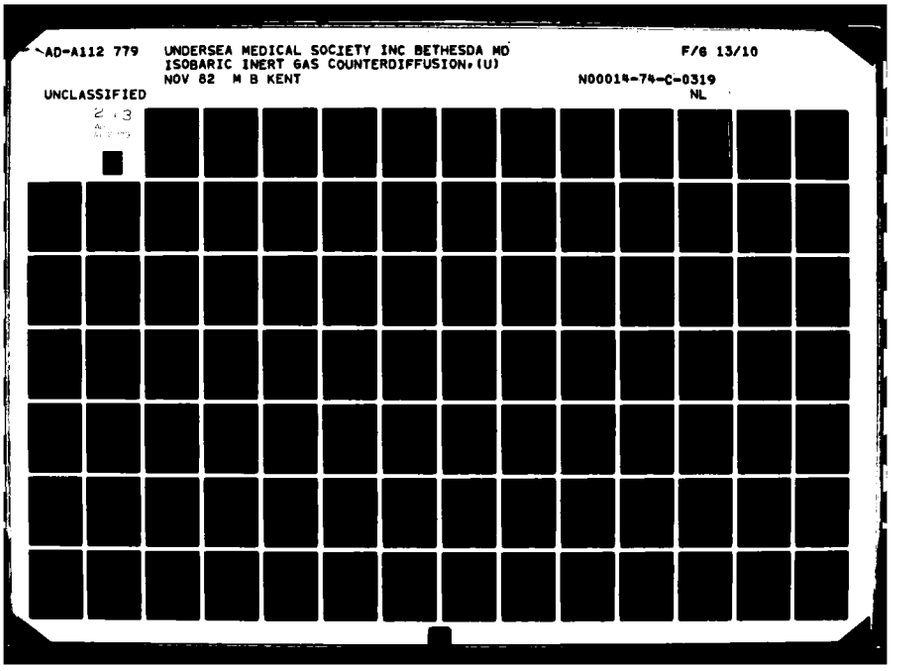
I said before that the gas had to contact the most permeable layer first in the two-layer sequence. The only thing that is necessary is for the relative permeabilities to be different for the right membrane or the right layer. If there are layers with different semi-permeabilities, they have to be arranged in the proper sequence, i.e., if you don't get supersaturation with one arrangement, switching the two gases should produce it. This is an important and interesting corollary to this simple model. Also, there is an optimum ratio of the thicknesses of the two layers that yields the maximum supersaturation or the maximum amount of dissolved gas in the system.

Fig. 2 - transient situation schematic

The transient situation, as Fig. 2 shows, will be the sum of two exponentials. The total response can be a simple exponential, an overshoot which initially goes to a higher total pressure and then comes down to a steady state, a decrease below the steady state followed by a return to the steady state, or a situation in which the first exponential starts to come up to the steady state and then the second exponential takes over, producing a two-humped response. Any of these four types of transient behavior is possible.

Fig. 3 - oil-water membrane

Figure 3 shows the simple experimental device we built to test our model. We saw bubbles at the interface at a pressure of only one atmosphere of helium or nitrogen. We would have achieved an even greater


AD-A112 779
UNDERSEA MEDICAL SOCIETY INC BETHESDA MD
ISOBARIC INERT GAS COUNTERDIFFUSION.(U)
NOV 82 M B KENT
F/6 13/10
N00014-74-C-0319
NL
UNCLASSIFIED
2 . 3


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS 1963 A

effect by using helium and nitrous oxide.

Figure 4 shows a second but similar experiment, using solid rather than liquid membranes, such as silicone rubber and ethyl cellulose. The gases were again nitrogen and helium. The curve represents the theoretical prediction from the model, and the circles represent the experimental data points. The fit is very good; the model seems to work well for all the conditions we've tried.

We also looked at what happens in a membrane blood oxygenator which gets rid of carbon dioxide and perhaps dissolved nitrogen that may be present in the blood, and which is in contact on the other side with pure oxygen. We wanted to see whether bubbles formed in the blood

Fig. 5 - blood oxygenator model

oxygenator. We assumed, as Fig. 5 shows, that there was one layer that had a film of blood with a thickness representative of the blood flow rate, and another membrane, usually silicone rubber. Oxygen passed in one direction, and nitrogen and carbon dioxide moved in the other. In this situation we identified a second mechanism, which we called exchange rate supersaturation. Other investigators have called it the single-layer model. It works as follows: there is a resistance -- perhaps a membrane or another physiological structure -- and blood or another fluid on one side of the resistance, supplying a particular gas, and another gas on the other side of the resistance. The layer or resistance allows one gas to penetrate in and be taken up by the blood faster than the substances dissolved in the blood can pass out in the other direction. An example of this situation is an air-filled balloon in a helium or hydrogen atmosphere: the balloon expands because the hydrogen or helium penetrates into the balloon faster than the air can escape, so there is

an increase in the total amount of gas within the system. Our theoretical results with this model, however, were not exciting (Fig. 5). There was some supersaturation, and the dashed and solid curves show the maximum and minimum estimates. Depending on whether you are at the blood entry into, or exit point from, the oxygenator, there are different degrees of supersaturation. The maximum in any situation would be 150 to 200 torrs.

Finally, although counterdiffusion generally has negative effects, we were able to use it beneficially to produce a commercial device for analyzing gases. Figure 6 shows a prototype of this device. A reference

Fig. 6 - measuring device

gas passes through one chamber, and a sample gas flows through the other chamber. A pressure transducer is connected to the inner compartment, so that the pressure you read will indicate the composition of the gas. The difficulty in design was to devise a technique to make the membranes extraordinarily thin and yet strong enough to withstand fairly high pressures. We have done that, and the device measures gases such as oxygen-nitrogen mixtures, nitrous oxide, ammonia, and half a dozen other gases, with a time constant of 5 seconds. After a gas switch, the meter changes in about 5 seconds. I'll close with that glimpse of one of the useful aspects of counterdiffusion.

Discussion

Q. Would your first model, with the oil-water interface, fit the ear counterdiffusion situation?

A. No, it fits the skin. It is important to realize that the skin can be very thin. The skin should be thought of here as a place for many millions of circulatory and lipid-aqueous locations.

Q. Would you agree that, strictly speaking, only the solid membrane model is really diffusion-limited? The oil-water model would have some micro-circulation, wouldn't it?

A. Yes, that's certainly what the theory would say.

Q. At what pressures will your gas analyzer work?

A. With the nitrogen and helium, we had pressures up to 0.5 atmospheres. But in other cases I don't think we went over 1 to 200 mmHg.

Q. With the analyzer, does there have to be a different area of the membrane or a different thickness for each gas pair?

A. If you want optimum response, the pair of membranes should be set at the right thickness ratios, and they should be made of the right materials. But in practice, one membrane pair would probably do for several different binary mixtures.

Q. Doesn't this device work on the same principle as one developed by Folkman in Boston several years ago?

A. No, that was a transient device, while ours is steady state. It gives you a continuous and accurate record of the composition of the gas stream.

Q. What were the pressure transducers you used?

A. Ones that are commercially available.

Q. What is the accuracy of the device?

A. It is within a few percent, certainly less than 5 percent.

MULTIPLE INERT-GAS BUBBLE DISEASE: A REVIEW OF THE THEORY*

David E. Yount

This paper is a review of the theory of multiple inert-gas bubble disease. The organization is etiological, that is, the two factors required to produce the disease—nucleation and supersaturation—are considered in that order. Although the novel aspects of the theory pertain mainly to supersaturation mechanisms, rather than to nucleation, a discussion of nucleation is appropriate because it can tell us what happens when a state of supersaturation is achieved and how much supersaturation is required to produce signs and symptoms.

Before dealing with the two main topics, we shall attempt to define more precisely several of the terms that will be used. First, we shall define "exogenous gas bubble disease" as a disease syndrome associated with the formation, via external causes, of gas bubbles in blood or tissue. Two conditions permit bubble formation in blood or tissue: 1) the presence of gas or other nuclei and 2) the existence of a state of dissolved-gas supersaturation. It follows that "decompression sickness" is a form of exogenous gas bubble disease in which a state of supersaturation is achieved by reducing the ambient pressure. Similarly, "multiple inert-gas bubble disease" is a form of exogenous gas bubble disease in which a state of supersaturation is achieved by using two or more inert gases, either sequentially or simultaneously. An example of sequential use is the switching of the breathing mixture from nitrogen-oxygen to helium-oxygen. An example of simultaneous use is the breathing of a nitrogen-oxygen mixture by a subject immersed in a helium-oxygen environment.

Decompression sickness and multiple inert-gas bubble disease differ primarily in the manner in which the state of supersaturation is achieved. Hence, we can anticipate that much of what is known about the former disease syndrome will be applicable to the latter. Furthermore, since compression and decompression frequently involve the use of more than one inert gas, it is not uncommon for a critical level of supersaturation to be produced synergistically, i.e., through the simultaneous action of decompression and inert gas exchange which separately might be harmless.

Nucleation Theory

The relevance of nucleation theory to exogenous gas bubble disease is suggested by four ab initio considerations. The first is the generality of symptoms and the fact that almost any body organ or part can be affected. Second is the fact that humans consist mainly of water. Third, bubble formation is a general property of aqueous media, and fourth, the thresholds for bubble formation in vitro are remarkably similar to those for the onset of symptoms in vivo.

* In the final report, the figures will be reduced and inserted above their respective legends, as indicated in the text.

Three additional observations suggest that bubble formation is initiated by stable gas nuclei. The existence of nuclei of some type is implied by the fact that bubble formation often occurs at supersaturation pressures of the order of one atmosphere, whereas the theoretical cavitation strength of pure water is more than 1000 atmospheres. Stability is implied by the phenomenon of denucleation. A gas filling is indicated by experiments in which samples are denucleated by degassing or by the application of static pressure. Solid or liquid nuclei, being essentially incompressible, would not be affected by pressurization.

The existence of stable gas nuclei is a scientific paradox. Nuclei larger than about 1 μm in radius should float to the surface of a standing liquid, whereas smaller ones should collapse rapidly due to the surface pressure $2\gamma/r$, where γ is the surface tension and r is the radius of the liquid-gas interface. In the crevice model (Harvey, Barnes, McElroy, Whiteley, Pease, and Cooper 1944), stability is maintained by using the walls of a gas-filled crevice to support an interface that is ordinarily flat. (As the radius r approaches infinity, the surface pressure $2\gamma/r$ approaches zero.) This mechanism presumably accounts for the familiar observation of a series of bubbles forming continuously at some point on the inner surface of a drinking glass filled with a supersaturated liquid, such as beer or champagne. This process may also operate in vivo, for example, in the spaces between adjacent cell membranes.

There is by now considerable evidence that the main initiators of bubble formation in a bulk liquid are spherical gas nuclei stabilized by an outer shell or skin composed of surface-active molecules (Yount 1979a; Yount, Yeung, and Ingle 1979). Such a skin opposes the inward surface "tension" $2\gamma/r$ with an outward skin "compression" $2\Gamma/r$. The skin is gas-permeable initially and during decompression, but it can become impermeable if the ambient pressure is increased rapidly by a sufficiently large amount. Thus the pores between the skin molecules close if the magnitude of the compression is large enough. Bubble formation occurs whenever the Laplace condition

$$p_{ss} > 2\gamma/r \qquad (1)$$

is satisfied, i.e., whenever the supersaturation pressure p_{ss} exceeds the surface pressure $2\gamma/r$.

The surfactant model is essentially a description of the way nuclear radii respond to changes in ambient pressure. The model predicts that there should be a one-to-one correspondence between the parameter r_o^{min} and the number of bubbles generated by a particular family of pressure schedules. By passing gelatin samples through Nuclepore filters prior to compression, it has recently been demonstrated (Yount, Yeung, and Ingle 1979) that r_o^{min} is the initial radius of an actual physical structure capable of initiating bubble formation in gelatin.

Below about 8 atm, the surfactant model predicts that the family of pressure schedules which yield a fixed bubble number N will be described

by a linear relationship between the supersaturation pressure p_{ss} and the initial increase in static pressure p_{crush} or, equivalently, between the allowed pressure reduction $P_1 - P_2$ and the exposure pressure P_1:

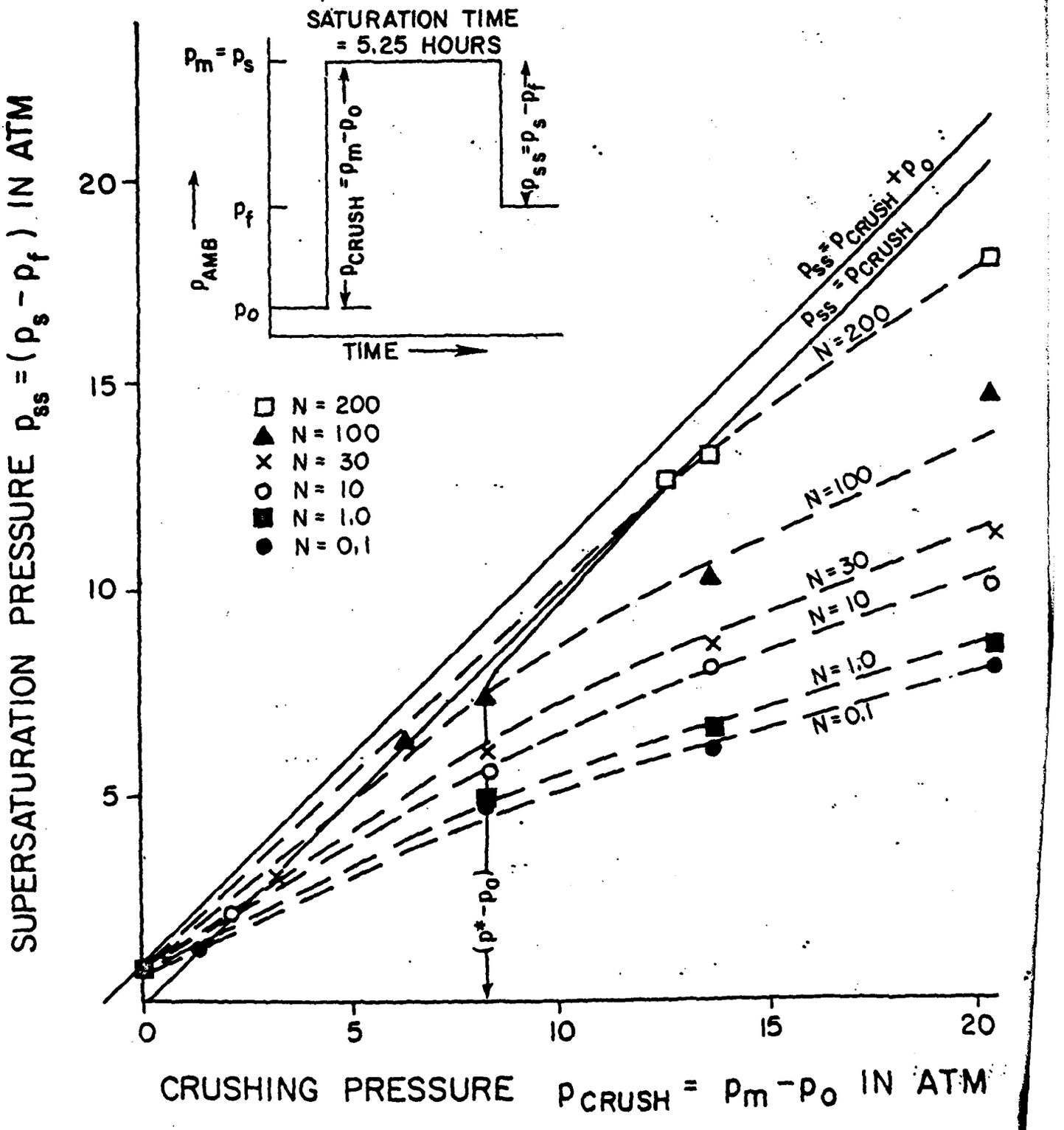
$$p_{ss} = a\, p_{crush} + b \qquad (2a).$$
$$P_1 - P_2 = c\, P_1 + d \qquad (2b)$$

For compressions larger than about 8 atm, the nuclear skins become impermeable. Impermeability is characterized by a decrease in slope and by a departure from the linearity predicted by Eqs. 2a and b. The decrease in slope occurs because the pressure inside a gas-impermeable skin increases as the radius and volume decrease. The increase in internal pressure aids the elasticity or compression strength of the skin in resisting further decreases in radius.

The surfactant model is compared with data on bubble formation in gelatin in Fig. 1 (Yount, Yeung, and Ingle 1979). The qualitative predictions outlined above are confirmed by these data, and the quantitative agreement between the model calculations (dashed lines) and the data points is excellent.

Fig. 1. Supersaturation pressure p_{ss} versus crushing pressure p_{crush} for isopleths of constant bubble number N = 0.1, 1, 10, 30, 100, and 200. Dashed curves are predictions of the surfactant nucleation model (from Yount, Yeung, and Ingle 1979).

In Fig. 2, the predictions of the surfactant model are compared with a compilation of decompression data for humans (Yount 1979b). Although the available data for humans are highly variable, the similarity between these results and the bubble counts in Fig. 1 is


SATURATION TIME
= 5.25 HOURS
$p_m = p_s$
p_f
p_o
p_{AMB}
$p_{CRUSH} = p_m - p_o$
$p_{ss} = p_s - p_f$
TIME
N = 200
N = 100
N = 30
N = 10
N = 1.0
N = 0.1
$p_{ss} = p_{CRUSH} + p_o$
$p_{ss} = p_{CRUSH}$
N=200
N=100
N=30
N=10
N=1.0
N=0.1
$(p^* - p_o)$
SUPERSATURATION PRESSURE $p_{ss} = (p_s - p_f)$ IN ATM
CRUSHING PRESSURE $p_{CRUSH} = p_m - p_o$ IN ATM
0
5
10
15
20

Yount 1

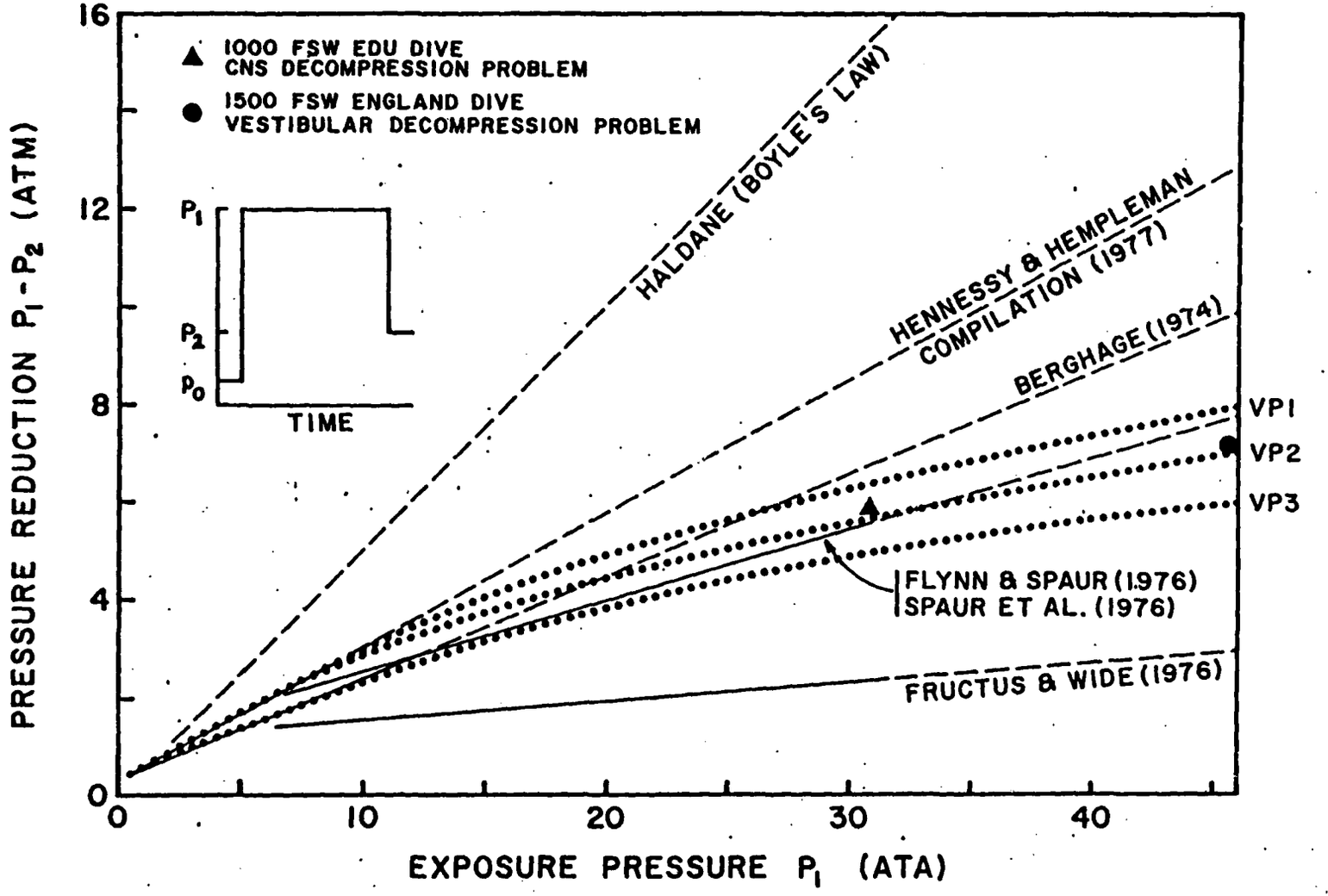
remarkable. Again, the qualitative features of the model are confirmed.

Fig. 2. Pressure reduction limits for humans. Below $P_1 = 10$ ATA, the available data can be summarized by the straight line $P_1 = 1.407\ P_2 + 0.50$ ATA, derived from the compilation of Hennessy and Hempleman (1977). At higher pressures, the data fall well below this line and are better described by surfactant nucleation model calculations, such as VP2 (from Yount 1979b).

The fundamental hypothesis that lines of constant effective dose ED are also lines of constant bubble number N has been subjected to a direct test by Watt and Lin (1979), who used a perivascular Doppler probe to detect gas emboli in the rat posterior vena cava caudad to the renal veins. Their results are plotted in Fig. 3 along with the ED-50 points for rats exposed to 6, 12, and 18 atm abs by Berghage, Gomez, Roa, and Everson (1976). As expected, the subsymptomatic line for $N \sim 1$ measured by Watt and Lin (1979) lies just below the ED-50 pressure reductions of Berghage and his co-workers (1976). Furthermore, both data sets agree very well with surfactant model predictions (solid lines). Finally, it should be noted that the Doppler bubble-detection thresholds determined by Watt and Lin (1979) for a second dive performed 24 - 96 hours after the first exposure are significantly higher than those obtained on the first dive. We believe that acclimation of this type results from a depletion of the reservoir of gas nuclei on previous exposures.

It is evident from the data in Figs. 1, 2, and 3 that the degree of supersaturation required to produce a given bubble number, effective dose, or level of incidence is a strong function of the initial compression P_{crush} or the exposure P_1. This observation is particularly relevant to multiple inert-gas bubble disease since inert gas manipulation permits a state of supersaturation to be induced isobarically, i.e., without compression or decompression. Thus, whereas all of the data points in Figs. 1, 2, and 3 lie in the pressure region

$$P_{ss} \leq P_{crush} \tag{3a}$$


1000 FSW EDU DIVE
CNS DECOMPRESSION PROBLEM
1500 FSW ENGLAND DIVE
VESTIBULAR DECOMPRESSION PROBLEM
P1
P2
P0
TIME
HALDANE (BOYLE'S LAW)
HENNESSY & HEMPLEMAN COMPILATION (1977)
BERGHAGE (1974)
VP1
VP2
VP3
FLYNN & SPAUR (1976)
SPAUR ET AL. (1976)
FRUCTUS & WIDE (1976)
PRESSURE REDUCTION P1 - P2 (ATM)
EXPOSURE PRESSURE P1 (ATA)
0
4
8
12
16
0
10
20
30
40

Yount 2

Fig. 3. Pressure reduction thresholds for bubble formation in rats. This comparison of the effective dose data of Berghage, Gomez, Roa, and Everson (1976) with the Doppler bubble detection data of Watt and Lin (1978) suggests that lines of constant effective dose ED are also lines of constant bubble number N, as has been assumed in applying the surfactant nucleation model to exogenous gas bubble disease in rats and humans (from Young 1978).

data obtained isobarically may extend into a different pressure region

$$P_{ss} > P_{crush} \tag{3b}$$

where

$$P_{ss} = (\tau - P_{amb})_{max} \tag{4}$$

is the maximum supersaturation where

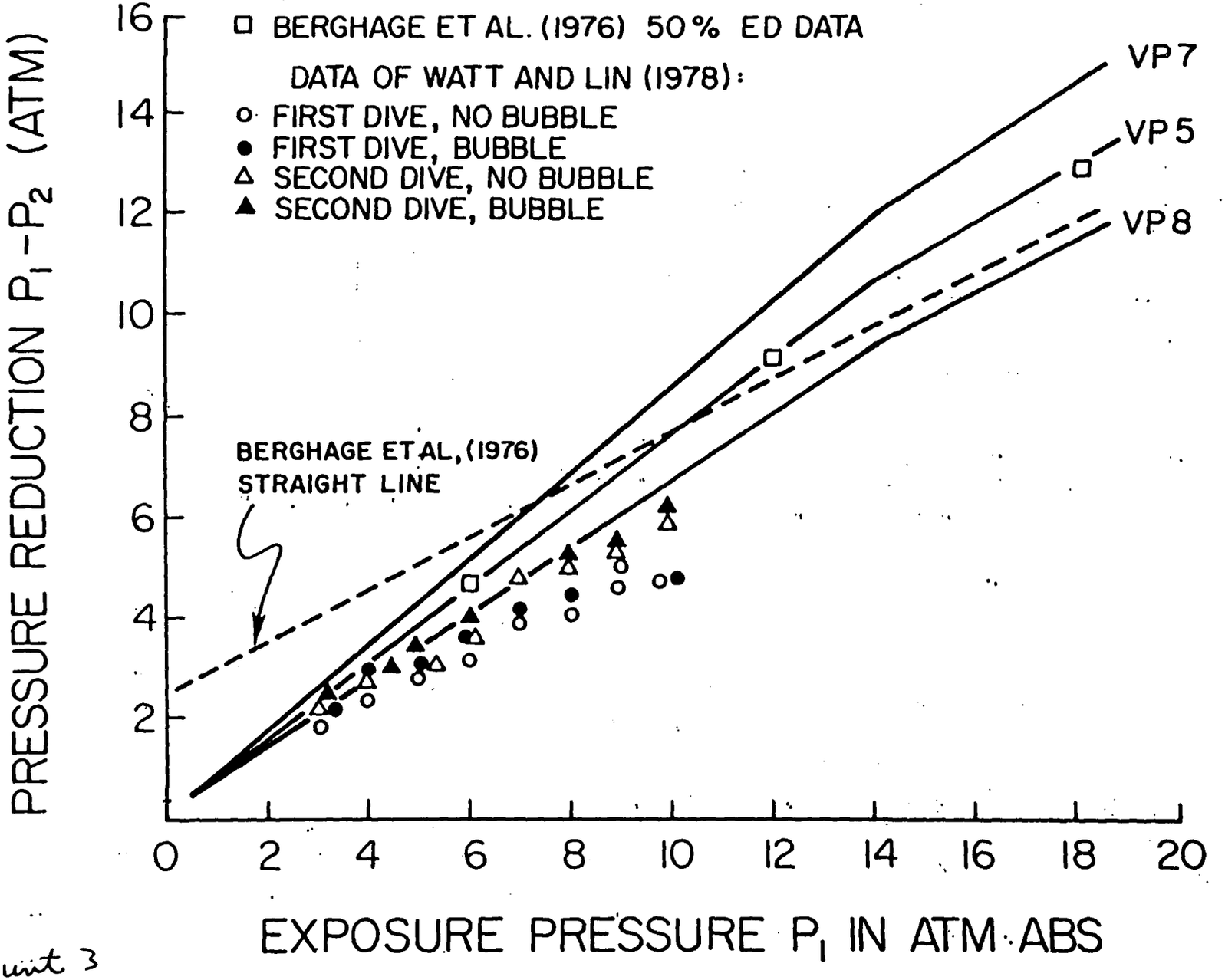
$$P_{crush} = (P_{amb} - \tau)_{max} \tag{5}$$

is the maximum over pressure or crushing pressure, and where τ is the dissolved gas tension and P_{amb} the ambient static pressure.

The pressure region defined by Eq. 3b can also be reached by exposure to high altitude or by using slow compressions or stepped compressions which permit a significant rise in the dissolved gas tension τ while the ambient pressure P_{amb} is still increasing. For the schedule shown in Fig. 4, the supersaturation is given by

$$P_{ss} = P_s - P_f \tag{6}$$

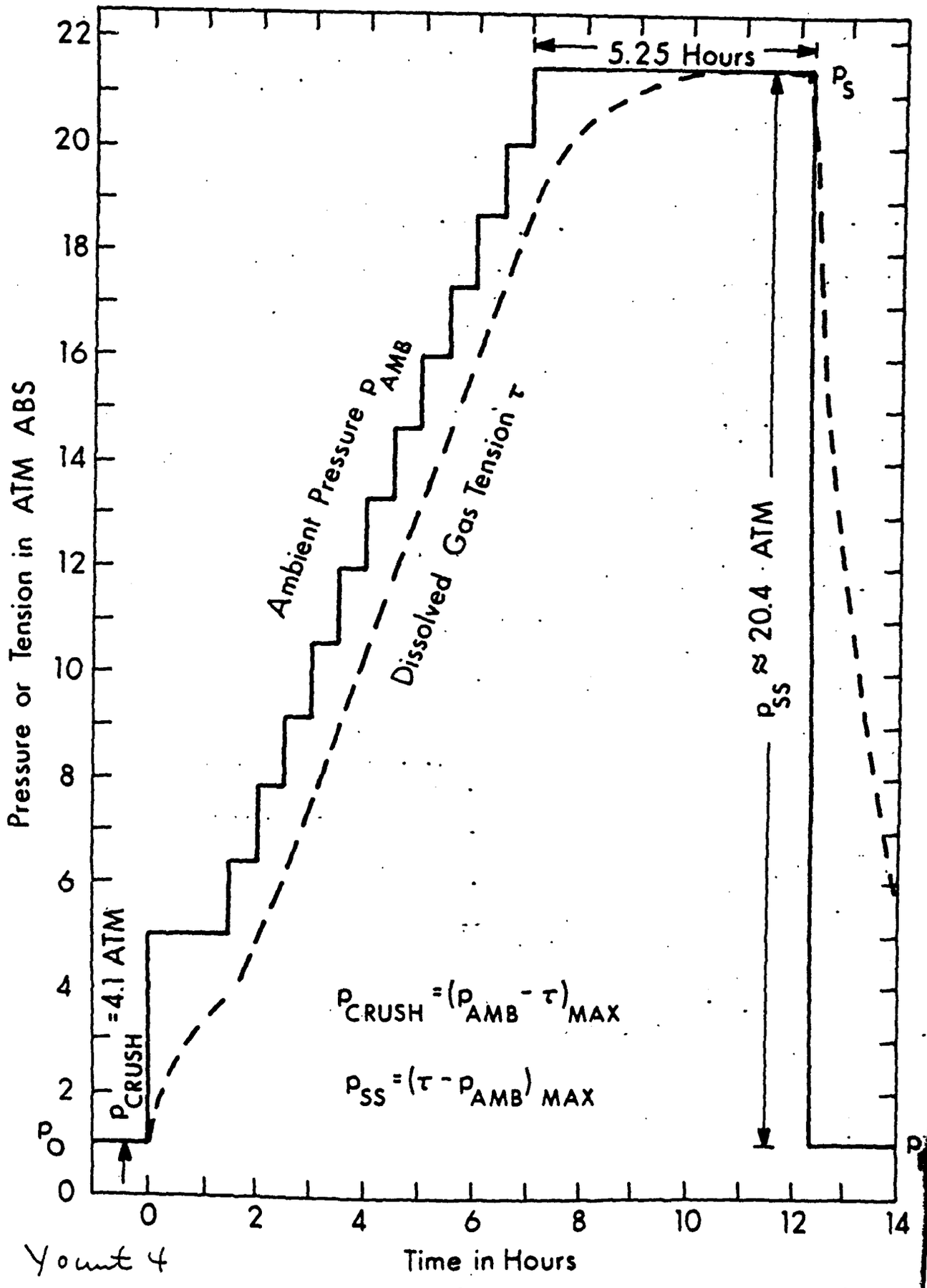
where P_s is the saturation or equilibration pressure and P_f is the final pressure at which the observations are made. By design, the maximum overpressure P_{crush} occurs on the first step and is simply the magnitude of the initial compression.


BERGHAGE ET AL. (1976) 50% ED DATA
DATA OF WATT AND LIN (1978):
FIRST DIVE, NO BUBBLE
FIRST DIVE, BUBBLE
SECOND DIVE, NO BUBBLE
SECOND DIVE, BUBBLE
VP7
VP5
VP8
BERGHAGE ET AL, (1976)
STRAIGHT LINE
PRESSURE REDUCTION P_1-P_2 (ATM)
EXPOSURE PRESSURE P_1 IN ATM·ABS
0
2
4
6
8
10
12
14
16
18
20

Yo unit 3

Fig. 4. Pressure schedules used to investigate bubble formation in the region $p_{ss} > p_{crush}$. The definitions of p_{ss} and p_{crush} are symmetric in that p_{ss} given by Eq. 4 is the maximum supersaturation while p_{crush} in Eq. 5 is the maximum overpressure or crushing pressure. For this schedule, the maximum overpressure is achieved on the first step and is 4.1 atm. The maximum supersaturation is 20.4 atm (from experiments by Yount and Yeung).

Our interest in the variables p_{ss} and p_{crush} is due in part to the experimental observation (Yount and Strauss 1976) that bubble counts in gelatin depend only upon these pressure differences and not upon the absolute pressures per se. Furthermore, since p_{crush} is determined in a stepped compression by that increment which has the largest overpressure, any other increments, whether they precede or follow the largest, will have no effect. These generalizations are confirmed by the gelatin results plotted in Fig. 5, which were obtained with a class of pressure schedules analogous to that shown in Fig. 4. The measured points extend well into the region defined by Eq. 3b, and over much of this region, the dashed lines calculated from nucleation theory (Yount 1979a) give an accurate description of the data. Satisfactory agreement with the aberrant points at large p_{ss} and at large p_{crush} can be obtained by taking into account the thickness of the nuclear skins.

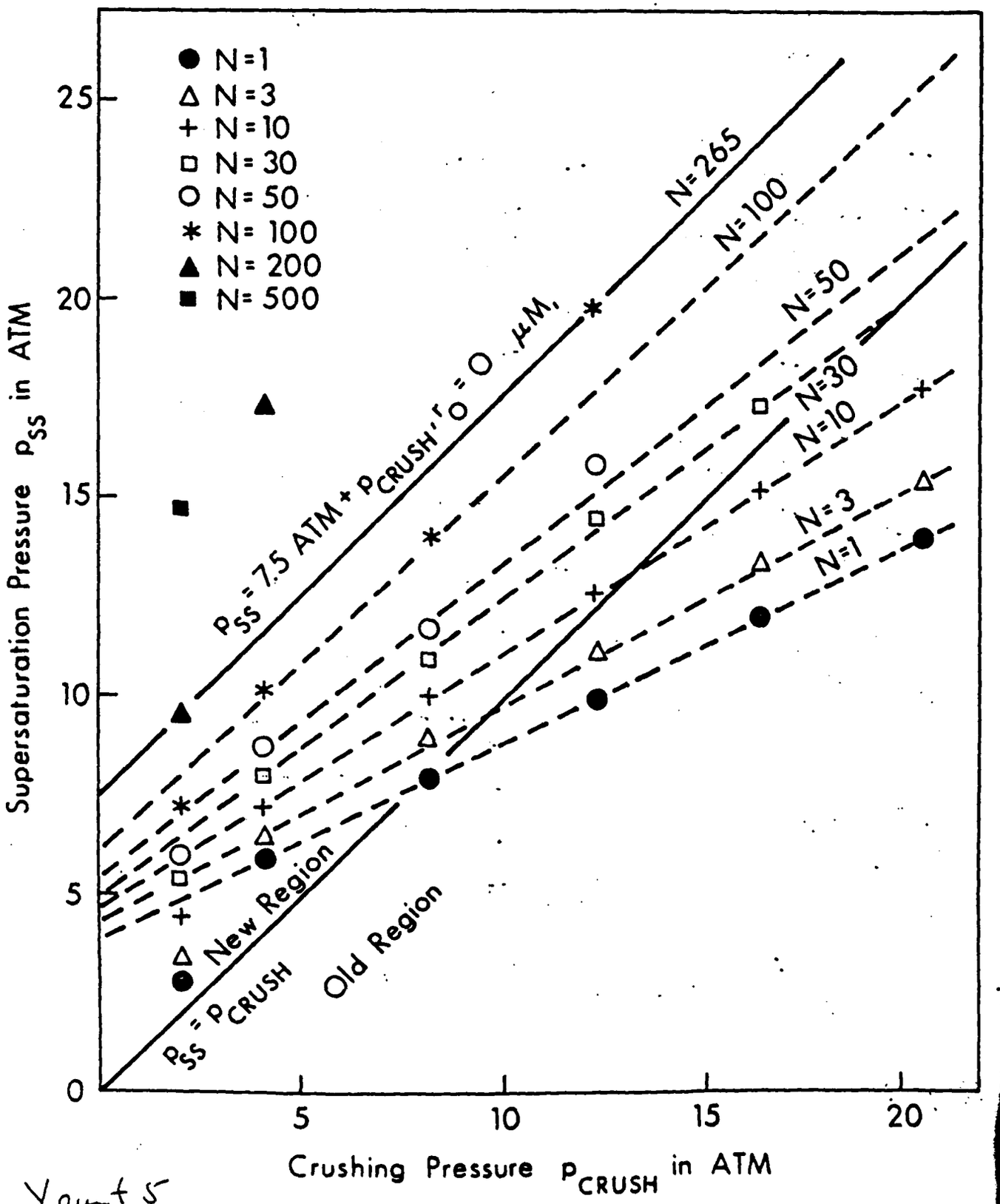

5.25 Hours
P_S
Ambient Pressure P_{AMB}
Dissolved Gas Tension τ
$P_{SS} \approx 20.4$ ATM
$P_{CRUSH} = 4.1$ ATM
$P_{CRUSH} = (P_{AMB} - \tau)_{MAX}$
$P_{SS} = (\tau - P_{AMB})_{MAX}$
P_O
P_F
Pressure or Tension in ATM ABS
Time in Hours
0
2
4
6
8
10
12
14
16
18
20
22

Yount 4

Fig. 5. Supersaturation pressure p_{ss} versus crushing pressure p_{crush} for constant bubble numbers $\hat{N}$ = 1, 3, 10, 30, 50, 100, 200, and 500. These data demonstrate that the region $p_{ss} > p_{crush}$ is physically meaningful and accessible to experiment through the use of stepped compressions such as that shown in Fig. 4. Over much of the new region, dashed lines calculated from the surfactant nucleation model continue to give an accurate description of the data (from experiments by Yount and Yeung).

Fig. 6 is the dive profile used by Lambertsen and Idicula (1975) and their associates to investigate the effects of various respired gas mixtures at ambient helium-oxygen pressures up to 1200 fsw. Clearly this is a stepped compression. Furthermore, the steps at 400, 700, and 900 fsw are of sufficient duration to permit equilibration of the gas tension τ with the ambient pressure p_{amb}. It follows that p_{crush} for this profile is 400 fsw, rather than 1200 fsw, and hence (from Fig. 2) the allowed supersaturation is only about half of that which would be permitted after a continuous rapid compression to 1200 fsw. It is also important to point out that in a dive of such long duration, the prophylactic benefits of a large initial compression may be significantly attenuated by the in vivo regeneration of gas nuclei during exposure.

The prediction that the supersaturation tolerance of a subject should depend strongly upon compression rate as well as compression magnitude follows directly from nucleation theory and cannot be derived from conventional analyses of inert-gas exchange. The relevance of nucleation theory to the etiology of gas bubble lesions in the skin and in other tissues exposed to the ambient gas mixture during chamber dives is even more profound. The time required for such tissues to equilibrate with the external gas may be very short. The gas tension τ would then follow closely the ambient pressure p_{amb}, so that the overpressure p_{crush} would be small--even during a continuous compression. Exposed


N=1
N=3
N=10
N=30
N=50
N=100
N=200
N=500
N=265
N=100
N=50
N=30
N=10
N=3
N=1
$P_{SS} = 7.5\ ATM + P_{CRUSH}$, $r_o = 0\ \mu M$,
$P_{SS} = P_{CRUSH}$
New Region
Old Region
Supersaturation Pressure P_{SS} in ATM
Crushing Pressure P_{CRUSH} in ATM
0
5
10
15
20
25

Yount 5

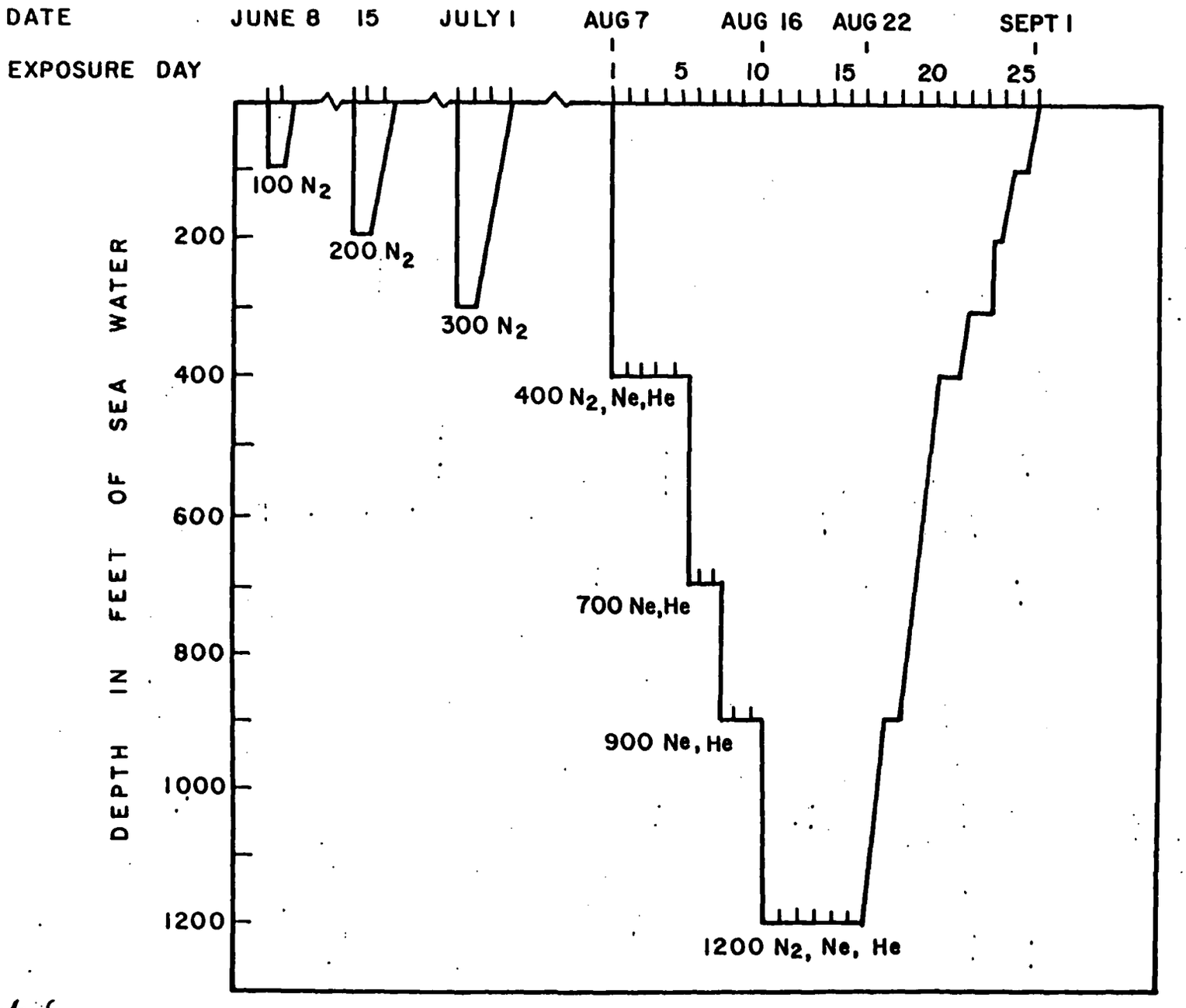
Fig. 6. Dive profile used by Lambertsen and Idicula (1975) to investigate the effects of various respired gas mixtures at ambient helium-oxygen pressures up to 1200 fsw. The value of p_{crush} for this profile is 400 fsw, rather than 1200 fsw, and hence (from Fig. 2) the allowed supersaturation is only about half of that which would be permitted after a continuous rapid compression to 1200 fsw.

tissues would then have a much lower supersaturation tolerance than deeper tissues with a longer time constant for gas uptake. This would not be a serious problem during decompression at rates slow enough to permit dissolved gas to exit the faster tissues. However, large supersaturation pressures can be achieved and maintained in exposed tissues via the isobaric mechanisms reviewed in the next section. The combination of large supersaturations and small tolerances would make the skin and other exposed tissues particularly vulnerable to multiple inert-gas bubble disease.

Multiple Inert-Gas Supersaturation Theory

1. Deep-tissue or whole-body supersaturation

In 1959, Hannes Keller pointed out the theoretical advantages of a shift from helium to nitrogen during decompression (Tepper, Lightfoot, Baz, and Lanphier 1979). The basic idea is illustrated by the rudimentary example shown in Fig. 7 (Yount 1978). Only one tissue compartment is involved, and the tissue half-times for two different inert gases in this compartment are 20 minutes and 40 minutes, respectively. No other gases or vapors are present. The compartment is subjected to a pressure of 4 atm abs for a period of 80 minutes. The faster gas (Fig. 7a) requires a 27-minute decompression, and the slower gas (Fig. 7b) requires a 29-minute decompression. By switching from the faster gas to the slower gas at the midpoint of the exposure (Fig. 7c), the decompression obligation is reduced to zero. In a practical diving table based on this idea (Keller and Buehlmann 1965), the time to decompress from a 120-minute exposure to 130 fsw was 15 minutes. Without inert-gas


DATE
JUNE 8
15
JULY 1
AUG 7
AUG 16
AUG 22
SEPT 1
EXPOSURE DAY
1
5
10
15
20
25
DEPTH IN FEET OF SEA WATER
200
400
600
800
1000
1200
100 N2
200 N2
300 N2
400 N2, Ne, He
700 Ne, He
900 Ne, He
1200 N2, Ne, He

Yount 6

Fig. 7. Illustration of how inert gas switching can be used to gain a decompression advantage. The faster gas (a) requires a 27-minute decompression, and the slower gas (b) requires a 29-minute decompression. By switching from the faster gas to the slower gas at the midpoint of the exposure (c), the decompression obligation is reduced to zero (from Yount 1978).

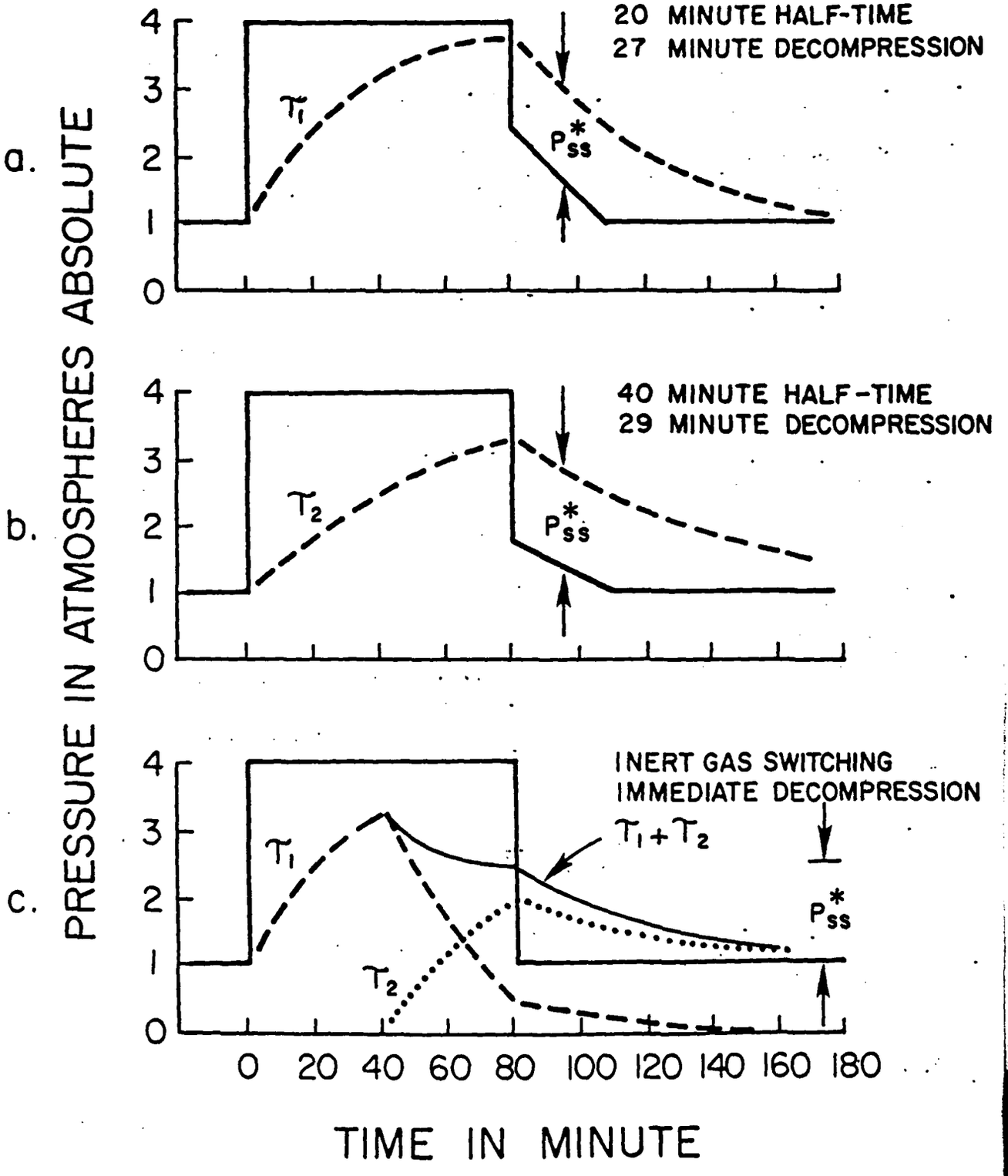
switching, 210 minutes would have been required.

The ratio of the tissue half-times between nitrogen and helium is assumed by Keller and Buehlmann (1965) to be 2.65. For a diffusion-limited system, this result can be derived from Fick's law

$$\dot{q} = ADS(\Delta p/\Delta x) \qquad (7)$$

where $\dot{q}$ is the flux or the diffusion rate for a gas with diffusion coefficient D and solubility S in the barrier material. The area of the barrier is A, its thickness is Δx, and the pressure drop across the barrier is Δp. The ratio $\Delta p/\Delta x$ is referred to as the pressure gradient.

Since the diffusion coefficient D is inversely proportional to the square root of the molecular weight of the gas, the flux ($\dot{q}$) is proportional to the solubility and inversely proportional to the square root of the molecular weight. Similarly, the rate at which a material saturates is proportional to $\dot{q}/S$, the rate at which gas enters divided by the quantity of gas that the material can contain. Assuming that the solubilities for the barrier and for the material being saturated are the same, then the "saturation speed" is independent of the solubility and inversely proportional to the square root of the molecular weight. The ratio of the "solubility speeds" for N_2 and He is


a.
20 MINUTE HALF-TIME
27 MINUTE DECOMPRESSION
T_1
P^*_{ss}
b.
40 MINUTE HALF-TIME
29 MINUTE DECOMPRESSION
T_2
P^*_{ss}
c.
INERT GAS SWITCHING
IMMEDIATE DECOMPRESSION
$T_1 + T_2$
T_1
T_2
P^*_{ss}
PRESSURE IN ATMOSPHERES ABSOLUTE
0 1 2 3 4
0 20 40 60 80 100 120 140 160 180
TIME IN MINUTE

Yount 7

$$(4/28)^{\frac{1}{2}} = 1/2.65 \qquad (8a)$$

and the ratio of tissue half-times is

$$(28/4)^{\frac{1}{2}} = 2.65/1 \qquad (8b)$$

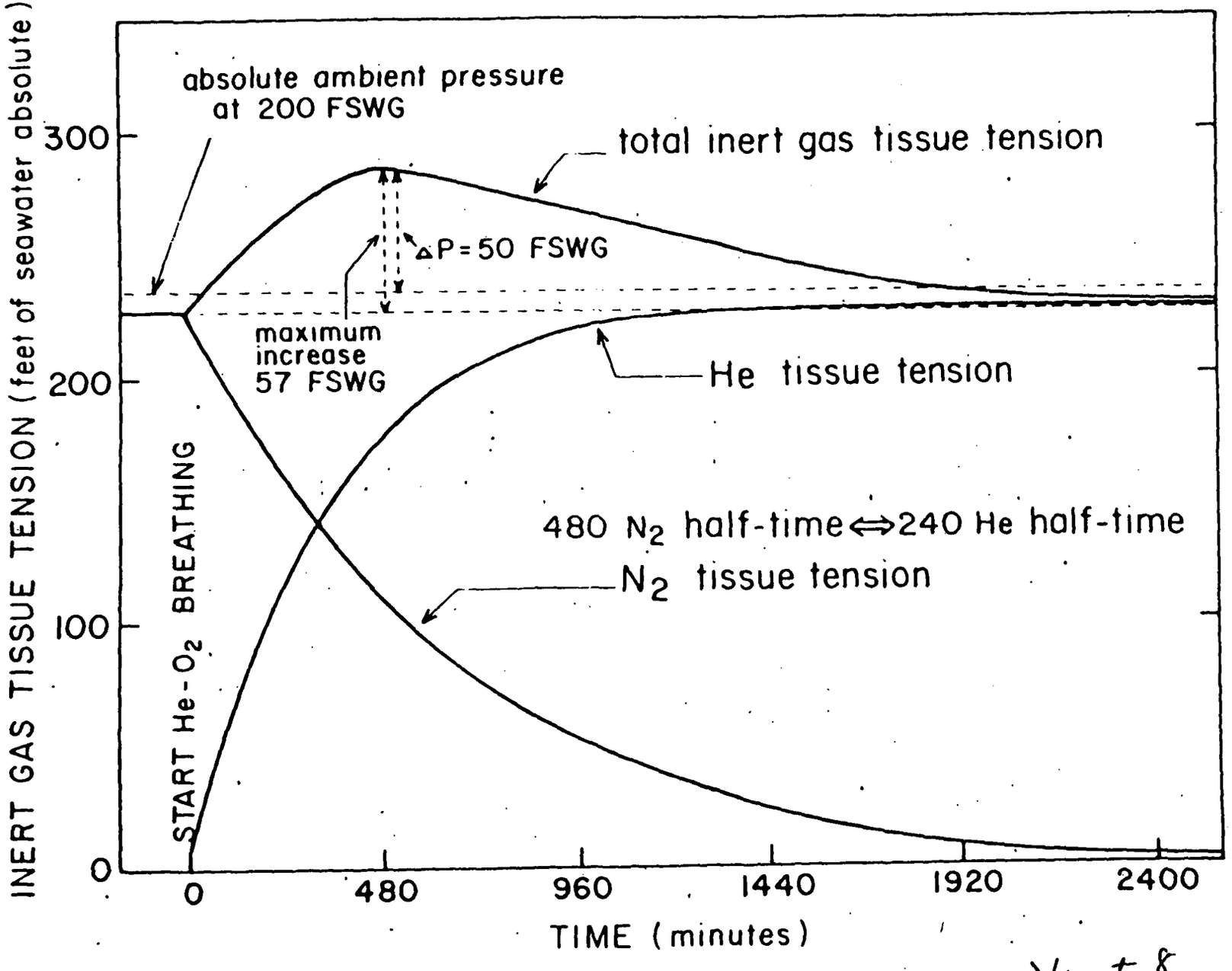
Keller and Buehlmann (1965) postulate that the system is diffusion-limited by the rate for inert-gas exchange of blood in the lungs. In this case, the ratio of half-times for nitrogen and helium would be applicable to the whole body, i.e., to all tissue compartments. These authors also state, "it is possible to obtain a desaturation of the body with a switch of gases without any change in pressure." This phenomenon, which we might now call "isobaric counterdiffusion desaturation," is evident in Fig. 7c, where a decrease in the total dissolved tension $\tau_1 + \tau_2$ begins half way through the exposure at the moment the two inert gases are switched.

Of course, if isobaric counterdiffusion desaturation can be achieved by a judicious manipulation of inert gases, then isobaric counterdiffusion supersaturation can be produced by a simple reversal. This possibility is illustrated in Fig. 8 (Lambertsen and Idicula 1975) for hypothetical half-times of 240 minutes for helium uptake and 480 minutes for nitrogen elimination. The ambient pressure is constant at 200 fswg, yet the dissolved gas tension increases by as much as 57 fswg. Assuming an oxygen window of about 7 fswg, the net supersaturation is 50 fswg.

Fig. 8. Illustration of how inert gas switching can be used to achieve a state of supersaturation by isobaric counterdiffusion (from Lambertsen and Idicula 1975).

To determine whether the supersaturation achieved in Fig. 8 would produce symptoms of multiple inert-gas bubble disease, we refer again to Fig. 2 (Yount 1979b) and particularly to the compilation of Hennessy and Hempleman (1977):

$$P_1 = 1.407\ P_2 + 0.50 \text{ atm abs} \qquad (9a)$$


absolute ambient pressure
at 200 FSWG
total inert gas tissue tension
ΔP = 50 FSWG
maximum
increase
57 FSWG
He tissue tension
480 N2 half-time ⇔ 240 He half-time
N2 tissue tension
START He-O2 BREATHING
INERT GAS TISSUE TENSION (feet of seawater absolute)
300
200
100
0
0
480
960
1440
1920
2400
TIME (minutes)

Yount 8

$$P_1 - P_2 = 0.289\ P_1 + 0.36\ \text{atm} \qquad (9b)$$

For an exposure of 200 fswg = 7.06 atm abs, the allowed pressure reduction is 2.40 atm = 79 fswg. This exceeds the supersaturation obtained in Fig. 8, and hence deep-tissue symptoms would not be expected. Cutaneous gas bubble lesions are entirely possible, however, if this level of supersaturation is present in the skin during a chamber dive to 200 fswg. (Recall the discussion in the last paragraph of the section on nucleation theory.)

The phenomenon of isobaric bubble growth *in vivo* has been simulated by Van Liew and Passke (1967), who measured the rate of diffusion into and out of subcutaneous gas pockets on the backs of rats. When the pockets were filled initially with SF_6, a volume increase of a factor of two was observed after four days' exposure to an air environment. Bubble growth and bubble shrinkage via isobaric counterdiffusion *in vitro* were observed by Strauss and Kunkle (1974), who subjected gelatin samples to nitrogen-helium and helium-nitrogen switching, respectively. Strauss and Kunkle (1974) concluded that switching from nitrogen to helium during the treatment of decompression sickness would make the disease worse rather than better.

Perhaps the most remarkable demonstration of deep-tissue or whole-body supersaturation is that reported by D'Aoust, Smith, Swanson, White, Harvey, Hunter, Neuman, and Goad (1977). These authors used Doppler ultrasonic techniques to detect gas bubbles in the posterior vena cava of goats that were switched from a nitrogen-oxygen to a helium-oxygen environment at various constant pressures. The data which they obtained at 7 atm abs are shown in Fig. 9. A detailed discussion of these same results in terms of nucleation theory has been given by Yount (1978). Particularly noteworthy are the early onset and long persistence of bubble signals, which reflect not only the deep-tissue time constants, but also the broad size distribution of gas nuclei *in vivo*. In effect, the rising supersaturation sweeps through the nuclear field, probing to smaller and smaller radii.

2. Isobaric counterdiffusion through a lipid-aqueous bilayer

Graves, Idicula, Lambertsen, and Quinn (1973) have pointed out that isobaric supersaturation can be achieved via counterdiffusion of two disparate gases through a liquid-aqueous bilayer. Applying Fick's law to the steady-state configuration shown in Fig. 10, we obtain

$$\dot{q} = AD_f S_f (P_1 - P_A)/\Delta x_f = AD_a S_a (P_A - P_2)/\Delta x_a \qquad (10a)$$

for the gas diffusing to the right and

$$\dot{q} = AD'_a S'_a (P_1 - P_B)\Delta x_a = AD'_f S'_f (P_B - P_2)/\Delta x_f \qquad (10b)$$

for the gas diffusing to the left. Solving for P_A and P_B, we find a net supersaturation at the lipid-aqueous interface of

Fig. 9. Doppler bubble counts versus time after inert gas switching from nitrogen to helium in goats at 7 atm abs. Primary bubbles are recruited only while the local supersaturation is rising. In effect, the rising supersaturation sweeps through the nuclear field, probing to smaller and smaller radii. Once formed, however, primary bubbles *in situ* can serve as generators of secondary cavities via tissue cleavage and free-gas migration, a process which continues until the supersaturation is relieved (from D'Aoust, Smith, Swanson, White, Harvey, Hunter, Neuman, and Goad 1977).

$$(P_A + P_B) - (P_1 + P_2) = \frac{(\Delta x_a \Delta x_f)(P_1 - P_2)(D_f S_f D'_a S'_a - D_a S_a D'_f S'_f)}{(D_a S_a \Delta x_f + D_f S_f \Delta x_a)(D'_a S'_a \Delta x_f + D'_f S'_f \Delta x_a)} \quad (11)$$

Since P_1 is greater than P_2, the criterion for supersaturation by this mechanism is (Graves, Idicula, Lambertsen, and Quinn 1973)

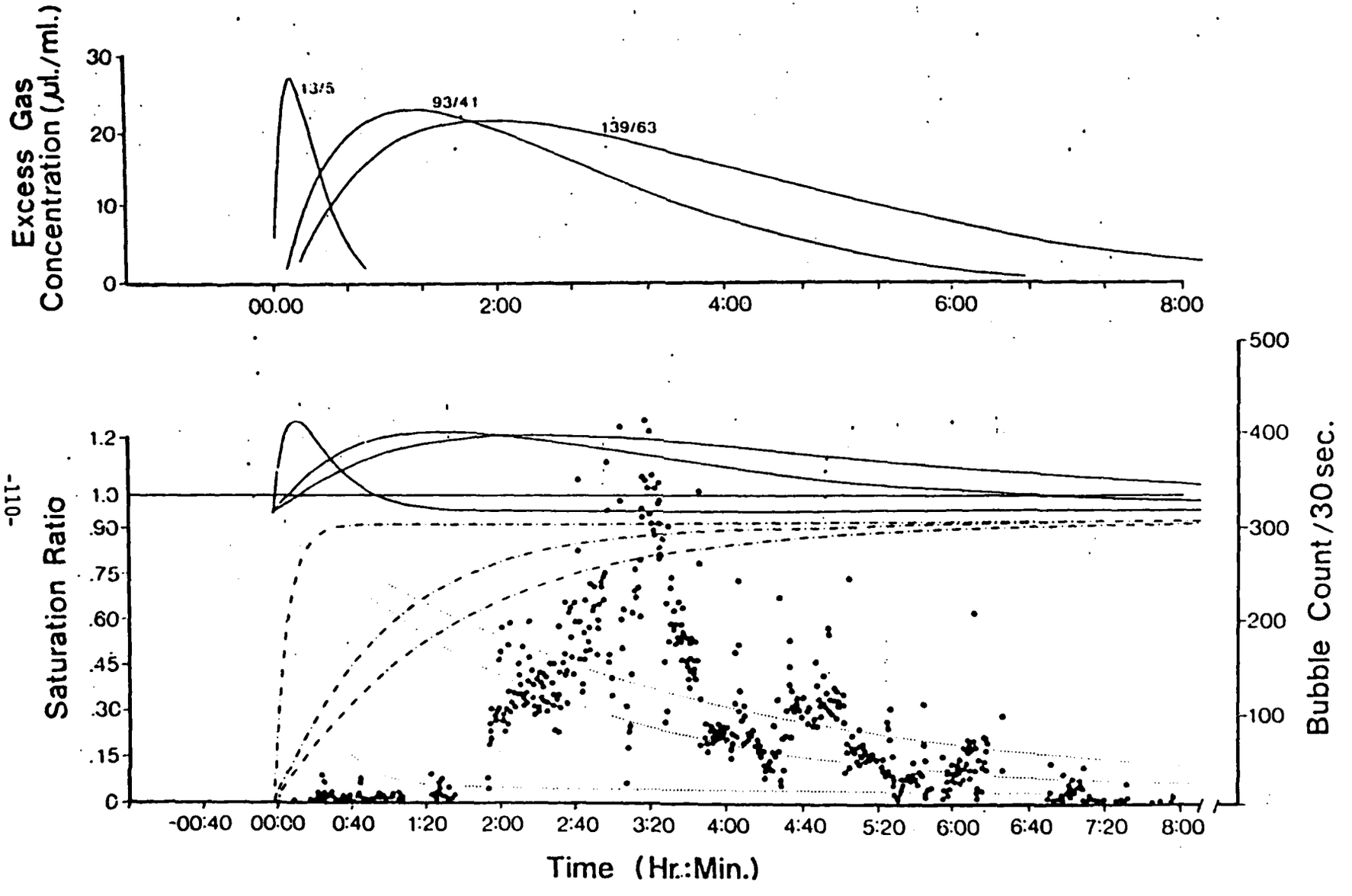
$$D_f S_f D'_a S'_a > D_a S_a D'_f S'_f \quad (12)$$

The maximum supersaturation is achieved when the layer thickness are in the ratio (Graves, Idicula, Lambertsen, and Quinn 1973)

$$(\Delta x_a / \Delta x_f) = (D_a S_a D'_a S'_a / D_f S_f D'_f S'_f)^{\frac{1}{2}} \quad (13)$$

The degree of supersaturation that can be achieved by this mechanism approaches 30% of the absolute pressure (Graves, Idicula, Lambertsen, and Quinn 1973). This would exceed the deep-tissue pressure reduction tolerances shown in Fig. 2 at exposure above 5-10 atm abs, and it could result in cutaneous gas bubble lesions at even lower pressures. (Again recall the discussion in the last paragraph of the section on nucleation theory.)

An investigation of the kinetics of isobaric counterdiffusion at a lipid-aqueous bilayer has been carried out by Karreman and Lambertsen


Excess Gas Concentration (µl./ml.)
30
20
10
0
13/5
93/41
139/63
00.00
2:00
4:00
6:00
8:00
Saturation Ratio
1.2
1.0
.90
.75
.60
.45
.30
.15
0
500
400
300
200
100
Bubble Count/30 sec.
-00:40
00:00
0:40
1:20
2:00
2:40
3:20
4:00
4:40
5:20
6:00
6:40
7:20
8:00
Time (Hr.:Min.)

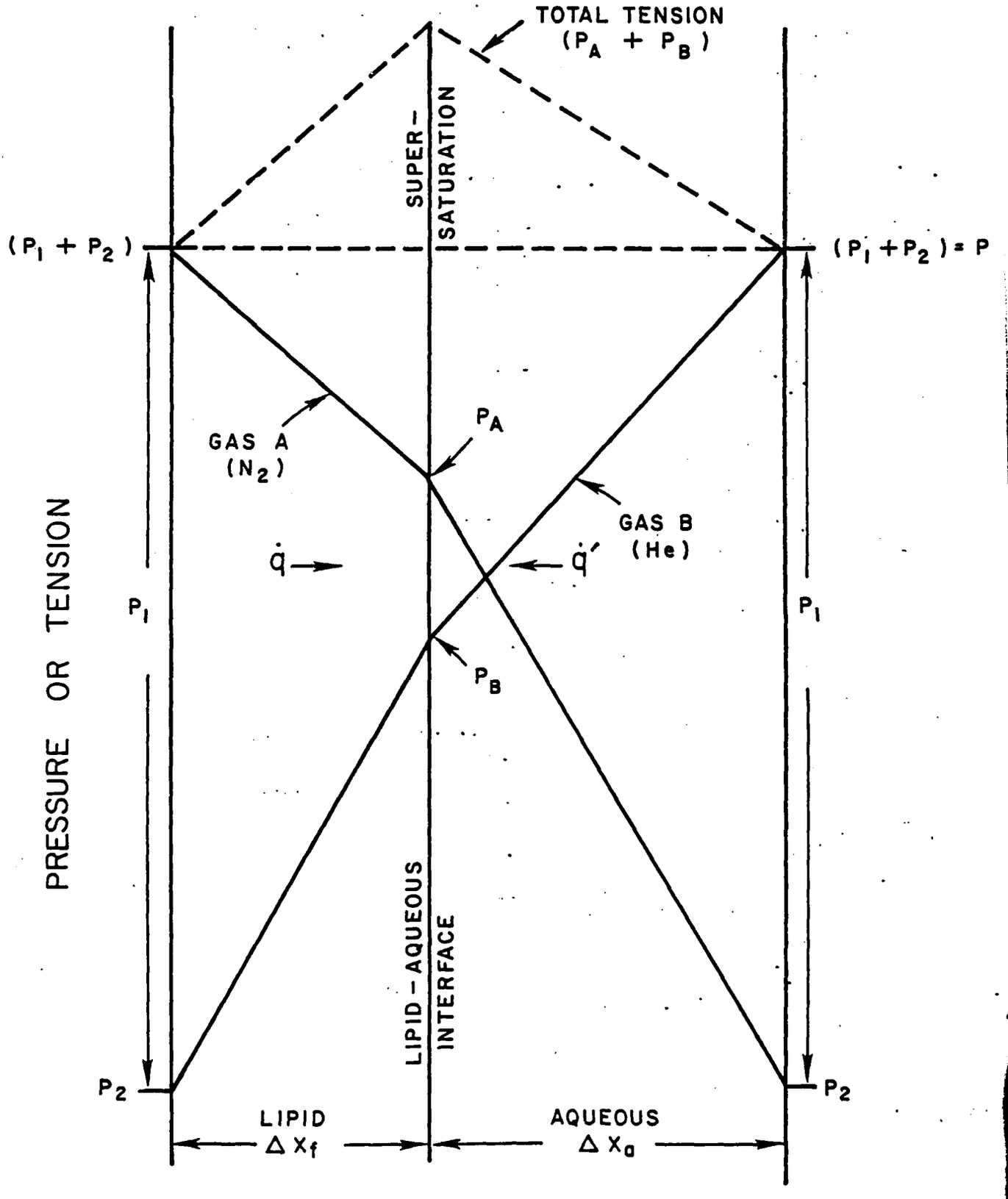
Yount 9

Fig. 10. Isobaric supersaturation via counterdiffusion of two disparate gases through a lipid-aqueous bilayer (Graves, Idicula Lambertsen, and Quinn 1973). For Gas A (N_2) diffusing to the right, the pressure gradients are $(P_1 - P_A)/\Delta x_f$ and $(P_A - P_2)/\Delta x_a$. For Gas B (He) diffusing to the left, the pressure gradients are $(P_1 - P_B)\Delta x_a$ and $(P_B - P_2)/\Delta x_f$. The total dissolved tension $(P_A + P_B)$ exceeds the ambient pressure $(P_1 + P_2)$ throughout the bilayer, reaching a maximum at the lipid-aqueous interface.

(1977) using the approximation of Landahl (1953) that assumes the advancing diffusion front is linear. This idea is illustrated in Fig. 11. Karreman and Lambertsen (1977) found that for helium diffusing against nitrogen, the time required to reach a steady state is in the range 0.01 to 12.4 sec. The layer thicknesses assumed by these authors varied from 5 to 160 μm, where the first value may approximate the diameter of a capillary while the second is an estimate of the distance from a skin capillary through the dermis to the surrounding atmosphere. This circulation suggests not only that the steady state approximation of Graves, Idicula, Lambertsen, and Quinn (1973) is valid, but also that the dissolved gas tension in the skin would follow the ambient pressure rather closely--even during rapid compressions. Thus P_{crush} could indeed be small for certain peripheral tissues, as conjectured in the last paragraph of the section on nucleation theory.

3. Isobaric counterperfusion

Supersaturation via isobaric counterperfusion is depicted in Fig. 12 (Hills 1977). The more diffusible gas, Gas I, is adjacent to the barrier at ambient pressure on the left, while the blood on the opposite side of the barrier is initially saturated with the less diffusible gas, Gas II. The tension of Gas I in the mixed venous blood is P_1 and the


TOTAL TENSION
$(P_A + P_B)$
SUPER-
SATURATION
$(P_1 + P_2)$
$(P_1 + P_2) = P$
GAS A
(N_2)
P_A
GAS B
(He)
$\dot{q}$
$\dot{q}'$
P_1
P_1
P_B
PRESSURE OR TENSION
LIPID - AQUEOUS
INTERFACE
P_2
P_2
LIPID
ΔX_f
AQUEOUS
ΔX_a

Yount 10

Fig. 11. Kinetics of isobaric counterdiffusion at a lipid-aqueous bilayer. In the approximation of Landahl (1953), as applied by Karreman and Lambertsen (1977), the advancing diffusion front is assumed to be linear in a given medium. For layer thicknesses in the range from 5 to 160 μm, the time to reach a steady state varies from 0.01 to 12.4 sec.

tension of Gas II in the mixed venous blood is P_2. The tension P_2 is less than the ambient pressure P because some of the gas originally in the blood has diffused out.

In the steady-state configuration shown in Fig. 12, Fick's law gives

$$\dot{q}_1 = AD_1S_1(P - P_1)/x = \dot{Q}S_1^{\prime}P_1 \tag{14a}$$

for the gas diffusing to the right and

$$q_2 = AD_2S_2P_2/x = \dot{Q}S_2^{\prime}(P - P_2) \tag{14b}$$

for the gas diffusing to the left. Solving for P_1 and P_2, we find a net supersaturation at the interface between the diffusion barrier and the perfusion zone of (Hills 1977)

$$P_1 + P_2 - P = \alpha P(\beta_1 - \beta_2)/(1 + \alpha\beta_1)(1 + \alpha\beta_2) \tag{15}$$

where $\alpha = A/x\dot{Q}$, $\beta_1 = D_1S_1/S_1^{\prime}$, and $\beta_2 = D_2S_2/S_2^{\prime}$

Yount II

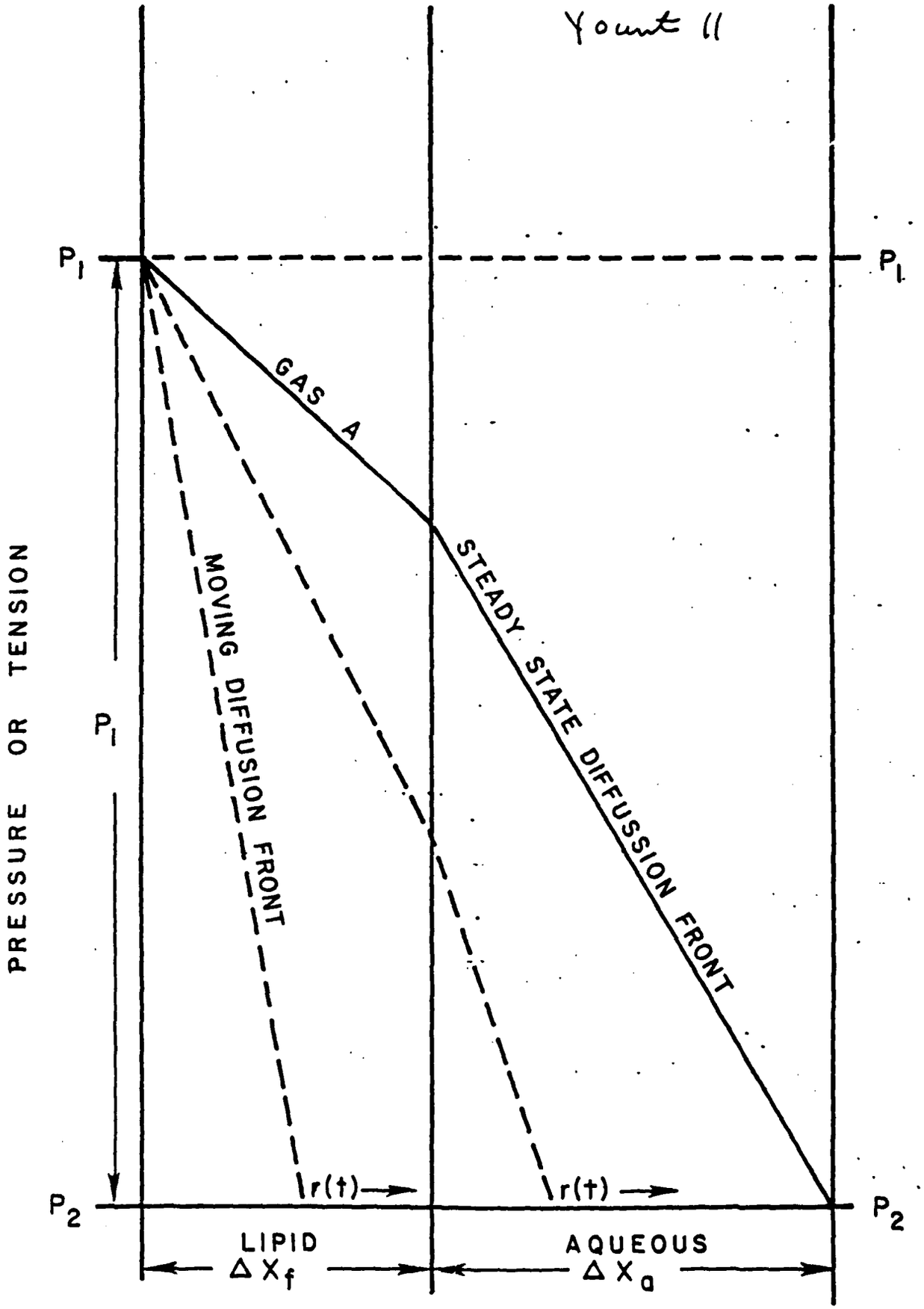

P1
P1
GAS A
STEADY STATE DIFFUSSION FRONT
MOVING DIFFUSION FRONT
PRESSURE OR TENSION
P1
r(t)
r(t)
P2
P2
LIPID
ΔXf
AQUEOUS
ΔXa

Fig. 12. Isobaric supersaturation via counterperfusion (Hills 1977). The more diffusible gas (I) is adjacent to the diffusion barrier at ambient pressure P. The less diffusible gas (II) is carried into the perfusion zone dissolved in the arterial blood at the same initial pressure. This configuration results in a steady-state supersaturation, not only of the perfusion zone, but also of the adjacent diffusion barrier.

The criterion for supersaturation via isobaric counterperfusion is

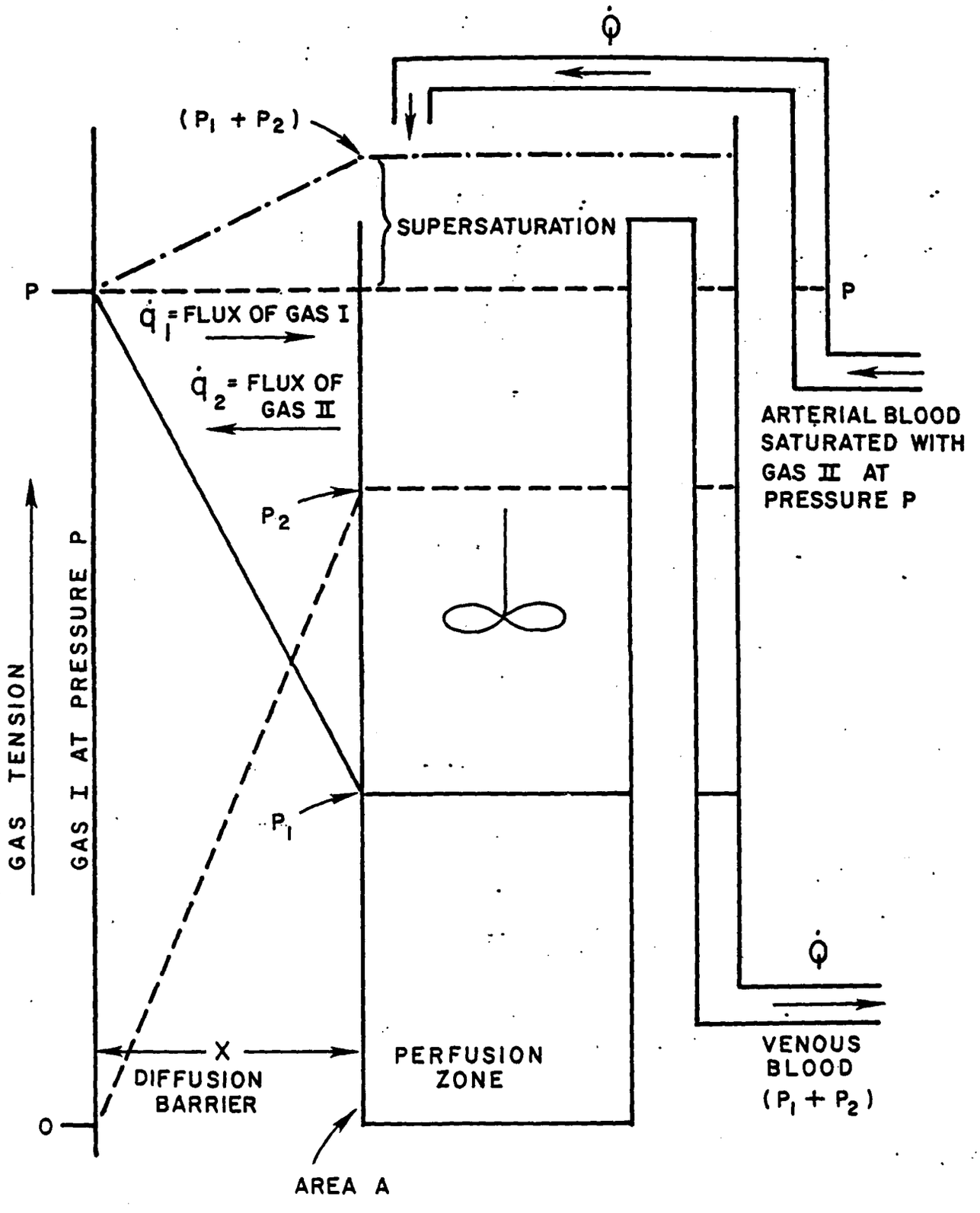
$$D_1 S_1 / S_1' > D_2 S_2 / S_2' \qquad (16)$$

For an aqueous tissue and aqueous blood, we have $S_1 = S_1'$ and $S_2 = S_2'$ Hence the only requirement is that D_1 is greater than D_2, i.e., that one gas diffuses faster than the other.

Hills (1977) emphasizes that this result applies to steady-state conditions. Hence if there are nucleation sites in the supersaturated media, bubbles can be produced continuously. Furthermore, the counterperfusion mechanism can explain bubble formation within the fluid compartments of the inner ear, where the presence of a suitable lipid-aqueous bilayer is questionable.

4. Chromatographic supersaturation

The phenomenon of simultaneous capillary perfusion and axial diffusion in a tissue cylinder has been investigated by Tepper, Lightfoot, Baz, and Lanphier (1979). The geometry considered by these authors is shown in Fig. 13a. The response time for radial diffusion is assumed to be very short compared to the capillary transit time, so that radial concentration gradients can be neglected. The relative importance of

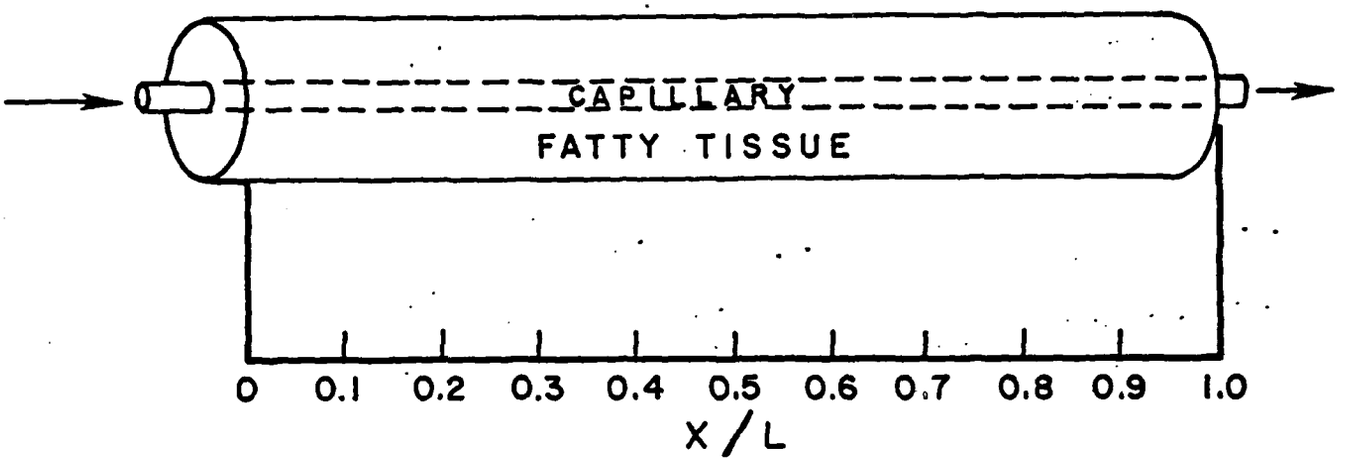

$\dot{Q}$
$(P_1 + P_2)$
SUPERSATURATION
P
P
$\dot{q}_1$ = FLUX OF GAS I
$\dot{q}_2$ = FLUX OF GAS II
ARTERIAL BLOOD SATURATED WITH GAS II AT PRESSURE P
P_2
GAS TENSION
GAS I AT PRESSURE P
P_1
$\dot{Q}$
X
DIFFUSION BARRIER
PERFUSION ZONE
VENOUS BLOOD $(P_1 + P_2)$
0
AREA A

Yount 12

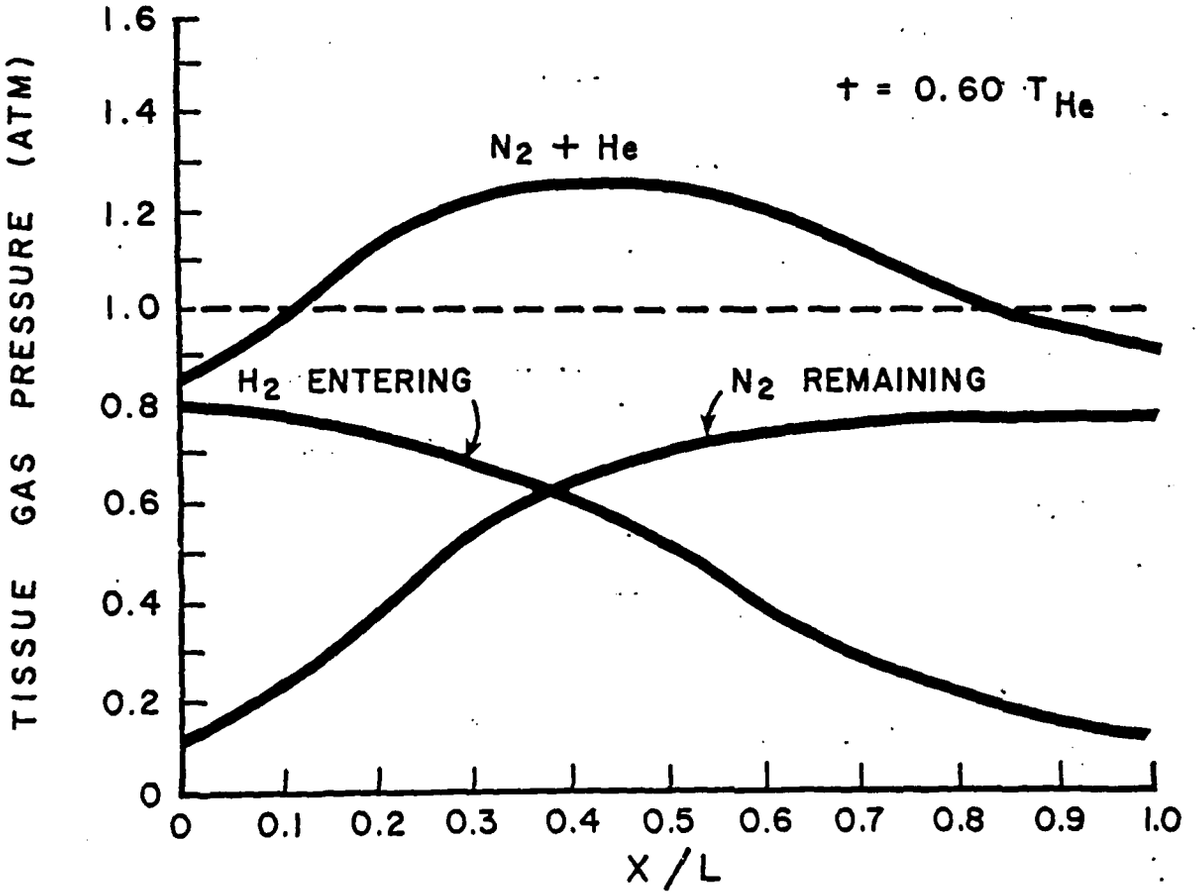
Fig. 13. Isobaric chromatographic supersaturation (Tepper, Lightfoot, Baz, and Lanphier 1979). In (a) a tissue cylinder is subjected simultaneously to capillary perfusion and axial diffusion. Radial concentration gradients are neglected. When the gas dissolved in the capillary blood is switched from nitrogen to helium, helium enters the system more rapidly than nitrogen is removed. The result is a transient supersaturation (b).

axial diffusion in the tissue compared with axial convection in the capillary can be characterized by the Péclet (Pe) number, which is the ratio of the response time for axial diffusion to that for removal of solute by convection from its volume distribution. As the Pe number approaches zero, axial diffusion becomes very rapid compared to axial convection.

Order of magnitude calculations by Tepper, Lightfoot, Baz, and Lanphier (1979) indicate that the Pe numbers for fatty tissues lie in an intermediate region, e.g., Pe $\sim$ 4. If the inert gas dissolved in the capillary blood is switched from nitrogen to helium, a significant supersaturation can result. This is illustrated in Fig. 13b for a shift at one atm abs from 80% nitrogen to 80% helium. The elapsed time is 0.60 of the helium response time T_{He}. Because of finite axial dispersion, there is a non-uniform concentration of each inert gas along the cylinder. Furthermore, the concentration of the helium that has entered is greater than the concentration of nitrogen that has been removed. A supersaturation of about 25% is the result. At $t = 1.4\ T_{He}$, the total inert gas tension can exceed the ambient pressure by as much as 40%.


CAPILLARY
FATTY TISSUE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
X / L

(a)


TISSUE GAS PRESSURE (ATM)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
t = 0.60 T He
N2 + He
H2 ENTERING
N2 REMAINING
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
X / L

(b)

Yount 13

5. Gas-induced osmosis

We shall end this section by describing another process which, although it is not a supersaturation mechanism per se, is frequently mentioned in the same context (Blenkarn, Aquadro, Hills, and Saltzman 1971; Hills 1972). This process is gas-induced osmosis—the transfer of a liquid solvent through a semipermeable membrane that inhibits the transfer and equilibration of a dissolved gas. The osmotic pressure OP for a tension differential Δp across a membrane is given by (Hills 1972)

$$OP = \sigma S(\Delta p)T/273 \qquad (17)$$

where T is the absolute temperature in degrees Kelvin, S is the solubility, and σ is the reflection coefficient, sometimes interpreted as the fraction of the solute molecules which are reflected upon striking the barrier.

Assuming that tissue membranes are, in fact, somewhat impermeable to dissolved gas (i.e., that σ is not equal to zero), osmotic pressure differences would be induced by the local gradients in dissolved gas concentration that occur during compression, as well as during decompression and inert gas switching. This could result in cell hydration, in cell dehydration, or even in cell death.

Discussion

The discovery of isobaric supersaturation of tissue has added a new dimension to diving theory. On the one hand, exposure to different inert gases, either sequentially or simultaneously, constitutes a potential hazard that must now be taken into account. On the other, inert gas manipulation provides an opportunity not only to improve diving practice, but also to investigate a number of problems related to diving physiology.

A remarkable illustration of this last point is given by the experiment of Cowley, Allegra, and Lambertsen (1979), who subjected the ears of New Zealand White rabbits to isobaric counterdiffusion at 1 atm abs. The rabbits breathed a mixture of 80% nitrous oxide and 20% oxygen while their ears alone were surrounded by helium. Subcutaneous pressure changes were detected by a fluid-filled needle inserted into the external ear and attached to a transducer-recorder system. The development of a gas phase in the tissue was signaled by a pressure increase from 0 mmHg to a maximum of 48 ± 10 (SD) mmHg. The mean time to reach the maximum pressure was 75 ± 10 (SD) minutes.

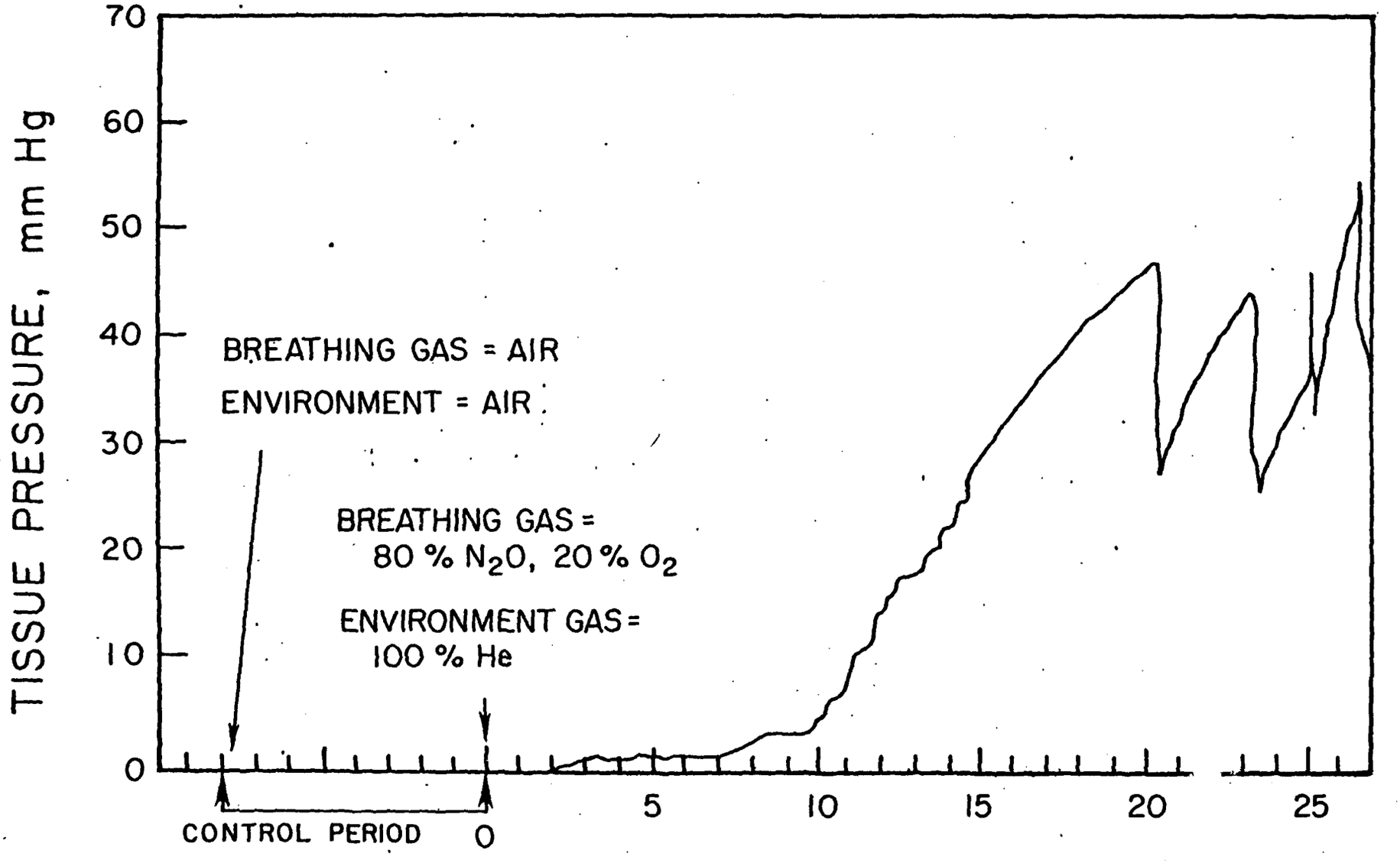
A representative tracing from the experiment of Cowley, Allegra, and Lambertsen (1979) is shown in Fig. 14. The increase in tissue pressure begins within 5 minutes after the breathing gas is switched from air to the nitrous-oxide mixture. In the interval from about 10 to 20 minutes, the tissue pressure appears to be approaching exponentially a steady-state level, presumably determined by the degree of supersaturation achieved in the rabbit ear under the given conditions.

Fig. 14. Subcutaneous pressure measured by Cowley, Allegra, and Lambertsen (1979) in the external ear of a New Zealand White rabbit subjected to isobaric counterdiffusion at 1 atm abs. Formation of a primary gas phase is signaled by the initial increase in pressure. Tissue cleavage, associated with a sudden increase in free gas volume, is indicated by a sharp decline. The cycle of exponential rise and sharp decline has important implications for the time course of gas elimination from the tissue.

After about 20 minutes, however, the exponential rise is abruptly terminated, apparently by cleavage of subcutaneous tissue which permits the free gas volume to expand. The cycle of exponential rise and abrupt decline is repeated again and again, generating a saw-toothed pattern with a gradual decrease in overall pressure during long exposure times. (See especially Fig. 5 in the paper by Cowley, Allegra, and Lambertsen 1979.)

The data of Cowley and his co-workers (1979), like those of D'Aoust, Smith, Swanson, White, Harvey, Hunter, Neuman and Goad (1977), have important implications for the time course of gas elimination from the tissue (Yount 1978; Yount 1979b). The primary event, once the required degree of supersaturation has been achieved, is the formation of a macroscopic gas phase, i.e., a bubble, from a microscopic gas nucleus. Whereas nuclei are stable and typically have radii less than 1 μm, bubbles are intrinsically unstable. Thus bubbles which form in lean gelatin samples ordinarily grow until the local supersaturation is relieved (Yount and Strauss 1976), while bubbles in tissue tend to expand until the deformation pressure δ (which is negligible in lean gelatin) increases to a value large enough to withstand the supersaturation and prevent additional gas from diffusing into the cavity (Yount 1978; Yount 1979b).

The data of Cowley, Allegra, and Lambertsen (1979) are of particular interest because neither of the above conditions prevails. The supersaturation is not relieved by the creation of the gas phase; rather, it is maintained at a more or less constant level by a steady-state counterdiffusion mechanism. Similarly, the tissue deformation


TISSUE PRESSURE, mm Hg
70
60
50
40
30
20
10
0
BREATHING GAS = AIR
ENVIRONMENT = AIR
BREATHING GAS =
80 % N_2O, 20 % O_2
ENVIRONMENT GAS =
100 % He
CONTROL PERIOD
0
5
10
15
20
25
TIME, MIN

Yount 1.4

pressure does not rise to the supersaturation level, but instead it is periodically discharged via tissue cleavage. This situation calls to mind the bubble chains seen in champagne or the "rosaries" of post-mortem bubbles reported by Albano (1970), and one can easily imagine a series of "secondary" bubbles originating at the site of a "primary" nucleus and discharging ultimately into the vasculature. This is not to say that intact bubbles move freely through tissue and capillary walls; rather, they are pools along the cleavage streams through which free gas migrates.

The above scenario is quite consistent with the data of D'Aoust and his group (1977), shown in Fig. 9. Primary bubbles are recruited only while the supersaturation is increasing, but secondary bubbles continue to be generated by the primary sites until the local supersaturation falls below the local deformation pressure. Furthermore, whereas a value of 48 ± 10 (SD) mmHg may be typical of a rabbit's ear (Cowley, Allegra, and Lambertsen 1979), the deformation pressures in blood and in other liquids must be negligible. Evidently, there is a gradient in deformation pressure, and it is this gradient that provides the force necessary to drive the cleavage streams of free gas out of the tissue and into the blood. The bubbles which form at the ends of these streams are not held in check by the tissue deformation pressure and may grow to many tens of microns. This facilitates detection by the Doppler apparatus, which continues to serve as a reliable monitor of the in situ liberation of dissolved tissue gas long after the formation of primary bubbles has ended. Since bubble size in tissue is ordinarily limited, perhaps to a few microns in radius (Rubissow and Mackay 1974), it may appear to an observer with poor visual resolution that all bubbles originate directly in the blood. Albano (1970), on the other hand, has emphasized the continuity of extra- and intravascular bubbles, and his work is in accord with the point of view expressed here.

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Q. Does your model take the thickness of the skin into account?

A. In our most recent work, we have adopted a model that takes skin thickness into account. We now have data to show that this is necessary, under extreme conditions — for example, when the side of the nucleus is so small that the skin thickness is a significant fraction of the radius.

Q. You made a comparison between the Berghage data and the findings of Watt and Lin, but since Watt used air and Berghage used helium-oxygen, do you think the comparison is valid?

A. The number of bubbles that form, as a first approximation, is independent of whether the gas involved is helium or nitrogen; this has been experimentally tested in gelatin. This doesn't mean that people are equally sensitive to the two gases; a lot more secondary bubbles may be released in the case of nitrogen than in a helium situation.

Q. Would you re-state the conclusion from your paper that you thought was so important?

A. The first point is that Pcrush may be smaller than we thought, if the gas tension rises significantly during compression. Those tissues that have extremely short time constants will have extremely low Pcrush, and instead of getting very high allowed pressure reductions -- 4 or 5 atmospheres -- we may actually be limited to 1 or 2 atmospheres. The vestibular region falls into this class -- if the respiratory gas is the same as the ambient gas, the Eustachian tube acts as another pathway. One could therefore have a gas tension in the vicinity of the round window or the vestibule that is close to ambient pressure as one compresses, which means that this region is not well protected by the compression of nuclei. This would be compatible with bubble formation in these areas, and explain why additional compression would have little effect on the size of the nuclei.

Q. This would clarify why Harvey's divers' itching was aggravated when they compressed an additional atmosphere on the same gas. The benefits of compression were less than the negative effects of the extra atmosphere of helium. The divers were clearly not yet equilibrated.

ISOBARIC SUPERSATURATION:

THEORETICAL MODELS*

R. S. Tepper

The use of multiple inert gases in combination or in sequence has become increasingly common in diving. The differences in the physical properties of the inert gases have generally been exploited to decrease the work of breathing at increased pressure, to balance the effects of nitrogen narcosis and the high pressure nervous syndrome, and to decrease the time required for decompression. In 1959, Hannes Keller (Keller and Buehlmann 1965) noted the theoretical advantage of switching the inspired inert gas from He to N_2 during decompression from a deep dive employing He. Such shifts subsequently became a central feature of the approach to deep diving described by Keller and Buehlmann (Keller and Buehlmann 1965; Buehlmann 1975). Only during the past decade has the diving community become aware of some of the possible hazards of simultaneous exposure to different inert gases or of shifting breathing media under constant ambient pressure.

In 1971, Blenkarn and his co-workers (Blenkarn, Aquadro, Hills and Saltzman 1971) first reported the occurrence of urticarial lesions in individuals breathing either N_2 or Ne while surrounded by He at a constant ambient pressure of 7 ATA. These cutaneous lesions were thought to be fluid filled and were attributed to gas-induced osmosis. Lambertser and his group (Lambertsen and Idicula 1975) reported similar cutaneous lesions while studying the effect of inspired gas density on respiratory work at increased ambient He pressures. Dissection of these lesions revealed confluent gas spaces rather than extravasation of fluid. This group subsequently produced both cutaneous lesions and fatal venous gas emboli in pigs breathing N_2O and surrounded by He at a constant ambient pressure (unpublished observations). They attributed these manifestations to isobaric supersaturation and bubble formation resulting from the difference in the rates of cutaneous counterdiffusion of the inspired and ambient inert gases. Lambertsen designated this phenomenon as the "isobaric gas counterdiffusion syndrome" (Lambertsen and Idicula 1975).

Graves, Idicula, Lambertsen and Quinn (1973) proposed a model, illustrated in Fig. 1, to explain how the steady-state, two compartment system with oil and water is able to produce supersaturation because of the differences in diffusivities and solubilities, and relative permeabilities, of the two inert gases. This model's shortcomings, however, are that it requires a specific orientation of the lipid-aqueous layer, and that it neglects convective transport by the blood. Both of these defects limit it as a model with realistic predictive ability.

* In the final report, the figures in this paper will be reduced and inserted above their respective legends in the text.

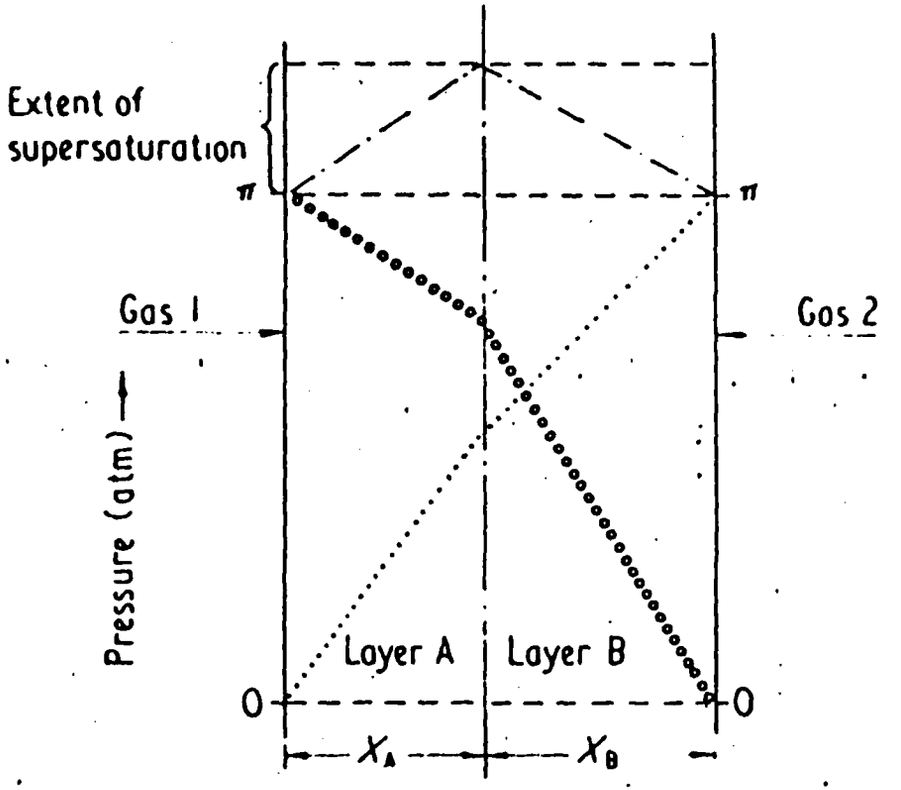
Fig. 1. Schematic showing supersaturation in a two-layer system during a counter-current diffusion experiment. In the real case, Gas 1 may be He; Gas 2, N_2; Layer A, H_2O; Layer B, oil. Partial pressure profile is indicated for each gas. Bubbles can form if at least one of the two layers is a liquid.

A closer approximation of the actual biological system has been proposed by Hills (1977). As depicted in Fig. 2, the diffusive resistance of the skin lies in series with the convective transport of a well-mixed blood supply. This model allows for supersaturation to occur solely from diffusional differences between inert gases in a single aqueous phase. Collins (1978) has measured the transcutaneous fluxes of several inert gases in piglets. Using Hills' model, his calculations of the relative counterdiffusion potentials of the different inert gases were in general agreement with the reported occurrences of isobaric supersaturation. This model makes it possible to predict which exposures to various inert gases may produce cutaneous supersaturation. However, the model's predictive ability is still limited by its use of steady-state analysis.

Analysis of transient responses

Although cutaneous counterdiffusion can produce a sustained steady-state isobaric supersaturation, it is important to examine the transient response of a system. This is best illustrated by the recent work of Cowley and Lambertsen (1979). These investigators were unable to produce bubble formation in either the cornea or anterior chamber of the eyes of animals breathing N_2O and surrounded by He at 2 ATA after 2 to 3 hours' exposure. Using the above model, with the cornea representing the diffusion barrier and the anterior chamber as the convective

Tepper



•••••• Effective partial pressure of Gas 1

..... Effective partial pressure of Gas 2

— — Sum of partial pressures

Fig. 2. Readily diffusible gas (I) washes away from outer surface of skin or membrane any less diffusible gas (II) that has permeated this barrier from perfused zone supplied with blood free of Gas I but saturated with Gas II at ambient pressure (P). By adding gas tensions, it can be seen that the stirred pool, and hence the overflow (venous blood), becomes supersaturated ($P_1 + P_2 > P$) as the system reaches steady state.

transport system in series, they subsequently estimated that it would require approximately 16 days to generate 1 ml of gas in the anterior chamber. This could have been estimated from the transient response time of the system, the time needed to reach steady state. It is therefore important to know whether the predicted steady-state values will occur during the time-span that is actually at issue.

The importance of transient analysis is further emphasized by the consideration of "deep tissue" isobaric supersaturation, a phenomenon first speculated about by Lambertsen and Idicula (1975). This phenomenon could result from an abrupt switch in the respired inert gas such that the first gas exits the tissues more slowly than the second gas enters. A switch from N_2 to He, the reverse of the presumably beneficial shift proposed by Keller and described by Buehlman (1975), could theoretically produce isobaric supersaturation. In contrast to the sustained steady-state bubble formation that can be produced by superficial counterdiffusion, "deep-tissue" supersaturation is not sustained and results from transient differences in the microcirculation.

Although several authors have discussed the theoretical possibilities of "deep tissue" isobaric supersaturation (Tepper, Lightfoot, Baz and Lanphier 1979; D'Aoust, Smith, Swanson, White, Stayton and Moore 1979), there has been no experimental verification of bubble formation resulting specifically from "deep tissues." D'Aoust and his co-workers (D'Aoust, Smith, Swanson, White, Stayton and Moore 1979) have documented

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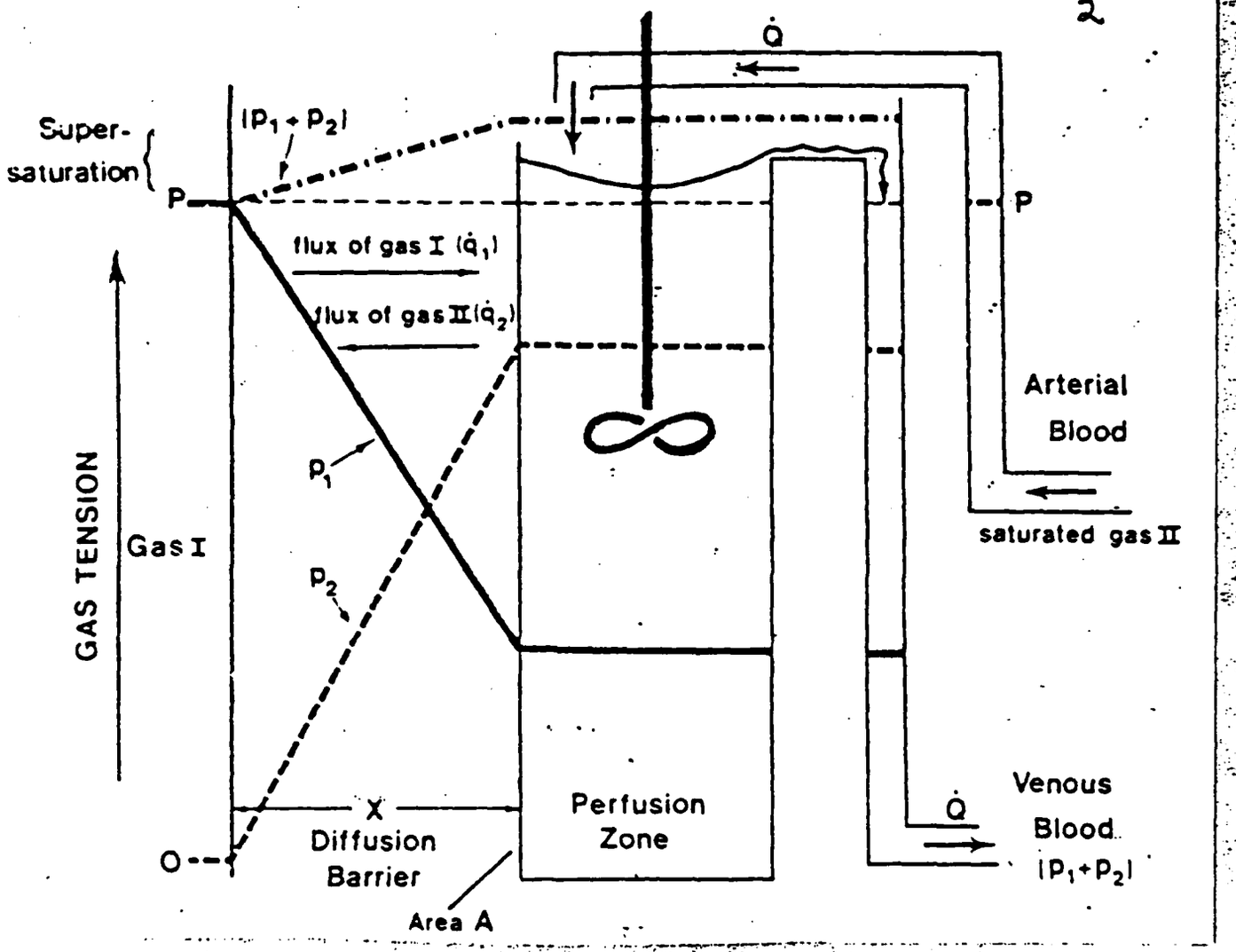

Q̇
Super-
saturation
(P1 + P2)
P
P
flux of gas I (q̇1)
flux of gas II (q̇2)
Arterial
Blood
saturated gas II
P1
P2
GAS TENSION
Gas I
X
Diffusion
Barrier
O
Perfusion
Zone
Area A
Q̇
Venous
Blood
(P1+P2)

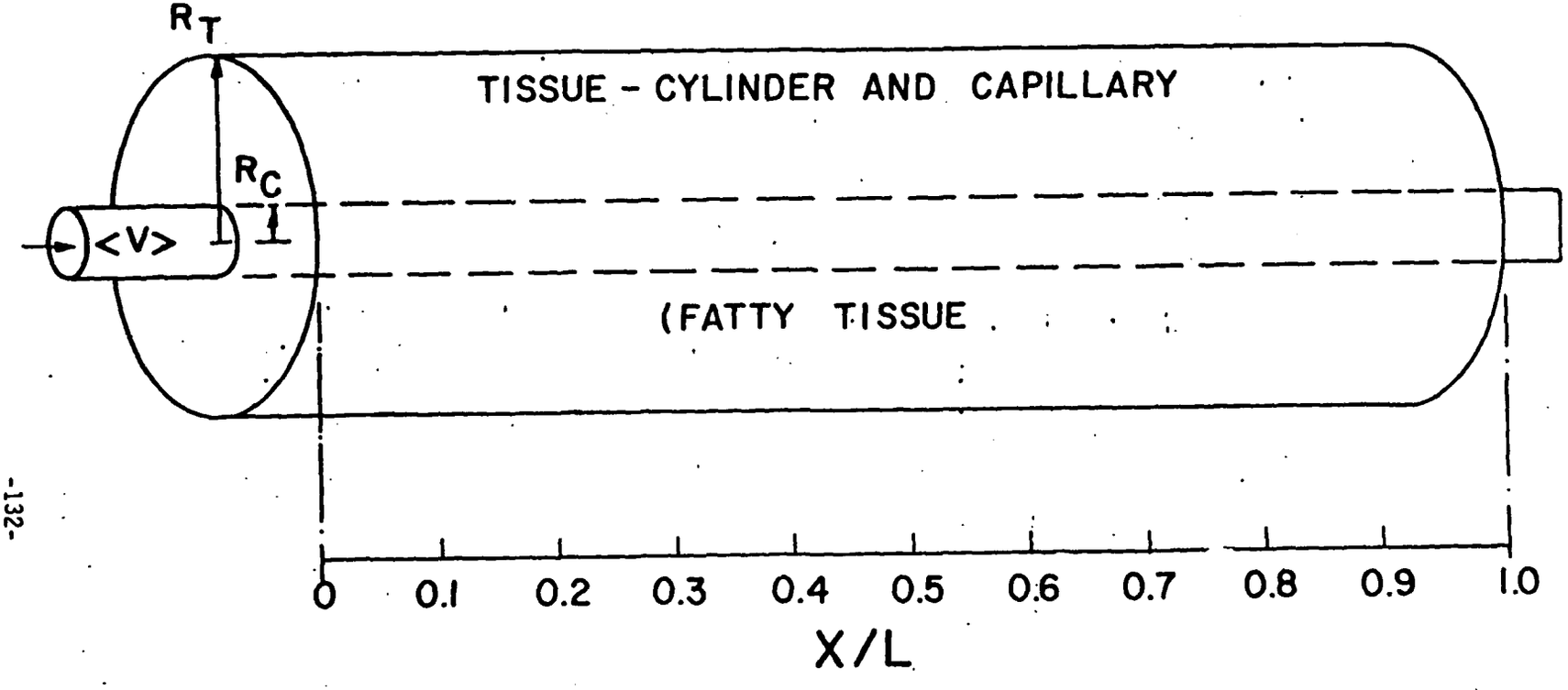
the occurrence of vena caval bubbles after an isobaric N_2 to He switch. It is, however, difficult to discriminate between the results of superficial and deep isobaric supersaturation because these workers' experimental design altered both the respired and ambient inert gas from N_2 to He.

Microcirculatory models

In considering "deep tissue" saturation, it is necessary to examine the various models of inert gas transport in the microcirculation. Most models are based on the idealized Krogh capillary-tissue cylinder unit, illustrated in Fig. 3. Krogh (1919) was interested in the transport of oxygen within skeletal muscle. He described the steady-state radial diffusion of gas within the extravascular space, neglecting convective transport within the capillary. Roughton (1952) subsequently provided the equation for the transient response. He concluded that the response time for radial diffusion was very short compared to the capillary transit time and that the radial concentration gradients can therefore be neglected. Hills (1970) used the same mathematical description, but employed a diffusion coefficient on the order of 10^{-10} cm^2/sec in contrast to the value of 10^{-5} cm^2/sec commonly cited in the literature. On this basis, Hills concluded that radial diffusion in the extravascular tissue is not only slow but is actually rate limiting. There is, however, no present justification for employing a diffusion coefficient so small.

Fig. 3. Schematic of capillary-tissue cylinder unit, as used in the Krogh model.

In contrast to the model with diffusional resistance distributed through the radial dimension of the extravascular space, Fig. 4 represents a lumped parameter model. Diffusional resistance is represented by a semi-permeable barrier localized between the capillary and an extravascular space, which is at a uniform concentration. The equations describing this model are usually simplified to facilitate their solution. Morales and Smith (1948) assumed a linear concentration gradient along the length of the capillary. In contrast, Ohta, Song, Groom and Farhi (1978) have assumed that the difference between the mean capillary


R_T
TISSUE - CYLINDER AND CAPILLARY
R_C
<V>
(FATTY TISSUE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
X/L

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3

Fig. 4. Model used to analyze experimental data; 3 compartments are shown on left, and parameters and variables on schematic. For tissue source, these include volume (V_t), solubility of tracer (a_t), and partial pressure (P_t); diffusion characteristics of barrier (area, thickness, geometry) are lumped into K. In blood, P_a and P_c represent partial pressures at either end of capillary, and a_b is solubility of tracer. Equations are mass balance equations for each compartment. MW is molecular weight of tracer gas.

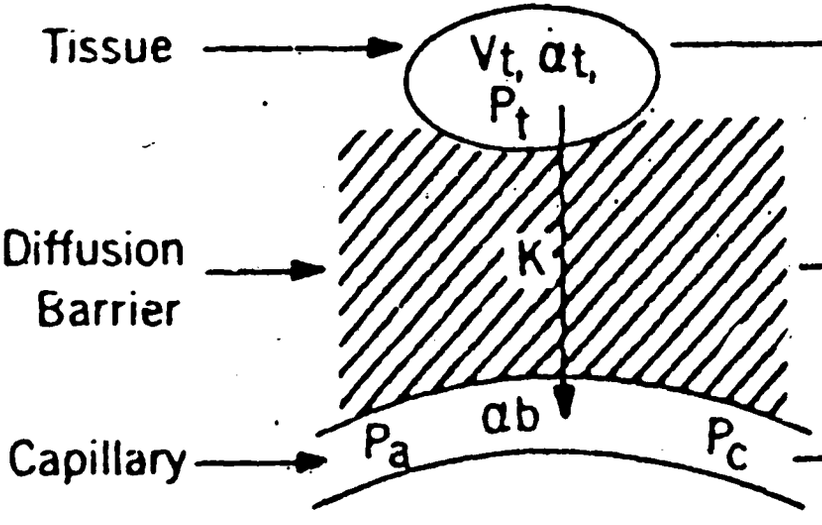
and end capillary gas tensions is small compared to the difference between the tissue and mean capillary tensions. This assumption becomes less tenable as the permeability barrier becomes negligible and during the latter phase of solute washout. The limiting case of no permeability barrier represents the perfusion-limited system assumed by Haldane and most researchers.

Tepper, Lightfoot, Baz and Lanphier (1979) have considered the chromatographic model, which is characterized by instantaneous equilibration in the radial direction and by a finite rate of axial diffusion in the tissue cylinder. These assumptions are made because the transient time constants for axial diffusion are comparable to those for convective transport and thus cannot be assumed to be infinite, as is assumed in both the perfusion and barrier-limited models. As illustrated in Fig. 5, the chromatographic model produces profiles within the tissue cylinder that are distinctly different from the uniform concentration usually assumed. The relative importance of diffusion in the microcirculation is usually assessed relative to the permeability barrier model, but there is neither anatomic nor physiologic evidence to suggest that lipid soluble inert gases should encounter an isolated diffusional barrier.

Implications of diffusivity

To determine the extent to which diffusion may limit the exchange of gases stored in tissues, Ohta and his co-workers (Ohta, Song, Groom and Farhi 1978; Ohta and Farhi 1979) measured the whole body and cerebral washouts of inert gases with the same lipid solubilities but different diffusivities. Figure 6 shows the logarithmic plots of inert gas elimination for the whole body and brain, respectively. In each plot, the slope of the dotted line represents the ratio of the diffusivities

Model **Equations** Tepper +



(1) $\dot{V}_G = V_t \cdot \alpha_t \cdot \dot{P}_t$

(2) $\dot{V}_G = -(P_t - P_c) \cdot K \cdot \frac{\alpha_t}{\sqrt{MW}}$

(3) $\dot{V}_G = -\dot{Q} \cdot \alpha_b \cdot P_c$

Fig. 5. Schematic of chromatographic model.

and the predicted curve of the barrier-limited model. The slopes of the plots were very near 1.0, the value predicted for a perfusion-limited model. These authors thus concluded that the rate of exchange of inert gases is limited only by the gas partition coefficient and the blood perfusion rate.

If, however, one examines the late phase of each washout, one consistently notes that the more rapidly diffusible gas is at a higher concentration and thus is washing out more slowly. This is demonstrated by the proportionately larger number of points above than below the curve in Fig. 6, as well as by examining the raw data in Fig. 7. A barrier-limited model cannot explain the slower washout of the more diffusible gas. Figure 8 is a theoretical plot of the washout of two inert gases with the same lipid solubilities and a 1.5:1.0 ratio of diffusivities, using the chromatographic model. Note the slower washout of the more diffusible gas. The logarithmic plot has a slope of 0.92, distinctly less than 1.5 and very close to 1.0. This occurs because more of the inert gas with the greater diffusivity returns to the proximal end of the tissue cylinder and thus slows its washout. As suggested by Tepper, Lightfoot, Baz and Lanphier (1979), such interaction of perfusion and diffusion should not be neglected. Figure 9 illustrates the marked difference in the predicted local and average tissue supersaturations for the chromatographic and perfusion-limited models after an isobaric shift from N_2 to He. In addition, the perfusion-limited model predicts supersaturation only in fatty tissues, while the chromatographic model predicts supersaturation even in aqueous tissues.

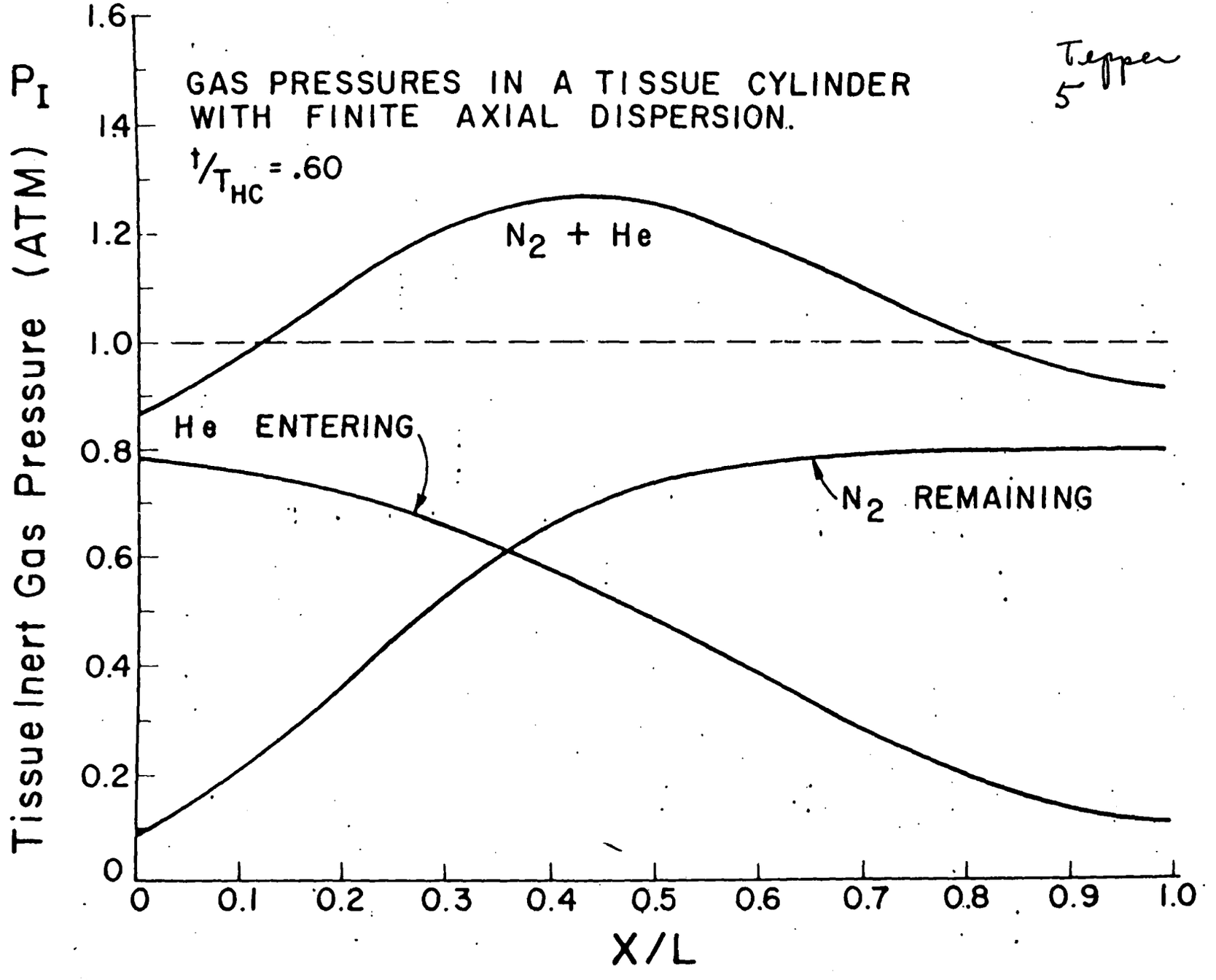
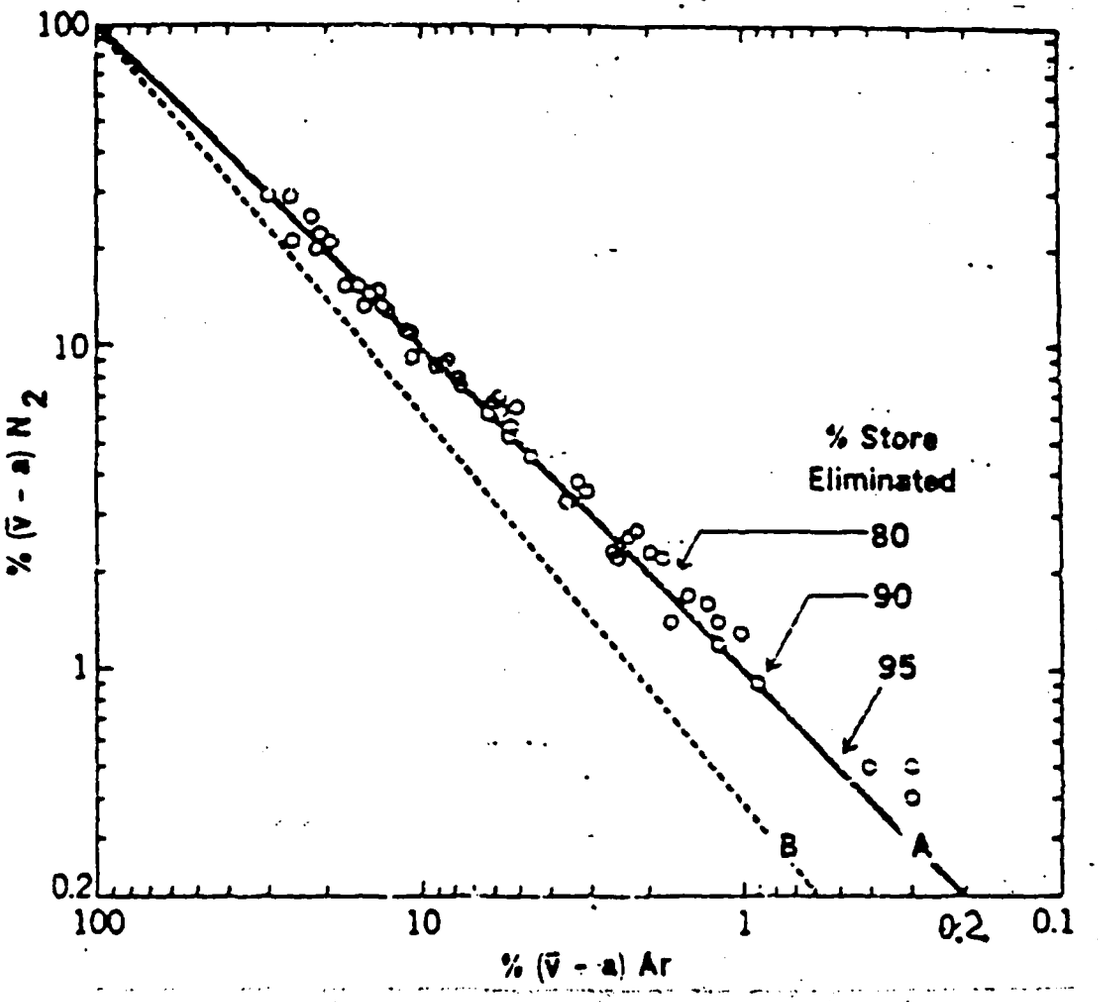
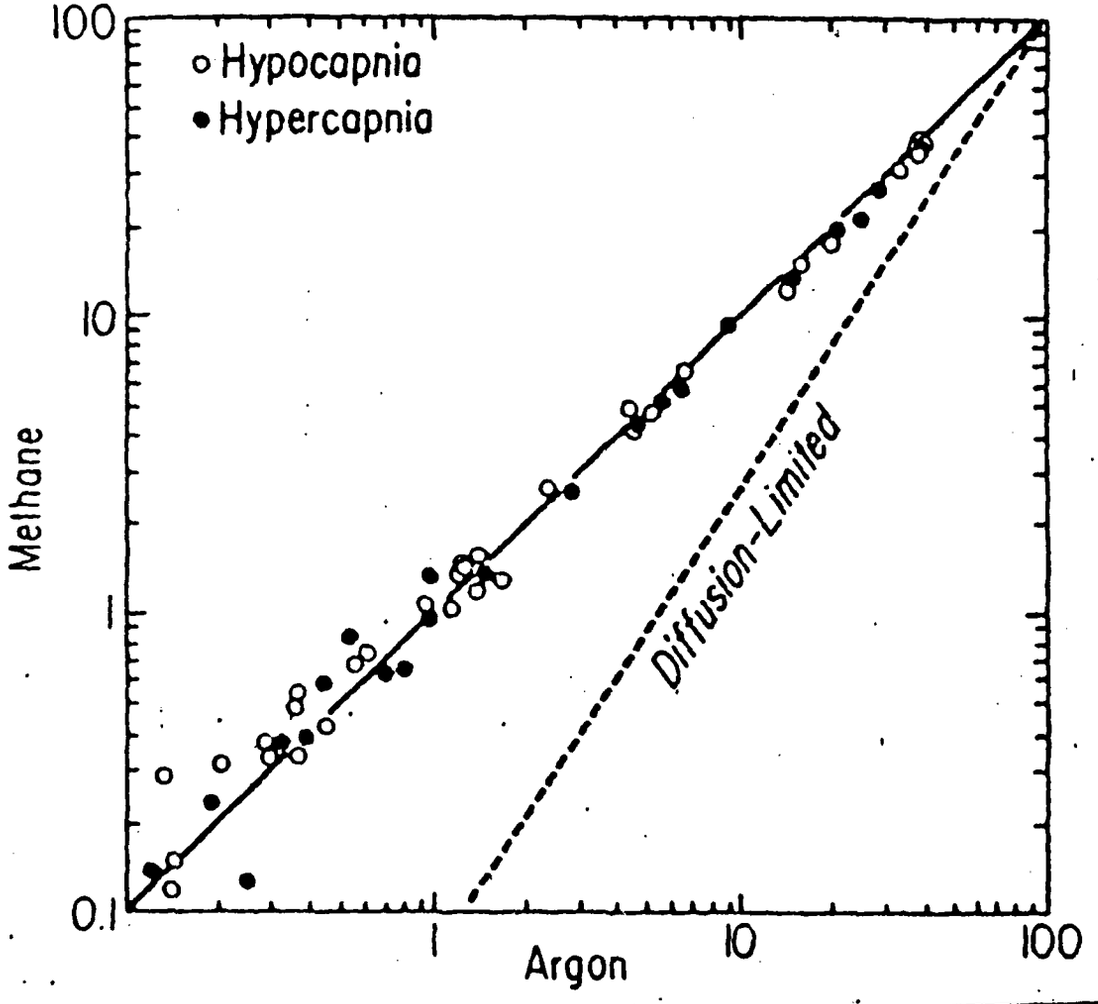

GAS PRESSURES IN A TISSUE CYLINDER
WITH FINITE AXIAL DISPERSION.
t/T_{HC} = .60
Tepper 5
N_2 + He
He ENTERING
N_2 REMAINING
Tissue Inert Gas Pressure (ATM) P_I
X/L
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Fig. 6A. Relationship between nitrogen and argon washout ($\bar{v}$-a)N_2 is plotted against ($\bar{v}$-a)Ar. Line A indicates expected relationship in situation in which gas washout is limited entirely by perfusion. Dashed line B depicts situation in which process is limited primarily by diffusion. Experimental points are scattered around line A. Arrows indicate points of washout at which a given percentage of initial gas store has been eliminated.

Fig. 6B. Methane washout plotted against argon washout. Solid line is the identity line and corresponds to a situation in which washout is limited entirely by perfusion. Dashed line indicates where data would be expected to fall in a diffusion-limited preparation. Experimental points are for both hypocapnia (open circles) and hypercapnia (solid circles).

Tepper 6A

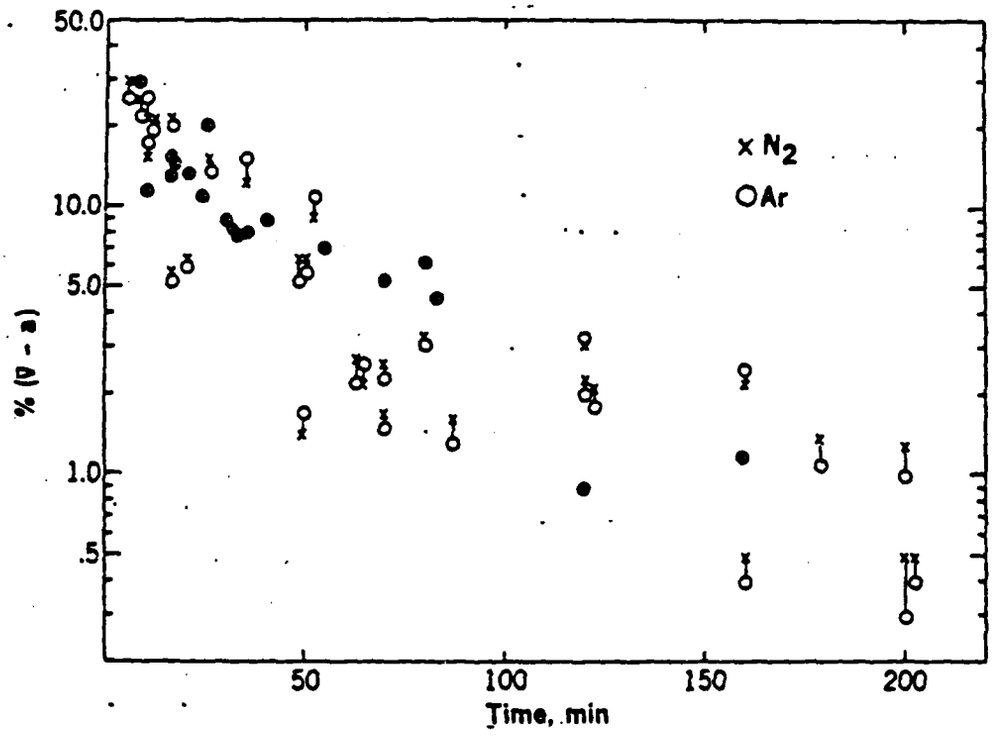



100
10
1
0.1
Methane
Hypocapnia
Hypercapnia
Diffusion-Limited
1
10
100
Argon

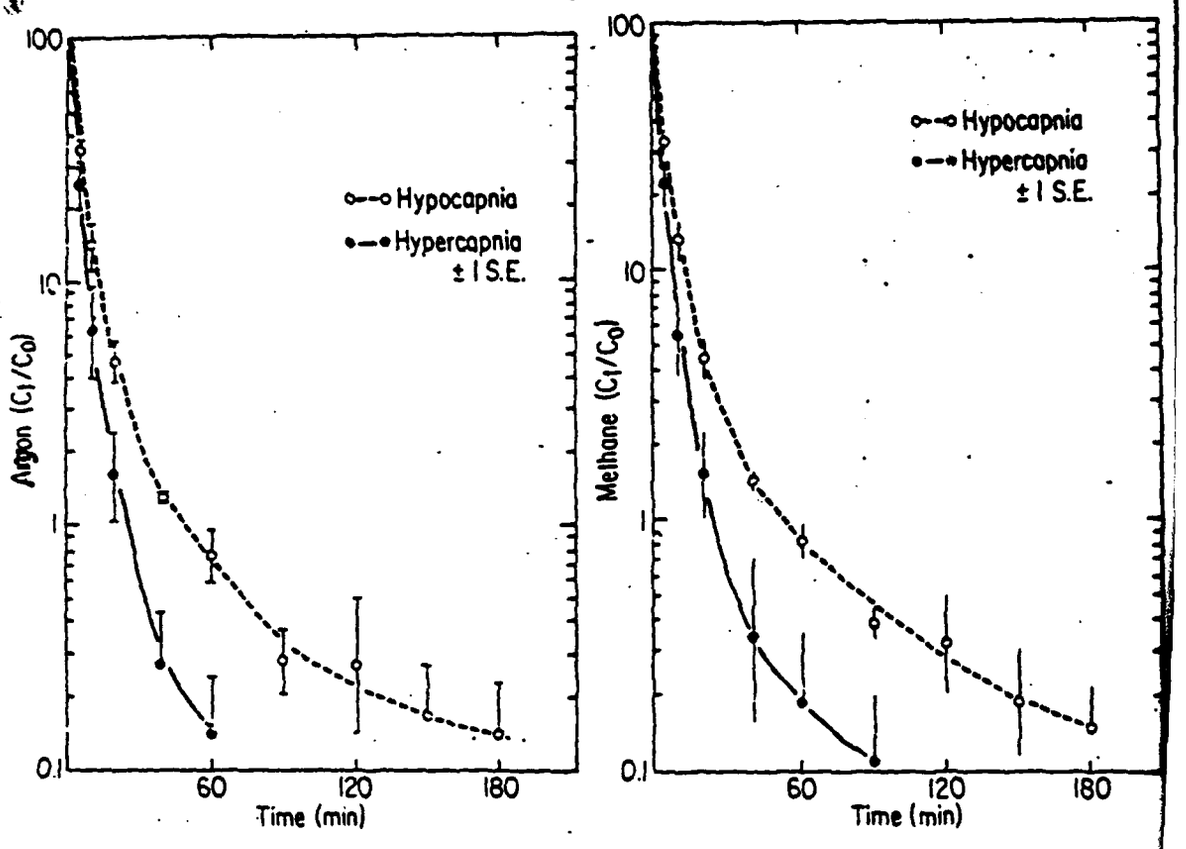
Tepper
6B

Fig. 7A. Washout of argon and nitrogen from body stores. Abscissa is time in minutes. Ordinate (log scale) is ($\bar{v}$-a) difference expressed as percent of initial blood level before washout. When values for Ar and N_2 expressed in this fashion are not identical in any 1 sample, the two data are connected. Scatter is caused by differences in behavior of individual animals.

Fig. 7B. Washout of argon and methane from body stores. Abscissa is time in minutes. Ordinate (log scale) is ($\bar{v}$-a) difference, divided by control value. Solid line is average of points from hypercapnic animals; dashed line, hypocapnic animals.

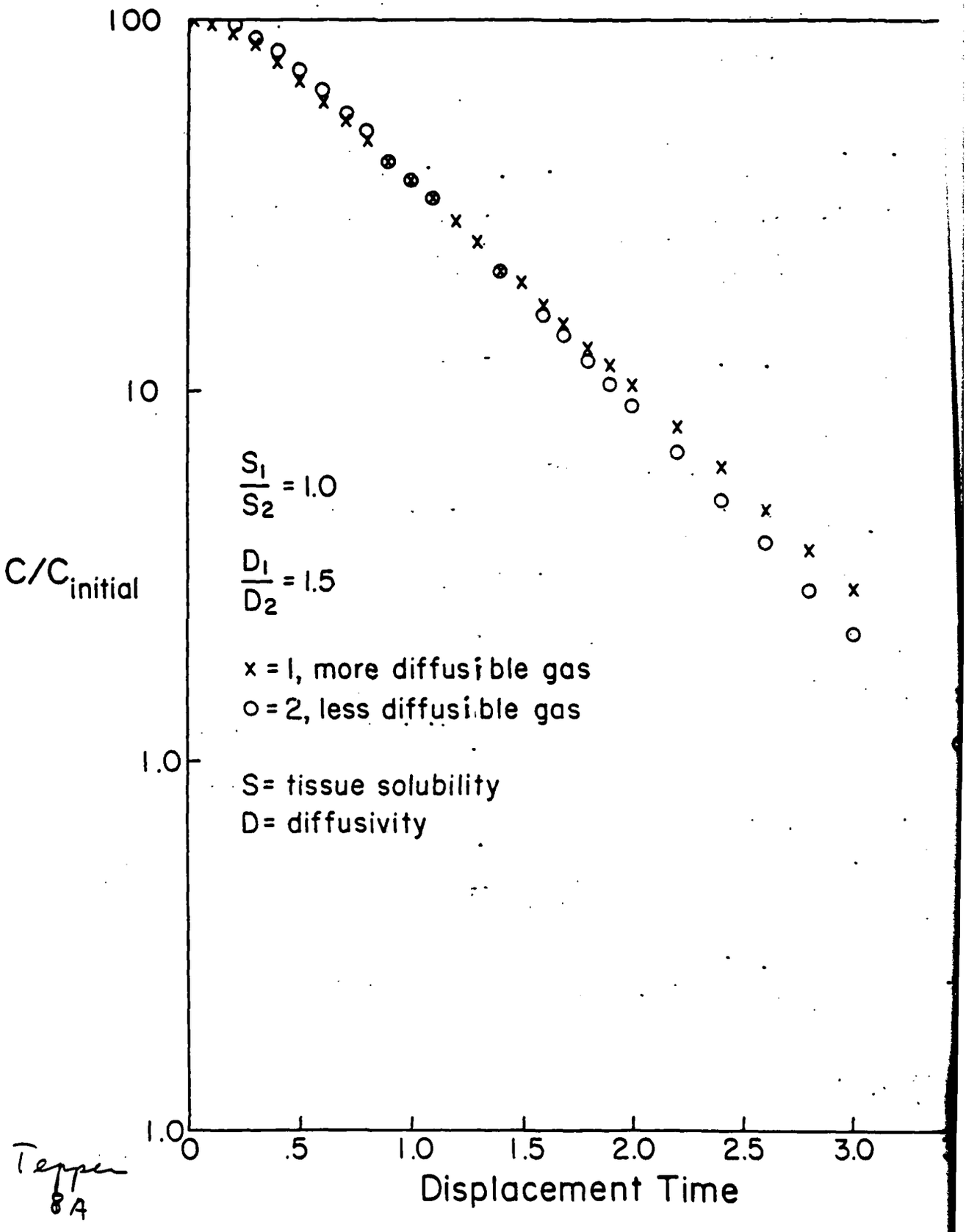


Tepper
:7A

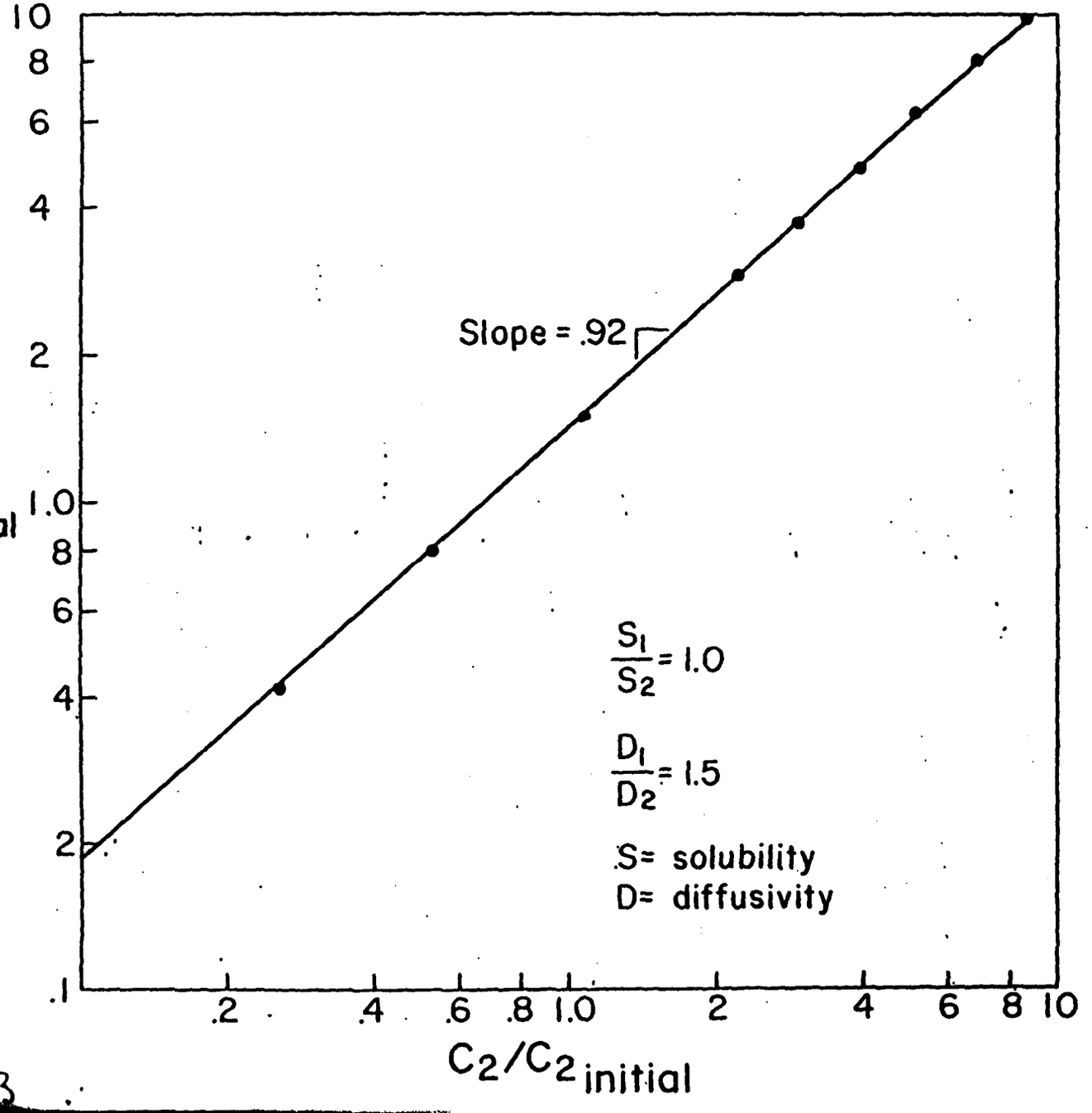

100
10
1
0.1
Argon (C_1/C_0)
Hypocapnia
Hypercapnia
± 1 S.E.
60
120
180
Time (min)
100
10
1
0.1
Methane (C_1/C_0)
Hypocapnia
Hypercapnia
± 1 S.E.
60
120
180
Time (min)

Tepper 78

Figs. 8A and 8B. Plots of washout for two inert gases with same lipid solubilities and a 1.5:1.0 ratio of diffusivities, using the chromatographic model.


100
10
1.0
1.0
$C/C_{initial}$
$\frac{S_1}{S_2} = 1.0$
$\frac{D_1}{D_2} = 1.5$
x = 1, more diffusible gas
o = 2, less diffusible gas
S= tissue solubility
D= diffusivity
0
.5
1.0
1.5
2.0
2.5
3.0
Displacement Time

Tepper
8A


10
8
6
4
2
1.0
8
6
4
2
.1
.2
.4
.6
.8
1.0
2
4
6
8
10
Slope = .92
$C_1/C_{1\,initial}$
$C_2/C_{2\,initial}$
$\frac{S_1}{S_2} = 1.0$
$\frac{D_1}{D_2} = 1.5$
S= solubility
D= diffusivity

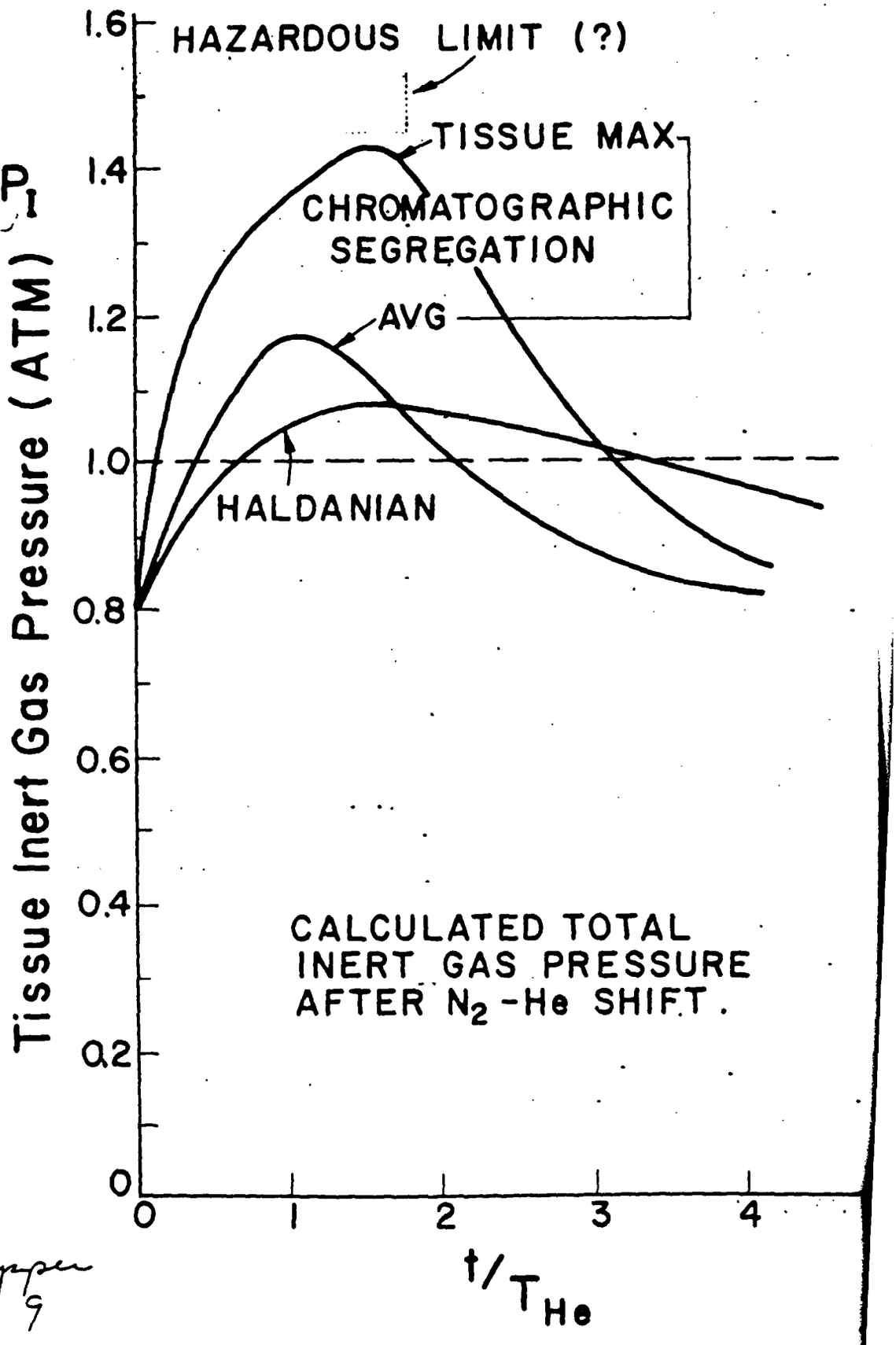
Tepper 88

Fig. 9. Difference in predicted local and average tissue supersaturations, using the chromatographic and perfusion-limited models.

Conclusion

Models are only gross simplifications of very complex systems and are at best no better than the anatomic, physiologic and mathematical assumptions upon which they are based. Steadfast adherence to a single model can limit both interpretation of experimental data and predictive ability, the two prime reasons for modeling.

Awareness of isobaric supersaturation has added a new dimension to diving theory and new opportunities to investigate the mechanisms controlling inert gas transport in the microcirculation.


HAZARDOUS LIMIT (?)
TISSUE MAX
CHROMATOGRAPHIC SEGREGATION
AVG
HALDANIAN
Tissue Inert Gas Pressure (ATM) P_I
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
0
1
2
3
4
t/T_{He}
CALCULATED TOTAL INERT GAS PRESSURE AFTER N_2 - He SHIFT.

Tepper
9

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Discussion

Q. The model's accuracy depends on the tissue, and whether or not the capillaries really are that parallel. The vascularity is never adequately taken into account in these cylindrical models.

A. I agree, but some investigators have begun to take vascularity into account.

Q. Does your cylinder model assume the same diffusion coefficient for the intra- and extracellular material?

A. I would be happy to use different coefficients, if you can tell me why they should be different. I am just lumping them together here.

Q. I think the intracellular diffusion coefficients are probably orders of magnitude lower than extra-cellular ones, as Ling has shown in his work.

A. The bulk of the physiological and circulatory literature shows clearly that Krogh's diffusion coefficients are accurate. In fact, it would be very difficult to explain gas exchange across the alveolar membrane if there were very low diffusion coefficients there.

Q. How did Ohta and Fahri generate the curve for the whole body washout data?

A. Line A in their figure (Fig. 6) is hand drawn, and their data points fit the slope of 1.0 very nicely.

Q. Why doesn't their plot go through 0.1 at the bottom?

A. Their axes are confusing; they only go down to 0.2. But I think their data show that the system is not totally diffusion limited; there is no permeability barrier.

COUNTER-TRANSPORT OF INERT GASES:

EFFECTS OF STEADY-STATE AND TRANSIENT GRADIENTS

B. A. Hills

When we first observed the cutaneous effects of the isobaric counter-transport of gases in the chambers at Duke University in March, 1970 (Blenkarn, Aquadro, Hills and Saltzman 1971), our first reaction was to make sure that there was no contaminant in the normoxic nitrogen supplied to the head-tents of the divers a few minutes beforehand. The magnitude of the disorder and its resemblance to classical "skin-bends" were striking, and yet in this case it was occurring without any decompression at a simulated depth of 200 feet during what would otherwise have been a fairly routine "saturation" exposure to normoxic helium. This extensive erythematous maculopapular eruption in all three subjects was totally unexpected and, naturally, caused my colleagues to abandon plans for a scheduled pulmonary study. Upon looking more closely at the subjects, however, it occurred to me that the urticaria terminated at the line around the chest, back and shoulders where the head-tent had been taped down to effect a gas seal.

This was particularly interesting since it meant that this "isobaric urticaria" was observed only where the skin was exposed to helium while the blood supplied to the cutaneous vessels had been equilibrated with nitrogen at the lungs at the same partial pressure. Hence it was concluded that this was a phenomenon caused essentially by the superposition of two steady-state gradients of different inert gases in opposite directions -- but only when the two gases were in a particular orientation. For instance, it occurs only when helium is adjacent to epithelium and nitrogen is intravascular, but not vice versa.

This situation also arises in the ear, so it was particularly interesting when the group at the University of Pennsylvania applied reverse gas gradients at 400 feet (Lambertsen 1976). Not only did they confirm our earlier findings at Duke but, without any decompression, they also produced vestibular disorders indistinguishable from those listed as symptoms of decompression sickness. Before discussing the mechanisms which have been proposed to explain how reverse gas gradients can induce this isobaric blood-epithelium phenomenon, it must be emphasized that both the cutaneous and vestibular manifestations refer to steady-state gradients rather then to any transient situation.

Steady-state vs. transient conditions

Steady-state conditions pertain in the inner ear or across the skin, since any helium diffusing across the epithelium or otherwise being transported towards the nearest vessels under the tension gradient will be removed by the perfusing blood, thus preventing any accumulation. An essentially similar situation arises for nitrogen in the opposite direction, so that this counter-transport of different gases results in essentially static gradients of both gases. It is my preference to call

this phenomenon "counter-transport" rather than "counter-diffusion," since diffusion is only one of many transfer processes which might be involved in the passage of inert gas molecules between blood and epithelium. "Counter-current" is certainly not an appropriate term, since it implies the transfer of one solute between two streams flowing in opposite directions rather than opposite paths for two solutes in a situation where only one medium, if any, needs to flow.

In other words, it is only the continuous removal of gas which has traversed the blood-epithelial barrier that makes steady-state conditions possible, thereby presenting the intellectual challenge of explaining the mechanism accounting for the isobaric cutaneous and vestibular phenomena.

By contrast, many more transient situations can occur in vivo where, upon switching breathing mixtures, one gas can diffuse into a tissue or tissue compartment faster than another can leave. This can result in transient supersaturation if the switching occurs in the wrong direction, i.e., from a less to a more diffusible gas. Therefore, gases are switched in the opposite direction during decompression, i.e., from helium to nitrogen, to take advantage of the transient unsaturation which can be induced. This reasoning has been exploited to great advantage in the multiple inert gas switches employed by Keller and Buehlmann (1965) in formulating the decompressions for their epochal diving experiments. Switching gases in the reverse direction, i.e., from less to more diffusible, to provoke gas phase formation is of largely academic interest, but the increase in the number of bubbles (D'Aoust, Smith, Swanson, White, Stayton and Moore 1979) and the increase in the probability of decompression sickness (Harvey 1977) found when this was done tends to confirm the rationale of Keller and Buehlmann. However, this confirmation calls into question one of the major axioms on which many decompression tables have been formulated, namely, that blood perfusion controls inert gas uptake and elimination from tissue.

In these transient situations we are probably concerned with different tissues than those in which symptoms can be provoked under steady-state conditions. This is fairly obvious since, in the transient situation, we can envisage a "back wall" to our tissue in which the blood is both the source of supply of one gas and a sink for the other. On the other hand, the steady-state counter-transport phenomenon requires a separate source for each of the two gases, each acting as a sink for the other, so we are probably dealing with a very different mechanism. In fact it would seem that the transient and steady-state manifestations of isobaric decompression sickness are different phenomena, and it is unfortunate that they are sometimes given the same name.

Mechanisms for steady-state isobaric decompression sickness

Though the transient manifestations of gas switching can be explained on the basis of the same models and arguments proposed for formulating decompression tables, this is not true for the steady-state phenomenon. The latter could be a red herring and may not be particularly important in commercial diving, but explaining it does present a tantalizing intellectual challenge.

There is little doubt that the real mechanism is related to the geometric requirements -- helium adjacent to epithelium separated from blood equilibrated with nitrogen, resulting in fixed gas gradients in opposite directions. When we first discovered the cutaneous manifestations (Blenkarn et al. 1971), I was working on gas-induced osmosis (Hills 1971), so this osmosis was offered as a possible explanation for the urticaria, since the gas gradients were ideally situated to effect a fluid shift in the direction of increasing nitrogen concentration. Though such shifts do undoubtedly occur, there is considerable doubt whether they would be large enough to cause cutaneous manifestations of the magnitude observed. On the other hand, it is easier to envisage how minimal fluid shifts across a membrane as physiologically active as Reissner's membrane could cause the vestibular manifestations. This reasoning is compatible with the results of some preliminary studies (unpublished observations) on four monkeys in which we found that nystagmus can be induced simply by ventilating one middle ear with nitrous oxide and the other with helium, having previously humidified both gases at body temperature. Moreover, the direction of nystagmus was reversed upon switching gases.

On the other hand, in the skin, any effects of osmotically induced fluid shifts are probably minimal compared with those of the bubbles formed and demonstrated so convincingly by Idicula, Graves and Quinn (1976). The ingenious explanation offered for those bubbles was counter-diffusion supersaturation (Graves, Idicula, Lambertsen and Quinn 1973), a concept which is based upon a tissue bilayer of two solvents for the two gases -- one aqueous and one fatty, and both of comparable thickness. Though this is a plausible mechanism to offer for isobaric urticaria, it is inappropriate to explain vestibular manifestations since there is no fat in the inner ear or, at least, there is no lipid layer of adequate thickness to cause any degree of supersatuation.

In this connection it must be remembered that, in vivo, we are not dealing with inert gases alone. Any local increase in total inert gas tension must be greater than the inherent unsaturation caused by the metabolic gases (Hills and LeMessurier 1969) before there can be a net supersaturation and, hence, before bubbles can form. The inherent unsaturation essentially arises from the metabolic conversion of oxygen into a much more soluble gas (CO_2), and must be incorporated into any predictions of overall supersaturation.

To return to the observation made above, the lack of enough fat in the inner ear to comply with the counter-diffusion model has led me to suggest that processes other than diffusion can influence the opposing gas gradients.

Counter-perfusion model

It is, perhaps, rather ironic for me to argue that blood perfusion as a process makes an appreciable contribution to gas tension gradients. However, if a circulation-controlled compartment representing the blood vessels is placed in series with a single diffusion barrier (i.e., a monolayer) to form the model shown in Fig. 1, then supersaturation can

Fig. 1. A readily diffusible gas (I) removes from outer surface of epithelium any of a less diffusible gas (II) which has permeated this diffusion barrier from the perfused zone supplied with blood free of gas I but saturated with gas II at the ambient pressure, P. By adding gas tensions, it can be seen that the effectively stirred pool and hence the overflow (venous blood) becomes supersaturated ($P_1 + P_2 > P$) as the system attains steady state. From Hills 1977.

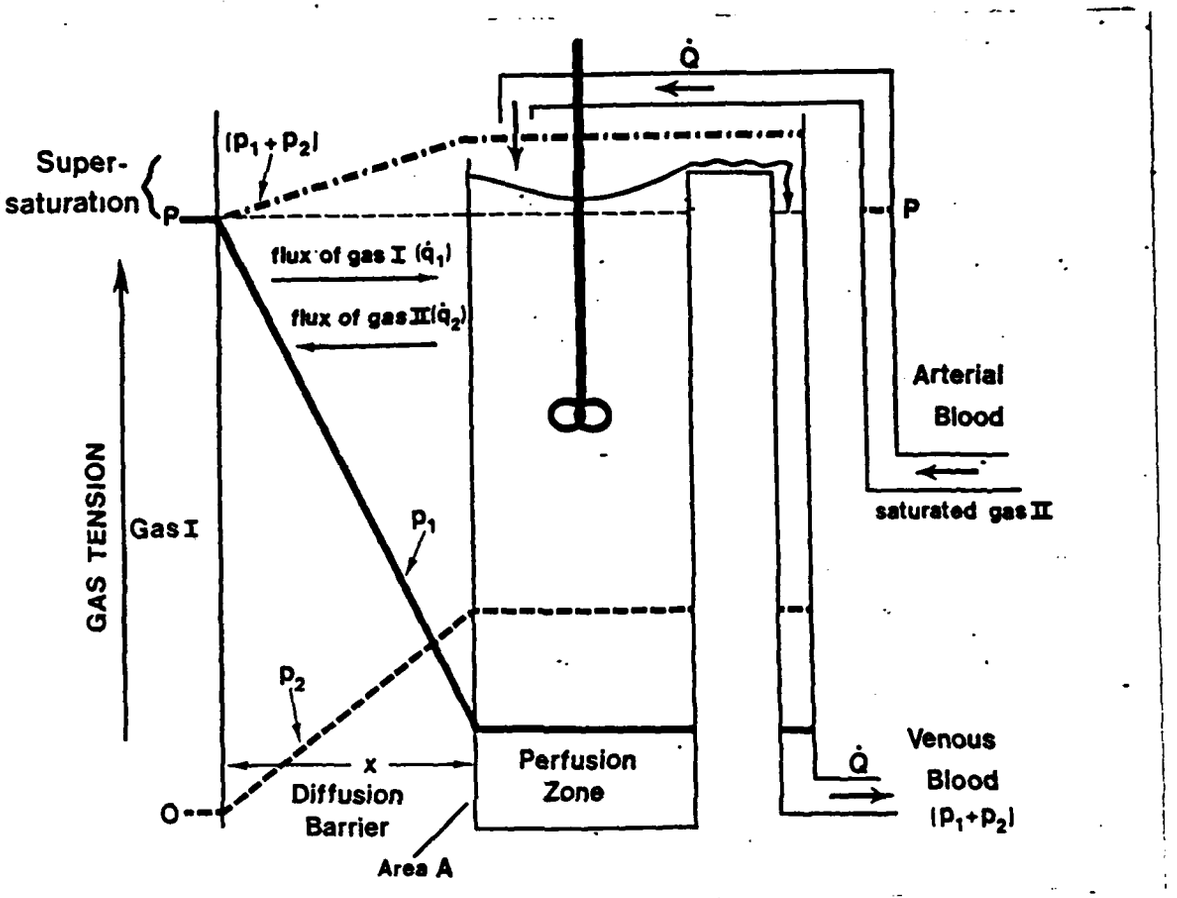
Q̇
(P1 + P2)
Super-
saturation
P
P
flux of gas I (q̇1)
flux of gas II (q̇2)
Arterial
Blood
saturated gas II
GAS TENSION
Gas I
P1
P2
x
Diffusion
Barrier
Perfusion
Zone
Q̇
Venous
Blood
(P1+P2)
O
Area A

Fig. 1.

be produced in the steady state without invoking any fat. This model has been presented (Hills 1977) as a "counter-perfusion" mechanism, although "counter-transport" might be a more appropriate term since the process also involves diffusion. In addition to its compatibility with the inner ear, the counter-perfusion model (Fig. 1) would indicate that the greatest level of supersaturation should occur in the vessels. This is compatible with the findings in experimental animals at the University of Pennsylvania (Cunnington, Lambertsen and Cowley 1978), where it was found that the opposing gas gradients cause a continuous stream of venous bubbles. Hence this model may be more appropriate than counter-diffusion for explaining the cutaneous as well as the vestibular manifestations of isobaric counter gradients. This was essentially the conclusion of Collins (1978) after his comprehensive study of counter-transport phenomena using many pairs of different gases and gases other than helium and nitrogen.

Conclusion

These arguments may sound very academic and appear to be divorced from the reality of naval or commercial diving, but isobaric decompression sickness has occurred in the field when a diver at about 150 feet breathed air on BIBS while still in the heliox environment of the bell. Moreover, vestibular symptoms are very common after transfer from the bell to the deck decompression chamber, i.e., from heliox to air. Hence it would seem desirable in commercial diving to minimize the likelihood of counter-gradients of nitrogen and helium occurring between the gas cavity of the middle ear and the blood perfusing the inner ear. Means which we have used to effect this and have tested to avoid vestibular problems in 40 man-exposures to 500 and 600 feet include:

(a) Use of Trimix to reduce the nitrogen gradient upon transferring from the bell to air in the deck decompression chamber.

(b) Compressing the first 100 feet while breathing air on BIBS in the bell to push some nitrogen into the middle ear and thus to reduce the nitrogen gradient upon switching to the deck decompression chamber during the subsequent decompression (although most of this N_2 would be washed out over a "saturation" exposure -- which could explain the higher preponderance of vestibular problems in this mode of diving).

(c) Slowly venting the bell with air for the hour or so before transfer to the deck decompression chamber.

Though our results do not prove that these measures were responsible for preventing vestibular symptoms, they are simple to incorporate into diving practice. They present no new hazards and, it is hoped, could reduce the incidence of the symptoms which opposing gradients of different gases can provoke -- whatever the mechanism(s) involved.

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SESSION III. CLARIFICATION OF TERMINOLOGY

Chairman: C. J. Lambertsen

Session III. Panel Discussion

Dr. Lambertsen: The purpose of this open discussion is to arrive at a systematic identification of words that will describe the variety of phenomena we have been discussing in the workshop so far. I have put on the board a rough outline of the different gas movement situations we have been talking about; the outline will serve as a base, to ensure that we are all talking about the same things (Fig. 1).

Fig. 1 here - Schematic of counterdiffusion terminology, drawn by Dr. Lambertsen

There are some surface-related phenomena that occur when the gas being breathed differs from the surrounding gas; we know the skin is involved, and that the eye is part of the body's surface. The ear is in the same category; we don't know whether the inner ear is involved in pathological processes, but we do know that something is happening to drive gas across the tympanic membrane. Continuing with surface-related events, the mucosa would have to be part of the picture, because we think of it as separate from the skin.

There are other exchange-related situations that occur beneath the body's surface: in the gut, the middle ear, and other deep tissues. And sometimes, both deep and surface-related phenomena occur simultaneously or in rapid sequence. With that as an introduction, let's open the topic of terminology up for discussion.

Dr. Farmer: Inner ear problems related to gas changes have been clearly identified, but there is no evidence that the middle ear is involved in these situations; the post-dive audiologic studies of the Predictive Studies IV divers do not show middle ear injury. It is possible that the middle ear played a role in these inner ear incidents; if there is heliox in the external auditory canal and the inner ear is saturated with heliox, and another inert gas mixture is introduced, there probably will be mixing problems across the round window membrane. I don't think changes in middle ear pressure per se play a major role, but I'm not prepared to exclude pressure changes from consideration altogether. In addition to any changes occurring across the round window membrane, a situation has occurred in which one compartment is differentially perfused, which makes it more than likely that something definitely has occurred in the inner ear. We need to devise a method of doing the tympanometry of pressure, taking into account that the characteristics of sound transmission change drastically with certain gases, such as helium. At Duke, we have calibrated transducers for helium down to 1000 fsw, and measurements obtained with those could be used. But I think the inner ear should be the focus of our immediate attention.

Discussant: Since we are talking about diving, a context in which the words "deep" and "surface" have specific meanings that

differ from the ones intended here, I think we should use other words to describe physiological counterdiffusion effects in the body. Another thing that should be clearly kept in mind is that there are both temporary (transient) and continuous (steady-state) phenomena.

Dr. Hemplemen: Looking at Dr. Lambertsen's list, I think we all ought to be able to agree to the use of the term "isobaric," which is unavoidable in discussing this phenomenon.

Dr. Lambertsen: Other words on the list that have been used are inert gases, counterdiffusion, supersaturation, deep tissue, subsaturation, counterperfusion, superficial, countercurrent, and mass transfer. It should be noted that gases other than inert gases, such as oxygen and carbon dioxide, are often involved in these situations; also, I have deliberately not used the term gas transfer, which is often misused.

Dr. Hempleman: We need words to describe the isobaric switching of ambient gas, and I think we should avoid words primarily related to modeling, like counterdiffusion and counterperfusion. To my mind, the one key word is supersaturation.

Dr. Vann: There are four possibilities externally that arise from the situation we're talking about: the breathing gas can be changed, or the environmental gas can be changed; both can be changed; neither can be changed; or either one can be changed. That is the "action" level -- there is also the symptom level, and the level of mechanisms. There should be three sets of words, one associated with each level.

I think it would be helpful to systematize the information we have obtained from actual experimental situations involving the phenomenon we're trying to define; with that as a base, perhaps we could talk more intelligibly about terminology.

The first case, at Virginia Mason and later at New London, involved breathing nitrogen initially and being surrounded by nitrogen; the symptoms were itching and pain, and presumably there was supersaturation. In the second experience, here at Pennsylvania, the divers started out breathing nitrogen and surrounded by helium; the symptoms were itching, skin lesions, and intravascular gas. In the third instance, again here at the Institute, the men were breathing helium and surrounded by helium, and at the end of the experiment they were breathing neon while surrounded by helium. Their symptoms were itching, skin lesions, and vestibular dysfunction.

At Duke, in the foutth experiment, the divers began the experiment both surrounded and breathing helium, and ended up breathing nitrogen in a nitrogen environment; the men developed itching and skin lesions. In the fifth case, the subjects started with both gases helium, ended up breathing nitrogen and surrounded by nitrogen, but had undergone air shifts during decompression -- in this case, both decompression after a deep dive and air shifts had been added. The symptoms were vestibular.

In the Keller-Buehlmann dive, they started out with helium and helium, and ended with nitrogen and nitrogen; theirs was an undersaturation situation, presumably. Finally, there is another combination that is used in the laboratory: begin with helium breathing while surrounded by nitrogen, and continue with the same gases throughout: no problems develop. Maybe reviewing these experimental situations will help us to find the right words to describe what we have seen.

Dr. Yount: It is important to remember, despite the fact that we have all agreed that the highest box on the terminology chart should say "isobaric," that we often encounter gas exchange problems during decompression; using the general term isobaric misses the synergism involved when gas exchange and decompression act cumulatively. I have developed a glossary of terms; after I present it, perhaps we could discuss it.

Exogenous gas bubble disease: A disease syndrome associated with the formation, via external causes, of gas bubbles in blood or tissue.

Decompression sickness: A form of exogenous gas bubble disease in which a state of supersaturation is achieved by reducing the ambient pressure.

Multiple inert gas bubble disease: A form of exogenous gas bubble disease in which a state of supersaturation is achieved by using two or more inert gases, either sequentially or simultaneously.

Isobaric supersaturation: A state of supersaturation produced at constant ambient pressure, for example via inert gas exchange or a temperature change leading to reduced solubility.

Isobaric multiple inert gas supersaturation: A state of supersaturation produced at a constant ambient pressure by using two or more gases, either sequentially or simultaneously.

Sequential inert gas supersaturation: A state of supersaturation produced by using two or more inert gases sequentially.

Simultaneous multiple inert gas supersaturation: A state of supersaturation produced by using two or more inert gases simultaneously.

Isobaric: at constant pressure. A process is isobaric over some time interval if there is no significant change of pressure during that interval. Mathematical definition: A process is isobaric over some time interval if this equation

$$\lim_{\Delta t \to +} \frac{\Delta P}{\Delta t} = 0$$

is satisfied throughout that interval. Practical definition for inert gas exchange: A process is isobaric if there is no significant change in pressure during a time interval long enough to permit a substantial exchange of inert gas.

Dr. Lambertsen: I think that glossary is an excellent beginning, and perhaps what we should do is assemble a small group at

another time to work on a glossary of terms describing this phenomenon. In the meantime, I'd like to propose a few words for discussion that I think are being misused. The first is "transport;" it is being used to mean the spontaneous and unforceful movement of molecules from one point to another, for example in diffusion, when it should properly be limited to situations in which something is being moved by means of a pump, such as the heart, from one place to another.

"Countercurrent" is a term borrowed from renal and thermal physiology, and it has specific meanings in those fields, but it is being misused here. "Perfusion" is another term that needs to be thought about. It is used in two ways in physiology: to mean pumping blood through vessels, as in the perfusion of tissues by blood, which is the correct meaning. In the other case, we misuse it when we say something is perfusion limited, by which we mean something that has to do with the movement of gases in the blood, or the delivery of gases in the blood; what is perfusing is a gas, not the blood. As long as this second definition is meant, there can't be such a thing as counter-perfusion because the flow in the capillary does not move in two directions. Perfusion is therefore another example of a word that should be used with care.

Dr. Lanphier: We also desperately need a synonym for "bubble." We have a tendency to misuse "embolus," but a bubble is not

an embolus until it lodges somewhere. We have not maintained that distinction during this workshop.

Dr. Farmer: Since the purpose of these workshops is information and its dissemination, and since we have been unable to reach a consensus on terminology, the report of this workshop should simply include the suggestions for terminology that have been put forward here.

Dr. Lambertsen: Let's end this session by saying that we will have another smaller meeting in the future, at which we will try to develop the terminology to describe the complex phenomenon we are dealing with; at that time, we will try to keep several aspects of the phenomenon, including clinical observations, operational considerations, and laboratory circumstances, in mind.

SESSION IV. IMPLICATIONS IN OPEN SEA AND CHAMBER OPERATIONS, DECOMPRESSION AND THERAPY

Chairman: R. C. Bornmann

Session IV. General Discussion

Dr. Bornmann: It is important to remember that certain dynamics having to do with the characteristics of the gas, the characteristics of the delivery, and the characteristics of the membrane determine whether or not bubbles will form; for example, if the order of presentation of the gases is reversed, nothing of practical consequence happens -- no bubbles occur. In our four-choice box, the presentation or inside-outside relation of the gases makes a great difference. The complex nature of the phenomenon we're studying should also be kept in mind. And further, when we analyze the practical risk involved, we need to determine what, theoretically, the possibility is that something will happen, and then to calculate, given the possibility under certain circumstances, what the likelihood in a specific instance is that it will happen. Finally, the magnitude of the risk that would occur if all of these things fell into place needs to be determined. We know that when a diver decompresses, there are bubbles all over the place, but very few of these divers develop decompression sickness.

Dr. Lambertsen: It will be helpful to list practical field or laboratory situations that involve a gas change under three categories: compression, decompression, and recompression. One example of an inert gas change that has been conducted for 40 or 50 years is helium diving after air saturation; this gas change might present problems if the dive was deep enough.

Another example would be saturation on a nitrogen-oxygen mixture at a depth of 60 or 100 fsw, and then going deeper in a helium excursion. Some of you may believe there could be problems in air excursions from air saturation at one or more atmospheres. Diving in a chamber in which the compression atmosphere is air but the diver is breathing helium-oxygen by mask, or any other breathing mixture by mask, should also be added to the list; we should consider in what situations a diver so exposed would be at risk.

During the decompression phase, shifting to air or nitrogen-oxygen to accelerate decompression after a helium dive or during a helium decompression is an example of an operational air shift. Further, even if the diver breathes helium-oxygen all the way to the surface, an air switch is involved when the diver reaches sea level or when he takes his mask off. Another decompression situation involving an inert gas switch might be a shift to oxygen during decompression on air or helium; although we are not used to thinking of oxygen as an inert gas, are there circumstances in which it does act like an inert gas that might pose a hazard of the type we're discussing?

The final category is recompression; the gas switches involved are common: after a helium dive, the diver surfaces and develops decompression sickness and is recompressed on air, or he dives on air and is recompressed in a helium

atmosphere. Or the diver breathes oxygen by mask and is recompressed. We should classify these and other operational gas switching situations as not hazardous, hazardous under limited circumstances, or hazardous in general.

Dr. Lanphier: There are some situations at normal pressure that should also be discussed. For instance, some concern has been expressed about difficulties that might arise when respiratory physiologists switch from sulfur hexafluoride to helium, and there are also anesthetic situations, such as switching from halothane breathing, that have the potential to be hazardous. There has probably not been much difficulty in the past because the concentrations of halothane are so low, and probably no one has been exposed to sulfur hexafluoride long enough to saturate on it.

Switching from air to helium does, according to our calculations, produce a fair amount of supersaturation, especially if the chromatographic model is correct. However, in diving this is apparently an innocuous event; has anyone made such a switch and then taken the animal or subject to altitude? That might provide us with an index of the hazard.

Discussant: Something of that sort was done in the Apollo program; they switched to a helium atmosphere and then went to altitude. There was more decompression sickness with helium than with nitrogen; the onset of decompression sickness occurred earlier.

Dr. Flynn: An isobaric category should be added to the list. For example,

in the Deep Submergence Rescue Vehicle (DSRV) program, we intend to transfer at 132 fsw from nitrox saturation to helium saturation. Another isobaric gas switch occurs when, in an experimental situation, there is trimix in the chamber and the physiologist wants to study the effects of helium breathing. Both of these situations involve washing out some nitrogen and washing in helium.

Dr. D'Aoust: Several diving companies have tried welding in an argon atmosphere while the diver breathes helium; this permits them to weld dry, and is another operational example of isobaric inert gas counterdiffusion conditions.

Dr. Lambertsen: It is important to remember that these categories of events are not mutually exclusive: any point during compression, decompression, or recompression at which the pressure is held steady is an isobaric point.

Dr. Hempleman: Another situation where there is one gas around the body and another is being breathed occurs during short excursions in water of moderate temperature when the diver is breathing helium but air is serving as the insulating blanket in the suit.

Discussant: We have been doing dives to as deep as 140 fsw for 10 minutes in a no-decompression dive or to 100 fsw for 60 minutes while the chamber is compressed with air and the diver is breathing helium-oxygen by mask. From what I have read about counterdiffusion, this sort of situation should present no hazard; however, we are planning to go

as deep as 300 fsw for 30 minutes soon. Has there been any operational experience, or are there theoretical considerations, that should be taken into account before we do that?

Dr. Hempleman: We have done dives of that sort in the past, but they have and should only be short dives; if the breathing system fails, the diver must be decompressed immediately into a zone of safety because he is breathing very high partial pressures of nitrogen and oxygen. Of course, this is not a counterdiffusion problem.

Discussant: Any time a diver comes off the mask for any reason, he takes on nitrogen; when he switches back to the mask, the same kind of situation would be created as with a helium switch after nitrogen saturation, especially in rapidly exchanging compartments. There don't seem to be problems except after a long period of saturation; short transitions don't appear to cause trouble.

Dr. Hempleman: In Link's early saturation work, a greater degree of nitrogen narcosis was observed than could be accounted for by the air partial pressure. I think it's possible that counterdiffusion may have been involved somewhat. There has also been the suggestion that the Link divers had some vestibular involvement. Also, in commercial diving it is common for the diver to breathe helium on mask in the deck decompression chamber when the bell is

in air. I have never heard of difficulties with this situation, even at 500 fsw.

Dr. Lanphier: We should be cautious about saying that certain situations are safe on the basis of a relatively limited exposure. When considering a situation such as the possibility of vestibular problems in the Link experiments, we should avoid saying that nothing untoward happened until the data have been looked at in that light.

Cdr. Smith: I am wondering whether there are percutaneous absorption risks in a rescue situation where a rescuer wearing a Scott Air Pack or a rebreather enters a gaseous or petroleum vapor atmosphere, at any pressure or at sea level pressure.

Dr. Lambertsen: The question is a very interesting one, and it should be investigated, but it goes beyond the scope of this workshop.

Dr. Vann: In the past, after a helium-oxygen dive we have recompressed the diver on air, or oxygen for the shallower Table 5 or Table 6. Are there circumstances in which we should consider using helium for recompression?

Discussant: One such situation occurs when a diver has had an omitted decompression or an air embolism and it is clear that recompression to 165 fsw is not going to save the diver's life.

Dr. Vann: Are counterdiffusion problems likely in the situation you described?

Discussant: Probably not, at least during the recompression phase, because any gas is being compressed. When helium has been used to recompress, it has been very effective, principally because helium makes more oxygen available to the tissues than nitrogen does.

Dr. Bennett: Counterdiffusion was one of the things we worried about at Duke, and the treatment John Miller and others have developed therefore calls for recompressing to 165 fsw and then saturating on 0.5 atmospheres of oxygen. We feel this technique is preferable to trying to judge whether going deeper on helium will provide a sufficient safety factor in a particular case.

Discussant: The Duke experience, which involves treating individuals whose decompression has been delayed by several hours, is very different from the omitted decompression or embolism situation that was posed earlier. Two examples of the omitted decompression or embolism problem are the accidents on the U.S.S. Chanticleer and the U.S.S. Skylark, in which the divers blew up from a tremendous depth and either walked into the chamber or regained consciousness while being recompressed on air, only later to lapse into unconsciousness and die. I think that either recompressing to 300 or 400 fsw with helium or saturating would have dealt with the gas phase and permitted these men to be stabilized. The question being posed is: Does the benefit

of the increase in static pressure outweigh the risk associated with counterdiffusion?

Discussant: There was a case of blow-up in the Gulf recently, where the man came up from 250 fsw. He was initially recompressed to 190 fsw on air because the rig didn't have any helium. After 6 hours at 190 fsw, they transferred him to a rig that had helium saturation capability, and this treatment was effective. The diver has some residuals, but the wonder is that he's alive at all.

Dr. Lanphier: In the perfusion-limited gas exchange model, one would predict, with a 2.6 to 1.0 nitrogen to helium ratio, that an isobaric shift at 165 fsw would cause some overpressure. If one shifted and recompressed an additional 200 fsw, the supersaturation would be destroyed. If one shifted at 60 fsw, there would be a smaller overpressure that would disappear with an additional 20 fsw of recompression. This phenomenon is a result of an oxygen window caused by increasing pressure at a greater rate than the gas pressure is increasing. At least theoretically, then, if a gas switch was accompanied simultaneously by recompression, overpressure problems might be avoided.

Discussant: Some recent gelatin experiments of Ed Beckman's show that bubbles formed at high pressures require higher pressures to eliminate. The implication for a treatment table would be that symptoms with onset at depth require treatment at

deeper depths than symptoms with shallow onset or surface onset.

Discussant: In an operational situation of a blow-up from 450 fsw after 30 minutes at that depth, and with helium saturation capability available, it is safe to say that the counterdiffusion effects can be ignored.

Dr. Bennett: In the Gulf, they often recompress to 165 fsw on air, and stay there for the prescribed treatment time. But at the end of the air treatment, if the patient isn't improving, they have to make a decision whether or not to switch to helium.

Discussant: Another difficult operational situation occurs when the NOAA Ops procedure is being used. For example, a diver is saturated on nitrox at 100 fsw, makes an excursion on nitrox to 250 fsw, and then presents with vestibular symptoms on his return to 100 fsw. There are three treatment options: the diver could be brought from the habitat in a bell and transferred to a deep diving system; he could be transferred into a nitrox environment at 100 fsw and then be recompressed deeper with helium; or he could be transferred at 100 fsw and then be recompressed deeper with nitrox. What treatment would be best in these circumstances?

Discussant: It would be best to recompress him to 200-225 fsw on nitrox, rather than using helium at that nitrox saturation level. I would not compound the vestibular problem

by switching gases; thus far, recompressing to 3 ATA deeper than symptom onset depth has worked well with inner ear problems.

Discussant: If you can compress faster than the transient potential supersaturation, you will be safe. If you have to switch to helium to go deeper, the best way to do it is just by topping off with it, slowly.

Discussant: Using the diffusion-limited model, there would be more and more driving force for gas coming into the tissue, the same driving force as is available for gas out of the tissue.

Dr. Lambertsen: It is essential to avoid setting up rigid rules about what can or cannot be done in certain instances. In actual operational situations, there are many factors to be considered: the oxygen partial pressure, the inert gas, the rate and degree of compression, the equipment available, and the seriousness and time limitations of the symptoms you are dealing with.

Discussant: It seems clear that the risks associated with counter-diffusion do not outweigh the need for prompt recompression. Vascular emboli are not a short-term problem with counter-diffusion — they do not develop for many hours.

Dr. Farmer: The vestibular incidents that occurred during decompression from a deep helium-oxygen dive and after an air shift were decompression sickness incidents rather than counter-diffusion or counterperfusion phenomena. I think a helium bubble that formed deep was stimulated by the air shift

to the point where it became clinically significant. The situation may have been aggravated by counterdiffusion effects, however. The diver with an inner ear problem should be recompressed with the same or similar breathing mixture as was used in the dive.

Dr. Lambertsen: Since what you are recommending runs counter to therapy and decompression theory, would you explain the basis for your opinion?

Dr. Farmer: It is based on my intuitive feeling that the bubble causing the problem is a helium bubble. Drs. Miller and Bennett agree with my treatment recommendations, although we have only subjective and clinical evidence to rely on.

Discussant: However, in cases other than those involving the inner ear, we have been using air for recompression of type I decompression sickness for decades, and this procedure has been effective, simple, and economical.

Dr. Lambertsen: And air treatment in those circumstances also has advantages, theoretically — that is the important part.

Discussant: The vestibular hit and the peripheral hit are physiologically not the same. The tissues involved in the peripheral event are perfusion limited. The vestibule, however, has a fluid reservoir, which acts both as a source and a sink for gas molecules, and there may be a diffusion barrier in the surrounding tissue. It is easy to imagine that the inner ear situation resembles that of the skin, in which a diffused

subcutaneous base lies under a horny diffusion layer. A similar situation would occur in any compartment, for example in the bowel, with nitrogen coming in through the wall and a helium reservoir inside the bowel. The cerebral spinal fluid, and perhaps the vitreous humor, are other examples.

Discussant: Dr. Hempleman, is it still your opinion that the percentage of inner ear injuries that occur in deep decompression sickness on very deep helium-oxygen dives is higher than for shallow or moderately deep helium-oxygen dives?

Dr. Hempleman: My opinion has altered only to the extent that I would now say that on such dives the likelihood of any type II incident is higher than experience at shallower depths would indicate; I would not now limit the statement to inner ear incidents only.

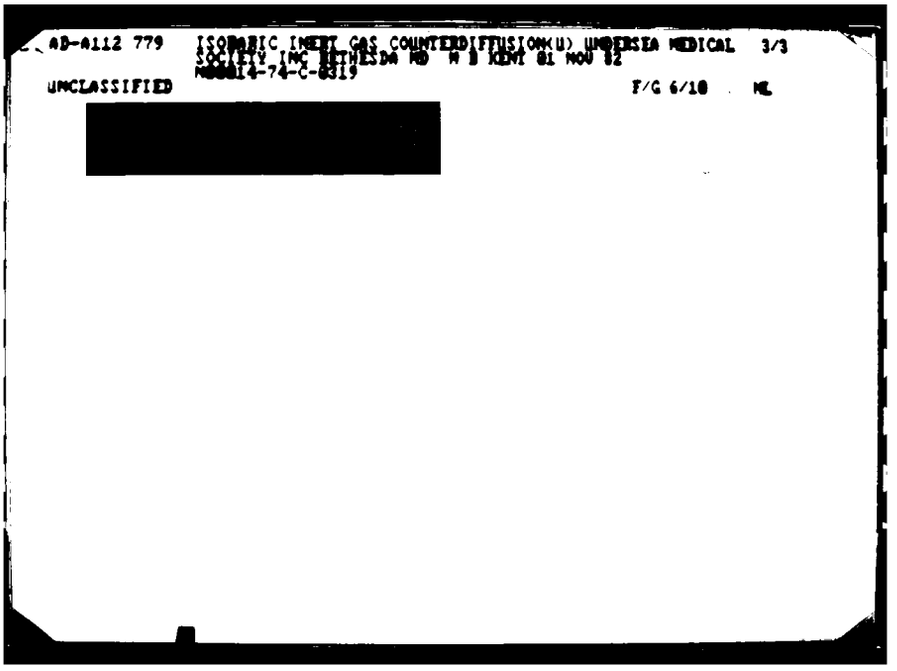
Dr. Lanphier: Dr. Bennett, would you expand on your statement that more oxygen is available to the tissues with helium than with nitrogen?

Dr. Bennett: In some experiments with cats, which have been published in the Journal of Applied Physiology, we measured the available oxygen in the cortex. We used 35 psi of oxygen, and added up to 132 psi of helium, and also did this with other gases such as nitrogen and argon. We found that when helium and oxygen were used, the amount of oxygen available was almost the same as if oxygen alone had been

used. The amount of oxygen became progressively less when nitrogen was used, and continued to fall with argon.

Dr. D'Aoust: Some other work that points to the mysteries of helium was done by Larry Raymond, who found that breathing helium-oxygen increased the time until ventricular fibrillation was reached by 25%, compared to nitrogen-oxygen breathing. He suggested that the diffusions of the two gases in the lung might be responsible.

Dr. Lambertsen: In closing the workshop, I would like to say that it has been successful -- many topics of interest have been raised, and several problems have been recast as questions for research, the results of which will appear over many years.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agencies and universities but all

The co-Chairmen were Prof. Dr. Ch
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