THE PHYSIOLOGICAL BASIS OF DECOMPRESSION

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THE PHYSIOLOGICAL BASIS OF DECOMPRESSION: AN OVERVIEW

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The exchange of dissolved inert gas between blood and tissue is controlled by blood flow and diffusion. To a first approximation, blood flow is the primary determinant. The exchange rate is proportional to the partition coefficient, the ratio of the tissue and blood solubilities. Diffusion has a modifying influence on gas exchange in heterogenous tissue. Weathersby provides a table of gas properties.

The interaction of perfusion and diffusion can be evaluated by analyzing the arterial to venous transit times of gas molecules in model tissues. Transit time analysis allows an entire exchange curve to be described by two parameters, the mean transit time and the relative dispersion. The relative dispersion is the standard deviation of the transit time distribution divided by the mean transit time.

An ideal, well-stirred tissue with a mono-exponential washout curve has a relative dispersion of unity. Whole-body washout curves are multi-exponential with relative dispersions of about three. The common representation of the body as a collection of ideal tissue compartments perfused at different rates has a dispersion of about two indicating that heterogeneous perfusion accounts for some of, but not all, the deviation from ideal behavior.

Experimental washout curves from individual tissues have dispersions of about two. Factors contributing to dispersions greater than unity include heterogenous perfusion, heterogenous solubility, diffusion between heterogeneous tissue regions, and countercurrent gas exchange between arterial and venous vessels.

Perfusion heterogeneity and countercurrent exchange were simulated by random walk methods in microcirculatory units with as few as four and as many as thousands of capillaries. In regions as thick as 1cm, rapid diffusion eliminated concentration gradients resulting from regional blood flow differences of 3:1, and perfusion controlled inert gas exchange. With larger flow differences, concentration gradients developed, and diffusion became a controlling factor. Diffusion parallel to capillaries and arteriovenous countercurrent gas exchange appeared to be unimportant in these 0.1cc tissue regions.

The distribution of blood flow to tissue changes frequently. When regional flow is high, perfusion dominates gas exchange. Diffusion dominates when flow is low. Flow distribution is regulated by the mean arterial pressure and local peripheral vascular resistance. Mean arterial pressure is determined by cardiac output and total peripheral vascular resistance. Vascular resistance is regulated extrinsically and intrinsically. The sympathetic nervous system provides extrinsic control

of perfusion by maintaining basal constriction of arterioles and precapillary sphincters. Metabolites, temperature, and local and systemic hormones provide intrinsic regulation of arteriole and sphincter tone.

Tissues differ widely in how they regulate blood flow. Metabolically active tissues such as brain, heart, and muscle exert strong intrinsic control. Blood flow to the brain and spinal cord is quite heterogeneous. Flow can be high in tissue masses as small as 0.2g and low in adjacent masses. Local flow can be zero for as long as two minutes. When flow is low in regions of this size or larger, diffusion is the primary gas transfer mechanism.

During immersion in cool or cold water, translocation of blood to the chest increases the central blood volume by about 700ml. This improves regional lung function but has little effect on pulmonary inert gas exchange which is rapid for low solubility gases such as nitrogen, helium, and argon. Cardiac output increases by 30%, systemic vascular resistance decreases by 30%, and tissue perfusion rises without changing the oxygen consumption. The plasma volume increases during the first 30 minutes of immersion as fluids move into the vascular space from tissue. This leads to diuresis at 30-120 minutes. Warm water immersion causes peripheral vasodilation which blocks the shift of blood into the thorax.

In thermoneutral water, the distribution of blood flow is similar to that in air, but flow is slightly higher to skin. In cold water, peripheral vasoconstriction decreases heat loss without increasing oxygen consumption. Below a critical temperature, vasoconstriction reduces blood flow to 10-15 ml/min/100g, and oxygen consumption rises with the onset of shivering. Vasoconstriction and reduced blood flow to fat and muscle can persist in cool water even during shivering.

Blood flow to fat and muscle are mediated intrinsically at first by low skin temperature and later by decreased core temperature through the extrinsic sympathetic and hormonal pathways. Skin and core temperature affect flow to skin and fat while perfusion of resting muscle is influenced only by its own temperature. Increases in blood flow at one location are frequently accompanied by decreases at another location. During exercise, increased muscle flow is accompanied by decreased flow to kidney and liver. A 20-fold increase in muscle flow is attended by decreased splachnic flow, but the spleen is generally not involved in decompresson sickness. "Slow twitch" or red muscle is highly vascular and exchanges inert gas rapidly but undergoes random changes in flow.

During exercise in cold water, muscle blood flow is lower than in thermoneutral water, but exercise keeps muscle warm and blood flow elevated even when the skin is cold. Blood flow to fat increases during exercise except in cold water immersion. At exercise levels below the anerobic threshold or onset of fatigue, physical conditioning has no effect on blood flow and does not influence inert gas exchange except, perhaps, by elevating resting flow after long periods of heavy aerobic exercise. Adaptation to cold reduces the prompt and extreme vasoconstriction which usually occurs upon immersion in cold water.

Alteration of local perfusion heterogeneity does not necessarily influence respiratory nitrogen exchange. Blood flow can be drastically redistributed at regional levels without greatly affecting whole-body nitrogen washout although nitrogen might be trapped locally. Rest in a cold environment, however, reduces whole body nitrogen exchange from skin, fat, and muscle while exercise significantly increases nitrogen exchange.

Whole body nitrogen elimination is increased and decompression risk reduced by factors which elevate blood flow. This has been demonstrated for exercise and for warm water immersion during oxygen breathing before altitude exposure. In diving, light exercise during decompression also reduces decompression time and risk. For exercise to be beneficial, however, bubbles must not be present. Exercise significantly increases DCS risk after decompression to altitude and during slow decompression from saturation diving where bubbles are common.

Other environmental or physiological conditions which may affect DCS risk by increasing perfusion and respiratory inert gas exchange include hypoxia, carbon dioxide inhalation, a supine body position, vasodilators, and negative pressure breathing. The vasodilator terbutaline and negative pressure breathing both reduced the incidence of precordial gas bubbles at altitude. DCS risk also can be affected by cold water immersion, positive pressure breathing, hyperoxia, and an erect body position which decrease perfusion and gas exchange. Pendergast provides a table of blood flows to various organs and tissues under a number of conditions.

The absorption of inert gas is not a major factor in altitude exposure but is of great importance during diving and caisson work. Conditions which influence absorption at pressure and elimination during decompression will have opposite effects on DCS risk. Faster gas exchange at pressure increases risk while faster exchange during decompression decreases risk.

Nitrogen exchange is least favorable for the diver who is warm while exercising on the bottom and cold while resting during decompression. These conditions may pose the greatest risk of decompression sickness. For a diver who exercises at depth and during decompression, the effect of temperature depends on the relative lengths of the bottom and decompression times. It would be better to be cool during a no-stop dive, but warm on the surface after the dive. On a dive with short bottom time and long decompression time, it might be better to be warm.

Divers and caisson workers both are exposed to conditions unfavorable to optimal gas exchange and decompression safety. They exercise at pressure and frequently rest during decompression while sitting in a cool, dry chamber. To stay warm at pressure, a diver may wear a hot water suit which raises perfusion and gas uptake. The hot water usually is turned off or the suit removed during decompresson which compromises elimination.

By preventing hypothermia, hot water suits have improved diver alertness and manual dexterity as well as the depth and time of useful work. They are essential to safe and efficient diving, but DCS risk would decrease if divers were warm and immersed (or supine if dry) during decompression. A diver who must decompress in cold water will be warmer if he exercises. Hypothermic and postural hypo-perfusion in both divers and caisson workers could be eliminated and DCS risk reduced by decompression in a hot-tub.

Helium is absorbed faster than nitrogen. A mixture of these gases provides no decompression advantage, but their difference in gas exchange kinetics can be used to advantage by switching from helium to nitrogen during decompression. As helium is eliminated faster than nitrogen is absorbed, decompression time is reduced. In animals, the DCS potency of nitrogen is greater than of helium but less than of argon.

A bubble might be viewed as a tissue with a high inert gas solubility into which gas diffuses from its surroundings. Diffusion and perfusion are in series when a bubble is present. Gas must diffuse back into tissue before it can be removed by blood flow. Perfusion sets the inert gas level in tissue, but diffusion controls the rate at which gas leaves the bubble. The principles of diffusion describe the growth and resolution of large subcutaneous gas pockets in tissue. Small bubbles resolve faster than gas pockets because of surface tension and curvature.

Metabolism controls oxygen and carbon dioxide in tissue to low and nearly constant levels. After a change in pressure, oxygen and carbon dioxide in a bubble equilibrate rapidly with tissue. Nitrogen in tissue slowly equilibrates with its partial pressure in the lung. The difference between nitrogen in a bubble and in tissue is a consequence of the conversion of oxygen to carbon dioxide and is known as the oxygen window. The oxygen window is the driving force for nitrogen elimination. It increases linearly with the inspired oxygen but levels off at high partial pressures which are determined by local blood flow and metabolism.

A bubble can resolve ten times faster during oxygen breathing than during air breathing. At partial pressures below about 2 ATM, oxygen is an innocuous replacement for inert gas. At higher partial pressures, its tissue tension increases, and it assumes some of the DCS potency of an inert gas. The influence of carbon dioxide on DCS risk appears to be small.

The rate at which gas enters or leaves a bubble depends on its diffusivity-solubility product, known as the permeability. If the gas diffusing in has a higher permeability than the gas diffusing out, a bubble will grow. This is counterdiffusion. Relative to helium or nitrogen, nitrous oxide has a high permeability and causes bubbles in tissue to grow rapidly. Carbon dioxide has a high permeability but a low tissue tension.

Helium has a greater permeability in aqueous tissue than nitrogen. A nitrogen bubble expands as helium diffuses in. The effect of counterdif

fusion in lipid tissue is less certain as there are no data on lipid solubility. If the lipid solubility of nitrogen is greater than of helium, the bubble will shrink. This is the rationale for recompressing a nitrogen CNS bend on helium.

Cutaneous counterdiffusion occurs when the skin of a diver (or animal) breathing a slowly diffusing gas (e.g., nitrogen or nitrous oxide) is exposed to a rapidly diffusing gas (e.g., helium). Bubbles can form when inward diffusion of the faster gas causes the skin to become supersaturated. During counterdiffusion of helium and nitrous oxide, the difference in diffusivity is so large that bubbles form at sea level. With helium and nitrogen, the smaller diffusivity difference precludes bubble formation below an absolute pressure of about 5 ATA.

Bubbles forming in the skin enter the venous blood, and after a delay, appear in central venous circulation. In animals, the bubble volume depends on the exposed skin area, and their mass is proportional to the absolute pressure. In situ bubbles are less damaging to pulmonary capillaries than injected bubbles.

There are two principal mechanisms by which bubbles can originate: de novo formation (from nothing) and formation from gas nuclei (pre-existing bubbles). Depending on the gas species, de novo formation in water requires supersaturations of 120-360 ATM while formation from gas nuclei occurs at supersaturations of only tenths of atmospheres, regardless of the gas species. Gas nuclei can be dissolved and bubble formation reduced by hydrostatic pressure treatment. In animals, bubbles form at supersaturations as low as 0.5-0.7 ATM, independent of animal species or absolute pressure, and hydrostatic pressure treatment reduces both bubble formation and DCS. These observations indicate that bubbles in animals originate from gas nuclei.

Gas nuclei appear to form during the relative motion of tissue structures. Viscous adhesion during this motion generates negative pressures which are hundreds of atmospheres in magnitude. The resulting supersaturation is mechanical in nature rather than gaseous and causes bubbles to form by a mechanism known as tribonucleation. Tribonucleation is responsible for gas cavities detected by x-ray and CT-scan in almost every joint of the body including the spine. These "silent" bubbles are known as vacuum phenomena and are seen in people who never have been decompressed.

The creation and destruction of gas nuclei appear to be in dynamic equilibrium. Factors such as exercise (particularly pre-dive weightlifting) promote the creation of nuclei. This increases bubble formation and DCS risk. Factors such as pressure treatment promote the destruction of nuclei. This reduces bubble formation and risk. Decreased risk has been reported following daily pressure exposure for caisson workers and for several animal species. Known as adaptation, this effect has been attributed to the elimination or consumption of gas nuclei. Adaptation is controversial, however, as it can be difficult to demonstrate and because DCS risk has been observed to increase during multi-day repetitive diving.

Bubble formation is rare in stationary tissues such as liver, kidney, or brain which lack the moving structures necessary for tribonucleation. In the skin, bubble formation is minimal during decompression but extensive during counterdiffusion. These bubbles probably originate from gas nuclei trapped in cutaneous tissue layers. As the bubbles expand, they develop into hard, raised, white, and bloodless lesions throughout the full skin thickness. The lesions dissect the tissue and seed the blood with gas. Bubble formation does not occur in the eylids, conjunctiva, sclera, or cornea during counterdiffusion. Perhaps these tissues lack gas nuclei.

Blood is naurally resistant to bubble formation. Gas from bubbles which form during decompression may enter the blood by dissecting the tissue as in counterdiffusion. Bubbles in the venous blood are carried to the heart where they can be detected by ultrasound. The correspondence between precordial bubbles and DCS is poor, but decompression risk increases with the bubble load. At Doppler bubble Grades of III or IV, about 5% of the inert gas is carried by bubbles while 95% is dissolved. At very high bubble loads during counterdiffusion or after extreme decompression, death can occur when gas displaces blood from the heart.

In normal hearts, venous blood passes directly to the lungs. Eighteen to 25% of the population, however, have right-to-left shunts which can allow venous bubbles to enter the arterial circulation. In the fetal circulation where the lungs are not functional, these shunts are completely open but usually close at birth. Diving during pregnancy can cause arterial bubbles in the fetus. Preliminary evidence suggests that incomplete closure right-to-left shunts may be responsible for arterial bubbles and some serious DCS in adults. Shunts can be detected by 2-dimensional echocardiography with bubble-contrast injection.

In reasonable quantities, the venous bubbles entering the lungs are filtered by the pulmonary circulation. At bubble loads above Doppler Grades III or IV, however, the pulmonary artery pressure rises, and bubbles can pass through the pulmonary filter into the arterial circulation. Bubbles arising from decompression or counterdiffusion cross the lungs more easily than injected bubbles but are less damaging the pulmonary circulation. During repetitive diving, bubbles trapped in the pulmonary circulation from a first dive can be compressed and enter the arterial circulation on a second dive.

Arterial bubbles are occasionally detected in asymptomatic humans, most often at high pressure. High pressure bubbles may cross the pulmonary filter more easily than low pressure bubbles which contain fewer gas molecules. Doppler signals which appear to be intravascular bubbles have been reported in goats at a stable depth of 1000 msw.

The dangers of arterial gas embolism are well known. Arterial bubbles have been proposed as a cause of spinal DCS, but venous bubbles and <u>in situ</u> or <u>autochthonous</u> bubbles also have their proponents. While this controversy awaits resolution and all three mechanisms may be active in the appropriate circumstances, the evidence appears to favor autochthonous bubbles as the most common initiating factor.

The brain is the principal target in embolic diseases rather than the spinal cord, and few diving physicians report that cerebral symptoms accompany spinal DCS. Compared to the brain, the spinal cord is resistant to ischemic injury. Venous infarction usually affects both grey and white matter and has a segmental distribution. Spinal DCS, on the other hand, appears as spotty, punctate lesions involving only the white matter. Vacuum phenomena within the spinal canals of non-divers are evidence for gas nuclei from which autochthonous bubbles might grow. Increased pressure as these bubbles expand within the spinal canal might lead to a compartment-like syndrome in which first the venous and then the arterial circulation were compromised. Hemorrhage would be a secondary occurrence.

"A fish just outside Constantinople,
Was caught in a net and in trouble,
He was brought to the top,
Where he fizzed and he popped,
Not caring was it Complement or Bubble?"

Enrico Camporesi
Karen Van Hoesen

Closely linked to these events are the biochemical effects that bubbles have on blood and tissue. Bubbles are foreign bodies which can disrupt cells and release or activate at least 20 proteins including the vasoactive substances bradykinin, complement, histamine, prostoglandin, and 5-hydroxytryptamine. These chemical mediators act rapidly (as in an insect bite) and are deactivated rapidly. Animal experiments have shown that DCS can be produced by introducing such mediators and prevented by removing them or by adding antagonists or inhibitors.

There is evidence that DCS may be caused by bubbles in the circulation which activate the complement system. DCS susceptibility can be reduced, for example, by depletion of complement proteins. Rabbits were made resistant to DCS by decomplementation, and humans who were sensitive to complement activation were found to be susceptible to DCS. Repetitive diving may cause decomplementation and result in the decreased DCS susceptibility known as adaptation. Individual complement sensitivity is highly variable and could explain the intra-individual changes in DCS susceptibility. Complement activation also may promote bubble formation in vitro by reducing surface tension.

Biochemical damage at a bubble's surface may be as or more important than mechanical effects due to a bubble's size. Local bleeding, changes in vascular permeability, thrombosis, and platelet clumping are readily understood biochemical events. Equally understandable, however, are mechanical effects such as ischemia, stretching of pain receptors, and dissection of tissue by bubbles. Which symptoms are mediated biochemically and which are mediated mechanically remain to be determined. Indeed, both mechanisms are probably active simultaneously and sequentially.

Decompression risk is determined in part by the dive profile and in part by individual susceptibility. Susceptibility has both random and causal components. The random component makes succesive decompressions a poor test of susceptibility. A lack of data makes epidemiological study of the causal component difficult. Obesity and high serum lipid levels are frequently implicated as risk factors, particularly in DCS shock during altitude exposure. Risk appears to increase with age, perhaps as result of chronic or degenerative disease. Vacuum phenomena of the spine, for example, are more common in the elderly. Some studies indicate that females are at higher risk than males, but this is an inconsistent finding. Bends are sometimes reported at the sites of injury, but not all injuries result in bends. Even when risk factors are statistically or scientifically significant, their clinical importance can be uncertain. Except in extreme cases, the applicability of risk factors to fitness to dive standards is difficult to ascertain.

Can and should decompression be bubble-free? Arterial bubbles are unquestionably hazardous and ought to be avoided either by conservative decompression procedures or by disqualifying individuals with the anatomical pathology that might cause them. Limiting or avoiding the less hazardous venous and extravascular bubbles is desirable, but perhaps not practical. Because bubbles form at low supersaturations, a bubble-free decompression procedure could be very conservative. The decompression time from a saturation dive, for example, might increase by a factor of 25 if bubble formation were forbidden.

Decompression sickness occurs in divers, caisson workers, aviators, astronauts, and people who dive at altitude or fly after diving. Its acute forms include limb pain, spinal symptoms (sensory and motor dysfunction), chokes, and a variety of cerebral symptoms. Accurate reports of DCS incidence can be difficult to obtain when the jobs of the affected individuals (e.g., astronauts or caisson workers) might be at risk.

The type of DCS symptoms which occur depends to some extent on the nature of the pressure profile. Spinal symptoms are most common after short deep dives but relatively rare during altitude exposure, after long (6-8 hr) low-pressure caisson profiles, or during the slow decompression from saturation dives.

Chokes are caused by sustained and high pulmonary bubble loads and are more common on long shallow dives and altitude exposures than on short, deep dives. Arterial bubbles would seem likely during chokes from the transpulmonary passage of venous bubbles. Since chokes are not associated with the pressure profiles which predispose to spinal DCS, arterial bubbles would not appear to be a common cause of spinal symptoms.

The observation that spinal DCS occurs most frequently after deep, short dives suggests that the tissues responsible for spinal symptoms are faster than those responsible for limb pain. It also implicates tissues which require higher gas tensions for bubble formation. It follows that a reduction in ascent rate or the introduction of shallow decompression stops might decrease the incidence of spinal symptoms. Maine scallop

divers were symptom-free when making slow ascents on a basket winch but developed spinal symptoms after rapid out-of-air or panic ascents.

Military records show that limb bends are more common than CNS bends. Military diving is usually confined to a single day. In recreational diving, the Divers Alert Network has found that CNS symptoms are more common than limb bends. Multi-day repetitive diving is a key risk factor in these accidents. Multi-day diving appears to stress the tissues responsible for spinal symptoms.

While the multi-day profiles of sport divers lead to increased DCS risk, multi-day exposures of caisson workers result in adaptation and reduced risk. These contrasting risks may be a result of differences in the pressure profiles. Sport dives are high pressure, short bottom time, and repetitive while caisson profiles are usually low pressure, long duration, and single exposure.

Spinal DCS in divers is generally more common than cerebral DCS, and cerebral symptoms are more common in aviators when chokes occur. This suggests the involvement of arterial bubbles in cerebral DCS. Cerebral symptoms have a more rapid onset than spinal symptoms, but most CNS symptoms occur within one hour. Once again, this suggests the involvement of faster tissues in CNS symptoms than in limb pain. DCS is more easily treated in aviators than in divers, perhaps because a bubble of a given size contains fewer gas molecules at altitude than at sea level.

Decompression pain can be relieved by relatively small increases in pressure. Inflating a pressure cuff around a joint affected by a limb bend eliminates or reduces the pain. During altitude DCS, ankle and knee pain are more severe when subjects are supine rather than standing. Extra pressure would reduce the size of an offending bubble. This could indicate reduced stress on surrounding pain receptors or perhaps reduced production of a painful biochemical mediator at a smaller bubble interface.

Decompression sickness has longterm as well as acute effects. Bone necrosis is the most certain of these and appears to result from inadequate decompression. Caisson workers are most frequently affected by bone necrosis, but the introduction of conservative caisson decompression procedures which would reduce this incidence has been resisted. Other longterm effects under investigation are cerebral and spinal DCS damage.

To reduce decompression risk, limits are placed on the extent and rate of pressure reduction and oxygen is used to minimize inert gas absorption and to accelerate elimination. For short pressure exposures, inert gas uptake is insufficient to cause hazardous bubble formation. For long duration or high pressure exposures, stage or linear decompression is used to limit bubble formation and allow inert gas to be eliminated in a (largely) dissolved state.

The safe decompression times on air for some dives can be greater than the Standard Navy Air Decompression schedules by a factor of 2-3.

Nitrogen elimination can be accelerated by pure oxygen or elevated oxygen partial pressures. This can make exposures practical which would be unsafe or too long for air decompression. When in-water decompression is hazardous, divers are removed from the water and recompressed on oxygen in a chamber. While effective, there is controversy concerning whether surface decompression causes a higher proportion of CNS symptoms than in-water decompression. The incidence of CNS decompression sickness is 0.1% in the British sector of the North Sea while it is 0.01% with the new French tables. DCS from surface decompression can occur many hours after the diver leaves the chamber.

Nitrogen-oxygen mixtures (oxygen enriched air) reduce gas uptake at pressure. The use of oxygen and nitrogen-oxygen at pressure and during decompression are the most effective methods for improving safety and reducing decompression time, but they are frequently opposed on the grounds of complexity and fire hazard. In Japan, for example, caisson workers are still decompressed twice a day using the split-shift procedure which is known to be hazardous.

Dive computers are becoming more popular, particularly among recreational divers and are responsible for an increasing number of DCS incidents. It is not known if this represents high risk or high usage, but it points to the limitations in our understanding of DCS mechanisms and in our ability to incorporate them into decompression algorithms. This is especially true for repetitive diving.

Diving at altitude requires reduced bottom times which are not well-defined. The most extensive experimental studies of altitude diving were conducted by Buhlmann in mountain lakes. For flying or altitude exposure after diving, a sea level equilibration period of uncertain length is necessary. Astronauts are affected by this uncertainty as they undergo weightless training underwater and sometimes fly shortly thereafter.

Before exposure to altitudes greater than 10-18,000 feet, aviators and astronauts must eliminate nitrogen from their bodies by oxygen breathing or stage decompression. An air break during an oxygen pre-breathe has a deleterious effect on DCS protection. The Apollo program avoided these problems by using 100% oxygen atmospheres in the vehicle and the suit used for extravehicular activity (EVA). The atmosphere in the Shuttle is air at 14.7 psia while the suit contains 100% oxygen at 4.3 psia (30,300 feet). A current protocol uses 4 hours of oxygen breathing in the Shuttle before decompression to suit pressure, but this protocol results in a 20% incidence of mild DCS and a 40% incidence of bubbles. These problems are eliminated by 8 hours of oxygen breathing at rest or by 3.5 hours of oxygen with exercise.

The most frequently used pre-EVA protocol decompresses the entire Shuttle to a 10.2 psia stage pressure with 28% oxygen atmosphere for 24 hours before further decompression to 4.3 psia. The microgravity environment causes redistributed perfusion and fluid losses. It is unknown if this significantly affects DCS risk. Officially, astronauts have not reported any DCS symptoms. Many of these problems will be alleviated in the Space Station by a 8.3 psia suit.

THE PHYSIOLOGICAL BASIS OF DECOMPRESSION

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EGRESS OF INERT GAS FROM TISSUE

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The simplest model proposed to describe inert gas excretion predicts that the log of venous inert gas concentrations, obtained during a washout experiment plotted against time, will be a straight line. Experiments always yield a curved line, which falls more rapidly than expected at first and more slowly than expected at later times. This indicates a spread in the distribution of tissue transit times with an unexpected surplus of very short transit times and a complementary surplus of very long transit times. The magnitude of this spread in transit times is assessed by means of the ratio of the standard deviation to the mean transit times, which we call the relative dispersion. Whole body relative dispersions of 2.5 are accounted for in part by considering whole body washout as the sum of 14 simple washouts. Individual tissues also have local tissue washout curves, which are curved on a semi-log plot, with relative dispersions around two rather than the value of one predicted for the simplest excretion models. Possible explanations are that tissues are not uniformly perfused, that there are regions of unusually high solubility in tissues, or that counter-current gas exchange causes a surplus of short transit times and long transit times. Non-ideal gas exchange takes place in tissue units from a few cm^3 to 0.06 cm^3.

INTRODUCTION

The simplest ideas about gas exchange fail to explain the comings and goings of N_2 for the whole body. In part this is because different tissues are differently perfused. But the simplest ideas fail again when applied to individual tissues. We will first define what we mean by the simplest ideas about gas exchange and illustrate the failure of the simplest ideas to explain whole body washout. We will then discuss the failure of the simplest ideas to explain gas exchange in individual tissues. Finally we will offer some suggestions about why gas exchange in tissues is complex rather than simple.

WHOLE BODY WASHOUT CURVES

The simplest idea about inert gas exchange supposes that inert gas molecules enter tissue with the arterial blood where they are instantaneously and evenly dispersed throughout the tissue. Venous blood at the same

concentration as the surrounding tissue removes inert gas. Kety (1), ascribes the first statement of this model to Zuntz (2) in 1897. Tissues so equilibrated with air and suddenly exposed to arterial blood with no nitrogen will gradually lose nitrogen. The loss should be exponential. That is, a semi-log plot of the nitrogen in venous blood normalized to its initial concentration and plotted against time, should be a straight line, as illustrated in Figure 1.

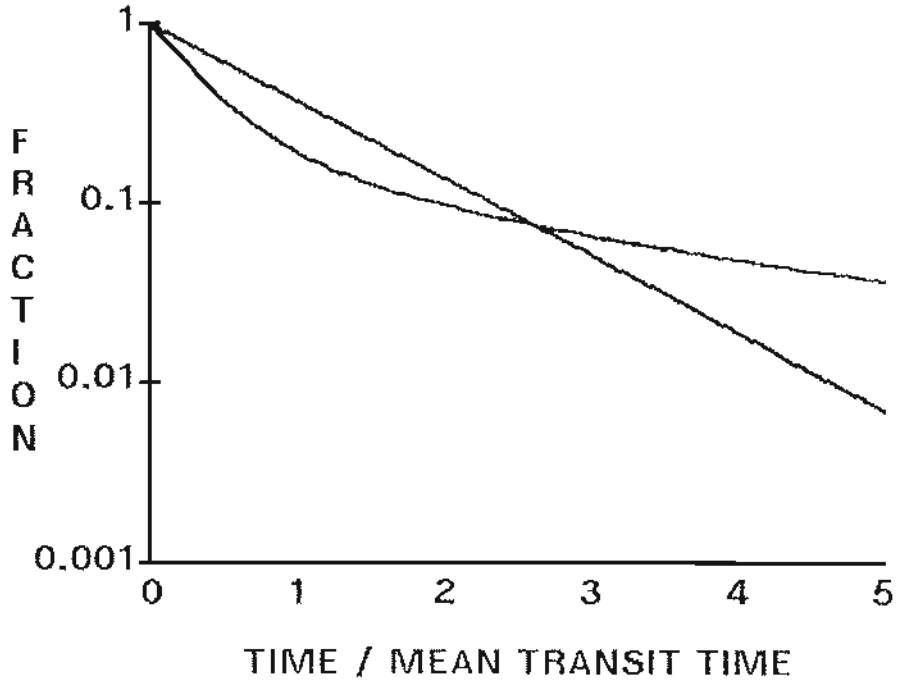

Figure 1. Normalized Venous Concentration. Concentrations of nitrogen following the breathing of a zero nitrogen gas. The straight line represents a theoretically well-mixed body, while the curved line is a reconstruction of published data (3). Concentrations are normalized by the original concentration.

Figure 1 also shows a reconstruction of normalized venous concentration from the data of Groom and co-workers (3). This line is clearly curved in the semi-log plot and this indicates that the idea that the body may be regarded as a simple well-mixed region is not correct. According to Kety this inadequacy has been appreciated at least since 1908 (4). From the shape of the curves we can see that some of the gas leaves the body more rapidly than predicted by the single exponential model while some of the gas leaves the body later than predicted by the single exponential model. The mean transit time for the gas molecules is the same for both curves shown in Figure 1. The average time for a gas molecule to leave the tissue is the same for both curves. We can use the standard deviation of the distribution of transit times divided by the mean as a quantitative measure of the departure of a curve from the single exponential depicted by the straight line in Figure 1. The ratio of the standard deviation of transit

times to the mean transit time (relative dispersion) is one for a single exponential distribution. The curved line of Figure 1 represents a sum of three exponentials used by Groom et al., to approximate data. Because some of the gas leaves the body earlier and some leaves later than it would if the distribution were a single exponential, the relative dispersion is 3.1 rather than 1.0.

Behnke and co-workers (5) also found that semi-log plots of venous nitrogen concentrations obtained during washout of nitrogen were curved. The ratio of standard deviation to mean in their experiments was 2.4. They proposed that there were in fact two regions. In one region the solubility of nitrogen was assumed to be similar to the solubility in water. In the other region, thought to be fat tissue, the solubility would have to be about five times that in water in order to account for the observed curvature of the semi-log plot. Only fat tissue is known to have a solubility so much greater than blood (6). Other tissues have N2 solubilities within 30% that of water. A weighted sum of two or three exponential terms will fit the data of inert gas washout experiments pretty well. Differences in gas solubility in different regions represent one possibility justifying the use of a sum of exponentials to describe the washout of inert gas. Another possibility is that each exponential term represents a contribution from different tissues with variable perfusion. Some of these tissues may be well perfused and others poorly perfused.

VARIABLE PERFUSION

Let us assume that each of many tissues is well-mixed and behaves simply so that the semi-log plot of washout is a straight line for each tissue. Then, if we know the flow to each tissue, we should be able to reconstruct the whole-body curve. Figure 2 shows a distribution of flows to different tissues which we have drawn from a composite of the literature. The data comes principally from studies in which radioactive microspheres were injected into dogs (7, 8) with supplementary information on skin, fat, and bone drawn from studies on the baboon (9) and the rhesus monkey (10).

The tissues are listed in order from the most highly perfused tissue, brain at the top, to the least well perfused at the bottom, bone. There is a one-hundred-fold range in perfusion from bone to brain. Now if we know that for the tissue number i the perfusion is k_i ml/ml-min and the proportion of the cardiac output going to that tissue is w_i, and we assume the gas has the same solubility in tissue as in blood, then we can write down for the distribution of transit times f_i,

$$f_i = w_i \, k_i \, e^{-k_i t} \qquad [1]$$

The integral of f we call F, and the normalized venous concentrations v/v_0. v/v_0 is equal to 1-F, so we can calculate, (1, 12)

$$v/v_\emptyset = \sum_{i=1}^{14} w_i e^{-k_i t} \qquad [2]$$

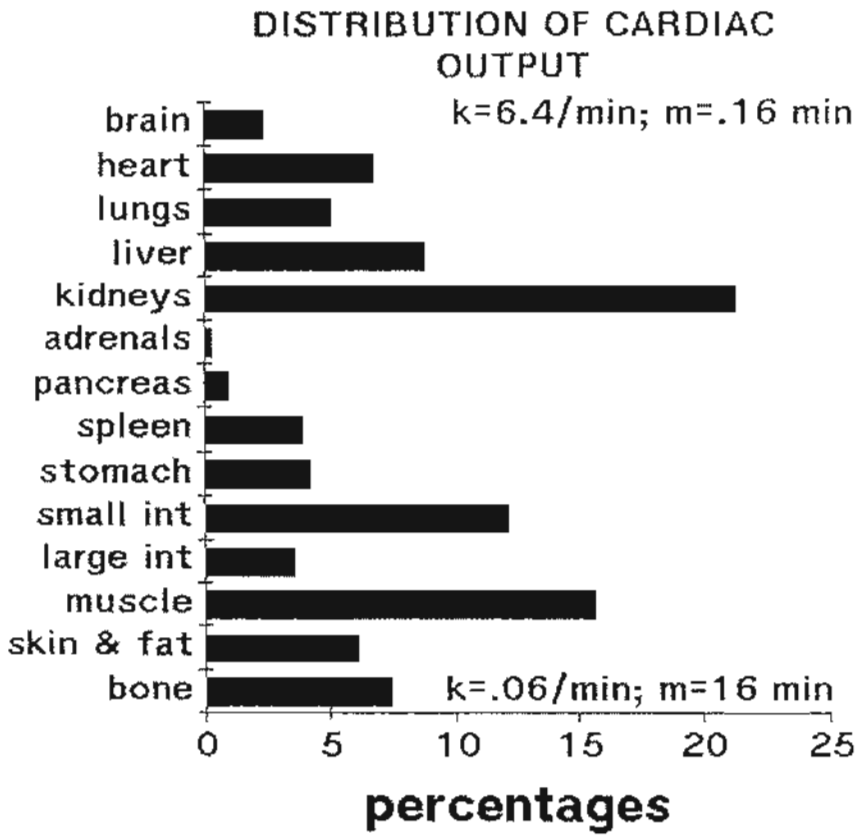

Figure 2. Distribution of Cardiac Output. The percentage of cardiac output distributed to tissues is shown in order of perfusion from poorly perfused tissues (bottom) to well perfused tissues (top). Perfusion constants (k) and corresponding mean transit times (m) are shown for the best perfused (brain) and most poorly perfused tissues (bone).

We have calculated the washout using Equation 2 and the data of Figure 2, assuming that each of the 14 tissues is a perfectly mixed compartment. The results of these calculations are compared in Figure 3 with the curve published by Groom and co-workers.

The curve derived from tissue flow is a bit straighter than the curve describing nitrogen washout data. The experimental spread between fast washout and slow washout is greater than predicted by the sum of tissue washouts. The ratio of standard deviation to mean (relative dispersion) for the sum of tissues model is 2.1. This is clearly larger than the value of 1 to be expected for a single exponential but is also clearly smaller than the values of 3.1 and 2.4 calculated from data in the literature on nitrogen washout (3, 5). We conclude that some other factor besides variation in flow probably contributes to the curvature of these semi-log plots.

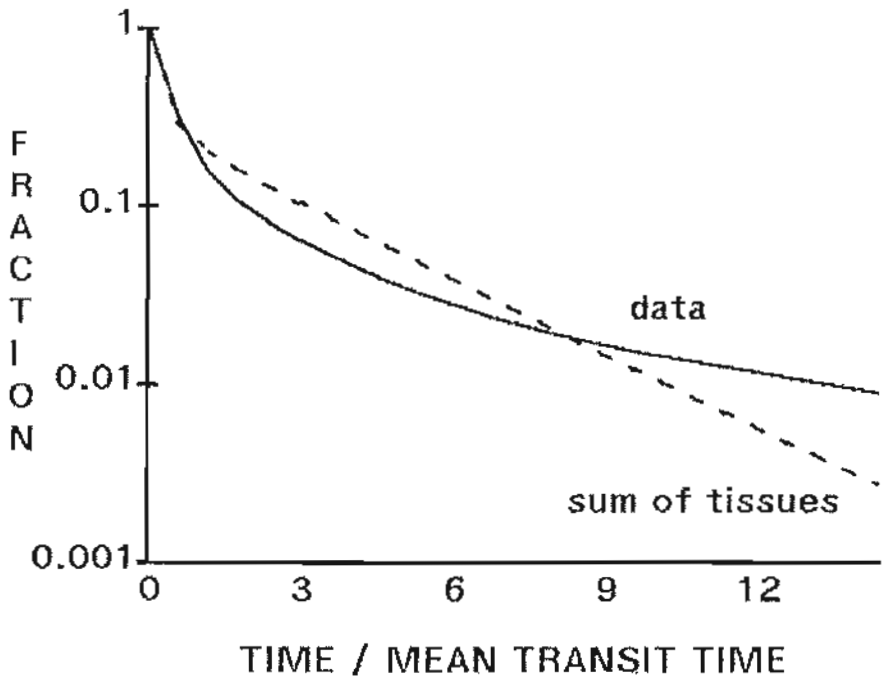

Figure 3. Mixed Venous Nitrogen Washout. The dashed line shows the expected washout from the 14 tissue compartments of Figure 2. Solid line is from data (3). Initial concentration is used to normalize the concentrations as in Figure 1.

Were it not for additional evidence based on studies of isolated tissues, the conclusion would not be a very secure one. The presence of an unaccounted tissue taking three percent of the cardiac output with a perfusion, say one-third the least perfusion we have used, would give us a relative dispersion around 2.5. Alternatively, a three-fold error in the perfusion estimated for fat tissue would also give us relative dispersions close to those we have computed from data on nitrogen washout.

TISSUE WASHOUT CURVES

We do not need to rely on whole body washout curves in order to assess gas exchange in individual tissues. It is also possible to do studies of inert gas washout on isolated tissues (11) or with probes that obtain measurements from isolated portions of tissues in an intact animal (12). These studies show that semi-log plots of washout are curved rather than straight. In analyzing tissue experiments we must use formulas appropriate to these measurements. For a wash-in experiment in which there is a sudden change from zero to a new arterial concentrations of gas, which we will call c_a, the tissue concentration c_t is,

$$c_t = (c_a/m) \int_{\emptyset}^{t} (1-F)dx \qquad [3]$$

m is the mean transit time. For a sudden step down from equilibrated concentrations c_a to 0.

$$c_t = c_a - (c_a/m) \int_{\emptyset}^{t} (1-F)dx \qquad [4]$$

Weathersby and co-workers (12) used a gamma camera to follow tissue concentrations of radioactive xenon and then sums of exponentials were fitted to the data. Equations 3 and 4 provide the relations needed to calculate means and standard deviations from the fitted exponentials. They calculated means and standard deviations of transit times for many tissues.
These calculations revealed that regions judged to be a few centimeters cubed in volume had ratios of standard deviations to means (relative dispersion) always greater than one and usually greater than two. This suggests that factors leading to the curved semi-log plots of inert gas washout must be sought in regions smaller than a few centimeters cube in volume and must be present in most tissues.

MICROCIRCULATORY EXCHANGE

How about regions so small they might contain just a few capillaries? Flow in capillaries varies from minute to minute and need not be the same in adjacent capillaries. Homer and Weathersby (13) developed a computer simulation of gas transport in a cluster of four capillaries. A molecule was placed at random in one of the four capillaries and a random walk begun to which convective motion was added whenever the molecule was in the capillary. The time required to arrive at the venous end of a capillary was recorded. This was done many times in order to obtain a mean transit time and a standard deviation of transit times. The relative dispersion was always very close to one even when the spread in flows was so great that all the flow was directed to one capillary and the flows were fixed at zero in the other three. Variations in capillary spacing and countercurrent orientation of capillaries also did not raise the relative dispersion even to 1.1. The reason is that molecular diffusion is quite rapid compared to the flow at this level of the circulation.

Diffusion is so rapid that four capillaries is much too small a unit to study. Suppose a molecule first entering a tissue remains there an average of 11 minutes (3). After 11 minutes of random diffusion in three dimensions five percent of the molecules will have escaped a cube 6mm on a side. Such a cube contains hundreds of thousands of capillaries. Since some molecules have shorter residence times than the mean and some longer residence times, our 6mm cube is only an approximate measure of the volume of tissue, which should form the basic vascular unit to be considered in reckoning gas exchange. The details of flow within a unit a tenth this size (a 600 micron cube), for example, will be of little importance as a

source of curvature for the semi-log plots because diffusion is rapid enough so that regions of such a size are well-mixed and as our simulation showed, give rise to relative dispersion close to one even if the flow is very non-uniform.

Regions of tissue ten times larger than 6mm on a side are well isolated. We may expect regions of non-uniform flow separated by 60mm to contribute to the curvature in semi-log plots without much influence from molecular diffusion. These same conclusions hold for inhomogeneities in solubility. Heterogeneities in fat content distributed over distance of 600 microns or less will change the mean transit time but the relative dispersion should not be affected very much. If fat containing regions are separated by distances greater than 6mm, then both the mean transit time and the relative dispersion may be increased.

If the basic vascular unit to be considered in understanding the curvature in semi-log plots are the typical contents of pieces of tissue as large as .2 gms (6mm cube) then we must consider vessels as large as 80 microns in diameter and many thousands of capillaries. Arterioles as large as 80 microns in diameter often are paired with a venule whose flow is counter-current to the arteriolar flow. Accordingly, the geometry of vessels from 80 microns down to capillary size must be considered in trying to understand the source of curvature in the semi-log plot.

Calculations (13) showed that a gas molecule within a 100 micron arteriole will rarely arrive at a capillary without first having left the vascular space from a vessel larger than a capillary. Exits also usually take place by diffusion from tissue directly into vessels much larger than capillaries. Accordingly, counter-current exchange could play an important role in the motions of inert gas in tissue.

SIMULATION OF EXCHANGE IN A VASCULAR TREE

In order to study gas exchange in a tissue block with several levels of branching in its vascular tree, we have developed a computer simulation. Anatomical dimensions and branching structure of our tissue model are based on a series of articles providing the necessary quantitative information about the rat spinotrapezius muscle (14), (15), (16), (17), (18), (19). The model represents a tissue sandwich 12.3 mm by 12.3 mm by 0.76 mm, with a volume of 100mm^3. Blood flows into the system through three feeder arterioles. Each arteriole has a diameter of 79 microns. These arterioles run along the rim on three sides of the sandwich. They are accompanied by complementary venules whose flow runs counter-current to the arteriolar flow. Figure 4 displays the disposition of feeder vessels within the basic tissue module.

Figure 5 shows how the feeder vessels join the next vascular level, the arcade network.

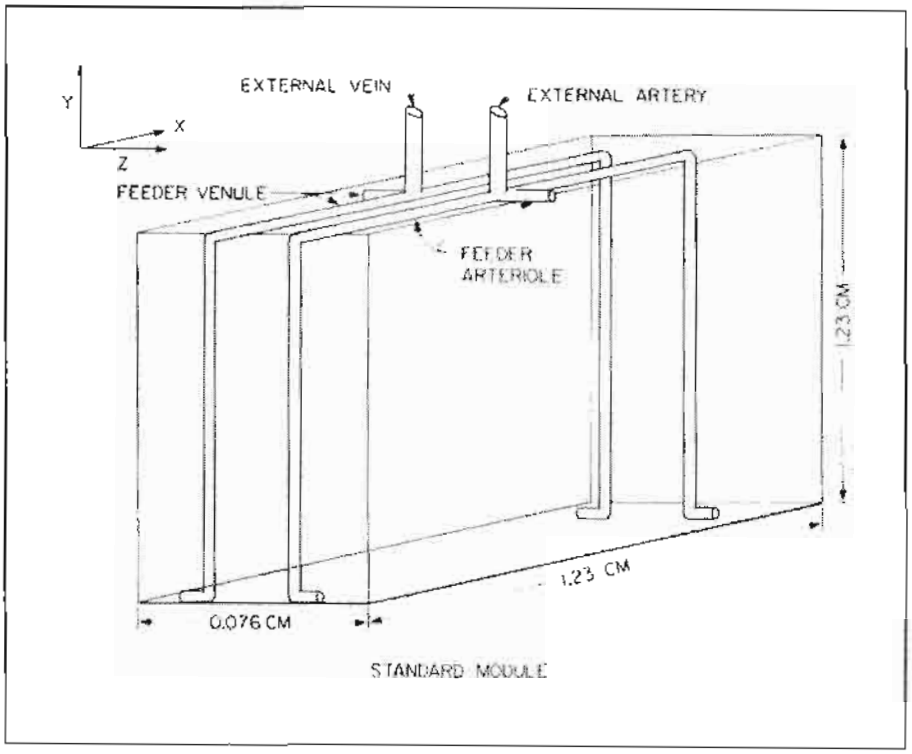

Figure 4. Feeder Vessels.

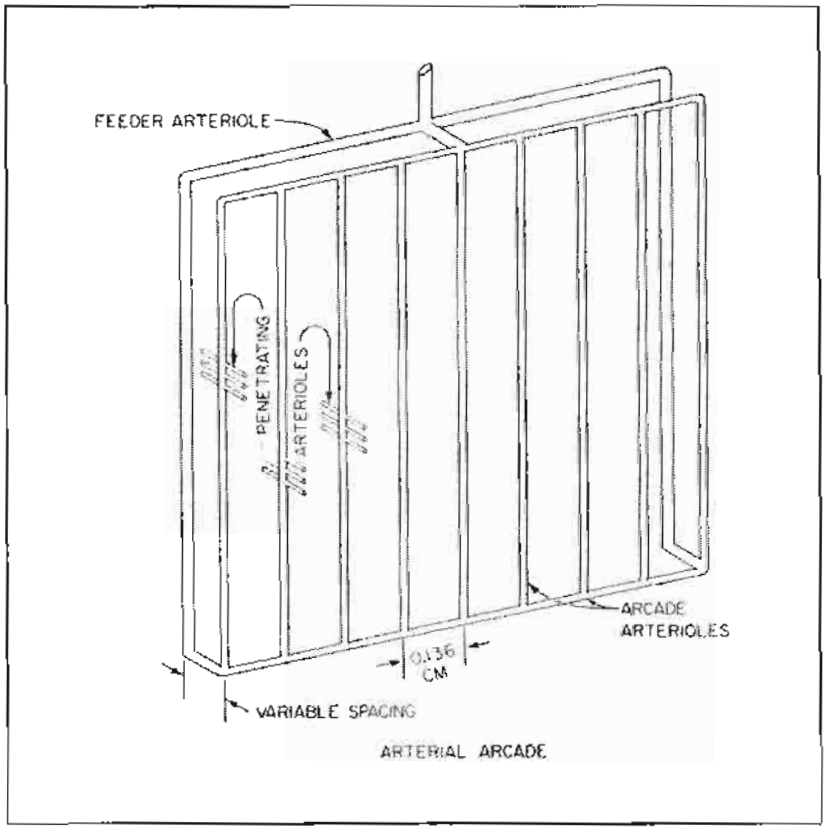

Figure 5. Feeder, Arcade, and Penetrating Arterioles.

The blood from the three feeder arterioles empties into a network of arterioles 45 microns in diameter located in a plane beneath and parallel to the surface of the sandwich. The total length of these network vessels is 130mm. A complementary venous network lies beneath the surface of the opposite side of the tissue sandwich. The network arterioles give rise at right angles to penetrating arterioles 17 microns in diameter that run from one face of the sandwich to the opposite face. Capillaries arise at right angles from the penetrating venules. The capillaries join to the penetrating venules that carry blood to the venous network. Figure 6 summarizes the relationships among the smaller vessels.

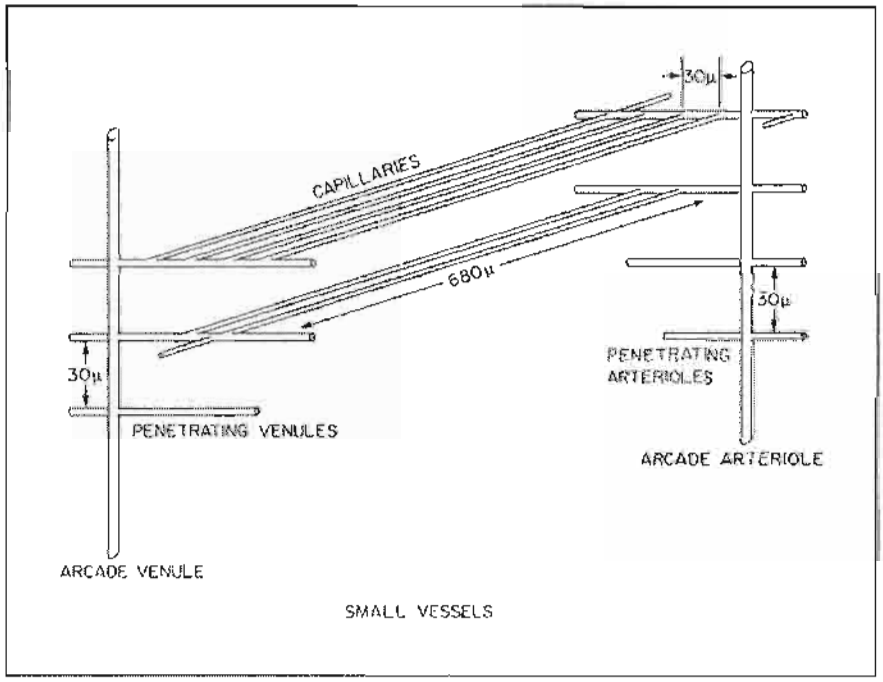

Figure 6. Relationships of small vessels. Capillaries join the arterial penetrating vessels to the venous penetrating vessels.

Table 1 shows the number and diameter of vessels in our simulated tissue block.

BRANCH LEVEL	DIAMETER (uM)	NUMBER
Capillary	5.7	190,000
Penetrators	17	3,700
Arcade network	45	9
Feeder Arteriole	79	3

Table 1. Number and Diameter of Model Vessels.

The most prominent difference between our simulation and the observed characteristics of the rat spinotrapezius lies in the branching between 45 micron vessels and capillaries. Observations indicate that the single level of 17 micron penetrating vessels is in fact represented by three orders of branching vessels ranging in diameter from 7.4 to 26 microns. Capillary densities of 1140/mm^2 and lengths of 680 microns agree well with published data (16). Densities and branching structure linking 45 microns and 79 micron vessels are also well matched to available data (14-19).

The simulation begins with the placement of a gas molecule at the beginning of a 79 micron feeder arteriole. Each step consists of 1) a check to see if the trip has finished or a boundary has been crossed, 2) addition of blood flow to the motion of the molecule if it is in a blood vessel, 3) addition of the random motion of diffusion, and 4) return to step 1. When boundaries are crossed the particle is translated to the opposite boundary, which is equivalent to assuming that the tissue is made of side by side replications of the same basic unit we have already described. When the particle finally arrives at the end of a large feeder venule that trip is over, the time required to complete the trip is recorded and a new trip begun. The program is tested by comparing selected results with those of previous simpler simulations and with relative dispersions, which are known for simple cases such as a single well-mixed compartment (13). The results of many trips are used to compute the mean transit time and the standard deviation of the transit time distrubtion. The mean is a selected parameter of the simulation and therefore the simulation results should agree closely with the value selected, as it does. The standard deviation, however, varies with the mean, the diffusion coefficient and the uniformity of perfusion. The relative dispersion, therefore, will depend on the uniformity of perfusion and the diffusion coefficient.

HETEROGENEOUS PERFUSION

Figure 7 compares the distribution of transit times for a uniformly perfused arcade with one in which 94 percent of the flow was directed to the middle third of the tissue through three of the nine vertical 45 micron arcade vessels (Fig. 5). This left each of the remaining six with just one percent of the flow. The ratio of flows in the high-flow vessels to that in the low-flow vessels was 100 to 1.

The uneven flow is represented by an excess of very short and of very long transit times and consequently its relative dispersion is 2.4 rather than 1. The simulation of even perfusion has more transit times clustered close to the mean of 11 minutes and accordingly has a relative dispersion close to 1.

The relative dispersion depends on several other characteristics of the uneven flow. Just how uneven is the flow? If flow in the well perfused regions is 100 times that in the poorly perfused regions then one can expect a greater relative dispersion than if the flow in the well perfused regions is only three times that of the poorly perfused region. Another factor is the spacing between regions of high flow. Uneven flow between adjacent capillaries has very little effect on the relative dispersion even

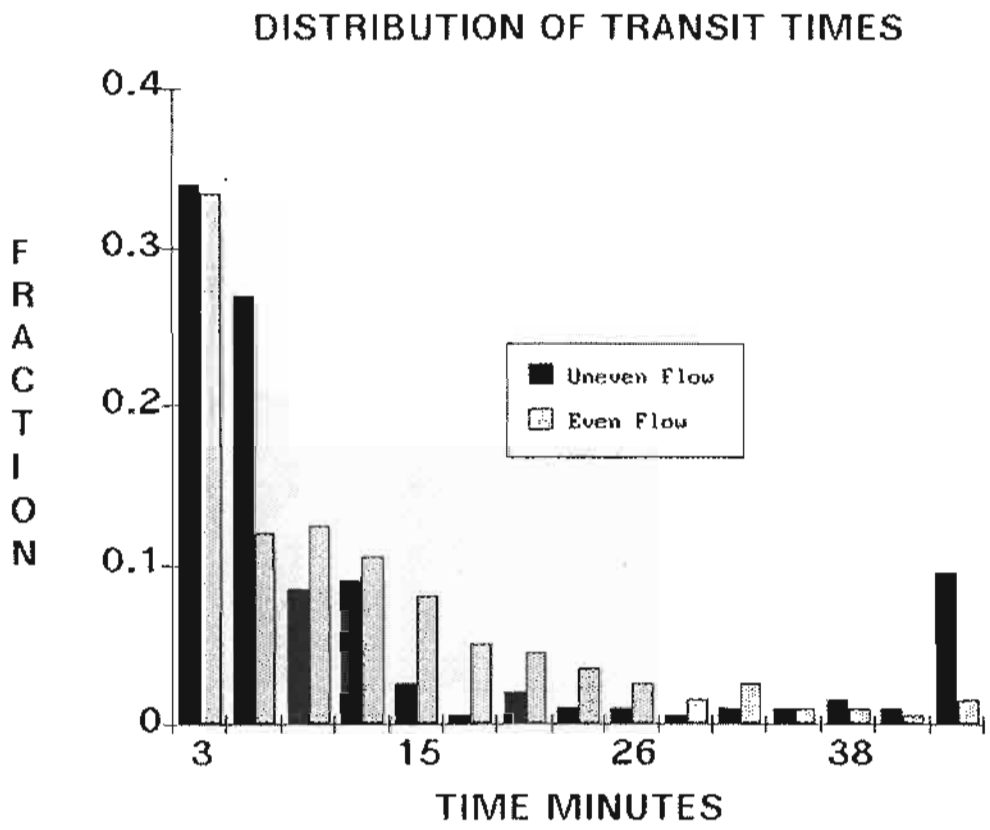

Figure 7. Transit Times. Solid bars represent the results of simulation with uneven flow through the arcade network. Shaded bars represent even flow. Mean transit time 11 min, diffusion coefficient 0.5 x 10^{-5} cm^2/sec.

if one capillary is completely stopped. The reason is that diffusion mixes the molecules from high-flow and low-flow regions. The effective flow is just the tissue average in that region. But diffusion is less effective in mixing over long distances. The effects of high flow to low flow ratios and of spacing between high flow regions were examined with simulations which varied these factors. The results are summarized in Figure 8.

Relative dispersions also depend on the choice of mean transit time and of diffusion coefficient. A larger diffusion coefficient will lead to greater mixing of molecules in the low flow and high flow regions and hence would give smaller relative dispersions. More rapid flow and a shorter mean transit time would leave less time for mixing and hence lead to larger relative dispersions. Relative dispersions above 2 were only achieved when high-flow to low-flow rates were 100 and high-flow regions were at least 4mm apart.

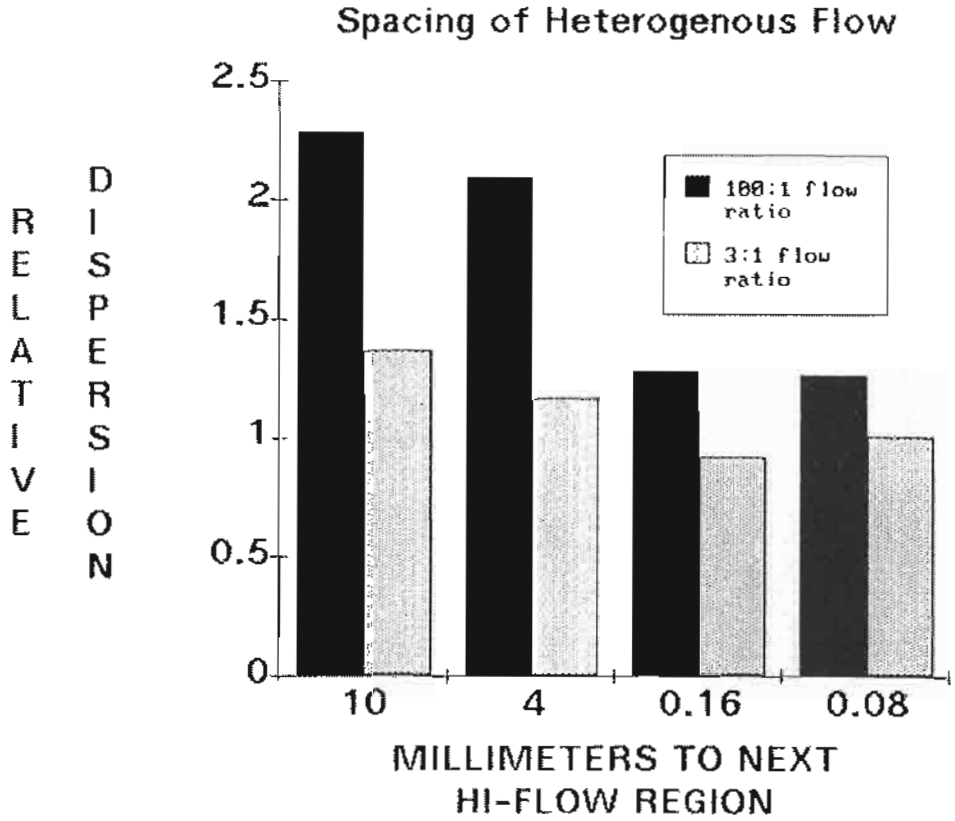

Figure 8. Effect of Flow Spacing and Flow Ratios and the Relative Dispersion. Dark bars show the relative dispersion for 100:1 (high-flow: low-flow) ratios with various spacings between high flow regions. Light bars display the results for 3:1 flow ratios. Ten and 4mm spacings were achieved by setting uneven flow through arcade vessels. Smaller spacings of high flow were simulated by setting uneven flows in penetrating vessels. Mean transit time 11 min, diffusion coefficient 0.5 x 10^{-5} cm^2/sec.

These results can be given additional perspective by comparing these relative dispersions with the ones that have been measured in tissue. Local relative dispersions for xenon washout are about 2 to 2.2 (12). By treating the sum of tissue flows as parallel compartments we can calculate that in order for the whole body relative dispersions to amount to 2.5, the individual tissues must have relative dispersions of about 2, rather than the well-mixed value of 1 (13). Figure 8 shows that our simulation spans these values if the flow ratios are 100:1 or greater, and the high-flow regions are separated by 4mm or more. Flow ratios of 3:1 prove inadequate even with a separation of 10mm.

COUNTER-CURRENT GAS EXCHANGE

Xenon washout curves have means twice as large as those predicted from flow measurements with radioactive microspheres (11). Could the 1 to 3% fat in muscle account for a two-fold discrepancy between the mean expected from experiments with radioactive microspheres and the mean found by analyzing xenon washout curves? Cerretelli and co-workers (11) have concluded that it is unlikely that this discrepancy is due only to the presence of fat in skeletal muscle. They suggest that counter-current exchange might be at least, in part responsible.

Inert gases are distributed to tissues not by capillaries but principally by arterioles larger than 20 microns. The last vessel entered from the tissue before the molecule leaves the vascular unit is apt to be a venule larger than 20 microns. Figure 9 illustrates a tabulation of which vessels serve as sources and sinks in our simulation.

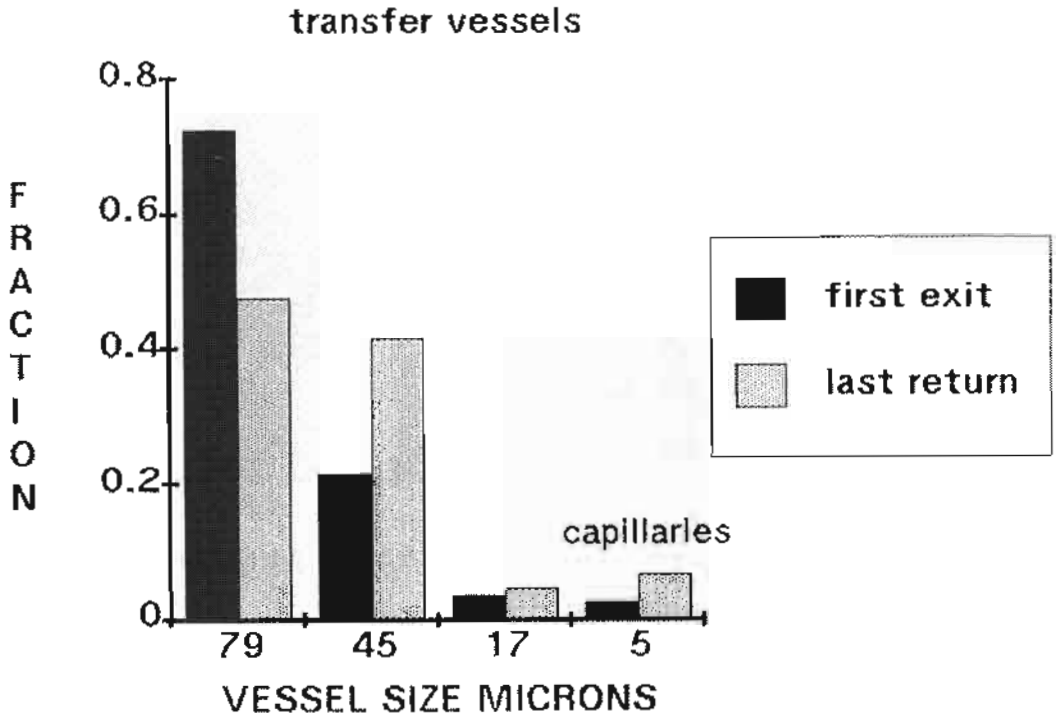

Figure 9. First Exit and Last Return Vessels. The simulation set 50% of flow through the side feeder vessels and 50% to the central feeder vessel. All other vessels were uniformly perfused. The fraction of first exits from the vascular space and last returns is shown for each size of vessel. m = 11 min; diffusion coefficient = 0.5×10^{-5} cm^2/sec

Because many molecules enter tissue from the larger arterioles counter-current exchange can take place. If a vein is nearby, a molecule having left a large arteriole may frequently enter a large vein and then enjoy an exceptionally rapid passage out of the vascular unit. It will also happen

that molecules about to leave the vascular unit in a vein may leave the vein, enter adjacent tissue, and then enter the adjacent arteriole and be thrust away from the exit. Such a molecule will experience an unusually long transit time before leaving the vascular unit. The presence of unusually short-paths and of unusually long-paths will lead to a larger relative dispersion than exists without the rapid exchange between vessels. If the vessels are far enough apart and the tissue evenly perfused, relative dispersion will be close to one and will be larger in simulations with the counter-current vessels close together. Figure 10 displays the effect of distance between counter-current vessels on the relative dispersion.

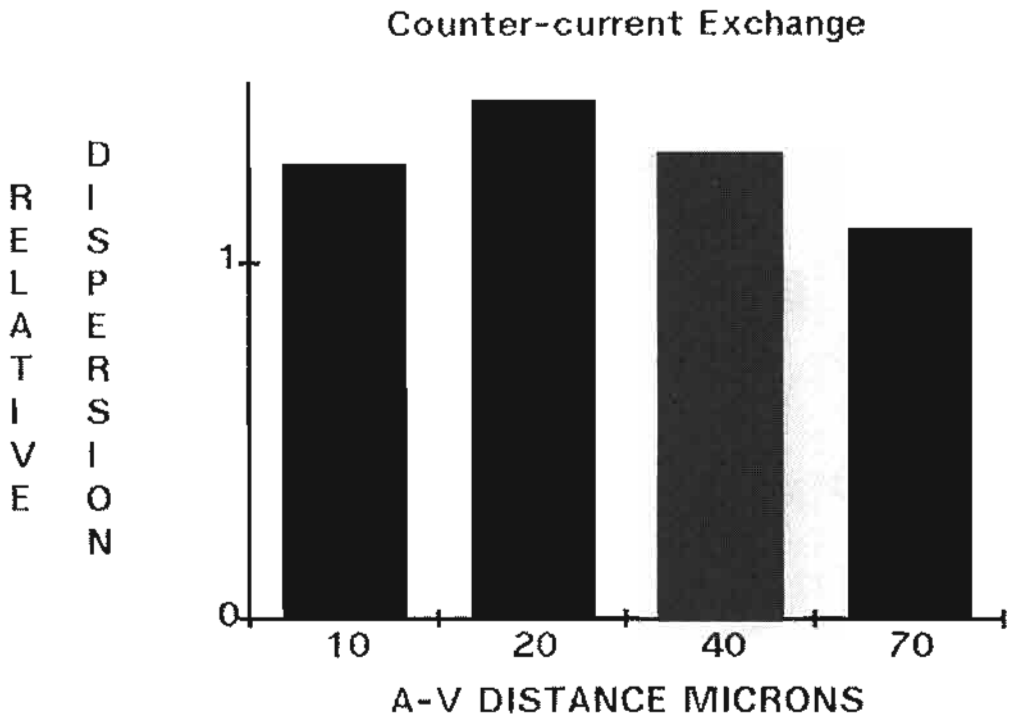

Figure 10. Relative Dispersion and Counter-Current Separation. Simulations set 90% of the flow to perfuse the counter-current vessels. Spacing between adjacent feeder vessels was varied as shown. Diffusion coefficient 0.5×10^{-5}, mean transit time 11 minutes.

Figure 10 shows that simulations in which the counter-current vessels were separated by 70 microns had relative dispersions near 1. As the separation is decreased, the relative dispersion increases to 1.4 and then decreases again at very short distances. The reason for the decrease is not presently known.

DISCUSSION

Whole body washout curves will not be understood without considering the washout in individual tissues. To a first approximation the whole body washout curves reflect the fact that some tissues are more highly perfused than others. Taking this into account and assuming the simplest model to apply for each individual tissue still does not quite account for the curvature observed in the semi-log plots of whole body washout curves. The relative dispersion is larger than one would predict from considering whole body washout to be the sum of many simple washout curves each with a relative dispersion of 1. Studies of washout of radioactive xenon from isolated tissues also show that the relative dispersion is greater than one in tissue regions as small as a few cubic centimeters in size (12). What is the source of this non-ideal, heterogeneous behavior? The three principal candidates are heterogeneous flow, heterogeneous solubility, and counter-current gas exchange. Computer simulation of a random walk through tissues can be used to find the time for a gas molecule to traverse a tissue. By repeating this random walk many times the mean and variance of the tissue transit times may be estimated and the relative dispersion of the simulation compared to the relative dispersion calculated from data or from other theoretical models. Such computer simulations of the traversal of gas molecules through tissue have convinced us that the heterogeneous factors must be distributed on a scale larger than a tissue volume containing a few capillaries. Heterogeneous flow or solubility so fine grained that it occurs between neighboring capillaries would not increase the relative dispersion above 1.1. Diffusion of gas through tissue is sufficiently rapid to blur the effects of uneven flow between adjacent capillaries. Uneven solubility similarly spaced we also believe would not be detectable, though we have not yet attempted simulations with uneven solubility. Counter-current flow in adjacent capillaries would not increase relative dispersions much above the ideal value of one.

With our most recent simulation of a tissue supplied by a vascular unit beginning with three 79 micron arterioles and containing 190,000 capillaries, we can assert with confidence that ratios of 3:1 between maximum flow and minimum flow could not account for relative dispersions of 2 no matter how arranged within our tissue module. Flow ratios of 100:1 would, on the other hand, be adequate if adjacent regions of fast flow were separated by at least 4 mm of slowly perfused tissue. Similar dimensions seem likely to hold for the required spacing of heterogeneous solubility. That is portions of fat tissue should be spaced about 4 mm apart or further if we are to account for a relative dispersion of 2 on the basis of fat distribution within a tissue.

Our simulations show that counter-current flow in our small module would not account for the relative dispersion of 2. Our simulation module is, however, not large enough to provide a reliable assessment of the contribution of counter-current exchange to the relative dispersion. We must simulate a tissue region large enough so that the largest vessels of the unit usually deliver a gas molecule to the next branch level of the vascular tree rather than to tissue. In our simulation the largest vessels usually do not deliver a gas molecule to the next branch level since the molecule will usually have already left the vessel before the flow reaches

the next branch level. This means that previous levels of branching almost certainly contribute to counter-current exchange and hence our simulations can only place a lower limit on the contribution of counter-current exchange to the relative dispersion. A more accurate assessment would require a simulation which included larger counter-current vessels.

Clearly we have much more to learn about inert gas exchange. The simulations we have already done should be extended to calculate explicitly the effects of heterogeneous solubility. They must also be extended to larger tissue modules so that we can obtain a better assessment of the possible contributions of counter-current exchange to the larger than expected relative dispersions.

A more detailed accounting of flow distribution within tissues is also needed. Published distributions of flow within .75 gram regions of skeletal muscle show just enough variability in perfusion to account for a relative dispersion of 2 if high-flow regions were spaced several samples apart (20). Since these distributions were obtained by pooling data from several animals, it is to be expected that some of this variation represents variability between animals, and if the same data were considered for each animal separately, then one might conclude that the variability apparent in .75 gram regions could not account for the observed relative dispersions. On the other hand heterogeneity on a smaller scale might be obscured in such large samples. Our simulations show that data on samples as small as 0.1 gms may be needed to fully appreciate the possible importance of heterogeneous flow within tissue to inert gas exchange.

Data on the distribution of small regions of fat tissue within tissues is also needed. The scale should be similar to that needed in the flow distribution. Separate information on flow distribution within the fatty regions of individual tissues is also needed since, if flow is substantially lower in the fat tissue than in surrounding aqueous tissue, the relative dispersion will be increased beyond what might be expected from the solubility differences alone. Attention should especially be given to the distribution of fat in relation to counter-current vessels. We have no simulations to assist us yet, but we believe that counter-current effects may be more prominent if a large reservoir of gas is held near the counter-current vessels in a region of fat.

Finally, we also need quantitative summaries of vascular branching on a scale substantially larger than what we presently have. These studies should be done on those tissues most susceptible to decompression sickness, since the details of just how much fat, how much flow heterogeneity, and how much counter-current exchange takes place can only be accurately determined on a tissue by tissue basis. In the kidney, counter-current exchange is possibly the dominating cause of heterogeneous gas washout. In the knee perhaps it is heterogeneous flow, and maybe in the central nervous system fat distribution is very important.

BIBLIOGRAPHY

1. Kety SS. The theory and applications of the exchange inert gas at the lungs and tissues. Pharmacol Rev 1951; 3:1-41.

2. Zuntz N. Zur Pathogenese und therapie der durch rasche Luftdruckanderungen erzeugten Krankheiten. Fortschr d Med 1897; 15:632-639.

3. Groom AC, Song SH, Ohta Y, and Farhi LE. Effect of anesthesia on rate of N_2 washout from body stores. J Appl Physiol 1974; 37:219-223.

4. Boycott AE, Damant GCC, and Haldane JS. The prevention of compressed-air illness. J Hyg (Lond) 1908; 8:342-443.

5. Behnke AR, Thomson RM, Shaw LA. The rate of elimination of dissolved nitrogen in man in relation to the fat and water content of the body. Am J Physiol 1935; 114:137-146.

6. Weathersby PK and Homer LD. Solubility of inert gases in biological fluids and tissues: a review. Undersea Biomedical Research Dec 1980; 7(4):277-296.

7. Adachi H, Strauss HW, Ochi H, and Wagner HN Jr. The effect of hypoxia on the regional distribution of cardiac output in the dog. Circulation Research 1976; 39:314-319.

8. Kawashima Y, Okada K, Kosugi I, In-Nami H, et al. Changes in distribution of cardiac output by surface-induced deep hypothermia in dogs. J Appl Physiol 1976; 40:876-882.

9. Hales JRS, Rowell LB, and King RB. Regional distribution of blood flow in awake heat-stressed baboons. Am J Physiol 1979; 237:H705-H712.

10. Hoffbrand, BI and Forsyth RP. Validity studies of the radioactive microsphere method for the study of the distribution of cardiac output, organ blood flow, and resistance in the conscious rhesus monkey. Cardiovasc Res 1969; 3:426-432.

11. Cerretelli P, Marconi C, Pendergast D, Meyer, Heisler N, and Piiper J. Blood flow in exercising muscles by xenon clearance and by microsphere trapping. J Appl Physiol 1984; 56:24-30.

12. Weathersby PK, Mendenhall KG, Barnard EEP, Homer LD, Survanshi S, and Vieras F. Distribution of xenon gas exchange rates in dogs. J Appl Physiol 1981; 50:1325-1336.

13. Homer LD and Weathersby PK. How well mixed is inert gas in tissues? J Appl Physiol 1986; 60:2079-2088.

14. Gray SD. Lack of capillary << rarification >> in skeletal muscle of spontaneously hypertensive rats. In Hypertensive Mechanisms, Rascher W, Clugh D, Ganten D (Eds); F. K. Schattauer Verlag, Stuttgart - New York, 1982:204-207.

15. Engelson ET, Skalak TC, and Schmid-Schonbein GW. The microvasculature in skeletal muscle: I Arteriolar network in rat spinotrapezius muscle. Microvasc Res 1985; 30:29-44.

16. Engelson ET, Schmid-Schonbein GW, and Zweifach BW. The microvasculature in skeletal muscle: II Arteriolar network anatomy in normotensive and spontaneously hypertensive rats. Microvasc Res 1986; 31:356-374.

17. Engelson ET, Schmid-Schonbein GW, and Zweifach BW. The microvasculature in skeletal muscle: III Venous network anatomy in normotensive and spontaneously hypertensive rats. Int J Microcirc: Clin Exp 1985; 4:229-248.

18. Skalak TC and Schmid-Schonbein GW. The microvasculature in skeletal muscle: IV A model of the capillary network. Microvasc Res 1986; 32:333-347.

19. Schmid-Schonbein GW, Skalak TC, and Firestone G. The microvasculature in skeletal muscle: V The arteriolar and venular arcades in normotensive and hypertensive rats. Microvasc Res (in press).

20. Piiper J, Pendergast DR, Marconi C, Meyer M, Heisler N, and Cerretelli P. Blood flow distribution in dog gastrocnemius muscle at rest and during stimulation. J Appl Physiol 1985; 58:2068-2074.

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DISCUSSION

DR. VANN: In terms of a more traditional approach to inert gas exchange, can you, Dr. Homer, relate the relative dispersion of mean transit times to the more familiar tissue half-times?

DR. HOMER: If you know all the tissue half-times and the proportion of cardiac output associated with each, you can calculate a relative dispersion with a simple formula. You can't go back the other way because the relative dispersion and the means are constructed of many components.

DR. KUNKLE: I noticed in your results that most inert gas exchange occurred in vessels larger than 79 microns. Why, then, do we have capillaries? I suppose the answer is that oxygen transport is different from inert gas transport. There are many penetrators in your model which can be simultaneously fed by a relatively few arcades. The number of penetrators that are open at any time is determined by the oxygen concentrations in the capillaries. How do you couple perfusion and metabolism in your model?

DR. HOMER: We're not coupled to metabolism at all. Everything delivered to an arcade ends up in one of the penetrating vessels. We control the flow in the penetrating vessels by telling it what it's going to be, so that we can, for example, make the flow even along all penetrating vessels, or even cyclic. We can build up a cycle of 10 vessels and have one flow in the first 2, another flow in the next 2 and so on. We force that way. It's not metabolically interactive right now.

DR. KUNKLE: Are your results sensitive to that approximation?

DR. HOMER: At that scale, it depends on the separation. It's very sensitive to the flow distribution if the separation between high and low flows is 4 millimeters or larger. It's virtually insensitive to flow distribution if the high flow regions are separated by 0.16 millimeters or smaller. We haven't yet explored the in-between region.

DR. KUNKLE: So adding metabolism to physiologically determine which penetrators are open (instead of just assigning them) might be an interesting future development.

DR. HOMER: Yes, it might be, but one of the advantages of this system is that it's much less costly in computing time than a boundary value solution. The disadvantage is the difficulty of dealing with the oxygen. An oxygen molecule somewhere in tissue might have a certain probability of going into a mitochondria, except for regions where the oxygen tension is high. I haven't figured out a way to solve that problem yet.

DR. LOEWENHERZ: Are you assuming differences in regional saturation of dissolved gas, or are you assuming full saturation or equilibrium at the time the model is run?

DR. HOMER: There are no equilibrium assumptions, but the solubility is presumed uniform through this tissue, and the diffusion coefficient is assumed uniform through all of it.

DR. LOEWENHERZ: So you're assuming a maximum dissolved gas gradient from intravascular to tissue all the time?

DR. HOMER: No, I'm not assuming anything about a gradient. I'm taking an individual molecule and marching it through the tissue to see how long it takes to get from the arterial inlet to the venous outlet. This is also a disadvantage of the method, because I can't tell where the gradients are. For the reason related, I haven't got a boundary value solution to this problem.

DR. VAN LIEW: It seems to me that your computer model is like a pinball machine. You watch a molecule bounce around and count how long it takes to get out.

DR. HOMER: Yes, that's exactly the idea.

DR. WARD: I can't quite follow what's happening at the interface between two different tissues. You say you're not making an assumption of equilibrium at the interface. What is the boundary condition? How does the molecule cross from one tissue module to another?

DR. HOMER: I check to see whether the last step of each cycle has taken a molecule beyond the physical dimension of the module. If it is outside the module, I reflect it to the other side and that's equivalent to stacking modules together.

DR. WARD: Does that mean that there's no physical barrier?

DR. HOMER: That's correct. It's equivalent to a tissue of infinite extent but composed of identical repeating units.

DR. WARD: Then you have an average diffusion coefficient for the entire tissue?

DR. HOMER: Yes.

DR. JAMES: Were you suggesting that perfusion in tissue is not a limitation. Brian Hills has shown, for example, that significant areas of connective shut-down periods of up to 6 hours.

DR. HOMER: I wouldn't choose to say that it's not limited by perfusion. It's important to know what size areas shut down and for how long and what distances are so small that rapid diffusion can overcome a shut-down region. I'm not familiar with the work you've cited, but if the regions shut down were on the order of 10 millimeters apart, that should lead to an altered relative dispersion. If the shut-down regions were less than two-tenths of a millimeter apart, however, it should not be detectable as a change in a relative dispersion. Our initial aim is to understand the size of regions that are important to open or shut down before one begins to see an effect.

DR. JAMES: Presumably, lymphatic gas transport is a factor in accounting for the very large volume of tissue that a gas molecule can have access to over the 11-minute period that you described. This volume, I believe, was on the order of 200 milligram of tissue.

DR. HOMER: I'm sure that there are many anatomic features, including the lymphatics, that we have neglected in our simple approach.

DR. KINDWALL: You describe a fascinating diffusion-limited or perfusion-limited approach to inert gas exchange, but the presence of bubbles makes quite a difference in the gas exchange curve when we're dealing with the decompression of divers. If a change is wrought by the presence of bubbles, what kind of vessel would bubbles have to block, or what kind of tissue would have to be totally blocked to influence a gas exchange curve? Would it be as great as or larger than a 79-micron vessel?

DR. HOMER: If the principal mechanism were the blockage of the vessels, the vessels would be 45 micron or larger in size to have an effect. A gas bubble does more than block off a vessel, however. If it's in tissue, it becomes a little home for gas molecules and would absorb gas like a piece of superfat, but we haven't simulated that yet.

DR. MILLER: You say the greatest inert gas exchange occurs in vessels 45-80 micron or larger in size. These are the size of arterioles and venules that are most vasoactive. Consequently, these are the blocks of tissue that would be most susceptible to shunt driven by temperature

change, exercise, metabolism, and other things that modify the uptake and distribution of not only gases but drugs as well.

DR. HOMER: Yes, it promises to be a real mess! Actually, it's even worse, and your point is a good one. On a larger scale, say up to 300-micron vessels, circulatory control becomes even more complex, and separate tissue units can interact, but we've got to start with something simple before doing something intelligent!

DR. VANN: What are the roles of perfusion and diffusion? How do the two break down? Which is more important? Where is it more important? What tissues would you say have more diffusion than perfusion?

DR. HOMER: I not only won't say, but I wish the rest of you would stop trying to think about it that way.

DR. VANN: When we're dealing with bubble formation that results from gaseous supersaturation, the roles of perfusion and diffusion become important because bubbles might form at the site of the highest inert gas partial pressure. A diffusion-limited tissue, if such exists, would have a higher tissue tension during decompression, would it not?

DR. HOMER: I think the largest partial pressures on decompression have to exist in tissue. I don't know whether that's where bubbles form, but I doubt that either diffusion or perfusion can be ignored. Both are important when you're talking about normal tissue blood flows.

DR. VANN: Which would predominate in most cases?

DR. HOMER: I don't even know how to begin to answer that question. I've stopped trying.

DR. VAN LIEW: I agree with you. The words "perfusion limited" and "diffusion limited" have some tricks in them and we should probably not use them until we get those tricks figured out. One approach might be to double tissue blood flow and observe how that affected the washout rate.

DR. HOMER: In all our simulations the mean transit time is inversely proportional to the flow rate. If you double the flow, you reduce the mean transit time by half, but you can also affect transit time by changing the diffusion coefficient.

DR. VAN LIEW: But diffusion coefficients don't change as much as blood flow, which can change dramatically under different circumstances.

DR. HOMER: Absolutely. In my model, though, I can make molecules with marvelous diffusion coefficients.

DR. KUNKLE: Does your model explain the benefits of hyperbaric oxygen therapy? Even if the arterioles are blocked by bubbles, perhaps oxygen can still get to the tissues by diffusion out of the larger feeders rather than in the small capillary beds where oxygen transport normally occurs.

DR. HOMER: It might be so, but I think that's a more fundamental idea than my model. I don't think it depends on the model.

DR. VANN: Let me ask you about several specific forms of diffusion in tissue. For example, in shunts between arterioles and venules which have been seen by Hoenig, for oxygen, and by Piiper, could an A-V shunt change a fast tissue into a slow tissue?

DR. HOMER: We don't have any A-V shunts in the sense that there are any special shortcuts for the red cells, although there is roughly a threefold range in the red cell transit time in these particular simulations. I would not expect it to make a large difference in any case because the gas mostly leaves large blood vessels.

DR. VANN: I was referring to diffusion shunts between arterioles and venules.

DR. HOMER: Sure, I think shunting by diffusion occurs all the time.

DR. VANN: Is this important for calculating inert gas exchange in tissue?

DR. HOMER: Yes, I think it is. If we bring arterial and venous vessels even as small as 79 micron closer together, we get increases in relative dispersion as a result of diffusion between them.

DR. VANN: Is this very important, or only slightly important?

DR. HOMER: I don't know the answer to that one yet. In this particular simulation I would have to say that it is of intermediate importance, but I also know that the vessels in this simulation are small, so I think that we'll have to wait for simulations of 300- and 100-micron vessels. Then I'll be able to tell you if for example, 10% of the gas goes across the 300-micron vessel while most of it crosses in a 200-micron vessel. I can't say that right now because the tissue module is too small.

DR. LAMBERTSEN: In measuring whole body gas exchange, you measure what comes out and decompression sickness results from what hasn't come out. What do you think about that?

DR. HOMER: One of the reasons for being interested in this kind of simulation is that it's a way of condensing into a single number the very long inert gas washout tails. I don't know if it will be the final answer, but we can compare two different curves. For example, one that has a very long and slow output with one that has a much faster output. After correcting for the means, which speed or delay tissue gas exchange, we may be able to determine if the tissue with the long tail has a larger relative dispersion. I think we are studying the right thing in looking at the relative dispersion.

DR. VANN: You described some of Dr. Weathersby's work in which one interesting feature was that the uptake of a tracer gas continued its increase after the gas was removed from the breathing medium.

DR. HOMER: That's not the experiment I described.

DR. VANN: Nevertheless, it raises another interesting question concerning inert gas exchange. After the subject stopped breathing the tracer gas, did its uptake continue because of diffusion between heterogeneous tissues or are there other explanations? Dr. Weathersby, would you care to comment on those studies?

DR. WEATHERSBY: The work that Dr. Homer presented concerned radioactive xenon in dogs whereas the work Dr. Vann referred to is the kinetics of radio nitrogen in human knees. It had the unexpected result of an increase in the concentration of nitrogen in the knee, even during the washout phases of the experiment. We suggest a flow-coupled-with-diffusion explanation for those results in the paper, but it's certainly not the final word on the subject.

DR. HOMER: Yes, I would say that life is more complicated than our simulations!

DR. VANN: Let's look at another situation involving both perfusion and diffusion. This is the case of longitudinal diffusion in the K rough cyclinder where radial diffusion distances are small enough so that radial diffusion is virtually instantaneous, but long capillaries have large longitudinal diffusion distances. Does this longitudinal diffusion limitation cause a significant variation from a well-stirred, ideal tissue compartment?

DR. HOMER: No, but it's difficult to be quantitative. Longitudinal diffusion limitation might give you relative dispersions of 1.02 or 1.08 but not as much as 2.

DR. VANN: Dr. Gerth and I are currently modeling whole body nitrogen elimination experiments using a series of exponential compartments and a linear compartment. We recognize the limitations of this approach and would like to ask your advice as to how we could improve upon our description of whole body elimination. We also perform maneuvers that vary the distribution and magnitude of blood flow throughout the body. How can we improve our description of inert gas exchange over the simple, traditional exponential compartment?

DR. HOMER: I don't know the answer to that. That question has come up at NMRI also. The modeling approaches that we take only work when there is stability during an experiment. As soon as you want to change the blood flow, the rules for the mathematical approximations become far too complicated. For example, take the case of the mean transit time which changes with the flow. In an experiment where you're fitting sums of exponentials to a washout curve, and the flow is changed in the middle of the experiment, you can't calculate a single mean transit time. It gets even worse if you want to calculate variances or describe individual compartments. You might have a chance of solving the exact boundary value problem if you had several million computers.

EFFECT OF EXERCISE, THERMAL STATE, BLOOD FLOW ON INERT GAS EXCHANGE

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Nitrogen elimination is dependent, at least in part, on tissue perfusion. Tissue perfusion, in turn, is dependent on perfusion pressure and vascular resistance. Perfusing pressure is determined by cardiac output ($\dot{Q}$) and total peripheral resistance. Vascular resistance is set by a balance between extrinsic and intrinsic regulations as modulated by hormonal release. Exercise results in an increase in $\dot{V}O_2$ that is proportional to the workload, leading to an increase in muscle blood flow, vasoconstriction in inactive vascular beds and increased $\dot{Q}$. Divers are exposed to immersion (WI), quite often in cold water, and are required to exercise. Immersion per se results in an increase in $\dot{Q}$. If the WI is in warm water, most peripheral tissues have increased blood flow, while in cold water the reverse is true. The vasoconstriction in response to cold is a thermoregulatory dive that persists even during exercise, leading to a blunted exercise hyperemia. These alterations in peripheral blood flow can alter nitrogen elimination. Perhaps more importantly, there are heterogeneities in blood flow within tissues so that even though total body washout appears normal, a local tissue could have a sufficient volume of gas to result in a decompression problem.

This symposium was organized to examine the physiological and environmental factors affecting decompression and decompression sickness. One of the primary factors that influences gas exchange at the level of the tissue, and subsequently decompression, is the level of perfusion of that tissue. The distribution of the total blood flow to various tissues, and within those tissues, is an important factor in determining the characteristics of total body decompression. The purpose of this review is to consider the factors that determine the perfusion to organs and tissues. A typical dive protocol involves a descent, time on the bottom, and ascent. The diver can be passive or exercising during any one or all three phases of the dive. Other than chamber dives, divers are typically immersed in water and, more often than not, the diver suffers from cold stress during the dive. To address these issues, this

review will examine rest and exercise in air, during water immersion (WI) in thermal neutral water (TNW), and during water immersion in cold water (<TNW). We will also attempt to evaluate the effects of alterations in perfusion during exercise or environmental stress on total body nitrogen washout.

Perfusion of an organ or tissue (q) is dependent on the mean arterial diving pressure gradient (ΔP_a) and the local vascular resistance (R) in that organ or tissue. To determine the tissue perfusion we must evaluate the role of these two parameters. The ΔP_a is determined by the mean arterial pressure (P_a) and the end capillary pressure, typically considered zero. The determinants of the P_a are cardiac output ($\dot{Q}$) and total peripheral resistance (TPR). The sum total of the vascular resistances determines the TPR. It is important, therefore, to examine the factors that determine $\dot{Q}$ and the local vascular resistances of independent vascular beds. Table 1 is comprised of a list of vascular units (organs or tissues) with their approximate weight, total blood flow, blood flow per unit tissue, percentage of total blood flow, oxygen requirement and oxygen extraction at rest and during exercise in air and during WI in either TNW or water below thermal neutrality (1,2,3,4,5,6,7,8,9). An examination of the data for resting air reveals that the metabolic demand of tissues and the blood flow is quite variable. To understand the control of this system, we must review selected principles of vascular control. The blood flow to a vascular unit is determined by a balance between extrinsic control and intrinsic regulation as modulated by hormonal responses. It is generally agreed that there is a basal tone in a vascular bed which can be potentiated or inhibited by increases or decreases in sympathetic tone (1,2,3,4). Selected vascular beds have quite variable responses that are dependent on the density and sensitivity of receptors. The response to increases in sympathetic tone are general and therefore their effect has to be modulated by local factors or intrinsic regulation. The intrinsic regulation would appear to be primarily a response to the buildup of metabolites (P_i, ADP, AMP, adenosine, lactic acid) in local tissues and is supported by local temperatures and mechanical changes as well as perhaps local neuro control (1,2). The modulation of extrinsic vasoconstriction by intrinsic regulation is responsible, at least in part, for the matching between q and metabolism in those tisues that demonstrate this relationship. The balance between extrinsic and intrinsic control is modulated by both local and systemic hormones. Specifically, epinephrine acting on B_1 and B_2 receptors causes a vasodilation in selected tissues, while norepinephrine acts on alpha receptors and tends to cause

Table 1

Representative values of blood flow, oxygen consumption, and extraction from various organs during rest and maximal exercise under various environmental conditions

Condition	Variable	Units	Brain	Heart	Kidney	Liver	Skin	Bone	Fat	Muscle	Total
Air	Wt	kg	1.4	0.3	0.3	1.5	2.0	27.0	15.0	35.0	82.5
Rest	BF	$l \cdot min^{-1}$	0.70	0.24	1.20	1.28	0.20	0.81	0.75	1.75	6.95
	BF	$ml \cdot 100g^{-1} \cdot min^{-1}$	50	80	400	85	10	.3	.5	5	—
	BF/Q	%	10	4	19	19	3	10	11	24	—
	VO_2	$ml \cdot min^{-1}$	60	35	14	60	10	20	20	60	279
	$(a-\bar{v})O_2$	$ml \cdot 100ml^{-1}$	8	14	2	4	2	4	4	6	—
Exercise	BF	$l \cdot min^{-1}$	.70	1.10	0.72	0.77	.80	.81	2.63	14.00	21.50
(max)	BF	$ml \cdot 100g^{-1} \cdot min^{-1}$	50	350	240	51	40	3	17.5	400	—
	BF/Q	%	3	5	3	4	4	4	12	65	—
	VO_2	$ml \cdot min^{-1}$	60	170	14	60	10	20	40	3000	3374
	$(a-\bar{v})O_2$	$ml \cdot 100ml^{-1}$	8	18	2	8	2	4	2	20	—
Immersion	BF	$l \cdot min^{-1}$	0.70	0.30	1.80	2.25	0.30	0.81	1.12	2.80	10.01
Rest 35°C	BF	$ml \cdot 100g^{-1} \cdot min^{-1}$	50	100	600	150	15	3	7.5	8	—
	BF/Q	%	7	3	18	22	3	8	11	28	—
	VO_2	$ml \cdot min^{-1}$	60	35	14	60	10	20	20	60	279
	$(a-\bar{v})O_2$	$ml \cdot 100ml^{-1}$	8	11	1	3	3	4	2	2	—
Exercise 35°C	BF	$l \cdot min^{-1}$	0.70	1.10	0.72	0.77	0.80	0.81	2.63	13.5	21.03
	BF	$ml \cdot 100g^{-1} \cdot min^{-1}$	50	350	240	51	40	3	17.5	37.5	—
	BF/Q	%	3	5	3	4	4	4	13	65	—
	VO_2	$ml \cdot min^{-1}$	60	170	14	60	10	20	40	2700	3074
	$(a-\bar{v})O_2$	$ml \cdot 100ml^{-1}$	8	18	2	8	10	4	2	.20	—
Rest 20°C	BF	$l \cdot min$	.84	.34	1.40	1.50	.20	.81	.15	.70	5.00
T_r1.5°C	BF	$ml \cdot 100g^{-1} \cdot min^{-1}$	60	120	466	100	1	3	1	20	—
	BF/Q	%	17	7	28	30	4	16	3	14	—
	VO_2	$ml \cdot min^{-1}$	70	53	14	60	10	20	20	240	487
	$(a-\bar{v})O_2$	$ml \cdot 100ml^{-1}$	8	16	1	4	5	3	14	.34	—
Exercise 20°C	BF	$l \cdot min$	.70	1.10	.72	.77	.60	.81	1.50	8.80	15.00
T_r1.5°C	BF	$ml \cdot 100g^{-1} \cdot min^{-1}$	50	400	240	51	3	3	10	250	—
	BF/Q	%	5	7	5	5	4	5	10	59	—
	VO_2	$ml \cdot min^{-1}$	60	170	14	60	10	20	40	1800	2174
	$(a-\bar{v})O_2$	$ml \cdot 100ml^{-1}$	9	15	2	8	2	2	3	.20	—

vasoconstriction. The systemic hormones angiotension II and vasopressin cause vasoconstriction while most of the autocords result in vasodilation (kinins, histamine, serotonin), and there are many more to be discovered later (1,2). The relative role of these various control mechanisms is determined by the primary function of each vascular bed. For example, the brain, heart, and muscle are metabolically active and therefore have high levels of intrinsic regulation, whereas vascular beds that serve support functions such as liver, kidney, and skin have a high degree of extrinsic control. In order to consider the control of q during exercise, immersion, or response to cold, we will have to consider how each of these alter extrinsic, intrinsic, or hormonal control of the vascular beds of all tissues. To accomplish this goal, data for blood flow for various environmental conditions are presented in Table 1 and will be discussed in the subsequent sections. In addition, the role of $\dot{Q}$ will be considered, as it determines P_a and therefore perfusion pressure.

Air

During rest in air, the $\dot{Q}$ ranges from 4-6 $l \cdot min^{-1}$ and supplies blood to the vascular beds as indicated in Table 1. As can be seen in Table 1, blood flow ranges from 3 to 400$ml \cdot 100g^{-1} \cdot min^{-1}$ and the $(a-v)O_2$ differences varies from 2 to 14. Under these conditions, the P_a is $\sim$ 90 mmHg, providing an adequate perfusion pressure. The distribution of $\dot{Q}$ at rest is primarily to the support tissues with kidney, liver, and skin getting almost 50% of the $\dot{Q}$, while muscle, heart, and brain receive $\sim$ 35% of the $\dot{Q}$.

When a subject begins to exercise, there is an increase in $\dot{V}O_2$, $\dot{Q}$, blood flow to muscle (q_m) and heart (q_h), while blood flow to kidney and liver decreases (see Table 1). These changes occur in a graded manner that is matched to the exercise metabolism. Specifically, as oxygen consumption increases from 0.279 to 3.374 $l \cdot min$, $\dot{Q}$ increases from 6.95 to 21.50 $l \cdot min$ at the rate of 6$l\dot{Q}$ per lO_2, while q_m increases from 5 to 400 $ml \cdot 100g^{-1} \cdot min^{-1}$ at the rate of 100 $mlO_2 \cdot 100g^{-1} \cdot min^{-1}$ per lO_2. In spite of the decrease in vascular resistance that results from the muscle vasodilitation, there is an increase in systolic and mean blood pressure, while diastolic blood pressure is unchanged by exercise. In man the increase in mean arterial pressure is critical to provide the perfusion pressure required to overcome the vascular resistance of muscle capillaries. Immediately at the onset of exercise, muscle tissues are excited and contract, utilizing energy. The combination of the buildup of metabolites from

metabolism, output of mechanoreceptors, and possibly output of intrinsic nerves causes a vasodilitation around those muscle fibers that are active (1,2). This implies that the muscle fiber types recruited determine to a great extent the vascular response. Concurrent with the recruitment of motor neurons there is an increase in sympathetic tone, resulting in an increase in vascular resistance throughout the circulation. The combination of a generalized increased resistance with local vasodilitation in metabolically active tissues redistributes the cardiac output toward exercising muscle and away from non-metabolically active tissues. The redistribution of $\dot{Q}$ is one mechanism of increasing q_m; however, the sympathetic drive increases heart rate and the inotropic state of the heart so that, as venous return is increased by the pumping action of the muscle, $\dot{Q}$ increases. As exercise workload is increased, both heart rate and stroke volume increase linearly with $\dot{V}O_2$ up to their maximal levels. When the heart rate exceeds 100 $b \cdot min^{-1}$, there is an increase in norepinephrine that is proportional to the increase in HR (1,2). The increased norepinephrine causes a further vasoconstriction in the splanchnic and renal blood flow. Due to the increase in mean arterial blood pressure, blood flow to relatively passive vascular beds, such as fat, increases, while vascular beds with a high degree of autoregulation (like the brain) vasoconstrict and do not have an increase in blood flow. At the outset of exercise, the skin vasculature is vasoconstricted; however, as the Tc increases, the skin vasodilates and can achieve flows of 40-80 $ml \cdot 100\ ml^{-1} \cdot min^{-1}$ (4,7).

At the onset of exercise, q_m adjusts very rapidly, while $\dot{Q}$, P_a, $\dot{V}O_2$, HR, and SV are somewhat slower, however, still rapid. There is an obligatory anaerobic energy component which consists primarily of utilization of ATP and CP and a small but significant glycogen -lactic acid. It is most likely that the buildup of these metabolites turns on $\dot{V}O_2$ as well as q_m. As exercise increases, maximal q_m, $\dot{Q}$, and $(a-v)O_2$ are achieved and energy is again supplied by glycogen-lactic acid (anaerobic glycolysis) which leads to significant elevation in muscle and consequently blood lactic acid. If the adjustment of q_m, $\dot{Q}$, or $\dot{V}O_2$ is delayed, the energy contributed by glycogen-lactic acid increases and could prevent a subject from exercising long enough to achieve steady state $\dot{V}O_2$. The utilization of anaerobic metabolism requires $\dot{V}O_2$ and consequently q_m to remain elevated during recovery from exercise for about 2-5 min. Although lactic acid (if produced in sufficient quantities) may remain in the blood for 20 min to 1 hr, it is consumed by basal or exercising metabolism and does not contribute per se to post-exercise $\dot{V}O_2$. It is important to note, however, that if T_c and/or catecholamines are

elevated, $\dot{V}O_2$ and q_m will remain elevated during recovery. Intermittent exercise can be considered as a simple extrapolation of a series of single adjustments, if the time interval in between bouts is considered in light of the recovery time from each exercise bout.

Response to Immersion

The application of the physiological response to decompression sickness typically would involve an aquatic environment as well as exercise. Just entering the water alters the resting cardiovascular state. Typical values for blood flow during head out water immersion (WI) in water of thermal neutral temperature are presented in Table 1 (1,2,3,4,6,7,8,9). The immersion per se results in a translocation of blood to the chest which increases cardiac output (10,11). In spite of the increase in $\dot{Q}$, mean arterial blood pressure either does not change or only increases slightly (10). As can be seen from Table 1, blood flow is generally increased and redistributed in spite of the fact the $\dot{V}O_2$ is unchanged. This implies an overriding of autoregulation in beds of high tone, i.e., heart, brain, muscle as well as extrinsic alteration in beds of low intrinsic tone. This can be explained by a generalized reduction in sympathetic tone which would affect all vascular beds. A decrease in sympathetic tone is consistent with the observed decrease in heart rate (HR) and catecholamines seen in immersion (10,11). In addition, there is a fluid shift (and perhaps electrolytes) from the tissue to the plasma compartment resulting in an increase in plasma volume (PV) over the first 30 min of WI (11). The increase in cardiac stretch, along with the increase in PV, results in a diuresis, natruresis, and kaluresis (between 0.5 and 2 hrs of WI) (11). It would appear that hormone release (atrial natruretic factors) or inhibition (antidiuretic hormones, aldesterone) along with renal sympathetic nerve activity play an important role in renal function and appear to blunt increases in plasma volume (11). Plasma volume would appear to be tightly regulated, presumably as part of blood pressure regulation.

The cardiovascular changes described above are time-dependent such that after $\sim$ 2 hrs of WI most variables have returned to air levels which the renal functions may take 2-4 hrs to return to air levels. Subjects who have been immersed for 4 hrs most likely still have elevated central venous pressures (11) and probably have reduced tissue water and electrolyte levels. If subjects are rehydrated during WI, the $\dot{Q}$ may remain elevated during WI (11).

Exercise in TN water provides a metabolic dive similar to that of exercising in air (12,13,14,15,16,17,18,19). The modulation of the extrinsic vasoconstriction by intrinsic dive to increase blood flow is similar and therefore peripheral blood flow adjustment is similar under the two conditions. The maximal values of flow expected under these conditions are shown in Table 1. The only exception to this similarity is skin BF which would be slightly elevated due to the higher skin temperature in water ($37^{o}C$) than air ($20^{o}C$). One would conclude that no significant alterations in cardiovascular control would result from exercising in thermal neutral water when compared to air controls.

Most diving is performed in water below thermal neutral water temperature. The exposure to cold water results in dramatic alterations in cardiovascular control both at rest and during exercise. The mechanical aspects of immersion in cold water are not significantly different from WI in TN water (12,13,14,15,16,17,18,19); however, the vascular response is quite different. Two levels of cold can be considered. The first is sufficient to cause a peripheral vasoconstriction and reduced heat flux such that T_c or $\dot{V}O_2$ would not change (critical water temperature, CW) (20). This water temperature (CW) is dependent on body size, muscle mass, fat thickness, and water movement and typically ranges from $28-32^{o}C$ (5,20,21). With water temperature below an individual's CWT, the vasoconstriction is potentiated, T_c decreases, and $\dot{V}O_2$ increases (5,13,14,15,18,19,22,23,24). The vasoconstriction has been demonstrated by measurement of total limit blood flow which is reduced from 10 to 5 $ml \cdot 100ml^{-1}min^{-1}$ (1,2,4,7,25). This vasoconstriction has been attributed to cutaneous beds and has been considered to be of little importance (4,5). More recently, we have shown that all muscles have a reduced blood flow; and as there are 25-50 kg of muscle, the impact on both temperature regulation and the circulation is very important (9,21,26). The reduction in blood flow to cold stress would appear to be mediated initially by skin temperature and subsequently by decrease in core temperature. It is our postulate that these vasomotor responses are mediated by an increase in sympathetic tone leading to increased extrinsic tone. The idea is supported by the dramatic increase in circulating catecholamines observed in cold water exposures (12). Further support can be argued as heart rate is decreased by parasympathetic tone while stroke volume is increased by an increase in positive inotropic state resulting from increased sympathetic tone. Table 1 presents blood flow data for various organs, estimated from published data (7,13,14,15,18,22,23,24,26,27).

The increased vasoconstriction would increase total peripheral resistance, resulting in an increase in afterload. The increased afterload would offset the immersion-induced increased preload and as a result $\dot{Q}$ would be similar during cold WI to air and well below warm WI (27). In this scenario mean arterial blood pressure would be elevated, implying a resetting of the baroreceptors.

In the case of the cold WI, the T_c would decrease as a function of T_w and exposure time (14,18). Although T_w affects the VC, it would not appear to affect $\dot{V}O_2$; however, as T_h decreases, there is a proportional increase in $\dot{V}O_2$. In spite of this thermogenesis, the extrinsic VC is potent enough to override the intrinsic VD trend resulting from the increased $\dot{V}O_2$.

The response to exercise in the cold provides a useful model as the intrinsic VD dive increases with $\dot{V}O_2$ as does venous return and sympathetic tone. Estimated changes in responses to maximal exercise are given in Table 1. As can be seen, blood flows in vascular beds with a predominance of extrinsic control; however, even in beds with high intrinsic control (autoregulatory), the blood flows are lower in the cold than in warm water. The reduced local blood flow results in a higher $(a-v)O_2$ difference, lower maximal $\dot{V}O_2$, and lower $\dot{Q}$.

The lower $\dot{Q}$ at maximal exercise could be a result of decreased output due to cardiac factors or to the absence of peripheral demand. At submaximal workload, $\dot{Q}$ is not significantly depressed when compared to warm water or air; however, skeletal muscle blood flow is depressed at all workloads. This would support the contention that the heart is not the limiting factor and that it is meeting the demands set peripherally. This may not be true, however, as the maximal heart rate is less than 160 $b \cdot min^{-1}$ with a maximal stroke volume. Due to the increased parasympathetic control, the heart rate may not be able to be increased which could limit $\dot{Q}$.

In addition to the circulatory limitations to oxygen delivery, pulmonary limitations have been suggested (28). It is generally assumed that the ventilation perfusion ratio improves with exercise and during water immersion. Recent evidence suggests that during WI the volume of blood in the chest increases, therefore decreasing gas volume (15); that there may be a widening of the A-a gradient (29); and in fact dog blood that is lower in temperature may not "unload" oxygen (30). These factors could affect oxygen delivery to tissue and in fact nitrogen elimination. Further investigation is needed into the role of ventilation during WI, especially in the cold.

Adaptation to Cold

Chronic exposure to a cold environment has been reported to alter the metabolic and cardiovascular response to cold stress. LeBlanc (31) has shown a local adaptation to immersion of the hand in cold water by fishermen who routinely undergo hand immersion in cold water. He has demonstrated that this response is generalized to immersion of the foot, and the response is present throughout the year. Both hand and foot immersion gave lower pressure responses in these cold-adapted subjects. The authors suggest a lesser degree of vasoconstriction in the cold-adapted hand and foot. The adaptation to total body cooling in Korean diving women demonstrated by Rennie (20) would appear to be a different response, as their work suggests a greater increase in total body insulation and resistance to heat loss than in diving women. The primary observation of these authors was that the shivering threshold of the diving women was much lower than the non-diving Koreans. The fishermen and divers can be compared to the Eskimo hunters who do not apparently have an adaptation to cold (32). The Eskimo principal adaptation would appear to be to create a microclimate that eliminates the cold stress. This has been subsequently demonstrated in Korean diving women who now wear wetsuits and, as a result, have lost their adaptation. Alacaluf and aborigines have sustained the ability to withstand decreases in skin temperature without elevations in metabolic rate. In summary, it is clear that exposure of a limb to a cold stimulus results in a prompt and extreme vasoconstriction (4,7), which diminishes with adaptation (31). Total body immersion in cold water results in a vasoconstriction and increased metabolism (5) which are blunted by adaptation (20,32). Further investigation is needed to determine the role vasoconstriction plays in these adaptive responses.

Nitrogen Washout

The primary purpose of reviewing blood flow and the factors that influence blood flow was to examine their influence on nitrogen elimination. To address this issue, we have modeled nitrogen elimination as it would be affected by changes in blood flow. Under most conditions, the time constants are fast enough that even though there were reductions in blood flow or redistributions of blood flow, this would not significantly influence nitrogen elimination. Under certain conditions, however, such as rest in the cold (T_c<1.5^{o}C), the decreased blood flow to skin, fat, and muscle could significantly affect nitrogen elimination. To examine this further, we model nitrogen

elimination assuming a simple exponential washout without diffusion limitations, the time constant of which was the ratio of effective tissue volume to perfusion. The data from Table 1 were utilized for these calculations and is presented in Figure 1. As can be seen, the nitrogen washout from all compartments is completed within 2 hrs in air (20°C), whereas in cold water ~ 0.5 l of nitrogen remains in the body after 2 hrs. This volume remains most likely in skin, fat, and muscle which are the tissues with reduced blood flow.

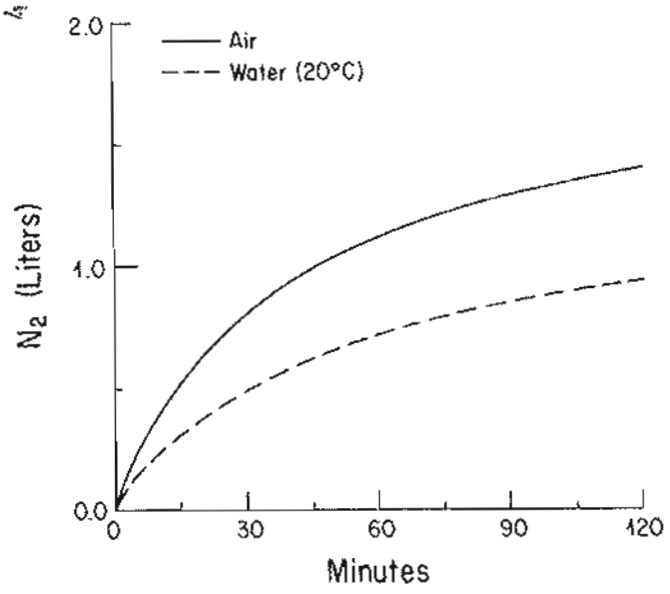

Fig. 1 Estimated nitrogen elimination (lN_2) is plotted as a function of time over 120 min period. The solid line represents N_2 elimination sitting in air with blood flow from Table 1A. The dashed line is N_2 elimination after 1 hr WI in 20°C water (t_c = 36°C), assuming the values for blood flow from Table 1E.

Nitrogen elimination from skeletal muscle at rest is plotted with a solid line in Figure 2. Nitrogen elimination under this circumstance is complete within ~ 2 hrs. This analysis assumes a homogeneous blood flow to the muscle. Recently, we have shown that there is large inhomogeneity in skeletal muscle (33). Assuming that one-half of the muscle is perfused at the mean flow and one-

quarter at a flow 1 SD above and one-quarter at a flow 1 SD below the average flow, we have calculated the nitrogen elimination from the total body (dashed line in Figure 2). Although the effect of this heterogeneity can be seen, it is relatively small and, in fact, may be undetectable by actual measurement. Perhaps more important than the total body washout is the washout from specific tissues. In this case, the variation in flow of X $\pm$ 1 SD makes a significant difference in the washout of nitrogen (Figure 3). This is very important, as total body nitrogen elimination would appear to be near normal; however, significant volumes of nitrogen could be trapped in localized regions of tissue and could result in local "hits" that are transparent when considering the "whole body." This modeling utilized muscle where we have published data demonstrating the heterogeneous nature of blood flow. In a recent study (unpublished), we have demonstrated a heterogeneity of blood flow in brain, nerve, bone, fat, and GI. This heterogeneity presumably could become larger under adverse expotential conditions and/or during exercise and therefore could play an important role in decompression sickness or accidents.

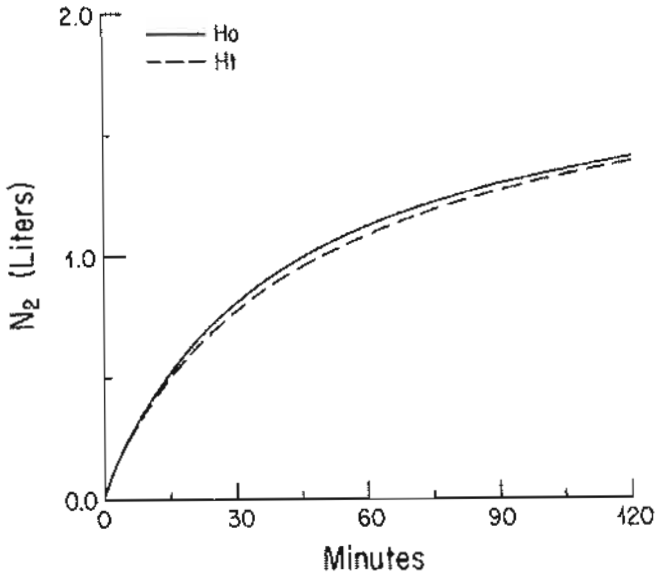

Fig. 2 Estimated nitrogen elimination (lW_2) is plotted as a function of time over 120 min period. The values are taken from Table 1A; however, Ho solid line is assuming that all tissues have the same flow. The calculations for Ht, dashed line, were based on a heterogeneity of blood flow ($\pm$1 SD) around the mean flows in Table 1A. See Table 2 for variations in blood flows used in the calculations.

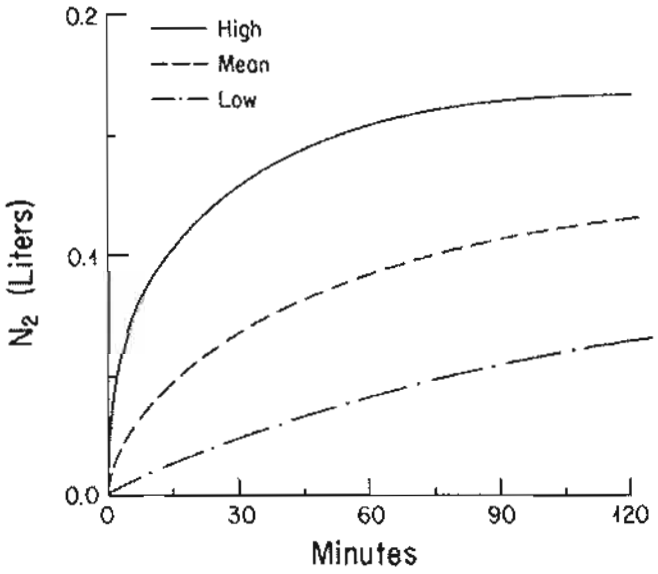

Fig. 3 Estimated nitrogen elimination ($1W_2$) is plotted as a function of time over 120 min period. The N_2 washout is from skeletal muscle, assuming the mean flow from Table 1A with 50% of the muscle at mean flow (mean), 25% at a flow +1 SD (high), and 25% -1 SD (low).

Inasmuch as the increased $\dot{Q}$ during exercise is directed to the skeletal muscle, and specifically to active skeletal muscle, $\dot{Q}$ increases proportionally to the increased $\dot{V}O_2$.

REFERENCES

1. Rowell LB. Cardiovascular adjustments to thermal stress. In: Handbook of Physiology: The Cardiovascular System. Shepherd JT, Abboud FM, eds. Bethesda, MD: American Physiological Society, 1983:967-1024.

2. Rowell LB. Human Circulation. Regulation During Physical Stress. New York, Oxford University Press. 1986.

3. Shepherd JT. Circulation to skeletal muscle. In: Handbook of Physiology: The Cardiovascular System. Shepherd JT, Abboud FM, eds. Bethesda, MD: American Physiological Society, 1983:319-370.

4. Johnson JM, Brengelmann GL, Hales JRS, Vanhoutte DM, Wenger CB. Regulation of cutaneous circulation. Fed Proc 1986; 45:2841-2852.

5. Nadel ER. Problems with Temperature Regulation During Exercise. San Diego, CA. Academic Press, 1977.

6. Balldin UI, Lundgren CEG, Lundvall J, Mellander S. Changes in the elimination of ^{133}Xenon from the anterior tibial muscle in man induced by immersion in water and by shifts in body position. Aerosp Med 1971; 42:489-493.

7. Bancroft H, Edholm G. The effect of temperature on blood flow and deep temperature in the human forearm. J Physiol (London) 1943; 102:5-20.

8. Krasney JA, Pendergast DR, McDonald BW, Powell E, Plewes JL. Regional blood flow responses to head out water immersion in the anesthetized dog. J Appl Physiol 1983; 52:29-35.

9. Thorsson O, Lilija B, Ahlgren L, Hermdal B, Westlin N. The effect of local cold application on intra-muscular blood flow at rest and after running. Med Sci Sport 1985; 17:710-713.

10. Arborelius MJ, Balldin UI, Lilja B, Lundgren, CEG. Hemodynamic changes in man during immersion with head above water. Aerosp Med 1972; 43:592-598.

11. Epstein M. Renal effects of head out water immersion in man: implications for an understanding of volume homeostatis. Physiol Rev 1978; 58:529-581.

12. Blomstrand F, Kaijser L, Matinsson A, Bergh J, Ekblom B. Temperature-induced changes in metabolic and hormonal responses to intense dynamic exercise. Acta Physiol Scand 1986; 127:477-484.

13. Costil DL. Effects of water temperature on aerobic working capacity. Res Quart 1966; 39:67-73.

14. Craig Jr. JB, Dovarak M. Comparison of exercise in air and in water at different temperatures. Med Sci Sports and Exerc 1969; 1:124-130.

15. Craig Jr AB, Ware DE. Effect of immersion in water in vital capacity and residual volume of lungs. J Appl Physiol 1967; 23:425-425.

16. Iampietro PF, Bass DE. Heat exchanges of men during caloric restriction in the cold. J Appl Physiol 1962; 17:947-949.

17. Holmen I, Bergh U. Metabolic and thermal response to swimming in water at varying temperatures. J Appl Physiol 1974; 37:702-705.

18. McArdle WD, Magel JR, Lesmes GR, Pechar GS. Metabolic and cardiovascular adjustments to work in air and water at 18, 25, and 33^{o}C. J Appl Physiol 1976; 40(1):85-90.

19. Toner MM, Sawka MN, Pandolf KB. Thermal responses during arm and leg and combined arm-leg exercise in water. J Appl Physiol 1984; 56:1355-1360.

20. Rennie DW, Covino BG, Howell BJ, Song SH, Kang BS, Hong SK. Physical insulation of Korean diving women. J Appl Physiol 1962: 17:961-966.

21. Veicsteinas A, Ferretti GT, Rennie DW. Superficial shell insulation in resting and exercising man in cold. J Appl Physiol 1982: 52:1557-1564.

22. Denison DM, Wagner PD, Kingaby GL, West JB. Cardio-respiratory responses to exercise in air and under water. J Appl Physiol 1972; 33:426-430.

23. Dixon RW, Faulkner JA. Cardiac outputs during maximal effort running and swimming. J Appl Physiol 1971; 30:653-656.

24. Hardy JF, Soderstrom GF. Heat loss from the nude body and peripheral blood flow at temperatures of 22^{o}C to 35^{o}C. J Nut 1985; 16:493-509.

25. Rowell L, Murray IA, Brengelman GL, Kraning K. Human cardiovascular adjustments to rapid changes in skin temperature during exercise. Circulation 1969; 24:711-724.

26. Park VS, Pendergast DR, Rennie DW. Decreases in body insulation with exercise in cold water. Undersea Biomedical Res 1984; 11:159-168.

27. Rennie DW, diPrampero P, Cerretelli PC. Effects of water immersion on cardiac output, heart rate and stroke volume of man at rest and during exercise. Medicina Dello Sport 1971; 24:223-228.

28. Brooks GA, Fahey TD. Exercise Physiology, Human Ioenergetics and its Applications. New York. John Wiley and Sons, 1984.

29. Cohen R, Bell WH, Saltzman HA, Kylstra, JA. Alveolar-arterial oxygen pressure difference in man immersed up to the neck in water. J Appl Physiol 1971; 30:720-723.

30. Gutierrec G, Warley AR, Dantzker DR. Oxygen delivery and utilization in hypothermic dogs. J Vascular Res 1986; 60:751-757.

31. LeBlanc, J. Local adaptation to cold of Gaspe fishermen. J Appl Physiol 1962; 17:950-952.

32. Hart JS, Sabean HB, Hildeo JA et al. Thermal and metabolic responses of coastal Eskimos during a cold night. J Appl Physiol 1962; 17:953-960.

33. Cerretelli P, Marconi C, Pendergast D, Meyer M, Neisler N, Piiper J. Blood flow in exercising muscles by xenon clearance by microsphere trapping. J Appl Physiol 1984; 56:24-30.

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DISCUSSION

DR. CHRYSSANTHOU: What are the implications of this presentation in the pathogenesis of decompression sickness?

DR. PENDERGAST: A first implication is that the likelihood of developing decompression sickness depends to a great extent on inert gas exchange which is influenced by the distribution of blood flow to various organs and tissues. This distribution can be altered by exercise and environmental stress which occur during diving.

A present absolute value of blood flow for various organs and tissues determined under various environmental conditions. Hopefully, these values will help others calculate the influence of exercise and environment on inert gas exchange.

A second implication, which Dr. Homer mentioned, is that blood flow within an organ or tissue is not homogeneous, and therefore there can be tissue volumes as small as 0.2 gram which may have a large remaining gas tension after the whole body is decompressed. I'm not too familiar with how bubbles form, but it's conceivable that a bubble in one of these poorly perfused tissue regions might not be sensed in the total body washout because of its small volume. We illustrate this by modeling the effects of immersion and heterogeneous blood flow on total body inert gas exchange. There can be large changes in perfusion heterogeneity which make very little difference to total body washout.

DR. BALLDIN: Dr. Pendergast, your work provides fundamental information for understanding the elimination of inert gases that influence the development of decompression sickness. You say that muscle perfusion increases tremendously with exercise in both air and water. Thus, exercise during decompression will increase the elimination of nitrogen from the muscles. Fat, however, dissolves much more nitrogen than muscle, and the temperature increase that occurs with exercise will cause an increase in subcutaneous adipose blood flow. Therefore, fat may be more important than muscle in the increased nitrogen elimination that occurs with exercise.

DR. PENDERGAST: I think this is a very important point and I'm glad that you brought it up. Fat, in many cases, is considered a passive tissue whose blood flow is controlled by the arterial pressure. During exercise, arterial pressure goes up so dramatically that fat blood flow increases from about 10 to about 40 millimeter per min per 100 gram. As Dr. Balldin pointed out, this can mean a lot more gas in fat rather than in muscle because of the fivefold greater inert gas solubility.

During cold, however, blood flow to fat, muscle, and skin is markedly reduced. It is quite complicated because the effects of compression, decompression, exercise, and cooling depend on their relative timing.

There is a big difference between inert gas exchange during cold water immersion and in air. Fat accounts for about half the difference, skin for about a third, and muscle for the rest.

DR. YOUNGBLOOD: As one of the running dogs of commercial diving and capitalism, I'd like to say that I find this very enlightening and very pertinent. For one of the first times, a scientific paper has connected the fundamental issues of the pathophysiology with some of the real field problems of decomposition sickness, such as hot water suits and other environmental factors.

DR. WHIDDEN: Exercise and shock appear to be very similiar at a metabolic level, represented, for example, by the relationship of cardiac

output to oxygen consumption. Have you attempted to relate respiratory quotient to free fatty acid and lactic acid metabolism as an indication of similar mechanisms in exercise and shock?

I ask this because Bagy and Miller in New Orleans have been looking at the role of exercise-generated lactate metabolism in depressing free fatty acids, which are a predominant fuel supply for cardiac output.

DR. PENDERGAST: The commonality between exercise and shock probably is metabolic. In shock, a large but inefficient protein catabolism produces some lactic acid which does inhibit free fatty acid metabolism. A large amount of substrate is utilized locally.

To my knowledge, no study has demonstrated that the raw fuel used has an impact on cardiac output and local muscle blood flow. There is a complicated relationship between the production of lactic acid, change in local and blood pH, change in the respiratory quotient, and the development of hyperventilation.

Your comments are appropriate metabolically, but no one has demonstrated either a peripheral or a central vascular effect that would be a primary determinant of the nitrogen elimination.

DR. CAMPORESI: You show blood flow to the spinal cord which is 20 times less than to the brain for mild exercise. During anesthesia or during rest, however, blood flow to the spinal cord is usually equivalent to the blood flow to the brain.

DR. PENDERGAST: Brain blood flow is very heterogeneous. During exercise, cerebellar blood flow goes up by a factor of four. In the rest of the brain, blood flow is more like that in the spinal cord. The important thing is that the index of dispersion discussed by Dr. Homer is the same in the spinal cord as it is in all compartments of the brain. Heterogeneity is what I was trying to illustrate would be equally as prevalent in all aspects of the brain in the spinal cord, in the bone, and in other tissues.

This may be complicated in the spinal cord, which already has a low flow. There are chunks of spinal cord and brain which get no microspheres during a particular injection, but there must be some flow over an extended period of time.

Heterogeneity, however, changes with time. In our observations, regional blood flow changes at intervals of about 2 minutes. While areas around slow twitch muscle tend to have higher flows than areas around fast twitch muscle, there also appear to be random heterogeneities. This probably has an impact on the volume of inert gas remaining in tissue.

CAPTAIN THALMANN: Dr. Pendergast, how does the skin temperature and the actual skeletal muscle temperature relate in terms of blood flow?

DR. PENDERGAST: The skin sensitivity brings about an immediate reduction in blood flow. Skeletal muscle blood flow can remain elevated, however, if the local temperature is high due to modulation of intrinsic hormonal, neural, and metabolic factors. If the muscle temperature is lower than normal, but lower than the high level that normally occurs during exercise, it would appear that the muscle becomes vasoconstricted as well.

During immersion, the skin temperature drops to water temperature immediately. This brings about a vasoconstriction that's about one-half the maximum. As the body cools down and the core temperature drops, there is a further decrease in blood flow. In experiments where the muscle temperature did not drop, blood flow remained normal. The three important factors are skin temperature, core temperature, and muscle temperature.

Muscle temperature seems to influence the muscle blood flow alone, whereas the skin and core temperatures seem to influence skin fat blood flow and, I think more importantly, the extrinsic vasoconstriction which would constrict the whole body as far as blood flow is concerned.

DR. GERTH: I'd like to comment on the questions of relevance of whole body gas washout studies to the issue of decompression sickness pathogenesis. The total volume of inert gas eliminated is probably less important than the shape of the washout profile from which we can derive information about the cardiovascular state of the body. In particular, the tail of a washout curve provides information about the mean microvascular performance which we have found to relate to the amount of decompression sickness protection acquired during oxygen breathing before altitude exposure. While the differences in the model nitrogen washout curves which Dr. Pendergast showed were small, there were changes in shape which can provide useful information.

DR. PENDERGAST: I didn't mean to suggest that whole body washout measurements are useless, but as Dr. Homer indicated, about 50% of the total body redistribution of blood flow within organs, tissues, and structures may be absolutely critical at the local level where decompression sickness occurs. These local sites may be hidden in the total body washout and significantly affected by a temporal redistribution of blood flow.

DR. LAMBERTSEN: One of the extrinsic neurogenic control mechanisms that seems to cut across almost every effect due to immersion, temperature effect, exercise, excitement, position and so forth, is the carotid sinus reflex which attempts to maintain constant blood pressure by way of sympathetic neural control. This control can vary widely over different tissues and organs. If one exercises, the increase in flow to the exercising muscle which may have some importance to that muscle, has to result in decreases in flow elsewhere. When one studies organs in which blood flow increases, there must be other regions not being studied where blood flow decreases in order to sustain blood pressure. This is relevant to the question of inert gas exchange where decreased blood flow and inert gas exchange can occur in many regions and yet not be observed. Could you comment on that?

DR. PENDERGAST: The question has two parts. The first part is that the sympathetic firing rate is dependent on the density of local receptors and on the sensitivity of those receptors. I think now we can characterize the density and sensitivity of both alpha and beta receptors on various vessels within various organs and tissues. More recent data explain those changes in the carotid baroreceptor and other mechanisms.

The second part is that although blood pressure is supported to a great extent by redistribution of cardiac output, there are changes in cardiac output that are important during exercise as well. These factors are modulated hormonally by the sympathetic nervous system and by local metabolic events in metabolically active tissues. In the case of cold, vasodilation is blunted by increase in sympathetic firing rate and because the muscle has a high density sensitive of beta-two receptors.

Inert gas exchange can be affected in other ways. We've shown in skeletal muscle that these can be regions of very high blood flow but very slow gas exchange. On the other hand, there can be regions where the blood flow is relatively low but gas exchange is rapid. We think that the high blood flow regions are not A-V shunts but functional conduits. The

very high flow allows blood to be recirculated and maintain the venous return.

If you stress that muscle and blood flow go down, we do not believe you compromise gas exchange but simply redistribute blood away from high-flow regions to low-flow regions. Thus you can still adequately perfuse the muscle and also provide blood flow to other organs and tissues. The net result as far as decompression is concerned is very complicated.

DR. LAMBERTSEN: Really, then, an increase in blood flow to muscle as a result of exercise might interfere with inert gas exchange in other tissues. Thus, the increase in blood flow that you describe as beneficial is in fact disadvantageous in the regions where decompression sickness is felt. It isn't felt presumably in the muscle where the exercises happen.

DR. PENDERGAST: I was using muscle as a model for heterogeneity in other tissues which are more important in decompression. As far as the exercise response, the skeletal muscle blood flow goes up by a factor of 20 or 30 Splanchnic blood flow, for example, goes down dramatically, but probably doesn't inhibit gas elimination.

CAPTAIN THALMANN: Let me put you on the spot a bit. When you test decompression schedules, you'd like to test the worst case, there's a controversy over whether a worst case is cold or warm. In one situation, you might exercise a cold diver on the bottom to overcome vasoconstriction during inert gas uptake and then let him rest during decompression when he is eliminating inert gas. In another situation, you might have a diver with the same exercise profile but who is kept warm throughout the entire dive. Which situation do you think is the worst--a cold, exercising diver who stays cold during decompression or an exercising diver who's kept warm for the whole profile?

DR.PENDERGAST: I'd like to beg the issue and say the worst possible scenario would be a diver who was warm on the way down and cold on the way up. If the skin is warm, you continue to perfuse the skin. If you exercise, fat blood flow goes up. The amount of gas you would put in fat would go up in the warm environment. Probably the other aspects wouldn't be too much influenced. The reason I can't really answer your question is that we do not know enough about blood flow to nerve, spinal cord, or brain in warm conditions. Not much happens to the blood flow to those tissues because they're not affected by skin temperature or even core temperature. However, that's only hypothesis, and there is no data to show that that's really true. If you're warm, you trap more gas while on the bottom. If you're cold, you may not eliminate it as well during decompression. Both the uptake and the elimination of inert gas are important, but it is difficult to say which one predominates in the situations you mentioned.

CAPTAIN THALMANN: What about bone? Is that completely passive to changes in muscle blood flow or does it have fairly active temperature sensitivity?

DR. PENDERGAST: I do not really know any quantitative data, but I can tell you that everybody considers bone a passive tissue with a very high resistance and relatively low flow excursions. On the other hand, there's such a heterogeneity of the blood flow within bone that some regions may have increases in flow where others have decreases. It's very difficult to assess, and it's a hard question to answer.

CAPTAIN THALMANN: Then you can't automatically assume that blood flow to bone increases during exercise?

DR. PENDERGAST: Everybody would postulate that there would not be an increase in bone blood flow.

DR. WHIDDEN: Do you believe that physical conditioning might be a significant factor in how an exercising person responds to decompression?

DR. PENDERGAST: Cardiac output at relatively low workloads is not much different in trained and untrained individuals. Untrained individuals, however, will become fatigued sooner, in which case there are very large differences. Aside from fatigue, there really aren't too many differences due to physical conditioning.

As far as exercising during decompression is concerned, exercise pushes blood primarily to high flow regions which are probably washed out reasonably well anyway. Fat perfusion does go up during exercise and that may, in fact, be a useful tool to speed the washout from fat. The heterogeneity of blood flow within organs and tissues, however, actually becomes greater not smaller during exercise, which would not help, but the washout from fat could improve because fat blood flow goes up as well as muscle blood flow during exercise.

DR. GERTH: I'd like to comment on the questions about whether the nitrogen washout from the whole body is related to the risk of bends. We have data from subjects breathing a 100% oxygen for certain periods before subsequent decompression to an altitude of about 30,300 feet (4.3 psia). Some subjects who exercised during a 3.5 hour oxygen prebreathe eliminated less gas than the same subjects under resting conditions. One subject, for example, eliminated much more gas in a condition of head-down rest than he did during seated exercise. Nevertheless, when we decompressed him after denitrogenation during head-down rest, he bubbled and bent, while after exercise denitrogenation he didn't bubble or bend. In other subjects, the overall amount of gas eliminated during exercising and resting denitrogenation is comparable, but subjects who exercise during denitrogenation bubble and bend considerably less than subjects who rest during denitrogenation. While the risk of bends does not seem to relate well to the total volume of nitrogen that is eliminated, it does relate to features of the elimination profile which I will describe tomorrow.

DR. BALLDIN: There are indications that increased whole body nitrogen elimination may decrease the risk of decompression sickness. We found, for instance, that oxygen breathing during immersion in warm water reduced the incidence of decompression sickness. In other studies, we saw that negative pressure breathing increased xenon elimination from adipose tissue and decreased the amount of intracardial gas bubbles during decompression to altitude. In addition, a vasodilating drug which increased perfusion also increased xenon elimination from adipose tissue and decreased the risk of decompression sickness in rabbits. On the other hand, exercise might increase the release of intracardial gas bubbles from the tissues. There is also some old information from Cook and Roth indicating that exercise increased the risk of decompression sickness at altitude, perhaps by some mechanical mechanisms.

DR. PENDERGAST: I think this is a valid point since with immersion or head-down tilt there are increases in perfusion because cardiac output goes up. To regulate blood pressure, there are time-dependent increases in perfusion to various tissues.

I think Dr. Balldin's point about the mechanical aspects of exercise also are very important. If you consider a cardiac output of 25 or 30 liters per minute, the turbulence of that blood flow is enormous and may be an important factor as well as the perfusion of skeletal muscle. The

mechanical contraction of the heart and skeletal muscle makes blood flow pulsatile rather than steady, and this may be important for bubble formation quite independent of inert gas exchange.

DR. JAMES: Dr. Pendergast, in your estimates of blood flow, measurements made with microspheres gave results which were twice as large as those made with xenon. I don't understand that. Do you have an explanation?

DR. PENDERGAST: I don't understand it either. The xenon washout curves parallel microsphere or venous outflow measurements by a factor of two across the physiological range of blood flows. As a relative measurement, you could say it's satisfactory. The estimation of blood flow from xenon washout requires knowledge of the blood tissue partition coefficient. The easiest explanation is that partition coefficient is inaccurate.

Although the partition coefficient is difficult to determine, it has been measured in the rat and dog, which have low levels of intramuscular fat that would affect the partition coefficient. Man has a much higher level of intramuscular fat than the dog. Whether this or another factor plays a role in this partition coefficient, we're not really sure. What we do know from our data and from what others have suggested that xenon becomes diffusion limited at very high flows. If this were the case, our validation curve would have a plateau in it. It doesn't. Other people have suggested vessel-to-vessel countercurrent diffusion. If that were true, the error would be greater at low flows than at high flows, but we do not see this. Our only reservation about the xenon washout technique is that we do not have an explanation of why it underestimates blood flow, but we're comfortable in using it as a relative measure because the underestimation is uniform at all flows.

DR. JAMES: What is the size range of the microspheres that you used?

DR. PENDERGAST: In our running dog experiments, which were the data that I showed, we used 8-25 micron microspheres in different experiments and together. The blood flows and the heterogeneities observed were not significantly different, irrespective of the size that is used. In our isolated perfused gastrocnemius experiments, we measure flow with microspheres, with an electromagnetic flowmeter, from the venous outflow, and from xenon washout. The xenon measurements are the only ones that disagree.

DR. JAMES: Is this discrepancy in flow estimation the same for the brain as it is for muscle?

DR. PENDERGAST: I can't say because in these experiments it's difficult to measure venous outflow and xenon washout in the brain concurrently. Other individuals have measured brain blood flow with xenon, and we've measured it with microspheres. If you put the data together, which is always difficult, they are similar. I wouldn't expect big differences from looking at the data from different studies.

RESPIRATORY INERT GAS EXCHANGE

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ABSTRACT

An accelerated inert gas elimination through the lungs may allow faster decompressions and improved diving safety. Physical exercise, mild hypoxia and carbon dioxide admixture to the breathing gas during lowered inert gas partial pressure are doubtful methods of increasing inert gas exchange due to their unwanted side-effects. Immersion, supine body position, raised ambient temperature and the application of negative pressure breathing and the use of a vasodilator may, however, substantially enhance the inert gas elimination. The increased inert gas elimination through the lungs may also be accompaned by an increased xenon133 elimination from the peripheral tissues and by an increased central and peripheral blood circulation. Immersion in warm water, negative pressure breathing and the use of a vasodilator have consequently been shown to decrease the amount of decompression intracardial gas bubbles and to decrease the risk of decompression sickness. The increased respiratory inert gas exchange and increased blood circulation should also cause an enhanced uptake of inert gas during raised ambient pressure. Thus, the environmental and other factors mentioned to influence the respiratory inert gas exchange should, therefore, be taken into consideration when testing decompression tables and diving equipment.

It is of great importance in diving activity to find methods which allow faster decompressions or improved safety against decompression sickness. An accelerated inert gas elimination to reduce the duration of the decompression may be accomplished by application of physical as well as physiological fundamentals (Lambertsen 1967). Increased partial pressure gradient of the inert gas, where oxygen toxicity may be a limiting factor, and increased activity of dissolved gas molecules for faster diffusion, are examples of enhanced inert gas elimination based on the application of physical fundamentals (Hills 1977, Vorosmarti, Barnard, Williams and Hanson 1978 and Kindwall, Baz, Lightfoot, Lanphier and Seireg 1975). A more physiological approach is to increase respiratory inert gas elimination by improving tissue perfusion and thus tissue gas elimination by different methods, such as changes in the ambient environment, physical activity, body position, respiration or by the use of drugs.

Physical exercise may increase the inert gas elimination through the lungs during oxygen breathing by an increased skeletal muscle perfusion

(Behnke and Willman 1941, Jones 1951, Dick, Vann Mebane and Feezor 1984) and be beneficial during decompression (Vann 1982). On the other hand, only small amounts of nitrogen are solved in the muscles and the circulatory adjustments to exercise may reduce the inert gas elimination in other more nitrogen solving tissues as for instance subcutaneous fat tissue. It is also reported that exercise might actually increase the incidence and intensify the symptoms of decompression sickness (Cook 1951 and Roth 1967).

Mild hypoxia has a stimulating effect on blood circulation as well as on ventilation and might thereby increase the inert gas elimination. It has also been reported that artificially induced hypoxia slightly reduces the frequency of symptoms of altitude decompression sickness (Smith 1951), but it does not appear to be a safe decompression routine in practical diving activity. Hyperoxia, on the other hand, has both been shown to decrease muscle blood flow and xenon133 elimination (Balldin, Lundgren, Lundvall and Mellander 1971) as well as cardiac output and to cause an unchanged muscle, fat and visceral blood flow (Plewes and Fahri 1983). A digital computer model indicated a minimal change in the pattern of nitrogen gas elimination by hyperoxia by the last authors.

Carbon dioxide admixture to the breathing oxygen may also improve nitrogen elimination during decompression probably by an increased peripheral blood perfusion, at least in some tissues, as well as by an increased lung ventilation (Margaria and Sendroy 1950). The influence on the incidence of decompression sickness seems, however, to be questionable when using carbon dioxide admixture to the breathing gas with both unchanged (Gray 1944) and increased risk (Hodes and Larrabee 1946). Balldin, Lundgren and Westling (1971) also pointed to that carbon dioxide accumulation by an increased respiratory dead space might increase the severity of decompression sickness once it occurs.

Among environmental factors influencing the inert gas elimination through the lungs, head-out immersion has been shown to substantially increase the the total body nitrogen elimination. When sitting subjects were immersed in thermo-neutral water of 35 ^{0}C, a mean of 40% increase in nitrogen volume were registered in a spirometer system over a 30 min period and an about 30% increase over a 2 hour period compared to a similar oxygen breathing period sitting dry in thermo-neutral temperature of 28 ^{0}C (Balldin and Lundgren 1972) (see Fig. 1).

In the explanation of these findings it was shown that immersion increased the cardiac output by about 30% using the dye dilution technique. This was concomitant with a central blood volume increase of about 0.7 l and an about 30% decreased systemic vascular resistance (Arborelius, Balldin, Lilja and Lundgren 1972a). The increased cardiac output during immersion is accompaied by an increase in peripheral circulation. Thus, a more than 100% increase in xenon133 elimination and thus in blood flow in leg muscular tissue was shown during immersion (Balldin, Lundgren, Lundvall and Melander 1971). An about similar increase in both blood flow and xenon133 elimination was also seen in subcutaneous adipose tissue (Balldin 1978), which may be a more important tissue due to the greater inert gas solving capacity in the fat tissue. The xenon eliminated from the tissues is finally eliminated from the body mainly through the lungs.

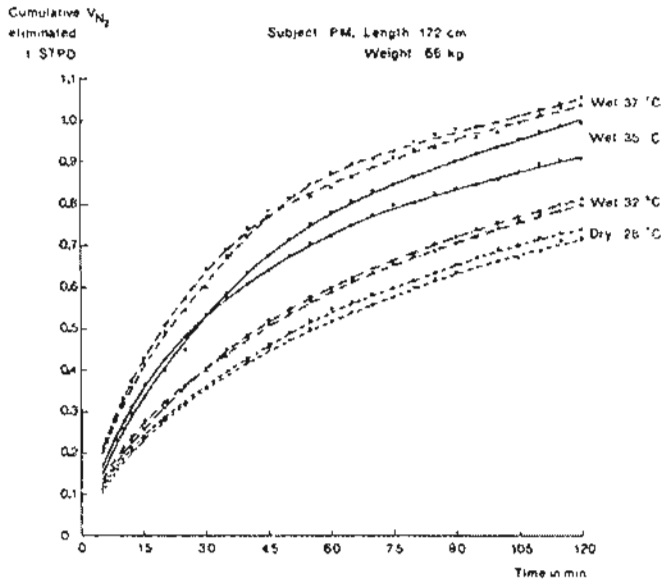

Fig. 1. Nitrogen elimination through the lungs during oxygen breathing sitting dry at 28°C and immersed at 32°C, 35°C and 37°C (from Balldin and Lundgren 1972).

The regional lung function was shown to be improved during immersion (Arborelius, Balldin, Lilja and Lundgren 1972b). Thus, a more even ventilation-perfusion ratio between the bases and apices of the lungs could be shown with xenon133 radiospirometry. This improvement was, however, considered insignificant for the enhanced nitrogen elimination during immersion as this elimination is largely blood flow dependent (Balldin 1973a). Only major deterioration in lung function during immersion might influence the exchange of nitrogen and other gases with low solubility in the blood and then in a negative way. Such deteriorations in lung function may be the lung vital capacity decreases or possibly atelectasis formation described during immersion and oxygen breathing (Balldin, Dahlbäck and Lundgren 1972, Dahlbäck and Balldin 1983 and Baer, Dahlbäck and Balldin 1987) (see Fig. 2) similar to findings during increased G-loads (Haswell, Tacker, Balldin, Burton 1986). The increased inert gas elimination (nitrogen as well as xenon) through the lungs during immersion may, thus, be explained mainly by the increases in both central and peripheral blood circulation and not by the improved ventilation-perfusion ratio of the lungs.

Changes in body position have in some ways simimlar influences on blood circulation as immersion. Thus, supine compared to erect body position increases the Xenon133 elimination and blood flow in muscular tissue by about 100% (Balldin, Lundgren, Lundvall and Mellander 1971) and in subcutaneous fat by about 35% (Balldin 1976). These increases are accompanied by an increase in nitrogen elimination through the lungs during oxygen breathing by a mean of 24% after 30 min of supine compared to erect body position and by 15% after 2 hours (Balldin 1973b).

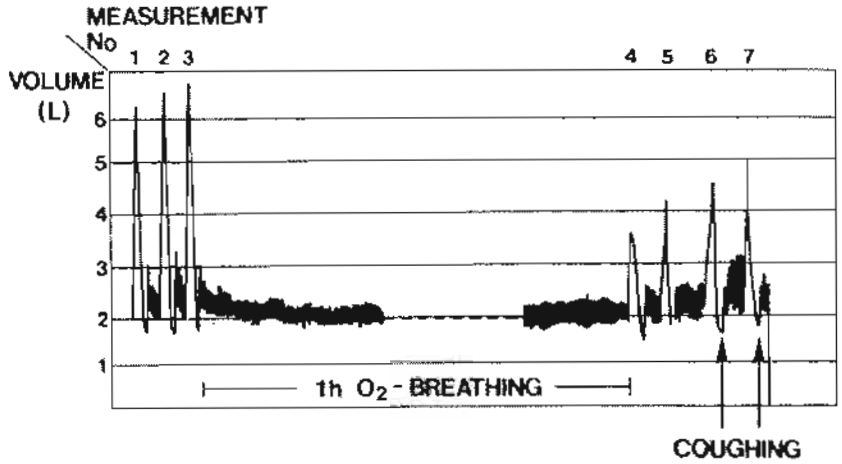

Fig. 2. Spirogram from a subject indicating reduced vital capacity after 1 h oxygen breathing during immersion (from Dahlbäck and Balldin 1983).

Temperature also influences the central as well as the peripheral blood circulatation and thus the inert gas exchange. The mean subcutaneous adipose tissue blood flow and xenon133 elimination during immersion was thus increased with 37°C (warm water) compared to 35°C (thermo-neutral water) by a mean of about 90% (Balldin 1978). A similar increase in total body nitrogen elimination through the lungs of about 6% was seen when the temperature was increased from 35°C to 37°C during 2 hours immersion (Balldin and Lundgren 1972).

When the temperature was increased in dry conditions from 28°C (thermo-neutral) to 37°C in sitting as well as in supine subjects the nitrogen elimination was increased by about 17% after 2 hours (Balldin 1973a). Heat stress has also been shown to increase whole body xenon washout in rabbits (Bove, Hardenbergh and Miles 1978). The combined effect of immersion and raised ambient temperature increased the nitrogen elimination by 49% after 30 min and 36% after 2 hours compared to sitting in dry conditions in thermo neutral environment and thus seemed to most effective (Balldin and Lundgren 1972). Similar increases in xenon133 elimination from adipose tissue in humans were found with immersion in warm water (Balldin 1978). The combined effect of raised temperature in dry conditions and supine compared to sitting body position increased the whole body nitrogen elimination by about 30% after 30 min as well as 2 hours (Balldin 1973b).

Lowered ambient temperature, on the other hand, decreases mainly the subcutaneous adipose tissue blood flow through vaso-constriction. In agreement with that, the total body nitrogen elimination during oxygen breathing could be shown to decrease slightly (about 10%) in the immersed subjects with lowered water temperature to 32°C (Balldin and Lundgren 1972). In the dry conditions a lowered ambient temperature to 25°C were not so consistent with both unchanged and increased nitrogen elimination in humans (Balldin 1973b). In rabbits cooling caused unchanged whole body xenon elimination in combination with an increase in muscle xenon elimination probably due to shivering (Bove, Hardenbergh and Miles 1978).

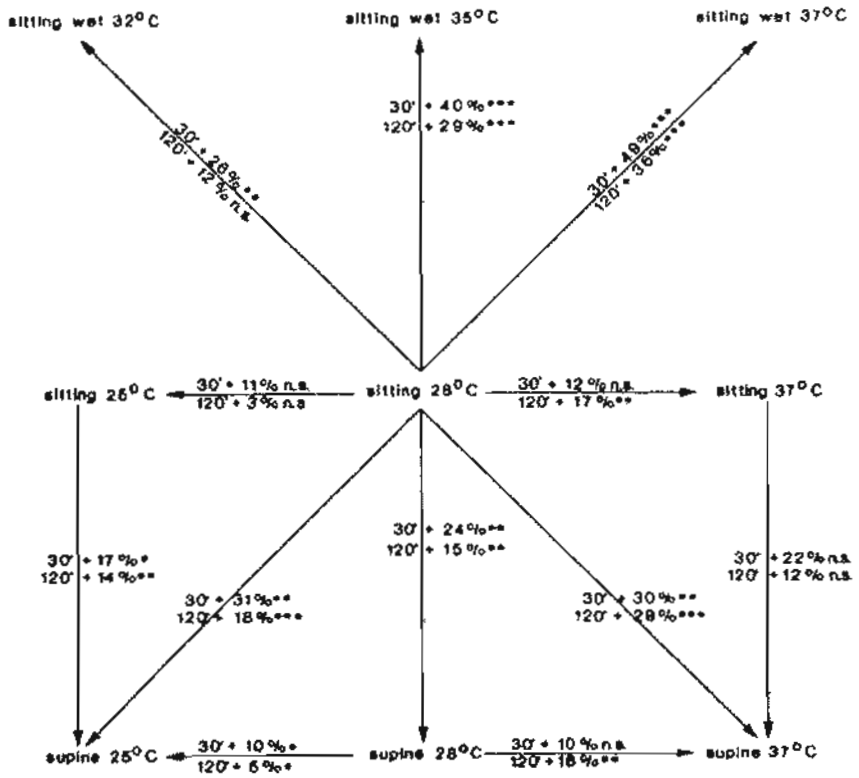

Fig. 3. Mean relative differences in tissue nitrogen volumes eliminated through the lungs after 30 and 120 min immersed at 32°C, 35°C, and 37°C compared to sitting dry at 28°C. Sitting and supine body positions in dry conditions are also compared in 25°C, 28°C, and 37°C. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ (from Balldin 1973).

The most effective way of increasing the nitrogen elimination, in these studies, namely the combined effect of immersion and raised temperature (see Fig. 3), was tested in actual decompressions in humans (Balldin 1973c). Denitrogenation by oxygen breathing for 25 min in water at 37°C or during dry thermoneutral conditions was followed by provocation of decompression sickness at an ambient pressure of 155 mm Hg (20.7 kPa). The occurrence of decompression sickness (bends) was 20% after warm water denitrogenation and 90% during dry thermoneutral conditions, thus supporting the effectiveness of the increased nitrogen elimination during warm water immersion.

Negative pressure breathing (NPB) has been shown to increase cardiac output as well as adipose tissue blood flow in humans (Balldin 1976). Thus 20 cm H_2O NPB increased xenon133 elimination in subcutaneous fat tissue by about[2] 70%. As a consequence of these findings it could also

be shown that denitrogenation during NPB compared to normal oxygen breathing decreased the amount and delayed the onset of intracardial gas bubbles detected with precordial Doppler ultrasound detector in decompressions to altitude (Balldin 1977). It also delayed the onset of symptoms and reduced the risk of decompression sickness.

Positive pressure breathing (PPB), in contrast to NPB, decreases the cardiac output (Balldin and Wranne 1980). PPB of 20 cm H_2O has also been shown to decrease xenon133 elimination from subcutaneous adipose tissue by about 40% (Balldin and Linér 1976), which consequently should impair inert gas elimination as well. PPB has, however, also been shown to reduce the atelactasis during oxygen breathing in immersion (Dahlbäck and Balldin 1983) and in diving (Dahlbäck and Balldin 1985) as well as at high G-loads (Tacker, Balldin, Burton, Glaister, Gillingham, Mercer 1987). Even though atelectasis may develop during oxygen NPB, and especially in combination with immersion, the improved blood circulation during NPB and immersion may be more important to gas elimination. As mentioned above, an increased inert gas elimination (e.g. nitrogen) depends more on improved blood circulation than on changes in ventilation, why NPB probably should be preferred to PPB in this respect.

The prophylactic use of drugs in diving operations as well as the therapeutic use of drugs for treatment of decompression sickness have been investigated in in many studies (cf Catron and Flynn 1982). Perorally administered terbutaline, a sympathomimetic beta-2-receptor stimulator with mainly vasodilator but also with bronchodilator effects, was shown to increase the xenon133 elimination in subcutaneous adipose tissue by more than 100% in humans (Balldin 1976). This increased inert gas elimination by terbutaline could also be shown to have a preventive effect on the occurrence of decompression sickness in rabbits, who were denitrogenated during oxygen breathing with terbutaline given prophylactically (Balldin and Linér 1978).

Whole body vibration should possibly release gas bubbles from the tissues and thereby increase inert gas elimination during decompression in diving or altitude activities in the same way as increased amounts of decompression bubbles are known to be released by muscle activity (Adams, Olson and Dixon 1979 and Balldin 1980a). However, whole body vibrations with 15 and 25 Hz, similar to single and twin rotor helicopter vibrations, did not release more venous gas bubbles as detected by precordial Doppler ultrasound technique (Balldin and Sporrong 1980).

The factors to increase inert gas elimination seem to be most important as prophylactics before gas bubbles have been formed in a decompression. Once decompression gas bubbles have been formed, the increase in inert gas elimination through the lungs, does not substantially help to eliminate the gas trapped in gas emboli in the circulation or as gas bubbles in situ. The elimination of inert gas from a bubble in the tissue or a gas pocket is slow compared to the elimination of gas solved in the tissue (van Liew, Bishop, Walder and Rahn 1965). The bubble might disturb the micro-circulation by blocking the blood flow and preventing the gas transport from the bubble. Preoxygenation prior to altitude exposure pre-

ceded earlier by a dive giving rise to silent bubbles is, thus, not as effective to reduce the risk of decompression sickness as is preoxygenation without a preceding dive (Balldin 1980b).

The above mentioned methods to increase inert gas elimination, e.g. immersion, raised ambient temperature, supine body position, NPB, vasodilators might be used to reduce the risk of decompression sickness in diving, at altitude or to some extent even in extravehicular space activity. On the other hand, they should also be taken into consideration in the gas uptake situation before decompression, for instance when a diver is at depth. In the situation with increased inert gas partial pressure the gas uptake will be increased in the same amount as the elimination is increased during decompression with reduced partial pressure of the inert gas. The ideal situation for a diver might be to be exposed to raised temperature, immersion or supine body position with negative pressure breathing after the administration of a vasodilator to increase gas elimination during decompression. Certainly, these environmental and other factors influencing the inert gas uptake and elimination should be taken into serious consideration when testing decompression tables and diving equipment.

REFERENCES

1. Lambertsen CJ. Basic requirements for improving diving depth and decompression tolerance. In: Proceedings of the Third Symposium on Underwater Physiology. Baltimore: Williams and Wilkins Co., 1967.
2. Hills BA. Effect of decompression upon inert gas elimination at constant inspired PO2. Undersea Biomed Res 1977; 4:A38.
3. Vorosmarti J Jr, Barnard EEP, Williams J, de G. Hanson R. Nitrogen elimination during steady-state hyperbaric exposures. Undersea Biomed Res 1978; 5:243-252.
4. Kindwall EP, Baz A, Lightfoot EN, Lanphier EH, Seireg A. Nitrogen elimination in man during decompression. Undersea Biomed Res 1975; 2:285-297.
5. Behnke AR, Willmon TL. Cutaneous diffusion of helium in relation to peripheral blood flow and the absorption of atmospheric nitrogen through the skin. Am J Physiol 1940-1941; 131:627-632.
6. Jones HB. Gas exchange and blood-tissue perfusion factors in various body tissues. In: Fulton JF, ed. Decompression sickness. Ch. IX, part II. Philadelphia and London: W.B. Saunders Co., 1951.
7. Dick APK, Vann RD, Mebane GY, Feezor MD. Decompression induced nitrogen elimination. Undersea Biomed Res 1984; 11:369-380.
8. Vann RD. The effect of exercise during decompression. Undersea Biomed Res 1984; 9: Suppl. p. 26.
9. Cook SF. Role of exercise, temperature, drugs and water balance in decompression sickness. In: Fulton Jf, ed. Decompression sickness. Ch. VIII, part II. Philadelphia and London: W.B. Saunders Co., 1951.
10. Roth EM. Space-cabin atmospheres. Part III. Physiological factors of inert gases. Scientific and technical information division. Office of Technology Utilization. National Aeronautics and Space Administration, Washington, D.C., 1967; NASA SP-117.

11. Smith HW. The effect of anoxia on the incidence of decompression sickness at 35 000 feet. Canada, NRCC, Associate committee on aviation medical research, Report No. 2. Clinical Investigation Unit, RCAF, Regina, January 1943. In: Fulton JF, ed. Decompression sickness. Philadelphia and London: W.B. Saunders Co., 1951.
12. Balldin UI, Lundgren CEG, Lundvall J, Mellander S. Changes in the elimination of 133xenon from the anterior tibial muscle in man induced by immersion in water and by shifts in body position. Aerospace Med 1971; 42:489-493.
13. Plewes JL, Farhi LE. Peripheral circulatory responses to acute hyperoxia. Undersea Biomed Res 1983; 10:123-129.
14. Margaria, R. Sendroy J Jr. Effect of carbon dioxide on rate of denitrogenation in human subjects. J Appl Physiol 1950; 3:295-308.
15. Gray JS. Present status of the problem of decompression sickness. U.S. AF, School of aviation medicine. Randolph Field, Texas 3 October 1944; Review No. 1.
16. Hodes R, Larrabee MG. The relation between alveolar carbon dioxide tension and susceptibility to decompression sickness. Am J Physiol 1946; 147:603-615.
17. Balldin U, Lundgren C, Westling H. The influence of added respiratory dead space on decompression sickness in goats. Försvarsmedicin (Stockholm) 1971; 7:33-38.
18. Balldin UI, Lundgren CEG. Effects of immersion with the head above water on nitrogen elimination in man. Aerospace Med 1972; 43:1101-1108.
19. Arborelius M Jr, Balldin UI, Lilja B, Lundgren CEG. Hemodynamic changes in man during immersion with the head above water. Aerospace Med 1972; 43:592-598. (a).
20. Balldin Ulf I. The effect of immersion and ambient temperature on the elimination of Xe133 from adipose tissue in man. Proceedings of the Sixth Symposium on Underwater Physiology. Federation of American Societies for Experimental Biology 1978; 329-334.
21. Arborelius M Jr, Balldin UI. Lilja B, Lundgren CEG. Regional lung function in man during immersion with the head above water. Aerospace Med 1972; 43:701-707. (b).
22. Balldin Ulf. Decompression sickness and nitrogen elimination in man: influence of immersion body position and ambient temperature with special reference to hemodynamics. (Thesis) University of Lund, Sweden, 1973; 51 pp. (a).
23. Balldin UI, Dahlbäck GO, Lundgren CEG. Changes in vital capacity produced by oxygen breathing during immersion with the head above water. Aerospace Med 1972; 43:768-774.
24. Dahlbäck GO, Balldin UI. Positive pressure oxygen breathing and pulmonary atelectasis during immersion. Undersea Biomed Res 1983; 10:29-44.
25. Baer R, Dahlbäck GO, Balldin UI. Pulmonary mechanics and atelectasis during immersion in oxygen breathing subjects. Undersea Biomed Res 1987; 14(3):229-240.
26. Haswell MS, Tacker WA Jr, Balldin UI, Burton RR. Influence of inspired oxygen concentration on acceleration atelectasis. Aviat Space Environ. Med 1986; 57:432-437.

27. Balldin UI. The effects of body position and a vaso-dilator on xenon133-elimination from sucutaneous fat. Undersea Biomed Res 1976; 3:379-385.
28. Balldin UI. Effects of ambient temperature and body position on tissue nitrogen elimination in man. Aerospace Med 1973; 44:365-370. (b).
29. Bove AA, Hardenbergh E, Miles JA Jr. Effect of heat and cold stress on inert gas (133xenon) exchange in the rabbit. Undersea Biomed Res 1978; 5:149-158.
30. Balldin UI. The preventive effect of denitrogenation during warm water immersion on decompression sickness in man. Proceedings of the First Annual Scientific Meeting of the European Undersea Biomedical Society, Stockholm 1973. Försvarsmedicin (Stockholm) 1973; 9:239-243. (c).
31. Balldin UI, Linér MH. Xe133 elimination from human fat during negative and positive-pressure breathing. Undersea Biomed Res 1976; 3:163-169.
32. Balldin UI. Borgström P. Intracardial gas bubbles at altitude after negative pressure breathing. Aviat Space Environ Med 1977; 48:1007-1011.
33. Balldin, UI and Wranne B. Hemodynamic effects of extreme positive pressure breathing using a two-pressure flying suit. Aviat. Space Environ Med 1980; 51(9):851-855.
34. Dahlbäck GO, Balldin UI. Pulmonary atelectasis formation during diving with closed-circuit oxygen breathing apparatus. Undersea Biomed Res 1985; 12(2):129-137.
35. Tacker WA, Balldin UI, Burton RR, Glaister DH, Gillingham KK, Mercer JR. Induction and prevention of acceleration atelectasis. Aviat Space Environ Med 1987; 58:69-75.
36. Catron PW, Flynn ET Jr. Adjuvant drug therapy for decompression sickness: a review. Undersea Biomed Res 1982; 9:161-174.
37. Balldin UI. Linér MH. The preventive effect of vasodilator on the occurrence of decompression sickness in rabbits. Aviat Space Environ Med 1978; 49:759-762.
38. Adams JD, Olson RM, Dixon GA. Use of the Doppler pre-decompressions. Preprint of 1979 Annual Scientific Meeting, Aerospace Medical Association, Washington, DC. 260-261.
39. Balldin UI. Venous gas bubbles while flying with cabin altitudes of airliners or general aviation aircraft 3 hours after diving. Aviat Space Environ Med 1980; 51:649-652.
40. Balldin UI, Sporrong A. Vibration and decompression gas bubbles. Proceedings of the Second Symposium of the Commission on Gravitational Physiology. The Physiologist 1980; Suppl. S-147-148.
41. Van Liew HD, Bishop B, Walder D, Rahn H. Effects of compression on composition and absorption of tissue gas pockets. J Appl Physiol 1965; 20:927-933.
42. Balldin UI. Influence of preoxygenation on intracardial gas bubbles and decompression sickness during flying after diving. Proceedings of the 5th Annual Scientific Meeting, European Undersea Biomedical Society, 5-6 July 1979, Bergen, Norway. Grimstad J, ed. 1980; 130-140.

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DISCUSSION

DR. VANN: Dr. Balldin, immersion tends to increase perfusion, and cold temperatures tend to decrease it. You studied immersion in warm water. Did you also look at immersion in cooler water to find the temperature at which you'd have no difference between immersion and dry air?

DR. BALLDIN: We studied immersion in 32°C water which increased the nitrogen elimination compared to sitting dry at thermoneutral temperature (28°C), but it was less than sitting at thermoneutral temperature in water (35°C). If we had decreased the temperature below 32°C, I'd say to 25°C in water, there might not have been any difference between nitrogen elimination sitting dry at neutral temperature. We didn't go further. We chose cool, neutral, and warm immersion and dry conditions.

DR. VANN: During hypothermia, would you expect to see a decrease in nitrogen elimination even though you were immersed?

DR. BALLDIN: It's more complicated than that, I think. If you decrease the temperature to the point of shivering, you increase the blood flow in the muscles and might decrease the flow in the subcutaneous adipose tissue. The result will probably be a decrease in the inert gas elimination.

DR. PENDERGAST: Our data indicate that vasoconstriction persists even with shivering and therefore the perfusion to both fat and muscle is reduced in cold water immersion.

DR. BALLDIN: You used 20°C water which is pretty cold compared to our 32°C.

DR. LUNDGREN: I want to comment on the question of what immersion and temperature do jointly or separately. We looked at changes in vital capacity as a measure of the movement of blood into and out of the thorax. We found that the 5-6% decrease in vital capacity which occurs with immersion in 35°C thermoneutral water was completely blocked by immersion in 37°C water (1). Thus, the circulatory effects of warm water immersion do not appear to rely on the redistribution of blood into the thorax, which would increase the preload and stroke volume of the heart. Despite the fact that the body was loaded with a water column at 37°C, just as in the 35°C experiments, we did not see that redistribution. In contrast, immersion in cool water, 20°C, increased the drop in vital capacity to around 12%. Incidentally, the vital capacity change can be blocked by prior application of tourniquets to the arms and legs. Upon release of the tourniquets, vital capacity is reduced once again.

DR. BALLDIN: The changes in ventilation are not so important, I think, to the inert gas elimination which is more dependent on blood flow.

DR. LUNDGREN: No, I'm not suggesting that there is any significant effect of changes in ventilation. My point is that when we think of the physiological mechanism whereby circulation is modified by immersion and temperature, it's interesting and somewhat perplexing that the hydrostatic effects of bracing the body from the outside by water are totally negated as far as intrathoracic blood redistribution goes, it seems, by increasing the temperature from neutral to 37°C.

DR. GILBERT: We did some nitrogen washout studies using males and females, 10 of each, in which they breathed 100% oxygen in three separate positions: sitting, supine and 6° head down-tilt. The 6° head-down tilt was the closest stimulation of the physiological redistribution of blood in space flight. We did correlations with all body parameters that we could measure, including respiratory volume, titer volume, total body fat,

respiratory rate, and the only statistically significant correlation was with total body water. The correlation with total body water was about 0.87 or 0.85, both on males and females. This seems to agree with your data on immersion in warm water where you would expect a redistribution of total body water. We did not detect any statistically significant differences in washout between any of the three body positions. Although, there were nonstatistically significant trends. The 6^{o} head-down tilt was a little bit better than the supine and the sitting washouts, except for sitting females who showed a statistically significant slower washout rate.

DR. BALLDIN: On the other hand, if you extend the period of nitrogen elimination more than 4 to 5 hours, the differences will become smaller because you only have a certain amount of nitrogen in your body. The greatest effects occur in the first 30 minutes to 2 hours, after which the effects decrease because little nitrogen remain.

DR. GILBERT: Yes, as time passed, we saw an increasing correlation with total body fat and a decreasing correlation with total body water. We couldn't go beyond about 3 1/2 hours because the nitrogen fraction became so small that half our mass spectrometer signal was error.

DR. VANN: Dr. Balldin, let me ask you or anyone else who would like to comment. What is the best way to simulate a microgravity environment on earth? We've been using a 6^{o} head-down tilt. Is there a better angle? Is immersion a better simulation?

DR. BALLDIN: My impression is that if you really want to simulate microgravity, the only thing you can do is do parabolic flights, and that's not simulation.

DR. VANN: We can't do that for 3 1/2 hours though.

DR. BALLDIN: No, not for more than 30 or 40 seconds, but all the other methods are with some disadvantages.

MR. WALIGORA: We've used the head-down position as the simulation for microgravity, but to establish a steady state takes a long time, so maybe you haven't gained anything over the supine position.

DR. PENDERGAST: Dr. Balldin, cardiac output and blood flow increase immediately upon immersion, but it's been recently shown that if dehydration occurs the cardiac output returns to preimmersion levels within an 1 1/2 to 2 hours, and the blood flow goes back to normal. Hormonal changes also are time dependent. How do these factors influence the overall washout?

DR. BALLDIN: Well, I'm sure that it will influence the overall washout, but most of our studies were only for 2 hours. We've extended some to 4 hours, but if there was a big difference in the first 30-60 minutes, that difference gradually decreases as the washout becomes complete. If the cardiac output and peripheral circulation changed during a 3- or 4-hour period, we would not detect it very well with our methods.

DR. YOUNGBLOOD: Would you predict a significant difference in nitrogen washout between sitting immersion and supine immersion breathing oxygen?

DR. BALLDIN: We didn't measure washout during supine immersion because immersion per se was more effective than the supine body position in dry conditions. On the other hand, body position is not very important during immersion.

REFERENCES

1. Kurss DI, Lundgren CEG, Pasche AJ. Effects of water temperature on the vital capacity in head-out immersion. In: Bachrach AJ, Matzen MM, eds. Underwater physiology VIII. Proceedings of the eighth symposium on underwater physiology. Bethesda, MD: Underwater Medical Society, 1981:297-301.

GAS EXCHANGES OF BUBBLES IN TISSUES AND BLOOD

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Background for this communication stems from experiments with big artificially-formed bubbles, subcutaneous gas pockets in rats (for example, 1-3), and mathematical studies (4-6). In some ways the rat gas pockets resemble the tiny bubbles that are associated with decompression sickness; the experiments allow a feet-on-the ground approach to the topic of bubble growth and decay in animal tissues. The mathematical studies lend perspective on the similarities and differences between decompression sickness bubbles and rat gas pockets.

The key to size changes of bubbles is the simple process of diffusion, which can have various manifestations in various circumstances. The main thrust of this communication is to review the diffusive interactions between the different gases in a bubble in a person's blood or tissue. This line of inquiry supplements the questions of bubble nuclei, bubble formation in supersaturated solutions, bubble distribution in animals or gels, and movement of bubbles from veins to arteries which have been reviewed recently by Daniels (7).

Diffusion Equations

The processes that make a bubble increase or decrease in size are simple enough that they can be predicted quite precisely if one has control of the bubble's surroundings. Mathematical descriptions which correspond very well to empirical observations have been presented many times. For examples: a) In accordance with theory, rates of exchange of nitrogen in subcutaneous gas pockets in rats were directly proportional to the difference of nitrogen partial pressure between inside the pocket and the animal's breathing gas over a range of pressure differences of -3.3 ATA (nitrogen enters the pocket) to +2.6 ATA (nitrogen leaves the pocket) (1). b) In accordance with a more complex theory, in vitro bubbles of oxygen of about 80 micrometers radius in oxygen-saturated water either grew or shrank; when the bubbles shrank, they disappeared completely within 20 min (8). c) Bubbles in sea water conformed to fairly simple diffusion equations in a variety of situations (9). d) Serial photographs of bubbles of n-pentane vapor in liquid n-tetradecane corresponded well with theory which included effects of surface tension, viscosity and liquid inertia (10).

Unfortunately it is difficult to apply these successful theories to practical conditions. Uncertainties about the environment of decompression-sickness bubbles in the body decree that experimental and mathematical treatments of bubbles are instructive, but not definitive.

A gas bubble contains many molecules of the various gas species that are in the bubble environment, all moving due to thermal diffusion. A bubble cannot be made up of only one gas, except fleetingly perhaps. If some gas species, such as carbon dioxide, is near a bubble, it will enter by diffusion -- it cannot be kept out. At a given time, some gas species may have a net entering tendency and others a net exiting tendency, but diffusion brings bubbles

toward a steady-state composition (11), so that usually all gases will be entering while the bubble is growing and all leaving while the bubble is shrinking.

The main constituent of a bubble is the inert gas in the man's breathing mixture -- thus the major gas in a bubble is nitrogen in a person breathing air or helium in a person breathing helium-oxygen. Equation 1) is a simplified diffusion equation that works well for gas diffusing through a membrane (12), for nitrogen diffusing out of a bubble in flowing blood in an in vitro system (13), and for describing the exchanges of nitrogen-containing subcutaneous pockets in air-breathing rats (1,14,15). It implies that the bubble is separated from its surroundings by an unchanging layer of material.

$$dV_{N2}/dt = (KA/L)\,(Pi - Po) \qquad 1)$$

In the equation, dV_{N2}/dt is rate of nitrogen gas passing across the boundary, K is related to the solubility and diffusivity of nitrogen in the boundary layer material, A is area of the exchange surface, L is thickness of the boundary layer, and Pi and Po are, respectively, partial pressure of nitrogen inside the bubble and in the bulk material beyond the boundary layer, that is, beyond the distance L. According to the equation, if partial pressure of nitrogen is greater inside than outside, nitrogen will have a net exit which promotes bubble shrinkage -- if the outside is greater than inside, nitrogen will enter, promoting bubble growth; the bigger the difference, the faster the rate of entrance or exit.

The total volume of a bubble is the sum of its components, which includes oxygen, carbon dioxide, and water vapor as well as nitrogen or other inert gas. Because each gas in the bubble is governed by an equation of the form of Eq. 1), the partial pressure of each gas comes as close as possible to its counterpart in the surroundings (11). After any large change in conditions such as compression, decompression, or change of breathing gas, there is an initial transient in which the various gases "jockey for position" to bring their respective diffusion gradients, Pi - Po, to a minimum, thus bringing the bubble to its new steady state of approximately constant composition (16).

Surface tension increases the total pressure inside the bubble and thereby increases the inside partial pressures of nitrogen and the other gases. The rules of surface tension indicate that a bubble should have a very large pressure inside when radius is very small, so gas should be absorbed rapidly. The logical extension is that there should be no pre-existing spherical bubbles in the body which could grow to troublesome size following a decompression; surface tension should prevent bubbles from ever getting started. However, observable bubbles do form, so there must be some sort of non-spherical bubbles or bubble nuclei in the body, or nucleation process, or remnant of pre-existing bubbles that can become bubbles again (17). Surface tension plays essentially no role in large bubbles, but can be the deciding factor as to whether a small bubble grows or shrinks precipitously. For example, the behavior of an oxygen bubble in oxygen-saturated water is almost completely dependent on surface tension since partial pressure differences between inside and outside are so small in this situation (8).

Equation 1) is a simple example of many possibilities for diffusion equations. All will contain terms related to geometry of the bubble and its surroundings, A and L in Eq. 1), and to the gas concentration gradient, Pi and Po. Equation 1) is not appropriate for small bubbles because of the implication that there is a given boundary layer or unstirred shell for diffusion around the bubble. A more general equation based on first principles of the

physical process of diffusion in spherical bubbles (5,6) reduced to the form of Eq. 1) for large bubbles such as subcutaneous gas pockets. According to derivations which appear elsewhere (5,6), it can be shown that Eq. 2) is a proper form of diffusion equation for small spherical bubbles which are close to a steady state of gas concentrations. It is essentially the same equation as that used by Epstein and Plessett (18) for bubbles in liquid.

$$dR/dt = K' (1/R) [1 - Po/Pi] \quad 2)$$

In Eq. 2), dR/dt is rate of change of the radius with time, K' is a constant which is related to solubility and diffusivity of nitrogen in the tissue or blood surrounding the bubble but slightly different from K in Eq. 1), and Pi and Po are, as before, partial pressure of nitrogen inside the bubble and in the general surroundings of the bubble, beyond the range of its diffusion gradient. The inside-to-outside partial pressure difference was divided by inside partial pressure to give the (1 - Po/Pi) term.

In Eq. 2), the area and length terms that were in Eq. 1) have disappeared -- the radius is now the only geometric term. The change of focus to actual size of the bubble, with all gas species accounted for, is possible because volume of one gas divided by that gas's fractional composition gives the total volume of the bubble:

$$Vol = V_{N2}/Fi \quad 3)$$

where Fi is dry gas fraction of nitrogen inside the bubble [PiN2 / (Ptot-PH2O)], Vol is volume of the bubble, Ptot is total pressure in the bubble, and PH2O is partial pressure of water vapor. Knowing the volume of the bubble, the focus can become the size of the bubble in terms of radius, R, of a spherical bubble.

$$R = (4 \Pi / 3 Vol)^{1/3} \quad 4)$$

A more complete form of Eq. 2) would have two more terms that add to the 1/R term (5,6). One of these has to do with stirring in the surroundings, such as clearance of gas from tissue by flow of capillary blood or the stirring effect of moving blood past a bubble in the blood stream. The stirring term is not important for small bubbles, although stirring sets the overall gas concentration in the surroundings of the bubble by washin or washout of inert gas. The other term is a transient term to account for the initial amount of gas that comes from or goes to the immediate surroundings of a new bubble or a bubble that moves to a new locality. This transient effect may be important for the transition from nucleus to bubble, but it is not very important for later growth or decay of sizable bubbles (6,19).

Equation 2) decrees that bubbles grow or shrink very rapidly when they are small. The 1/R term acts as an amplifier of rate, whether it is for growth or for decay and the other items outside the brackets also affect the rate of entrance or exit. If it were not for the 1/R term, the dR/dt would be constant, so R would decrease as a straight-line function of time. When R is big, 1/R is small and relatively constant, so a big bubble does tend to decrease as a straight line.

Rates of Radius Change

When the tissues and blood are denitrogenated in a person who breathes pure oxygen, the term in the brackets of Eq. 2) equals one -- the rate of radius change is just K'/R, so in a

decaying bubble the value of K'/R sets the maximal rate that can be achieved -- it is convenient to think of all other decay rates, when the tissue is not denitrogenated, as fractions of the maximal rate. In addition to the denitrogenation case, maximal rate is approached when the Po/ Pi ratio is small, such as when surface tension increases the pressure inside the bubble. When there is appreciable inert gas outside the bubble, rate of radius change can be considerably less than the maximal rate; in an air-breathing person, the rate is expected to be about 10% of the maximal rate. (See Oxygen Window below.) This emphasizes the value of oxygen breathing in causing bubbles to shrink -- an increase in inspired oxygen, by causing a decrease of tissue inert gas, can make bubbles shrink as much as 10 times faster. This sheds light on the options for deciding on treatment for decompression sickness -- there is a choice of making bubbles small by compression and thereby perhaps causing immediate relief of symptoms, or of administering oxygen to hasten absorption of the bubbles.

An interesting aspect of Eq. 2) is that maximal rate of radius change of a spherical bubble is independent of absolute pressure; in a denitrogenated tissue, a bubble can be expected to be absorbed at what appears to be the same rate before and after being subjected to compression. The greater pressure inside the bubble makes in-to-out diffusion greater in terms of numbers of molecules per time, but this is exactly balanced by the fact that more molecules are required to make a given size change. For example, consider a particular bubble which is expected to be absorbed in 10 min in an oxygen-breathing animal (4). If the animal is compressed to 3 ATA, the bubble is decreased to 70% of its original diameter, but then it decreases in radius at the same rate as before, so that it is completely absorbed in 7 minutes. In this example, compression caused a 30% decrease of duration of the bubble, as contrasted to the 10-fold difference between oxygen breathing or not.

Bubble Size

It may be helpful to focus on the absolute radius or diameter of bubbles. Presumably the physical size of a bubble in the human's physical body causes damage -- blockage of blood vessels, impingement on nerves, or interaction with blood elements. Volume occupied by a given number of gas molecules is inversely proportional to ambient pressure, but size of the bubble containing that gas follows a different rule: radius of a spherical bubble is inversely proportional to the cube root of the pressure. At 10 ATA, volume of a gas is one-tenth its 1 ATA volume, whereas radius is only about half its 1 ATA value. Thus compressions which cause relief of symptoms are due to relatively small decreases in bubble diameter.

There may be merit in expressing the pre- and post-decompression pressures in terms of a ratio as in the classical Haldane ratios; the maximal amount of gas (expressed as number of molecules or as gas volume under standard conditions) that could come out of solution in a decompression from 10 ATA to 5 ATA will be 5 times as great as that from 2 ATA to 1 ATA, but the volume of gas under the prevailing pressure will be the same, since it takes 5 times as much gas to form a bubble of given volume at 5 ATA as it does at 1 ATA; in this example, both decompressions follow a 2/1 ratio and both could give rise to the same maximal volume of evolved gas and the same sizes of bubbles. The sizes and volumes may actually not be the same because of differences in the way gas is cleared from the tissue under the two conditions (17). The work of Lin (20) indicates that the threshold to form bubbles at all is approximately a 2/1 decompression over an impressive range of actual pressures (10/5 to 2/1) and that a 50% incidence of bubbles occurs with a 5/1 decompression.

What volume of bubbles could potentially come from a given amount of tissue? Solubility of nitrogen in watery tissue has been quoted as 0.014 ml gas (ml tissue ATA)$^{-1}$. On decompression from 2 ATA to 1 or other 2/1 decompressions, the formation of bubbles can therefore be expected to clear the supersaturation of a volume of tissue or blood that is roughly 100 times the volume of the liberated gas. Thus the bubbles caused by degassing a unit of tissue are about 1% of the volume of the tissue for a 2/1 decompression, or 4% for a 5/1 decompression.

Oxygen Window

Bubbles are not expected to last indefinitely in the body -- eventually inert gas bubbles in blood or soft tissue are absorbed because Po/Pi for the inert gas is less than 1; the reason is related to the living tissue's metabolism. The so-called "oxygen window" or "inherent unsaturation" is due to the difference of oxygen in the bubble vs oxygen in the blood and tissues. Figure 1 depicts the principle.

The bubble's volume is the sum of the volumes of all gases, and also its total pressure is the sum of the partial pressures of all gases inside. Because oxygen and carbon dioxide in the bubble diffuse more easily than the inert gases, they tend to be very close to the low oxygen and carbon dioxide in the surrounding tissue or blood. Except when the tissue is supersaturated after a decompression, the nitrogen in the bubble will be elevated above that in the surroundings because the blood and tissue nitrogen is set by the nitrogen in the lung gas where oxygen is higher than tissue oxygen. Partial pressure of water vapor, not shown in Fig. 1, is a function of temperature only and therefore the same inside and outside.

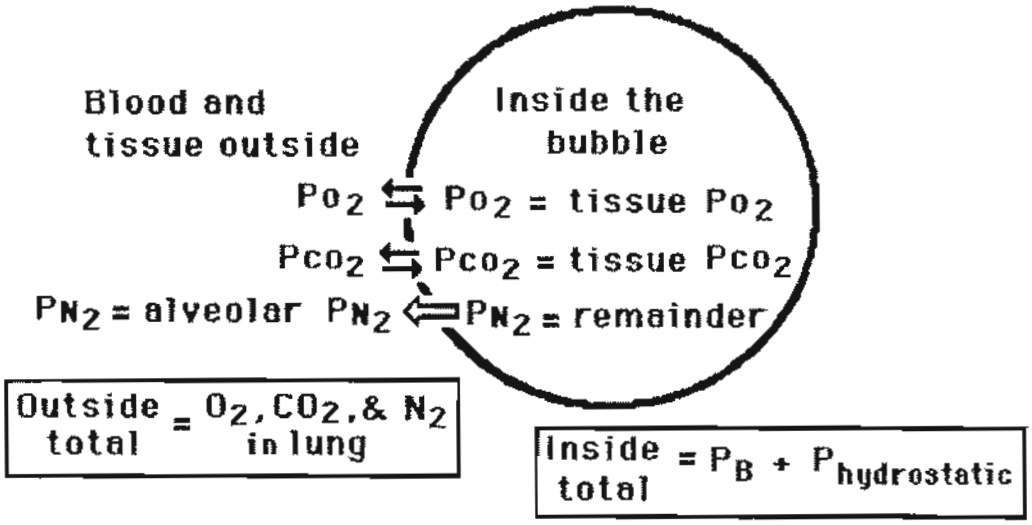

Figure 1. The "oxygen window" -- inert gas partial pressure inside a bubble is greater than outside because oxygen inside is close to tissue oxygen, and therefore less than oxygen in the breathing gas.

There can be many different oxygen windows in the body at the same time because tissues differ in their oxygen partial pressure (16). For examples, kidney cortex has a high blood flow and relatively low metabolism, so it has a high partial pressure of oxygen and small oxygen window; heart and exercising muscle have low flow relative to metabolic rate, so they have low partial pressure of oxygen and a big window. Because of the relationship of

tissue partial pressure of oxygen to blood carriage of oxygen on hemoglobin, the oxygen window increases with increasing oxygen partial pressure in the breathing gas but levels off when O2 is very high (16).

It is instructive to consider six cases in which the situation shown in Fig. 1 is changed:

1) If the lung gas contained no nitrogen, as in a person breathing oxygen, there would eventually be no nitrogen in the tissue and blood, so there would be a large gradient for nitrogen diffusion out of the bubble. The oxygen window would be at its maximum for the prevailing conditions.
2) Carbon dioxide could build up in a poorly perfused tissue and could dilute the bubble nitrogen so much that it would decrease the nitrogen exit rate, and therefore slow the decay of a shrinking bubble or even change a shrinking bubble into a growing one.
3) If there were a second inert gas inside the bubble, it would perforce decrease the partial pressure of nitrogen inside since the total pressure inside must be close to the atmospheric pressure (P B in the diagram). In an air-breathing person, this could cause entrance of nitrogen; if the entrance of nitrogen exceeded the exit of the second inert gas, the bubble would grow (see Growing Bubbles below).
4) Tissue partial pressure of oxygen tends to be the same at all degrees of compression but its counterpart in the bubble constitutes a different fraction of the total at different ambient pressures; the same can be said of carbon dioxide. Therefore when there is a change in total pressure, there is a transient phase while oxygen and carbon dioxide readjust by changing from the previous fractions to the new fractions (16).
5) A localized mechanical force such as apparently occurs in tribonucleation may initiate a bubble of water vapor -- it would disappear as soon as the force was removed unless some other molecules could diffuse in. In living tissues oxygen and carbon dioxide are always available and nitrogen is available in an air-breathing animal.
6) There is an exception to the idea that there is always an oxygen window: in arterial blood, the blood partial pressure of oxygen is the same as in alveolar gas, and blood partial pressure of nitrogen is the same as alveolar partial pressure of nitrogen. However, the high hydrostatic pressure in arterial blood would cause a hydrostatic pressure in the bubble that would increase partial pressures of all gases inside and promote outward diffusion of the gases as does the oxygen window.

Figure 2 illustrates how the washout process affects the gradients for diffusion. When a person is in a hyperbaric environment, various tissues take up inert gases at various rates and after decompression, the excess inert gas is washed out at rates that depend on the local blood flow and local ease of saturating the blood with inert gas. The figure describes a bubble in an air-breathing person who is compressed, as in treatment of decompression sickness. The upper panel shows that the bubble's inert gas partial pressure immediately goes to a high value. After a small readjustment due to changes of oxygen and carbon dioxide, the inert gas partial pressure stays constant until the end when surface tension increases the total pressure.

In the tissue the partial pressure of inert gas rises exponentially as nitrogen is washed in. The partial pressure difference is large at first, then decreases until it is just that due to the oxygen window. (Obviously this picture would be more complicated if there were excess gas in the tissue from a previous compression.) The results of the changes in partial-pressure driving force for diffusion are apparent in the lower panel. At time zero, when the person is compressed, the bubble's size decreases due to the compression; rate of compression is shown as very rapid to simplify the illustration. Then bubble size begins to decrease relatively rapidly due to the large inert-gas partial pressure difference before

inert gas has washed into the tissue. After that process is completed, decay of the bubble's size is due only to the oxygen window so the rate is essentially constant until finally at the end there is a rapid decrease in bubble size.

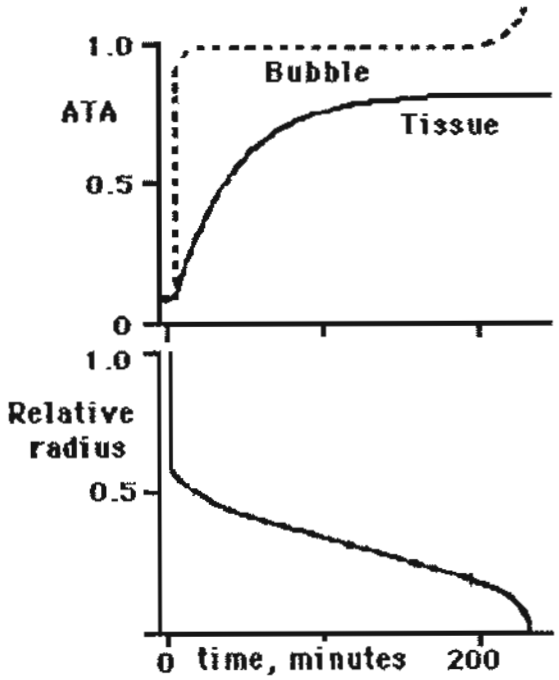

Figure 2. Upper panel -- partial pressure of nitrogen in bubble and tissue after a compression. Lower panel -- radius of the bubble. Compression is followed by phases in which the bubble is absorbed under the influence of the bubble- to-tissue nitrogen differences shown in the upper panel (Redrawn from (4)).

Growing Bubbles

The left panel of Fig. 3 shows a simulation of a bubble growing and decaying in a well-stirred medium which was previously saturated with inert gas at high pressure and then subjected to decompression; the gas washes out along an exponential time course similar to that expected in a person's tissues. Comparable simulations have been published by Meisel, Nir and Kerem (21). The time axis of Fig. 3 starts with the beginning of decompression. The bubble nitrogen is shown as the dashed horizontal line.

Medium nitrogen is above bubble nitrogen at first, then decreases until it is slightly below bubble nitrogen, comparable to the oxygen window in an air-breathing person. The simulation requires the assumption that there was a small pre-existing bubble; it grew rapidly while radius was small and inert-gas partial pressure outside was greater than inside; the bubble grew to several times its original radius, then after washout shrank fairly slowly due to the modest difference in partial pressure of nitrogen. At the beginning when the radius is small, the exchange of gas can be expected to be between the bubble and its immediate surroundings, but when the bubble has become large, exchanges from farther

away are necessary to provide the quantities of gas that are involved in the volume changes. At the end, radius was small again and even though the partial pressure of nitrogen difference was still modest, the bubble shrank rapidly (this diagram neglects the terminal increase of inside partial pressure of nitrogen due to surface tension; see Fig. 2).

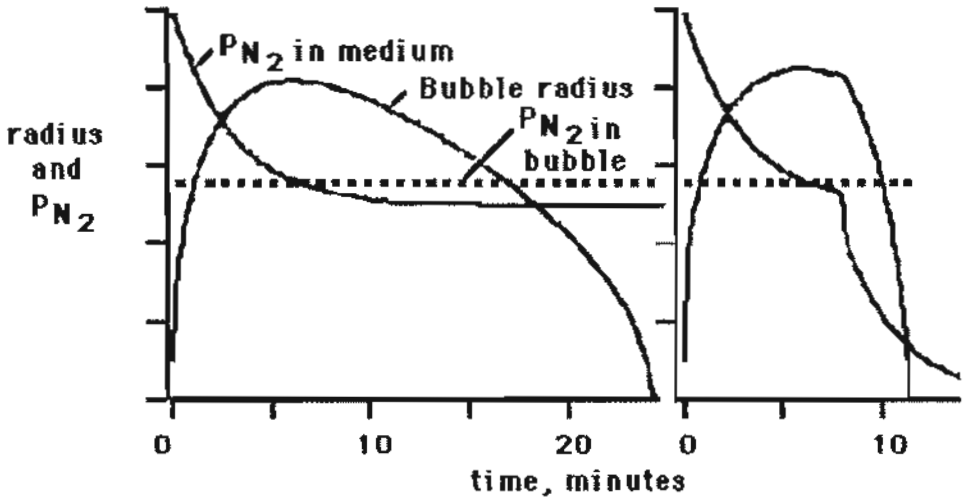

Figure 3. Simulations of partial pressure of nitrogen and radius of a pre-existing bubble after a decompression. Left panel -- the decompression is from 2 to 1 ATA in a system previously equilibrated with air and in contact with air after decompression. Right panel -- same as the left panel except that the system is in contact with pure oxygen at 8 min.

The right panel of Fig. 3 is the same situation as the left one, but there is a switch to oxygen during the decay phase. Nitrogen in the medium washes down to zero and the bubble goes into its rapid-shrinkage phase almost immediately.

The Fig. 3 diagrams oversimplify the situation. An in vivo bubble in a blood vessel would be expected to become cylindrical as it grew; the diffusion characteristics of cylindrical bubbles are somewhat different from those of spheres, but qualitatively the same. Bubbles in the body may break up into a stream of bubbles rather than reach the size shown in the figure and small bubbles may coalesce to give larger ones. A bubble may exhaust the amount of supersaturated dissolved gas in its surroundings so gas for additional growth must come to the bubble by diffusion from farther away or by being brought in by blood. The bubble would slow the local washout process if it slows or stops the local blood perfusion. Reactions of surface-active materials in the blood or tissue with the gas/liquid surface around bubbles may affect the diffusion rates across the interface. The tissue in the figure has a halftime for washout of 2 minutes and time scale for the figure is much shorter than the times (sometimes days) that are mentioned for duration of decompression sickness symptoms.

A bubble grows if more molecules enter than leave, and each gas species moves according to its own partial pressure difference between inside and outside the bubble. In the Fig. 3 cases, growth was caused by supersaturation but interactions of the bubble gas with the breathing gas can also cause bubble growth. Bubbles formed during decompression will contain the inert gas breathed before and during the decompression -- if the person is switched to a different inert gas to breathe, there will be exchange of the old gas for the new

in the bubble. If the new gas enters faster than the old exits, the bubble will have a transient phase of growth.

Figure 4 shows how this situation has been mimicked with experiments using gas pockets on the backs of rats. When the pockets contained nitrogen, there was a small increase in volume due to oxygen and carbon dioxide entering from the tissue, and then the pocket gas was absorbed over a period of 2 weeks. In contrast, pockets which originally contained sulfur hexafluoride doubled in size before they began to be absorbed; entrance of nitrogen from the air-breathing animals' tissues and blood exceeded the exit of SF_6. The gradient for nitrogen entrance is normal tissue partial pressure of nitrogen outside vs a partial pressure of nitrogen inside that could not reach or exceed the outside nitrogen level because of the presence of SF_6 inside. Eventually the pockets would contain nitrogen only; from then on absorption would be the same as when there was nitrogen originally. Pockets which originally contained neon followed almost the same time course as the nitrogen pockets. Nitrogen must have entered the neon-filled pockets, but apparently the neon's permeation rate is so near that of nitrogen that nitrogen entrance made no difference to total absorption rate of the pockets.

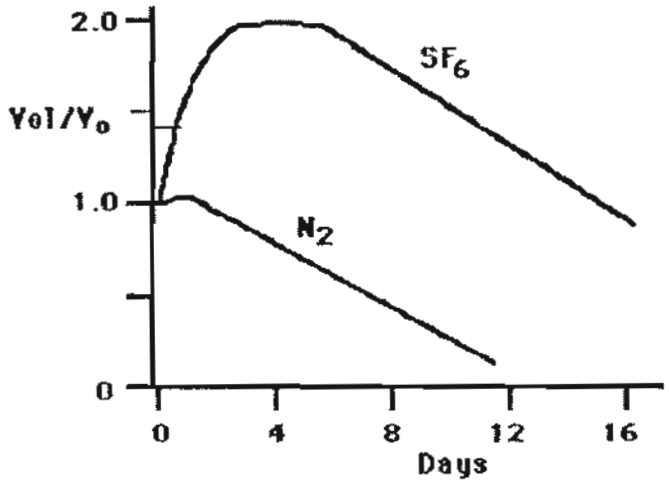

Figure 4. Growth of gas pockets that contain sulfur hexafluoride in air-breathing rats compared to pockets that contain nitrogen, also in air-breathing rats (redrawn from (22)).

If an inert gas in a bubble or pocket exits faster than nitrogen enters, the opposite of the Fig. 4 case occurs: while the fast gas leaves, there is an early shrinkage phase which gives way to the slower phase of the nitrogen-only case. This was observed with helium gas inside pockets in air-breathing rats (23). Note that if helium is a faster-diffusing gas than nitrogen, a bubble increase may occur when helium is outside a decompression sickness bubble and nitrogen inside, as when a person having nitrogen-containing bubbles in watery tissue is given helium to breathe. However, the outcome may be just the opposite for bubbles in or near fatty tissue, where solubility of helium is less than solubility of nitrogen, so helium may be the slower gas; a switch to helium breathing may cause an early shrinkage phase when bubbles are in fatty tissue.

Bubble growth due to two competing gases as in Fig. 4 are occasioned by having a gas in the bubble that is different from the breathing gas. Related cases are the phenomena known as

"isobaric supersaturation" and "isobaric counter diffusion". There the sum of the tensions of two gases in the tissues becomes higher than ambient pressure, either during the washin/washout after a switch of breathing gas (24,25) or due to gas permeation through the skin (26). After the resulting supersaturation causes bubbles to form, it is reasonable to envision each gas attempting to reach partial pressure equilibrium across the interior/exterior boundary of the bubbles and in so doing, each gas lowers the inside partial pressure of the opposite gas, causing the opposite gas to diffuse in.

REFERENCES

1. Van Liew HD, Schoenfisch WH, Olszowka AJ. Exchanges of N2 between a gas pocket and tissue in a hyperbaric environment. Respir Physiol 1968/1969; 6:23-28.

2. Van Liew HD. Effect of a change of perfusion on exit of nitrogen and oxygen from gas pockets. Respir Physiol 1971; 12:163-168.

3. Loring SH, Butler JP. Gas exchange in body cavities. In: Farhi LE, Tenney SM, eds. Handbook of physiology, Section 3: the respiratory system. Volume IV, Gas Exchange. Bethesda, MD: American Physiological Society, 1987:283-295.

4. Van Liew HD. Factors in the resolution of tissue gas bubbles. In: Lambertsen CJ, ed. Underwater physiology. Proceedings of the third symposium on underwater physiology. Baltimore, MD: Williams & Wilkins Co, 1967:191-204.

5. Van Liew HD, Hlastala MP. Influence of bubble size and blood perfusion on absorption of gas bubbles in tissues. Respir Physiol 1969; 7:111-121.

6. Hlastala MP, Van Liew HD. Absorption of in vivo inert gas bubbles. Respir Physiol 1975; 24:147-158.

7. Daniels S. Bubble formation in animals during decompression. In: Brubakk AO, Kanwisher JW, Sundnes G, eds. Diving in animals and man. Trondheim, Norway: Tapir Publishers, 1986:229-258.

8. Ward CA, Tikuisis P, Tucker AS. Bubble evolution in solutions with gas concentrations near the saturation value. J Colloid Interface Sci 1986; 113:388-398.

9. Wyman J Jr, Scholander PF, Edwards GA, Irving L. On the stability of gas bubbles in sea water. Sears Foundation J Marine Res 1952; 11:47-62.

10. Szekely J, Martins GP. Non equilibrium effects in the growth of spherical gas bubbles due to solute diffusion. Chem Engng Sci 1971; 26:147-159.

11. Van Liew HD. Tissue pO2 and pCO2 estimation with rat subcutaneous gas pockets. J Appl Physiol 1962; 17:851-855.

12. Chen PY, Van Liew HD. Krogh constants for diffusion of nitrogen and carbon monoxide in bladder tissue. Respir Physiol 1975; 24:43-49.

13. Hlastala MP, Farhi LE. Absorption of gas bubbles in flowing blood. J Appl Physiol 1973; 35:311-316.

14. Van Liew HD. Coupling of diffusion and perfusion in gas exit from subcutaneous pockets in rats. Am J Physiol 1968; 214:1176-1185.

15. Piiper J, Canfield RE, Rahn H. Absorption of various inert gases from subcutaneous gas pockets in rats. J Appl Physiol 1962; 17:268-274.

16. Van Liew HD, Bishop B, Walder-D P, Rahn H. Effects of compression on composition and absorption of tissue gas pockets. J Appl Physiol 1965; 20:927-933.

17. Piccard J. Aero-emphysema and the birth of gas bubbles. Proc Staff Meetings of Mayo Clinic 1941; 16:700-704.

18. Epstein PS, Plesset MS. On the stability of gas bubbles in liquid-gas solutions. J Chem Phys 1950; 18:1505-1509.

19. Hlastala MP. Transient state diffusion in rat subcutaneous tissue. Aerospace Med 1974; 45:269-273.

20. Lin YC. Species independent maximum no-bubble pressure reduction from saturation dive. In: Bachrach AJ, Matzen MM, eds. Underwater physiology VII. Proceedings of the seventh symposium on underwater physiology. Bethesda, MD: Undersea Medical Soc, Inc, 1981:699-706.

21. Meisel S, Nir A, Kerem D. Bubble dynamics in perfused tissue undergoing decompression. Respir Physiol 1981; 43:89-98.

22. Van Liew HD, Passke M. Permeation of neon, nitrogen and sulfur hexafluoride through walls of subcutaneous gas pockets in rats. Aerosp Med 1967; 38:829-831.

23. Tucker RW, Tenney SM. Inert gas exchange in subcutaneous gas pockets of air-breathing animals: theory and measurement. Respir Physiol 1966; 1:151-171.

24. Hills BA. Supersaturation by counterperfusion and diffusion of gases. J Appl Physiol 1977; 42:758-760.

25. Tepper RS, Lightfoot EN, Baz A, Lanphier EH. Inert gas transport in the microcirculation: risk of isobaric supersaturation. J Appl Physiol 1979; 46:1157-1163.

26. Lambertsen CJ, Idikula J. A new gas lesion syndrome in man, induced by "isobaric gas counterdiffusion." J Appl Physiol 1975; 39:434-443.

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DISCUSSION

DR. WARD: I would like to emphasize that the bubbles have to be sufficiently large so that surface tension effects are negligible. If surface tension is involved, all bubbles do not necessarily grow in an oversaturated solution. Sufficiently small bubbles will dissolve.

DR. KUNKLE: You mentioned that as the bubble grows large enough to cause a physiologic effect, it almost certainly won't be spherical. A spherical bubble has the minimum surface area to volume ratio. As it distorts or divides into several smaller bubbles, the surface-area-to-volume ratio will increase and the bubble should resolve more rapidly. Thus, distortion seems to be beneficial.

DR. VANN: Dr. Van Liew, would you review the difference between gas exchange in a small bubble as opposed to gas exchange in a subcutaneous gas pocket? The principles are essentially identical, are they not? Are there any differences besides the surface tension?

DR. VAN LIEW: In a small bubble, the gas can diffuse rapidly in several different directions. Therefore, there will be a steep concentration gradient around the bubble down which the gas will diffuse rapidly. In a big pocket, all of the rays of diffusion are parallel so that the gas will exert a back pressure that slows diffusion. Small bubbles grow or decay faster than large bubbles because of this divergence of the gradient. For this reason, a small bubble is much less dependent on stirring or removal of the gas in the far surroundings. After a small transient effect, inert gas exchange in big subcutaneous gas pockets is dependent on blood flow in distant tissue to remove the gas which diffuses from the pocket into tissue.

DR. VANN: Does diffusion or perfusion predominate in the growth and resolution of gas bubbles?

DR. VAN LIEW: For small bubbles as in decompression bubbles, I'd say diffusion predominates, but of course perfusion sets the tissue level. Inert gas exchange in a small bubble, however, is almost independent of the amount of stirring due to blood flow.

DR. VANN: So diffusion and perfusion are linked sequentially?

DR. VAN LIEW: Yes.

DR. VANN: Recompression with helium has been proposed for the treatment of refractory decompression sickness caused by nitrogen diving. Strauss and Yount demonstrated bubble growth in gelatin as a result of a change from nitrogen to helium. What is your assessment concerning a switch from nitrogen to helium when bubbles are present?

DR. VAN LIEW: If you have a nitrogen bubble in a watery medium and you put helium in the surroundings, the helium will diffuse in more rapidly than the nitrogen will diffuse out, so the bubble will increase in size.

DR. VANN: With regard to the treatment of nitrogen-oxygen decompression sickness by the use of helium-oxygen, is this a good idea?

DR. VAN LIEW: I don't know, but my studies suggest that if bubbles are present, it might not be a good idea to give helium because bubbles will get bigger. If bubbles are not present, maybe giving helium would be good because the tissues would denitrogenate more rapidly, as in denitrogenation by oxygen breathing. Perhaps helium is more important for bubble growth than for bubble formation. It is important to remember, however, that mathematical simulations of diffusion are not an end in themselves and are incorrect if they do not explain experimental observation.

DR. JAMES: These experiments were done a long time ago. This is reduction of volume of air in closed environments, respired gas 150 liters of air injected in all these experiments and I might say I haven't put the number of experiments in each group, but they're very large numbers. The respired gas is air, at 1 ATA ambient pressure, and the volume reduction is 10.38 percent, with 80-20 heliox. The pressure was 1 ATA surface pressure, 6 hours; it's just about double that at about 19.90%. At two atmospheres for 6 hours the volume reduction is almost 30 percent. Oxygen of course is very much better because of the inherent unsaturation. At 1 ATA hours there is almost a 4% reduction; at 2 ATA, about the same. Hildegard and Matson presented a paper in Palermo very recently in which they exposed rats to 3.5 ATA compressed air for hours, then decompressed and did all their experiments on the surface. And, they observed bubbles. Remember this is air decompression sickness. As they saw the bubbles getting down to very, very small dimensions, they switched over to allow the animals to breathe air. So, I think we've now got some real experimental data. These bubbles were actually observed in adipose tissue and of course in spinal cord containing about 30% lipid. They also just used air and showed that bubbles grow for many hours after reaching surface. I think they followed the bubbles up to about 6 hours, finding that the bubbles constantly expanded with air breathing.

This emphasizes that it is the product of the diffusion and solubility coefficients that controls the diffusion of inert gas in tissue. In a lipid tissue, this product is lower for nitrogen than for helium and so nitrogen is eliminated more slowly.

DR. VAN LIEW: You're saying the same thing I said, I believe. If you give an animal a gas to breath that is fast to enter, such as nitrogen in fact, a bubble will increase in size.

DR. JAMES: Exactly, yes.

RELATIONS OF ISOBARIC GAS COUNTERDIFFUSION AND DECOMPRESSION GAS LESION DISEASES

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Purpose and Perspective

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

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

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

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

The relationships of oxygen, decompression and counterdiffusion are clear on conceiving a decompression or therapy as a series of instantaneous (isobaric) periods in which all ongoing forms of gas exchange and gas effect exist simultaneously (as they do in reality).

A second personal goal is again to urge use of the term "Gas Lesion

Diseases," devised to encompass the several overlapping and impure pathologic states now obviously related and sometimes concurrent in exposures to unusual pressures and atmospheres (2). The still conventional blanketing designations of "Decompression Sickness" or "Gas

Embolism" are not adequate for present and future diving or hyperbaric medicine, and have led to use of such foolish terminology as "isobaric decompression sickness."

Table 1 indicates the scope of major forms of gas lesion diseases, different in their inducing circumstances or their consequences. The resulting symptoms or objective signs (e.g. neural, vestibular, cutaneous, or local pain may be similar or different, and do not themselves describe or represent the specific disease or fundamental mechanism. Table 2 emphasizes the clearly obvious fact that the ultimate primary basis for gas phase generation in decompression or in isobaric gas lesion diseases is an excess pressure of gases in peripheral tissues including peripheral blood. The complex consequences of bubble growth and bubble-tissue interactions are sequels to the primary event, without which no pathologic effects would occur. The table also emphasizes that the very occurrence of gas lesions and emboli in isobaric states indicates the pre-existence or continuous formation of "nuclei" in normal tissue fluids. Asterisks (*) mark venous gas embolism in four of the forms of gas lesion disease to call attention to the possibility that venous gas embolic process may conceivably lead to arterial gas emboli. While venous gas emboli affect blood and lung, arterial gas embolic phenomena should be considered as having access to all tissues and arterioles. It is therefore here cited as "systemic" embolization.

Table 1.

MAJOR FORMS OF GAS LESION DISEASES	SOURCE OF GAS PHASE
Pulmonary Overexpansion	Lung
Systemic Gas Embolism (Arterial)	
Pneumothorax	
Subcutaneous/Mediastinal Emphysema	
Iatrogenic or Traumatic Gas Embolism	Extrinsic
Venous*	
Arterial	
Systemic (Arterial)	
Decompression Sickness (Post Hyperbaric, Hypobaric)	Peripheral Tissue
Cutaneous	
Deep Tissue	
Venous Embolic*	
Systemic (Arterial)	
Superficial Isobaric Counterdiffusion Sickness (Stable State)	Peripheral Tissue
Cutaneous	
Vestibular	
Venous Embolic*	
Systemic (Arterial)	
Deep Tissue Isobaric Counterdiffusion Sickness (Transient)	Peripheral Tissue
Venous Embolic*	
Systemic (Arterial)	

Table 2.

GAS PHASE DEVELOPMENT IN DIVING DECOMPRESSION AND ISOBARIC COUNTERDIFFUSION

Inert gas uptake is not harmful in diving, inert gas elimination is not harmful, and decompression itself is not harmful.

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

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

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

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

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

Localization of gas phase development.

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

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

Table 3.

ISOBARIC INERT GAS COUNTERDIFFUSION (Superficial and Deep Tissue Forms)

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

"Superficial" isobaric counterdiffusion occurs through body surfaces when air or N_2-O_2 is breathed and the external environment is helium.

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

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

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

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

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

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

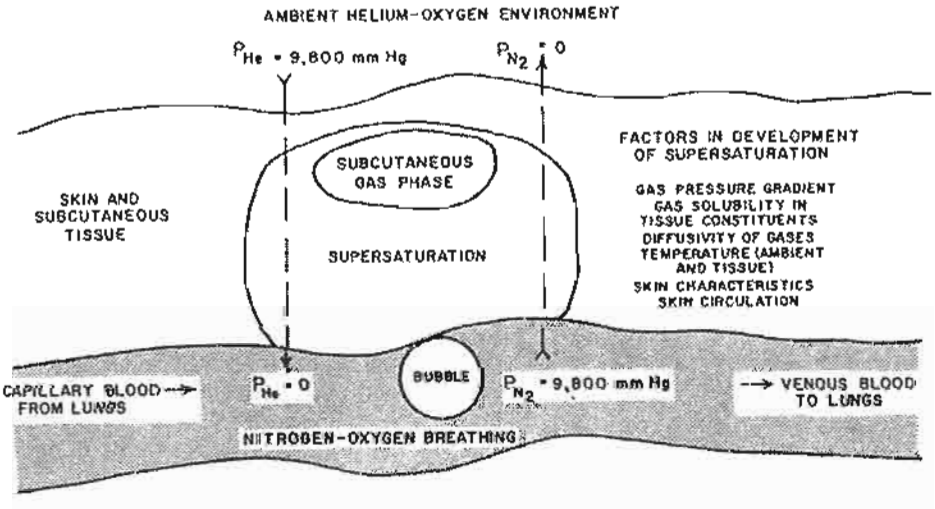

Fig. 1. Dermal Lesion in Superficial Isobaric Counterdiffusion.

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

The Phenomenon of Isobaric Inert Gas Counterdiffusion

Counterdiffusion was first recognized and named as the cause of gas lesion development in individuals who for a broad physiologic study (3) were saturated in a helium atmosphere at constant pressure and who then breathed neon-oxygen-helium and nitrogen-helium-oxygen mixtures at pressures equivalent to 400, 700, 900, 1200 fsw (3) (4) (5). These individuals developed severe cutaneous itching, the first symptom of a

larger problem that was partially solved by encompassing them in a gas-tight suit into which they exhaled. Only regions of helium-exposed skin, the scalp, hands, and skin of the face where the mask did not cover, continued to itch (3). Cutaneous symptoms encountered in previous experiments at a lower pressure were discounted as not attributable to gas lesion development (6).

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

DEPTH (ata)	EXPERIMENTAL CONDITIONS: Breathing Gas / Chamber Gas						
	Ne/He	N_2/He	Ar/He	N_2O/He	SF_6/He	He/N_2O	He/Ar
1		+	+	+	0	0	0
2		+	+		0		
3		+	+		0		
4	+	+	+		0		
7	+	+	+				
10	+	+	+				

Fig. 2. Exposures of Pigs to Superficial Isobaric Gas Counterdiffusion at Ambient Pressures From 1 to 10 ATA.

A (+) indicates that lesions were observed, an open circle (0) that no lesions were seen. The severity of lesions for any given depth and time was: $N_2O > Ar > N_2 > Ne$ (9).

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

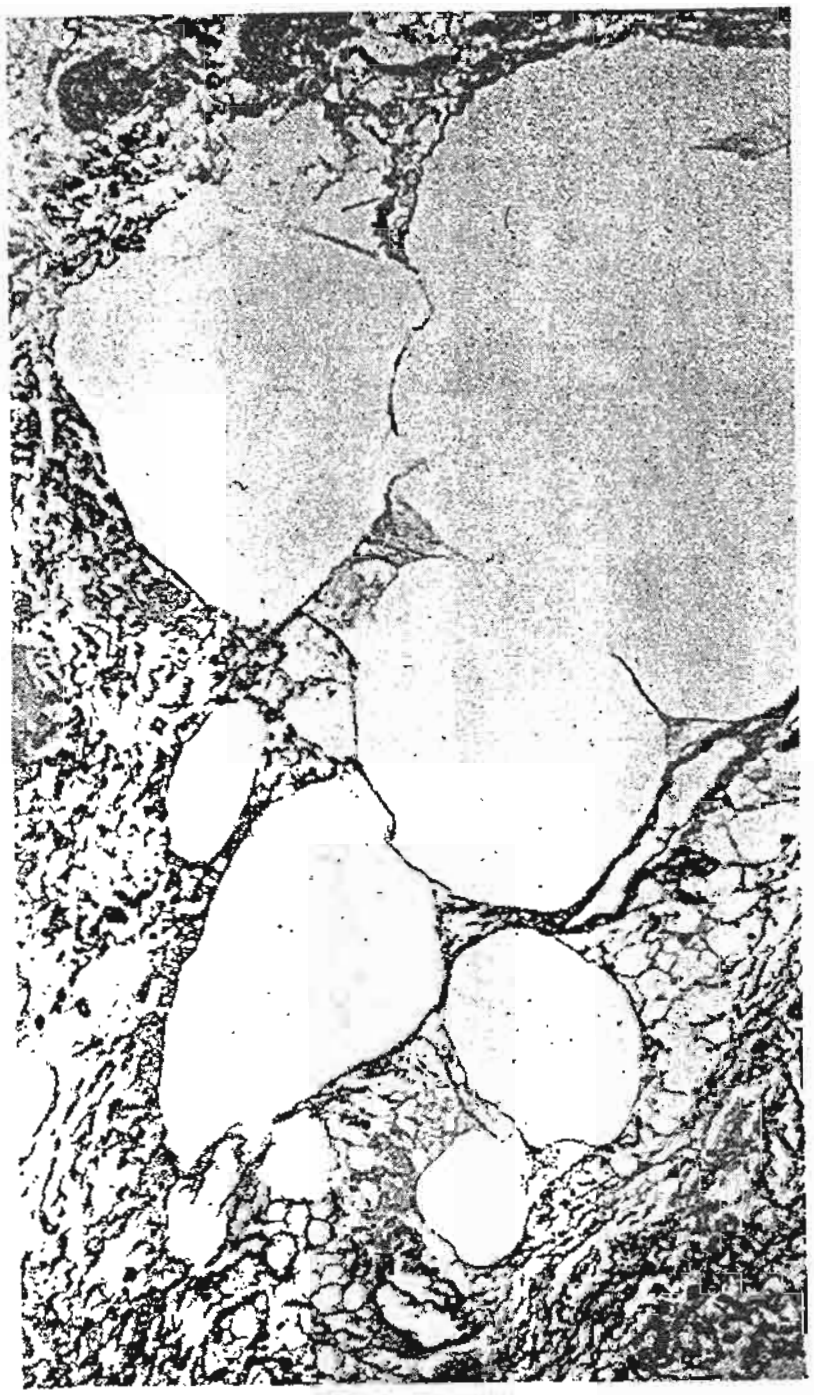

Fig. 3. Gas spaces in section of subcutaneous tissue of pig exposed to N_2O/He/1 ATA superficial isobaric counterdiffusion (From 23).

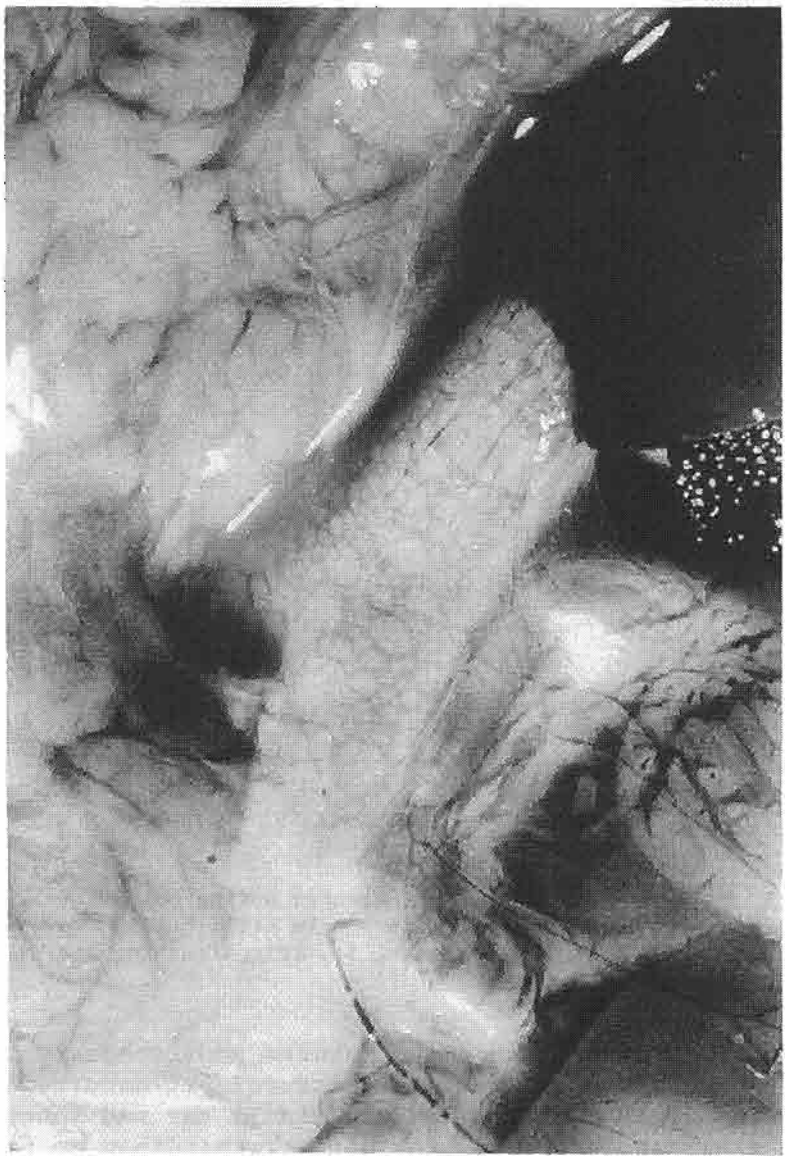

Fig. 4. Occurrence of massive amount of gas in inferior vena cava of pig following death due to N_2O/He/1 ATA superficial isobaric counterdiffusion (2).

"Superficial Isobaric Inert Gas Counterdiffusion."

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

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

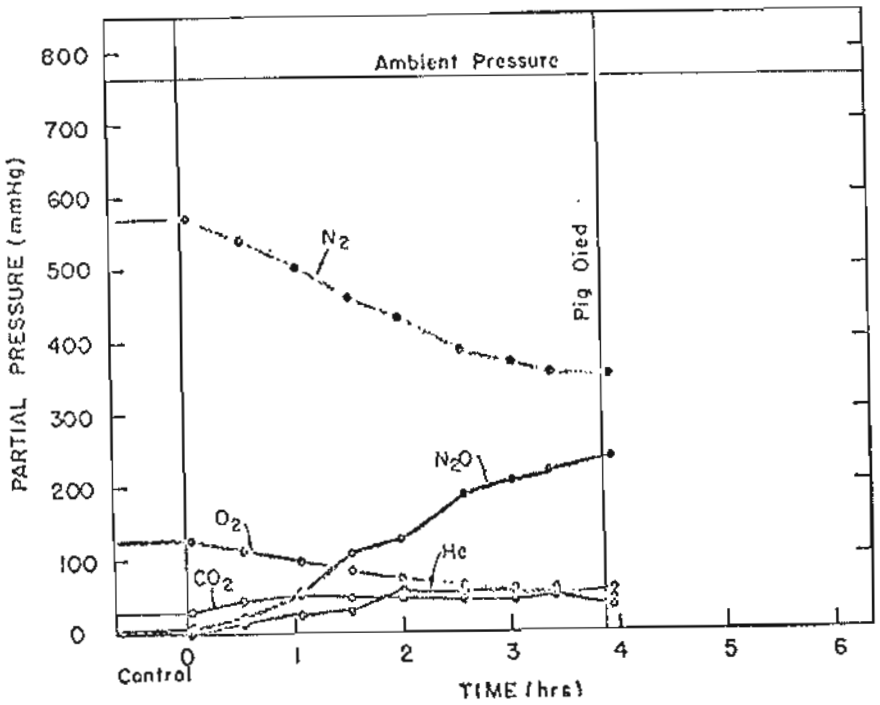

Fig. 5. Changes in Gas Partial Pressures During Superficial Isobaric Gas Counterdiffusion In Artificially Induced Subcutaneous Gas Pockets (23). (Pig Breathing N_2O-O_2, Surrounded by Helium).

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

20,000 mm. Hg.), diffuse through the tympanic membrane, then through the round window while the respired neon gas was escaping more slowly from the endolymph into the middle ear (4). Helium passage through the tympanic membrane of cats was measured, and found to be rapid (10) (11). To learn whether isobaric counterdiffusion would produce bubbles in endolymph we observed the round window by direct microscopy in guinea pigs breathing nitrous oxide at one and at two atmospheres with helium external to the round window (12). No bubbles appeared in the inner ear fluid after several hours of this exposure. The specific cause of this severe and incapacitating isobaric gas lesion in man therefore still remains an unsettled matter. It may relate to occurrence of as yet undetected arterial gas emboli.

The absence of effects of superficial isobaric counterdiffusion on the human eye is similarly unexplainable. Post-mortem photographs of the retina through the lens of the eye after prolonged counterdiffusion of pigs with nitrous oxide and helium at one ATA show gas bubbles deep, in the retinal vessels. In the human subjects who generated skin lesions there were never any symptoms, inflammation, or other evident effects of the early counterdiffusion process on vision conjunctiva, sclera, or cornea (4) (23) (13). When N_2O/He/2ata counterdiffusion was produced through the surfaces of the eye in rabbits, no bubbles or lesions had occurred by the time the exposure of the skin caused subcutaneous gas lesions, venous emboli and death (13). The eye has a surface area of the body where topical isobaric counterdiffusion occurs with no detectable adverse consequences.

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

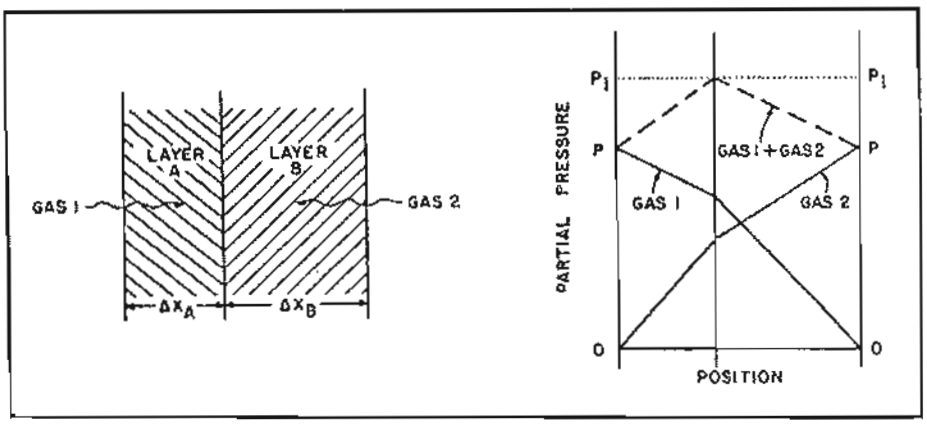

Fig. 6. Gas Partial Pressure Profiles Resulting From Steady Counterdiffusion of Two Inert Gases.

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

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

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

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

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

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

The Superficial Isobaric Inert Gas Counterdiffusion phenomenon deserves the designation as one of the "Gas Lesion Diseases" (4). In experiments with pigs at sea level, the process of N_2O/He/1 ATA superficial counterdiffusion could cause death within an hour and a half when the whole animal body was exposed to helium (9). To slow this rapid process

sufficiently in some experiments for detailed study, only the hind quarters of other pigs were exposed (by enclosing them within a helium-filled plastic bag). Removing the flow of gas emboli from the vena cava with a bubble trap prevented them from reaching the lungs and extended the life of the animal (14). This bubble trapping enabled measurement of the volume rate at which gas emboli were generated by counterdiffusion through a measured area of skin. It also allowed detailed study of the local lesion development, from initial to severe stages. With the animal breathing nitrous oxide and exposed to helium over the lower body and nitrogen over the upper body, the N_2O/N_2/1 ATA counterdiffusion produced no visible effect, but the N_2O/He/1 ATA counterdiffusion formed cutaneous gas lesions and venous gas emboli, disrupted skin capillaries, and had a grossly destructive effect on the skin and subcutaneous sites. A very sharp line of visible demarcation existed between the helium exposed region and the nitrogen exposed region.

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

This process of N_2O/He/1 ATA Superficial Counterdiffusion can be used as a controllable experimental tool to study early development of peripheral gas lesions and the progression of any pathophysiologic effects of gas emboli in the venous blood and "bombarding" the lungs.

The magnitude of effects on blood and lung can be experimentally controlled by changing the skin surface area which is subjected to counterdiffusion, or by changing the gas gradients, or by changing ambient pressure. If the area is small enough, there will be no increase in pulmonary artery pressure even though venous bubbles occur. With larger skin areas the gas embolism causes a rise in pulmonary

arterial pressure. In pigs which are monitored by venous and arterial Doppler probes, no bubbles appear to cross the lungs despite constant and continuous bombardment over six to eight hours. However, in one animal with a patent septal defect, death occurred early and gas bubbles were present in grossly visible amounts in arterial blood. It was only when normal pigs were near death from severe venous gas embolism that visible arterial emboli were found (17). Undetectable gas emboli could of course pass undetected, as suggested by the present of gas phase in deep tissues in port mortem examinations.

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

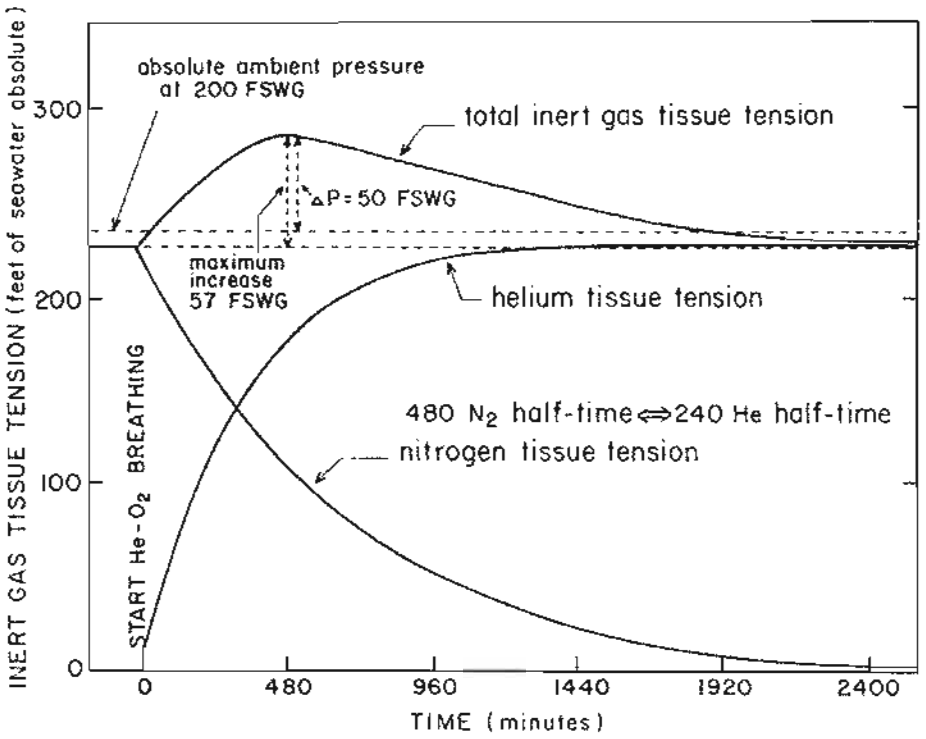

Fig. 7. Diagram of "deep tissue" isobaric supersaturation caused by breathing helium after prolonged exposure to N_2-O_2 mixture. Total inert gas pressure rises, and a composite supersaturation is maintained for many hours in "slow-perfusing" tissues. The opposite effect, an equivalent degree and time course of useful subsaturation, is subsaturation, is expected with breathing N_2-O_2 after prolonged exposure to helium (4).

"Deep Tissue Isobaric Counterdiffusion"

Inert gas counterdiffusion in another form can create supersaturation in the deep tissues, even when the skin is underwater or not exposed to a different inert gas. "Deep Tissue Isobaric Counterdiffusion" was selected as the name to designate the supersaturation or subsaturation which occurs when a diver "switches" from breathing one inert gas-oxygen mixture to a different inert gas carrier for oxygen (4) (15). After such a switch, from a "slower equilibrating" to a "faster equilibrating " gas (e.g. from air to helium-oxygen) a slowly perfused tissue saturated with nitrogen will become transiently supersaturated by entry of the more rapidly exchanging helium. This deep-tissue supersaturation continues for many hours, as predicted (4) and as D'Aoust demonstrated by bubble detection in goats (15). The process has not been widely encountered in man, but has been observed in helium exposures following shallow nitrogen saturation (22). A long transient of venous gas emboli can develop (7) (15), and it should for practical purposes of diving safety be assumed until proven otherwise that gas lesions generated by decompression in poorly perfused tissues will be expanded by "deep tissue isobaric counterdiffusion" (2). It is for this reason that helium should not be substituted for air breathing in treatment of severe decompression sickness resulting from air diving, without the degree of concurrent compression calculated to assure marked immediate reduction of bubble volume (as in Treatment Table 7A (18).

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

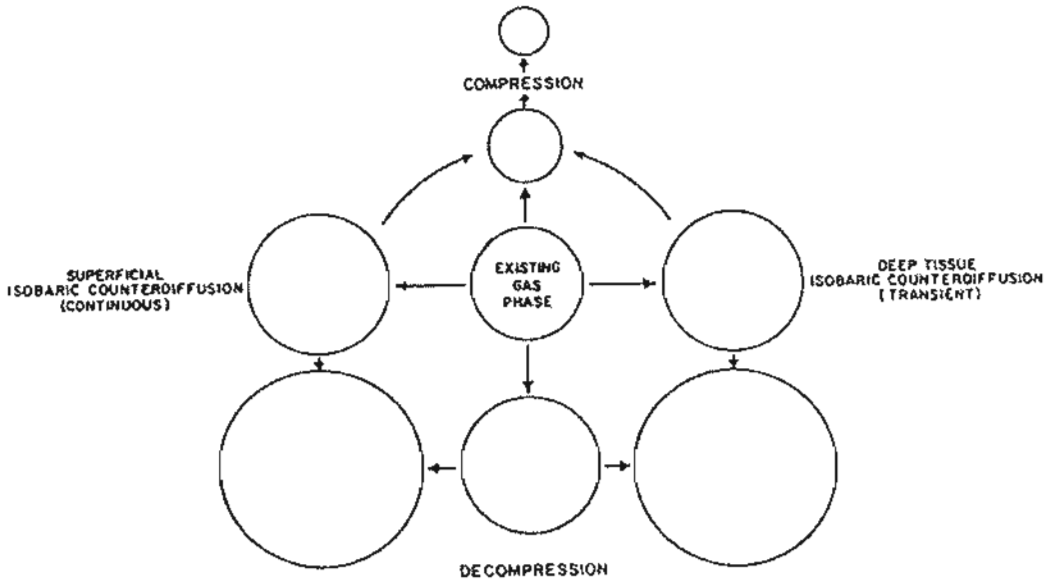

Fig. 8. Interactions among gas phase decompression, compression and isobaric states in several forms of gas lesion (2).

Interactions of Counterdiffusion Processes, Oxygen and Decompression

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

° Avoidance of mask breathing of air or N_2-O_2 while body surface or the ear canals are exposed to helium.

° Avoidance of an abrupt change from air or N_2-O_2 breathing to helium-oxygen at a constant or decreasing pressure.

° When it is clearly desirable during therapy for severe decompression sickness to proceed from air or N_2-O_2 breathing to prolonged exposure at a higher ambient pressure than is sensible for nitrogen, compression on helium is recommended despite the potential hazard of deep-tissue counterdiffusion supersaturation (18). Such change to helium should be accompanied by prompt compression and appropriate oxygen pressure, to counter the tendency for bubble growth or development.

° Switch from prolonged helium breathing to air or N_2-O_2 breathing to achieve deep counterdiffusion subsaturation is a desireable aid to prevention of decompression sickness in helium diving. In a pressure chamber it should occur by a change in ambient atmosphere rather than by mask breathing, to avoid superficial counterdiffusion. The transition should take place gradually, rather than abruptly, to avoid exaggerated sensations of narcosis which may be confused with vestibular effect.

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

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REFERENCES

1. Lambertsen CJ. Relations of decompression to use of oxygen: harmful effects and their prevention. In: Symposium on health examination of Divers - decompression/use of oxygen. Norwegian Petroleum Directorate Report, Stavanger, 1988.

2. Lambertsen CJ (ed.) Decompression sickness and its therapy. Proceedings of a symposium organized by the Association of Diving Contractors and the Institute For Environmental Medicine, University of Pennsylvania. New Orleans, Louisiana, 1 February 1978. Allentown, PA: Air Products and Chemicals, Inc. 1979.

3. Lambertsen CJ, Gelfand R, Peterson RE, et al. Human tolerance to He, Ne and N_2 at respiratory gas densities equivalent to He-O_2 breathing at depths to 1200, 2000, 3000, 4000 and 5000 feet of sea water. Aviat Space Environ Med 1977; 48:843-855.

4. Lambertsen CJ, Idicula J. A new gas lesion syndrome in man induced by "isobaric counterdiffusion." J Appl Physiol 1975; 39:434-443.

5. Graves DJ, Idicula J, Lambertsen CJ, Quinn JA. Bubble formation resulting from counterdiffusion supersaturation: a possible explanation for isobaric inert gas 'urticaria' and vertigo. Phys Med Biol 1973; 18:356-364.

6. Blenkarn GD, Aquadro C, Hills BA, Saltzman HA. Urticaria following the sequential breathing of various inert gases at a constant ambient pressure of 7 ata: a possible manifestation of gas induced osmosis. Aerospace Med 1971; 42:141-146.

7. D'Aoust BG, Smith KH, Swanson HT, et al. Venous gas bubbles: production by transient deep isobaric counterdiffusion of helium against nitrogen. Science 1977; 197:889-891.

8. Cowley JRM, Allegra C, Lambertsen CJ. Subcutaneous tissue gas space pressure during superficial isobaric counterdiffusion. J Appl Physiol 1979; 47:224-227.

9. Idicula J, Graves DJ, Quinn JA, Lambertsen CJ. Bubble formation resulting from the steady counterdiffusion of two inert gases. In: Lambertsen CJ, ed. Underwater physiology V. Bethesda, MD: Federation of American Societies for Experimental Biology, 1976; 335-340.

10. Dueker CW, Lambertsen CJ, Rosowski JJ, Saunders JC. Middle ear gas exchange in isobaric counterdiffusion. J Appl Physiol 1979; 47:1239-1244.

11. Ranade A, Lambertsen CJ, Noordergraaf A. Inert gas exchange in the middle ear. Acta Oto-Laryngol 1980; 371 (Suppl.).

12. Mynderse LA, Lambertsen CJ. Superficial isobaric counterdiffusion of the round window in the guinea pig. Institute For Environmental Medicine, 1983.

13. Cowley JRM, Lambertsen CJ. Isobaric gas counterdiffusion in rabbit eye. J Appl Physiol 1979; 47:220-223.

14. Cunnington JPW, Lambertsen CJ. Quantitation of spontaneous intravascular gas embolism during superficial isobaric gas counterdiffusion. Institute For Environmental Medicine Report, 1981.

15. D'Aoust BG, Lambertsen CJ. Isobaric gas exchange and supersaturation by counterdiffusion. In: The physiology and medicine of diving, Third Edition, Bennett PB, Elliott DH, eds. London: Balliere-Tindall,1983; 383-403.

16. Buhlmann AA. The use of multiple inert gas mixtures in decompression. In: The physiology and medicine of diving and compressed air work. Bennett PB, Elliott DH, eds. Baltimore, MD: Williams and Wilkins, 1969.

17. Pisarello JM, Fried M, Fisher D., Lambertsen CJ. Superficial isobaric counterdiffusion gas lesion disease - effects leading to mortality. In: Underwater Physiology VIII. Bachrach AJ, Matzen MM, eds. Bethesda: Undersea Medical Society, 1984; 101-106.

18. Lambertsen CJ, Miller RG. Treatment table 7A. Saturation decompression intermittent oxygen method for treatment of severe decompression sickness and gas embolism, or where onset of symptoms occurs prior to reaching surface. Institute For Environmental Medicine/Ecosystems/Solus Ocean Systems, 1980.

19. Albertine KH, Wiener-Kronish JP, Koike K., Staub ND. Quantification of damage by air emboli to lung microvessels in anesthetized sheep. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 57(5):1360-1368.

20. Albertine KH, Lambertsen CJ. Effects of superficial isobaric counterdiffusion venous gas embolism upon lung in the pig. Institute For Environmental Medicine Report, 1988.

21. Harvey CA, Lambertsen CJ. Deep tissue isobaric inert gas exchange: predictions during normoxic helium, neon and nitrogen breathing by men at 1200 feet of sea water. In: Underwater Physiology VI. CW Shilling, Kent MB, eds. Bethesda: Federation of American Societies for Experimental Biology, 1979; 343-358.

22. Harvey CA. Shallow saturation hyperbaric exposures to nitrogen-oxygen environments and isobaric switches to helium-oxygen. Undersea Biomed Res 1977; 4:A15.

23. Lambertsen CJ, Idicula J, Cunnington J, Cowley JRM. Pathophysiology of superficial isobaric counterdiffusion. Institute For Environmental Medicine Report, 1980.

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DISCUSSION

DR. JAMES: In view of the fact, Dr. Lambertsen, that you were unable to demonstrate inner ear bubbles under the experimental conditions that you described, I wonder if it's possible to consider an alternative mechanism. Someone yesterday pointed out that the initial size of a bubble after nucleation is not dependent on the absolute pressure, but the subsequent growth clearly is. If you form bubbles at 1200 feet of sea water as you did in the experiments, is it possible that these are, in fact, very small, very stable bubbles and that what you were seeing was an effect on the vestibular apparatus? It could have been brain stem or cerebellum, as well as inner ear. Did the subjects report any hearing disturbance as a result of the problem?

DR. LAMBERTSEN: There was no hearing loss. Are you asking if gas emboli reached the inner ear after forming elsewhere or whether bubbles were generated in the inner ear by an unknown mechanism?

DR. JAMES: No, I'm suggesting that there were small circulating bubbles that were extremely stable. It may not be just a labyrinthine mechanism. It could be brain stem or cerebellar.

DR. LAMBERTSEN: Yes, this is an alternate possibility.

CAPTAIN THALMANN: You concluded that the counterdiffusion mechanism showed that gas nucleated at 30 atmospheres. Have you established that there are preexisting gas nuclei using counterdiffusion?

DR. LAMBERTSEN: It's pure and simple conjecture, just like any talk about gas nuclei. This may show that even 38 atmospheres does not remove gas nuclei, or that they regenerate.

CAPTAIN THALMANN: In the dive where counterdiffusion occurred, you never had the opportunity to try to compress the divers to see if the problems would go away?

DR. LAMBERTSEN: No, we did not. We had the opportunity, but didn't take it.

DR. VANN: Let me pursue the question of the mechanism of bubble formation. Are we dealing with gas nuclei, or perhaps heterogeneous de novo nucleation. Normally, we think that de novo nucleation does not occur unless you are up around 200 or 300 atmospheres, but Dr. Gerth has found evidence that depending on available structures (he used crystal) nucleation occurred at 2 atm instead of 120 atmospheres. Perhaps something of this nature is going on within the layers of tissue. A test of this hypothesis might compress a dead animal hydrostatically to 1000 ATA and then do the experiment and see if you get a lesser cutaneous counterdiffusion, as opposed to a control animal which would be uncompressed, and maybe that would answer that question.

DR. LAMBERTSEN: Don't take too seriously my statements about demonstrating the preexistence of gas nuclei. I think it's quite obvious that gas emboli have formed. To distinguish different mechanisms of arriving at that state is way beyond this kind of experiment. It's probably not practical in mammals if you're going to have to compress to very high pressures. Those of you who are expert in gas nucleation won't miss the fact that there were several tissues that did not generate gas bubbles. These were aqueous tissues with essentially no fat. The lens of the eye and the round window generated no bubbles. In a marine animal preparation that can stand high pressures, you may find, as we did with the frog's web, that bubbles do not form.

DR. FRANCIS: Have you ever seen superficial or deep tissue counter-diffusion of the spinal cord?

DR. LAMBERTSEN: No.

DR. FRANCIS: Have you ever found arterial bubbles?

DR. LAMBERTSEN: Yes, at death, the arterial tree, particularly the retinal structure did have gas bubbles in it. This led us to think, as Dr. James was saying, that we probably had passage of very small bubbles across the lung into the systemic circulation which became obvious only after they had time to grow.

DR. FRANCIS: As this is a potential mechanism for spinal cord involvement, it would be interesting to see if you ever saw any pathology.

MR. IMBERT: Dr. Lambertsen, tig welding, which uses argon, is becoming a general process throughout the North Sea. Welders are exposed in a shallow water habitat for 6-8 hours breathing up to 1 bar of argon. Can you tell us if this is safe and what would be the effect of transferring a diver from a habitat containing argon at 360 meters to a helium-oxygen environment? Would symptoms of counterdiffusion occur?

DR. LAMBERTSEN: Isn't argon from tig welding rather impure?

DR. IMBERT: Let's say you've got 1 bar of argon in a habitat and the rest of it is heliox and then you transfer the diver back to a chamber where it's pure heliox.

DR. LAMBERTSEN: I doubt that there's any way to tell from past work what the end result would be, but animal experiments at several atmospheres beyond what you want to work at might give you the answer. We used 3 or 4 atmospheres of argon at very high pressure and found skin lesions did occur in animals.

MR. IMBERT: Would you expect the same symptoms at shallow depths as at deeper depths?

DR. LAMBERTSEN: I think the process becomes worse with greater depths and with greater partial pressures of the respired inert gas. It's less if you have a lot of oxygen present.

DR. DANIELS: There's no real problem for gas nuclei believers in the occurrence of counterdiffusion bubbles at 38 bar since there must be a range of nuclei sizes which show differential susceptibility to pressure. I would expect that bubbles would appear somewhat later at 38 bar than they do at 1 bar.

DR. LAMBERTSEN: It took about 45 minutes or so for the process to begin in humans at 300 and 400 feet and about an hour or so with animals. It took about 45 minutes at 1200 feet for skin itching, which was the first detectable sign.

DR. DANIELS: Once the transition from a nucleus to a bubble has occurred, however, the bubbles grow to a similar size very quickly. Just observing the end result caused by the macroscopic bubble is not sufficient to reveal differences in time. It is necessary to look at a much finer level to determine the point at which the nucleus becomes a bubble and how long it takes to get there.

DR. LAMBERTSEN: I think that's a fine idea and I think you should do that.

DR. YOUNGBLOOD: Dr. Lambertsen, as the High Priest of Oxygen Breathing, can you tell me if oxygen is totally innocuous insofar as counterdiffusion is concerned?

For example, we often store divers at low oxygen partial pressures and then lock out on as high an oxygen partial pressure as can be tolerated for the time. The hemoglobin is totally saturated, however, and there is

usually enough dissolved oxygen to handle the body's needs. Could oxygen create a brief counterdiffusion problem, perhaps at the alveolar capillary membrane? Might this be the cause of the transient pain which sometimes occurs at the onset of oxygen breathing during treatment of decompression sickness? While we often interpret this as bony pain, perhaps it represents the diffusion of oxygen into an periosteal or ligamentous microbubble.

DR. LAMBERTSEN: You're asking whether oxygen might behave temporarily as an inert gas. I haven't any more to offer there than you have, but if I had to choose which gas would be safest, I would choose oxygen because it will disappear, and the other gases will not.

DR. ZWINGELBERG: You've certainly shown that substantial volumes of helium enter the body as a result of transcutaneous diffusion. During the development of helium-oxygen decompression tables for bounce diving, we often have divers breathing helium in a dry air environment. Should we worry about counterdiffusion in this situation?

DR. LAMBERTSEN: In our pigs, which were counterdiffused by breathing nitrous oxide while surrounded by helium, the venous bubble trap collected gas at a rate of approximately 480 cc per hour per square meter, but your divers were surrounded by air rather than helium. This isn't a problem.

DR. PETERSON: Dr. Lambertsen, you mentioned that bubbles produced by counterdiffusion behaved differently with respect to effects on the pulmonary circulatory endothelium than did injected gas. Would you expect that there would be differences between an injected gas DCS model and a counterdiffusion model? Might the counterdiffusion model be better?

DR. LAMBERTSEN: There are three different ways in which to study the effects of gas emboli on the pathophysiology of decompression sickness. The first, is by injecting air bubbles, the second is by the counterdiffusion process, and the third is by decompressing animals. These processes are entirely different. There's no way in which you can pin down whether the isobaric approach is a better way than gas infusion, but gas infusion into an unsaturated animal is different from bubbles generation by decompression in an animal that's been exposed to high pressure.

Effect of Different Gases on Decompression Sickness

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Abstract

Molecules of oxygen, carbon dioxide, water, and one or more inert gases are dissolved in the diver's tissues by the time of decompression. For gases to have different effects in causing DCS by gas bubbles, some differences must be evident in gas uptake kinetics, rate of bubble nucleation, or rate of bubble growth. These phenomena theoretically depend on different combinations of gas solubility and diffusion coefficient. In experimental animals, helium is faster but less potent than nitrogen or argon; while in humans the ranking is unproven. Carbon dioxide is ubiquitous but apparently unimportant. Oxygen can add to DCS risk in animals but not in man at levels which avoid oxygen toxicity.

Introduction

In every hyperbaric exposure, there will be finite tissue partial pressures of oxygen, carbon dioxide, water vapor, and whatever inert gases the diver has breathed over the previous several hours. How they might contribute singly and in combination to an overall risk of decompression sickness (DCS) is the subject of this paper. I do not intend to present an encyclopedic review, as most papers on the subject do not contain statistically significant results. Instead I will review some theoretical possibilities, even at the risk of duplicating other presentations in this Workshop, and I will discuss a few of the experimental studies that seem most important.

The origin of any differences among gases must lie with different chemical properties of the candidate gases. The major properties are listed in Table 1. The entries in Table 1 are different from many such tabulations in the references listed below. I have attempted to list realistic parameters for actual biological tissues rather than the more commonly used parameters for water and olive oil. (I am told that bulk water and olive oil are difficult to find in a diver's body.) Several features are worth noting in the table. First, solubility in blood and tissue are similar for all the inert gases used in diving. For substantially different properties, more "exotic" gases such as N_2O and SF_6 are necessary. Note also the common approximation of diffusion coefficient decreasing as the square root of the molecular weight is not useful, since in many cases a heavier gas has a faster diffusivity.

Table 1
Chemical Properties of Gases in Tissue

Gas	M.W.	Solubility Blood	Solubility Tissue	Partition T / B	Diffusion	Permeability Ratio
H_2	2	.017	.018	1.1	3.6	3.2
He	4	.010	.012	1.2	5.4	3.2
Ne	20	.010	.016	1.6	2.2	1.7
N_2	28	.014	.012	0.9	1.7	1.00
Ar	40	.030	.024	0.8	1.0	1.2
N_2O	44	.46	.35	0.8	1.9	33.
SF_6	146	.009	.014	1.6	0.2	.2
O_2	32	-	.024	-	1.9	2.2
CO_2	44	-	.6	-	1.4	41.

Notes:
1. Solubility is expressed as Ostwald coefficient (ml of gas/ml of tissue per ATA at 37°C) with tissue chosen as skeletal muscle when possible (1).
2. Partition coefficient is ratio of tissue to blood solubility.
3. Diffusion coefficient is expressed as 10^{-5} cm^2/sec with values measured in water at 37°C (2,3) or temperature corrected if necessary (4) and multiplied by 0.55 as an average for muscle/water ratio (5).
4. Permeability ratio is the product of tissue solubility and diffusion coefficient normalized by the value for nitrogen.
5. Precision of solubility is estimated about to be about 20%, that of diffusion coefficients no better than 50%.

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Theoretical Considerations

With the standard presumption that excess gas accumulation into in-vivo bubbles is the proximate cause of DCS, we must step through the mechanisms by which different gases can affect DCS outcome. These can be via differences in gas uptake or elimination kinetics, by differences in the ability to initially form bubbles, by differences in bubble growth or shrinkage rates, or by differences in biochemical reactions mediated by the bubble surface.

Gas kinetics

Gas kinetics is an area of active investigation, as explained else-where in the Workshop by Homer. To a first approximation, gas loads into tissue with a (mean) speed proportional to blood flow divided by the tissue/blood partition coefficient of Table 1. Note that there is not even a factor of 2 difference in T/B partition among the gases listed, and that helium would be predicted to enter muscle slower than nitrogen. A different prediction could be possible, of course, for the as yet unknown anatomical tissues responsible for clinical DCS. A modifying

effect of gas diffusion coefficient is also present, but with our present knowledge, even the direction of this effect cannot be established with certainty. As shown in the presentation by Homer, any predictions based on either well mixed tissues or on single capillary models should be discarded.

Differences among gases are likely to be small enough that useful direct experiments would need to simultaneously study the kinetics of 2 or more gases in the same individual animal. The few reported exchange studies with simultaneous inert gases confirm that partition coefficient is important (6,7) but a clear effect of diffusion has not been measured.

Bubble nucleation

Once dissolved gas is in tissue, how can the different gases can affect bubble behaviour? First the bubble must form. (Theories concerned with pre-existing gas bubbles are outside the scope of this review and further more tend not to directly predict differences among gases.) Classical nucleation theory predicts only a marginal effect of gas species on nucleation in water (8). As shown by Hemmingsen and coworkers at this Workshop, bubble nucleation in pure water does not respect classical theory, and shows a strong dependence on gas species. Specifically helium bubble formation requires a much greater supersaturated partial pressure than do neon or nitrogen, and argon requires even less (9). A recently developed theory, consistent with these findings, relates gas nucleation potential in water to critical constants of the gas and focuses on the entropy required to form a 300 A diameter cluster of molecules within the water (10).

Bubble growth

With an existing bubble of any size or composition, subsequent growth or shrinkage depends on several gas properties in a complex manner. The general theoretical treatment of bubble growth is a severely nonlinear set of differential equations that requires many simplifying assumptions before a prediction is possible (11). In biological applications, the appropriate initial and boundary conditions are even more tenuous since the ultimate source and sink for gas molecules are blood vessels that are located at specific but generally unknown distance away. A general point for present purposes is that all gases in the tissue will be subject to the gas transport equations independently. Because dissolved gases in tissues are dilute in a chemical sense, all will diffuse without knowledge of any other gases present. For example, helium molecules saturated in tissues at 10 ATA will be surrounded by over 10,000 other molecules. The bubble itself will be made up of all the gas molecules that arrive at the bubble surface, and so will contain oxygen, carbon dioxide, water, and one or more inert gases.

For very short term events, the distant boundary conditions are not important and appropriate theoretical simplifications are available (12).

These general solutions predict that initial bubble growth rates from a supersaturated liquid increase with dissolved gas diffusion coefficient. By consulting Table 1, we would predict initial growth to be more rapid with hydrogen or helium than with nitrogen or argon. Over intermediate time scales both diffusion and solubility play a role. Under conditions that can be modeled as a steady state flux, such as the treatment by Van Liew elsewhere at this Workshop (13,14) the product of solubility and diffusion coefficient, the permeability, controls the growth rate. Normal diving gases are seen in Table 1 to have similar permeabilities so in this phase of growth helium would arrive at the growing bubble slightly faster than nitrogen. Note from Table 1 that carbon dioxide has a high permeability so it will accumulate even faster in this growth phase than the inert gases. The high permeability for N_2O may explain its ability to increase DCS risk, even when breathed after decompression by an animal(15).

Eventually the partial pressure gradients will dissipate and the bubble will approach an equilibrium composition. Chemical equilibrium will actually never happen because the inspired gas will probably change and because surface tension on the bubble will always provide a driving force for bubble shrinkage and disappearance. In a near equilibrium bubble, size will depend on the equilibrium property of gas solubility, with two conflicting effects. First the more soluble gas will have accumulated a larger number of molecules within the tissue, and thus available for bubble entry. However, the more soluble gas will have a greater tendency to keep its molecules in solution. From an examination of Table 1, we can see that that the first factor will dominate. With solubilities like 0.02 vs. 0.01 the more soluble gas will have twice the available molecules. Since both gases in this example have low solubility, nearly all of the available molecules of each gas will enter the bubble. Thus at this stage, the common diving gases will behave similarly but N_2O will be especially potent. The high solubility of carbon dioxide will allow CO_2 to be present in all bubbles, but its low and constant partial pressure of about 0.06 ATA will keep it a minority constituent, at least under hyperbaric conditions of several ATA of inert gas. No direct studies of gas differences in small tissue bubble kinetics are available because of the extreme difficulty in performing the necessary in-vivo experiment.

Surface biochemistry

Gas compositional differences in bubble induced pathology would be expected to be small, since the surface tension, the physical mediator of interfacial reactions, is only weakly dependent on gas composition. More important effects of the gases would be through their pharmacological effects away from the bubble, such as the action of SF_6 on pulmonary edema formation (16).

Small Animal Studies

In small non-mammalian species, Hemmingsen and colleagues have shown that visible bubble formation occurs in the same order as in water: argon is easiest to bubble, followed by nitrogen, with helium being most resistant (17,18). Appearance of decompression symptoms in fish were reported to show the same apparent ranking (19) but actually only argon was different from the other gases in ease of bubble formation (20). Qualitative studies of visible bubbles in several organs of guinea pigs also showed the same ranking (21).

The most informative animal studies with decompression sickness as an endpoint have been performed in mice and rats. Potency is defined as the partial pressure of a gas required to produce a given incidence of DCS. Several of these have been conducted in a way to achieve statistical significance. The earliest quantitative studies in mice showed a similar potency of nitrogen and helium after saturation exposures (22, 23, 24). Helium appeared to achieve its effect somewhat faster than nitrogen (22, 23) and there seemed a possibility of a specific advantage from an intermediate mixture. Also nitrous oxide appeared to be an even more potent gas for causing DCS (24), even when breathed after decompression (15).

The most thorough animal studies are those of Lillo (25). He used sufficiently large numbers of rats, controlled for intraspecies differences due to animal size and applied maximum likelihood with probabilistic models to extract the most quantitative information from his data. Saturation exposures established that helium is less potent than nitrogen by $9\pm2\%$, and that argon is $35\pm5\%$ more potent. He further found that He and N_2 combine linearly in adding DCS risk, but that mixtures of Ar with either of the two gases were closer to pure argon in potency than their fraction would indicate. Despite using over 1400 rats, there was no significant evidence of a mixture of 2 inert gases that was any safer than the safer component. More recent work by Lillo (26) has replicated the differential potency of He and N_2 and shown a 3-4 fold faster kinetics for helium.

Animal experiments on CO_2 effects were well reviewed by Berghage (27). With very high inspired CO_2 (like 60%!), frogs appeared more susceptible to visible bubble formation (28). Mice were slightly more prone to altitude DCS with higher inspired CO_2 (29). Berghage's own studies showed an increased DCS in mice up to about 0.01 ATA CO_2, but a decrease in rats for CO_2 up to 0.03 ATA CO_2. Thus the evidence is weak, conflicting and probably species dependent.

Animal experiments with O_2 are more numerous. Direct demonstration of DCS from pure O_2 exposures are confounded by oxygen toxicity. Thus oxygen potency is shown by an increased DCS incidence from exposures with a PN_2 of established potency and variably higher oxygen. Donald performed such a positive demonstration using 3.5 ATA of O_2 in goats

(30). There was a higher DCS incidence with that oxygen plus 2.0 ATA N_2 than with the same PO_2 and lower N_2, or with a lower O_2 and the full 2.0 ATA N_2. In later animal work oxygen was estimated to be 20-30% as potent as nitrogen for producing DCS (31). In 2 studies with rats, Berghage showed a finite but confusing oxygen potency with 2 ATA O_2 or more (32, 33). Berghage's studies were more internally consistent when reasonable treatments of oxyhemoglobin binding and carbon dioxide solubility were applied by Yount (34). Lillo's recent rat study produced an estimated oxygen potency at 88+7% (serious symptoms) and 38+4% (fatal DCS) compared to that of nitrogen (26). The animal studies thus show a convincing ability to produce "oxygen bends", at least when PO_2's of 2 or more ATA are used.

Human Experiments

As in many other areas of biology, we know less about men than about mice. In the decompression literature on humans there appears to be an irresistible urge to pretend knowledge based on a few DCS cases or a few dozen uneventful exposures.

For the inert gases, Behnke and Willamon estimated that helium is overall about half as soluble but somewhat faster than nitrogen in whole body uptake (35). After 12 hr exposures, Duffner found helium to be less potent than nitrogen in sudden decompression, though the experiments were not fully conclusive (36). Hempleman presented some preliminary data for helium as safer in short human dives (67), but the work was not carried to its conclusion.

Regarding CO_2, some World War II aviation work exposed 2 groups of 204 men to low or 0.12 ATA CO_2 before altitude decompression. No significant effect was reported in this largest reported study (38). A paper purporting to show human data on the subject actually is only a report of different DCS incidence following a major procedural change in otherwise uncontrolled tunnel work (39). In a recent series too small to detect changes in the incidence of DCS, Bell found that 2% CO_2 did seem to lower average Doppler scores (40).

Oxygen is clearly less potent than nitrogen in altitude exposures where oxygen breathing before and during the decompression is now routine. Oxygen has recently been put to a human test of 477 controlled dives with half near normoxic (.21 - .38 ATA O_2) and half at the highest O_2 allowed by O_2 toxicity concerns (1.0-1.5 ATA O_2, depending on exposure time) (41, 42). The study was designed to be sequential in exposure depth depending on the recent safety history of the trial. Overall analysis with maximum likelihood methods produced a best estimate of O_2 influence as zero, both for confirmed and marginal cases of DCS. The bends rate was low enough that the upper statistical uncertainty limit was an oxygen potency 40% as high as N_2. That is, at the outside an additional 1 ATA of inspired O_2 would contribute to DCS risk equivalent to an additional 0.4 ATA N_2.

Concluding Remarks

Overall, how much quantitative information can be applied to the calculation of human decompression procedures? The answer is almost none. Relative potencies of helium, argon, and nitrogen are well established in small animals and could be applied with some risk of interspecies differences. Direct application of animal rate data would be thwarted by inter-animal differences in circulation rates and by the likely differences in target organs implied by the differences in symptoms between animal and human DCS. Only for the potency of oxygen do we have direct quantitative human data. For now, decompression procedures that require gas choices will continue to be based on conjecture rather than understanding.

References

1. Weathersby PK, Homer LD. Solubility of inert gases in biological fluids and tissues. Undersea Biomed Res 1980; 7:277-296.

2. Verhallen PTH, Oomen LJP, Elsen AJJMvd, Kruger AJ. The diffusion coefficients of helium, hydrogen, oxygen, and nitrogen in water as determined from the permeability of a stagnant liquid layer in the quasi-steady state. Chem Eng Sci 1984; 39:1535-1541.

3. Himmelblau DM. Diffusion of gases in liquids. Chem Rev 1964; 64:527-550.

4. Reid RC, Prausnitz JM, Sherwood TK. The properties of gases and liquids. New York: McGraw-Hill, 3rd ed. 1977.

5. Kawashiro T, Campos Carles C, Perry SF, Piiper J. Diffusivity of various inert gases in rat skeletal muscle. Pflugers Arch 1975; 359:219-230.

6. Ohta Y, Fahri LE. Cerebral gas exchange: perfusion and diffusion limitations. J Appl Physiol: 1979; 46:1164-1168.

7. Rackow H, Salanitre E, Epstein RM, Wolf GL, Perl W. Simultaneous uptake of N_2O and cyclopropane in man as a test of compartment model. J Appl Physiol 1965; 20:621-627.

8. Weathersby PK, Homer LD, Flynn ET. Homogeneous nucleation of gas bubbles in vivo. J Appl Physiol 1982; 53:940-946.

9. Gerth WA, Hemmingsen EA. Gas supersaturation thresholds for spontaneous cavitation in water with gas equilibration pressures up to 570 ATM. Z Naturforsch 1976; 31A:1711-1716.

10. Finklestein Y, Tamir A. Formation of gas bubbles in supersaturated solutions of gases in water. Amer Inst Chem Eng J 1985; 31:1409-1419.

11. Scriven LE. On the dynamics of phase growth. Chem Eng Sci 1959; 10:1-13.

12. Subramanian RS, Weinberg MC. Asymtotic expansions for the description of gas bubble dissolution and growth. Am Inst Chem Eng J 1981; 27:739-748.

13. Hlastala M, Van Liew HD. Absorption of In Vivo inert gas bubbles. Respirat Physiol 1975; 24:147-158.

14. Van Liew HD, Hlastala MP. Influence of bubble size and blood perfusion on absorption of gas bubbles in tissue. Respirat Physiol 1969; 7:111-121.

15. Van Liew HD. Dissolved gas washout and bubble absorption in routine decompression. In: Lambertson CJ, ed. Underwater Physiology IV. Proceedings of the Fourth Symposium on Underwater Physiology. New York: Academic Press, 1971: 145-150.

16. Daniels S, Paton WDM, Smith EB. Use of exotic gases for the study of decompression sickness. In: Lambertsen CJ, ed. Underwater physiology IV. Proceedings of the Fourth Symposium on Underwater Physiology. New York: Academic Press, 1971:475-484.

17. McDonough PM, Hemmingsen EA. Bubble formation in crustaceans following decompression from hyperbaric gas exposures. J Appl Physiol 1984; 56:513-516.

18. Hemmingsen EA, Hemmingsen BB. Lack of intracellular bubble formation in microorganisms at very high gas supersaturations. J Appl Physiol 1979; 47:1270-1277.

19. D'Aoust BG, Stayton L, Smith LS. Separation of basic parameters of decompression using fingerling salmon. Undersea Biomed Res 1980; 7:199-209.

20. Yount DE. Application of a bubble formation model to decompression in fingerling salmon. Undersea Biomed Res 1981; 8:199-208.

21. Gersh I, Hawkinson GE, Jenney EH. Comparison of vascular and extravascular bubbles following decompression from high pressure atmospheres of oxygen, helium-oxygen, argon-oxygen, and air. Bethesda MD: Naval Med. Res. Inst. Rep. 5, Res Proj X-284, 8 Nov 1944.

22. Flynn ET, Lambertson CJ. Calibration of inert gas exchange in the mouse. In: Lambertsen CJ, ed. Underwater physiology IV. Proceedings of the Fourth Symposium on Underwater Physiology. New York: Academic Press, 1971:179-191.

23. Berghage TE, Donelson C, Gomez JA. Decompression advantage of trimix. Undersea Biomed Res 1978; 5:233-242.

24. Lever MJ, Paton WDM, Smith EB. Decompression characteristics of inert gases. In: Lambertsen CJ, ed. Underwater physiology IV. Proceedings of the fourth symposium on underwater physiology. New York: Academic Press, 1971:123-136.

25. Lillo RS, Flynn ET, Homer LD. Decompression outcome following saturation dives with multiple inert gases in rats. J Appl Physiol 1985; 59:1503-1514.

26. Lillo RS. Effect of N_2-He-O_2 mixtures on decompression outcome in rats following variable time-at-depth dives. J. Appl. Physiol 1988; In press.

27. Berghage TE, Keating LJ, Woolley JM. Decompression sickness in rats and mice rapidly decompressed after breathing various concentrations of carbon dioxide. In: Lambertsen CJ, ed. Underwater Physiology IV. Proceedings of the Fourth Symposium on Underwater Physiology. New York: Academic Press, 1971:485-496.

28. Harris M, Berg WE, Whitaker DM, Twitty VC, Blinks LR. Carbon dioxide as a facilitating agent in the initiation and growth of bubbles in animals decompressed to simulated altitudes. J Gen Physiol 1945; 28:225-240.

29. Gowdey CW, Philp RB. Etiology and treatment of experimental decompression sickness with special reference to body lipids. Military Med 1965; 130: 648-652.

30. Donald KW. Oxygen Bends. J Appl Physiol 1955; 7:639-644.

31. Rashbass C, Eaton WJ. The effect of oxygen concentration on the occurrence of decompression sickness. Alverstoke UK: Royal Navy Physiol. Lab. Rep. 10/57, July 1957.

32. Berghage TE, McCracken TM. Use of oxygen for optimizing decompression. Undersea Biomed Res 1979; 6:231-239.

33. Berghage, TE, McCracken TM. Equivalent air depth: fact or fiction. Undersea Biomed Res 1979; 6:379-384.

34. Yount DE, Lally DA. On the use of oxygen to facilitate decompression. Aviat Space Environ Med 1980; 51:544-550.

35. Behnke, AR, Willamon TL. Gaseous nitrogen and helium elimination from the body during rest and exercise. Amer J Physiol 1941; 131:633-638.

36. Duffner GJ, Snider HH. Effects of exposing men to compressed air and helium-oxygen mixtures for 12 hours at pressures of 2-2.6 atmospheres. Washington DC: Navy Exp. Div. Unit Rep. 1-59, 18 Sept 1958.

37. Hempleman HV. Decompression procedures for deep open sea operations. In: C.J. Lambertsen, ed. Underwater Physiology III. Proceedings of the Third Symposium on Underwater Physiology. Baltimore MD: Williams and Wilkins, 1967: 255-266.

38. Gray JS. Present Status of Decompression sickness. Randolf Field Tx: USAAF SAM Rev 1, 3 Oct 1944. Cited in Cook SF "Role of exercise, temperature, drugs and water balance in decompression sickness" in Decompression Sickness, R.F. Fulton, ed. Philadelphia: Saunders, 1951

39. Mano Y, D'Arrigo JS. Relationship between CO_2 levels and decompression sickness: applications for disease prevention. Aviat Space Environ Med 1978; 49:349-355.

40. Bell PY, Harrison JR, Page K, Summerfield M. An effect of CO_2 on the maximum safe direct decompression to 1 bar from oxygen-nitrogen saturation. Undersea Biomed Res 1986; 13:443-455.

41. Weathersby PK, Hart BL, Flynn ET, Walker WF. Human decompression trial in nitrogen-oxygen diving. Bethesda, Md: Naval Med. Res. Inst. Rep. NMRI 86-97, 1986.

42. Weathersby PK, Hart BL, Flynn ET, Walker WF. The role of oxygen in the production of human decompression sickness. J Appl Physiol 1987; 63:2380-2387.

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DISCUSSION

DR. IMBERT: I want to comment about the hydrogen diving experience in France. There are two ways to conduct decompression from hydrogen diving. One is an isobaric switch to heliox followed by standard decompression. The other is hydrogen decompression followed by helium decompression. These methods were used in hydrogen bounce dives in Sweden and in the U.S. by Peter Edell. Saturation diving, however, provides the simplest model to assess the decompression characteristics of hydrogen compared to helium or nitrogen. We have saturated 14 subjects with hydrogen. Professor Masurel studied these subjects with Doppler for intravascular bubbles. We compressed with helium-oxygen and then switched to hydrogen-oxygen after reaching the saturation depth. In one dive we switched back to helium. Bubble formation due to counterdiffusion occurred in two of three subjects and required recompression. Subsequent decompression took place at half the standard heliox rate of 45 minutes/meter. There were no bends. In another dive, we started decompression by selectively removing hydrogen by catalytic burning. To choose the decompression rate, we guessed that the solubility of hydrogen was 50% greater than helium and started with a decompression rate of 70 minutes/meter. By using Doppler monitoring for intravascular bubbles, we found this rate could be increased to 55 minutes/meter. When all the hydrogen was gone, we finished the decompression at the standard helium rate. For comparison, the decompression rate from a nitrous dive is 120 minutes/meter. If we consider the relative solubilities, a linear ascent at 50 minutes/meter eliminates approximately 2.2 millimole/hour of helium. Nitrogen elimination during the Nereide decompression also was approximately 2.2 millimole/hour. Because hydrogen has a larger solubility than helium, but both gases have similar ascent rates, we estimate that the helium estimation rate was about 2.7 millimole/hour.

DR. VAN LIEW: Dr. Weathersby, your solubility and diffusivity tables were for aqueous tissue. Would you comment on these values in fatty tissue?

DR. WEATHERSBY: Several years ago, I tried to do a complete tabulation of all English-language literature reports on solubility in any biological fluid or tissue. There were a number of tissues that we couldn't find answers for. In almost no case were the measurements in real tissues anything close to measurements in olive oil. In the rare cases where fatty tissues from animals were studied, the solubilities were closer to water than to oil.

DR. LAMBERTSEN: I would like to remind everyone that oxygen and carbon dioxide, which appeared in Dr. Weathersby's table on gas properties, are not equivalent to inert gases and have specific physiological effects that may well influence decompression. Hyperbaric oxygen interferes with CO_2 transport and elevates tissue CO_2 without effecting arterial CO_2. This can be equivalent to inspiring almost 7% CO_2 and can influence both autonomic and sympathetic nervous system function.

DR. MASUREL: We exposed many 70-kg pigs for 6 hours at 3.05 ATA with inspired CO_2 levels of 50 and 70 millibars. We observed no differences between these exposures.

DR. WEATHERSBY: I certainly didn't want to deny any direct biological effect of oxygen and carbon dioxide. In fact, this was part of our justification for setting up a large human trial on the effect of oxygen itself.

DR. VAN LIEW: Dr. Weathersby, when I put a sulfur hexafluoride bubble into a nitrogen-breathing rat, the bubble got bigger because the nitrogen diffused in faster than the SF-6 diffused out. This was the result of bubble-tissue inert gas exchange rather than pulmonary inert gas exchange. Dr. Lambertsen's talk has made me think about effects that gas switching might have on bubble formation and growth. Would you care to comment on the effects?

DR. WEATHERSBY: When people ask me about gas switches and say that they know a switch in one direction is safe, I point out that I'm not aware of any evidence to prove that the switch in the other direction would be unsafe. My jaundiced view of the field is that there is not a whole lot of quantitative data available to convince us what gas switches might be done glibly. I also share your concern that we may be getting in over our head in this case.

DR. VAN LIEW: If a gas switch in one direction is safe, wouldn't that be evidence that a switch in the other direction would be unsafe? It's a matter of the speed with which the gas moves in or out of either the bubble or the tissue which could lead to supersaturation.

DR. WEATHERSBY: Right, and the complex effects of diffusion in tissue gas exchange, as indicated by recent computer simulations, suggest that gas switches in either direction will influence inert gas exchange at the tissue level.

DR. IMBERT: Dr. Masurel detected bubbles with Doppler after switching from hydrogen to helium, and itching was observed, which is another characteristic of counterdiffusion. HPNS also occurred following the gas switch.

EXERCISE AND DECOMPRESSION SICKNESS

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ABSTRACT

Exercise influences both inert gas exchange and bubble formation. The effect of exercise on the risk of decompression sickness (DCS) is determined by the exercise severity and by where in a pressure exposure it occurs. At depth during diving, exercise increases DCS risk by accelerating inert gas absorption. During oxygen breathing at sea level, exercise accelerates inert gas elimination which reduces DCS risk during subsequent altitude exposure. Light exercise during decompression after diving accelerates inert gas elimination and reduces DCS risk if bubble formation has not been extensive. After decompression to altitude or following diving, however, exercise promotes bubble formation which interferes with inert gas elimination and increases DCS risk. Weight training before diving or altitude exposure appears to increase both bubble formation and DCS risk.

Nitrogen Absorption During Diving

Exercise influences the risk of decompression sickness (DCS) through its effects on inert gas exchange and on bubble formation. A diver who exercises at depth should absorb more inert gas than a diver who rests because exercise increases muscle perfusion. To test this hypothesis, we measured respiratory nitrogen elimination at sea level from divers who had just surfaced from no-decompression dives during which they had either rested or exercised (1). The divers breathed from a closed-circuit apparatus which controlled the oxygen to 21%, removed carbon dioxide, and maintained the inspired gas at ambient temperature. With a spirometer for a counterlung, a diver's nitrogen elimination was determined once a minute from the spirometer volume while he held his breath at functional residual capacity.

Figure 1 shows nitrogen elimination curves after 5 dives to 60 feet for 60 minutes. In the first hour after 3 resting dives, the diver eliminated a mean nitrogen volume of 565 ml. With exercise for the first 25 minutes during 2 dives, elimination rose 20% to 680 ml.

After 6 resting dives to 100 fsw for 25 min (Fig. 2), mean nitrogen elimination at one hour was 520 ml. With moderate exercise for the first 15 minutes of 5 dives, nitrogen elimination rose 60% to 830 ml.

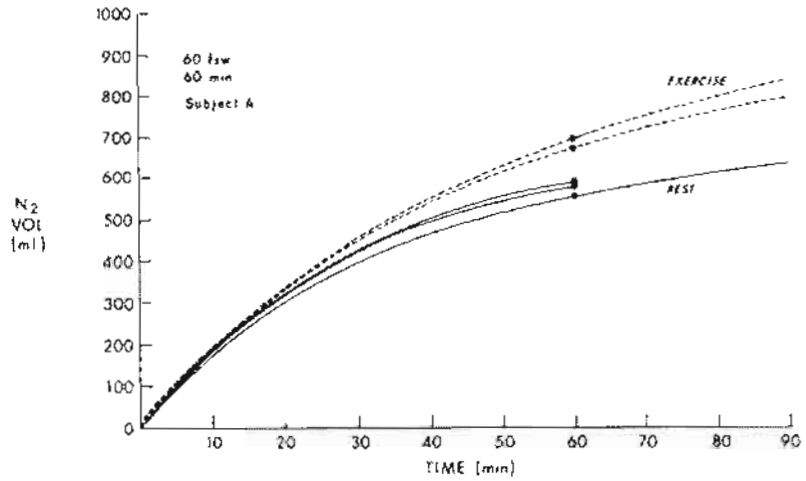


Figure 1. Respiratory nitrogen elimination from a resting diver after resting and exercising dives to 60 fsw for 60 min (1).

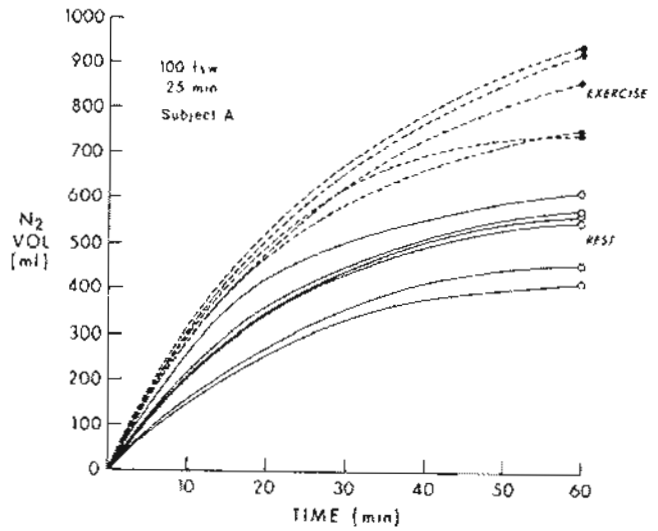


Figure 2. Respiratory nitrogen elimination from a resting diver after resting and exercising dives to 100 fsw for 25 min (1).

Following 3 resting dives to 130 feet for 10 minutes (Fig. 3), nitrogen elimination at 1 hour was 440 ml. With 5 minutes of exercise in 4 dives, mean elimination rose 64% to 720 ml. The difference in one hour nitrogen elimination between resting and working dives was statistically significant at $p<0.02$ for all 3 depths.

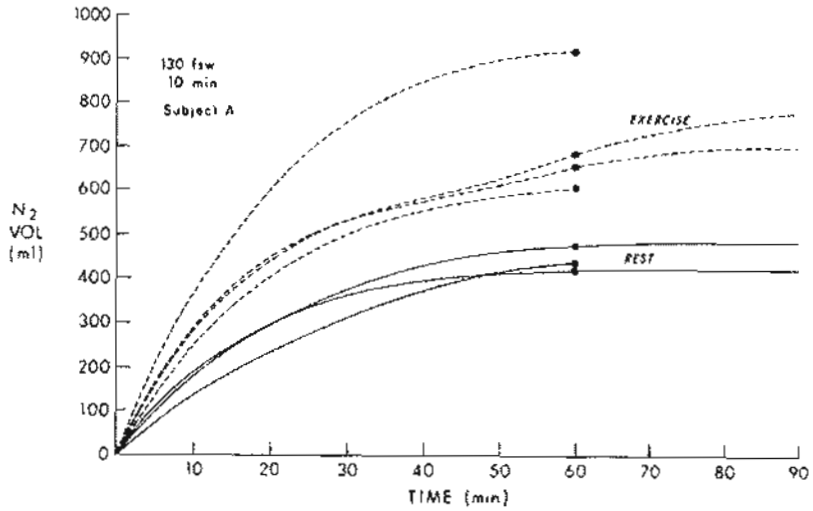


Figure 3. Respiratory nitrogen elimination from a resting diver after resting and exercising dives to 130 fsw for 10 min (1).

Because exercise elevates skeletal muscle perfusion, muscle was the most probable source of increased nitrogen elimination after the exercising dives. Despite this increase, however, and despite bottom times equal to the U.S. Navy no-decompression exposure limits, decompression sickness did not occur. Thus, skeletal muscle would not seem to be a primary site for DCS nor would nitrogen eliminated in one hour seem to be a sensitive index of DCS risk. Indeed, if decompression pain occurs in a small tissue, its contribution to whole-body nitrogen elimination could be masked by the larger volume of nitrogen released from muscle.

DCS Risk and Exercise at Depth

Several studies of decompression diving have observed an increase in DCS risk as a result of exercise at depth. In 1951, Van Der Aue reported that working divers developed 20-30% more decompression sickness than did resting divers after the same air decompression schedules (2). In 1972, Schibli and Buhlmann found that divers working in helium-oxygen needed 20 to 44% more decompression time than divers at rest (3).

We attempted to corroborate these observations with divers who worked for one hour at 100 fsw and rested during decompression (4). Four workloads were studied: rest in a dry chamber at an oxygen consumption of 0.5 lpm, light work swimming on a trapeze in a wetpot at an oxygen consumption of 1 lpm, moderate work at 2 lpm, and heavy work at 3 lpm. Oxygen consumption was measured in real-time as an index of workload using a closed-circuit mixed gas scuba which maintained the oxygen partial pressure at 0.7 ATM. The divers wore wetsuits and the temperature of the wetpot was 20-26°C.

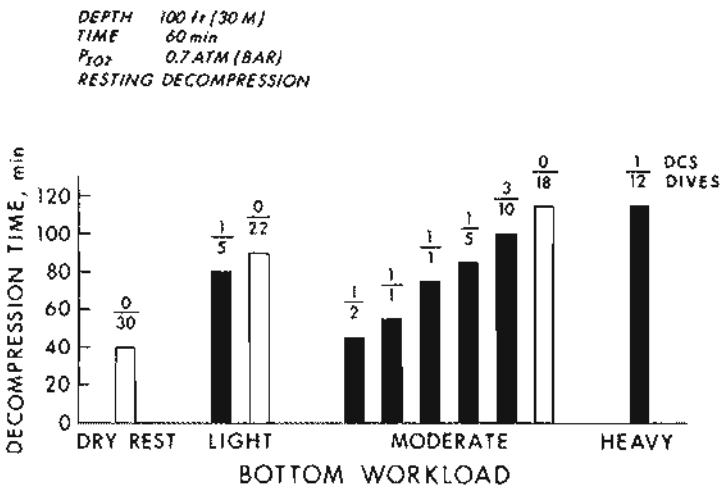


Figure 4. The effect of exercise at depth on decompression time and DCS risk (4).

Figure 4 shows the bottom workload on the horizontal axis and the decompression time on the vertical axis. Each bar represents a different decompression schedule. With the divers dry and at rest, a 40 minute schedule was tested safely in 30 trials. With light work in the water, one DCS incident occurred in 5 trials of an 80 min schedule. With 90 min of decompression, 29 dives were completed without incident. When the divers performed moderate work, there were 6 incidents in 7 schedules. The sixth schedule, 115 min long, was tested 20 times. In 2 tests, the diver did heavy instead of moderate work, and one DCS incident occurred.

Moderate exercise was actually the first workload tested. We did not initially appreciate the effect of exercise at depth, however, as indicated by the frequent DCS which occurred with the short schedules. Dry rest was tested next. Both rest at depth and dry decompression may have contributed to the short decompression time that was required. During the wet dives, nitrogen elimination during decompression was probably reduced by the progressive development of hypothermia. These results demonstrate that decompression schedules should be tested under their expected conditions of use. Should the conditions change, decompression requirements could increase by as much as 300%.

DCS Risk and Exercise Before Altitude Exposure

If exercise accelerates nitrogen absorption and increases DCS risk, might it not also accelerate nitrogen elimination and decrease risk? We tested this hypothesis during a NASA-supported study of altitude decompression. We measured respiratory nitrogen elimination with an open-circuit breathing apparatus from subjects who breathed oxygen for 3.5 hrs at sea level (5). The results are described in these proceedings (6). Oxygen breathing was followed by decompression in 9 min to an altitude of 30,300 feet (4.3 psia) where the subjects exercised for 4 hrs to simulate extravehicular activity in the Shuttle.

During the oxygen breathing period at sea level, the subjects were exposed to one of three conditions. In Condition 1, they were seated at rest. Blood tends to pool in the legs in this position. Condition 2 was supine rest with a 6° head-down tilt. This position is felt to simulate the circulation in microgravity where fluids shift towards the head. Condition 3 was seated exercise. Subjects exercised their arms and legs on an ergometer at a workload equivalent to a 2 mph walk.

Table 1 shows that in 9 trials of seated rest, there were 6 DCS cases for a 66% incidence. In 7 trials of head-down rest, there were 4 DCS cases for a 57% incidence. The mean onset time of symptoms was 70 min after seated rest and 143 min after supine rest. With seated exercise, no symptoms occurred in 10 trials. A chi-square test with correction for small sample size indicated that the difference between seated exercise and seated rest was significant at $p=0.009$. The difference between seated exercise and all resting studies was significant at $p=0.006$.

Table 1. Effects of exercise and body position on DCS risk.

	Seated Rest	Supine Rest	Seated Exercise
DCS	6	4	0
Trials	9	7	10
% DCS	66%	57%	0%
Mean DCS Onset Time	78 min	143 min	--

Table 2 summarizes our data and data from the Johnson Space Center on the effects of oxygen pre-breathe duration (7). With 3.5 hrs of oxygen breathing at rest, DCS incidences of between 30 and 66% were observed. Four hours of resting oxygen reduced the incidence to 21%, and 6 hrs reduced it to 10%. No incidents occurred with 8 hrs of resting oxygen, but this same degree of protection was achieved in 3.5 hrs with exercise.

Table 2. O_2 pre-breathe time before altitude exposure at 30,300 feet (7).

Source	Position	Work	Ascent Time	DCS/ Trials	Oxygen (Hours)	% DCS
Duke	Seated	Rest	9 min	6/9	3.5	66
"	Supine	Rest	9	4/7	3.5	57
JSC	Reclining	Rest	6	4/11	3.5	36
"	"	"	30	7/23	3.5	30
"	"	"	30	9/42	4.0	21
"	"	"	10	4/38	6.0	10
"	"	"	10	0/8	8.0	0
Duke	Seated	Exercise	9	0/10	3.5	0

Most of our subjects were students who engaged in vigorous sport. Four participated in basketball, weight training, or stair climbing which are stressful anaerobic activities that may predispose to bubble formation. These subjects developed DCS in 6 of 7 resting experiments. Two subjects, on the other hand, exercised aerobically by running long distances. These subjects completed 4 resting experiments without DCS or intravascular bubbles. The difference in DCS incidence between the aerobic and anaerobic subjects was significant at p=0.034.

The training effect which accompanies frequent aerobic exercise such as distance running has been shown to raise the basal metabolism (8). This might have accelerated resting nitrogen elimination in the aerobic subjects and may have placed them at a reduced DCS risk. Such an effect was also suggested by nitrogen elimination curves in the study described earlier (1). The diver in Fig. 5 made resting and exercising dives to 130 fsw for 10 min.

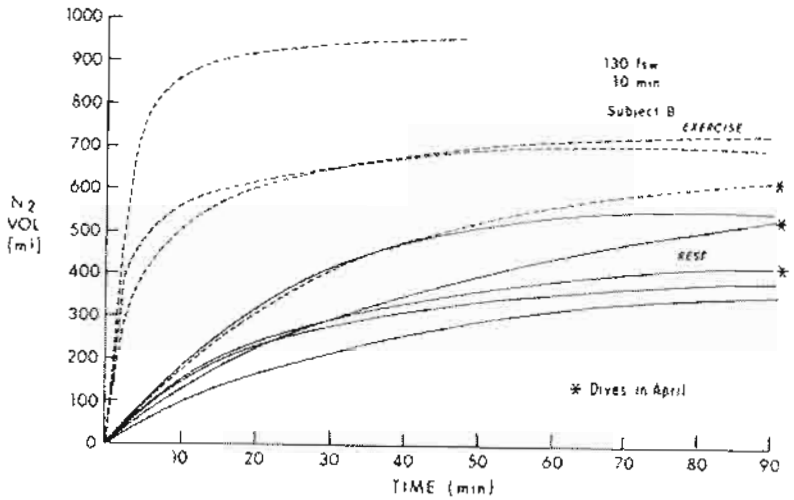


Figure 5. Respiratory nitrogen elimination from a resting diver after resting and exercising dives to 130 fsw for 10 min (1).

His nitrogen elimination after exercising dives was fast during a period when he was running or swimming daily. Four months later, however, he was inactive while studying for exams, and his nitrogen elimination was slow and was associated with itching and post-dive fatigue.

Exercise During and After Decompression

If exercise during oxygen breathing before altitude decompression reduces DCS risk, might not exercise during decompression from diving have a similar effect? Exercise during decompression, moreover, might limit the decreased perfusion which occurs as a result of immersion hypothermia. This possibility was recognized at the beginning of the twentieth century, and both Royal Navy and U.S. Navy divers were directed to exercise during their decompression stops (9,10). The practice was later discouraged, however, when the effects of exercise during and after decompression were confused.

Exercise during decompression was never tested, but in the 1940's, exercise after decompression was found to significantly increase the DCS incidence. After decompression to 38,000 feet of altitude, for example, Gray observed a 32% increase in incidence in subjects who did 5 push-ups and 5 deep-knee bends every 15 min (11). The increased incidence was equivalent to an additional 5,000 feet of decompression.

In diving experiments, Van Der Aue found a 34% increase in DCS incidence in divers who lifted 25 lb weights for 2 hours after no-stop dives to 40, 100, and 150 fsw (12). The confusion concerning the effect of exercise appears to have originated in the title of Van Der Aue's report. While he had tested exercise <u>after</u> decompression, he called his report, "The effect of exercise during decompression...."

To better define this effect, we investigated exercise during decompression from 1 hour dives to 100 and 150 fsw (4). The divers used the closed-circuit scuba described earlier and performed light exercise throughout the dive or rested during decompression. With light exercise during decompression (Table 3), a 60 minute long schedule was tested safely 26 times. With resting decompression, on the other hand, one DCS incident occurred in 5 trials of an 80 min schedule. A 90 minute schedule was tested safely 29 times.

With resting decompression after 1 hour of light exercise at 150 fsw, one DCS incident occurred in a single trial of a 195 minute schedule. The same diver, however, safely completed a 155 minute schedule when he exercised during decompression. In 28 trials of this schedule, there was one incident in a diver of unusually high susceptibility which was demonstrated several weeks later when he developed mild DCS symptoms during commercial air travel.

Table 3. The effects of light exercise during decompression on decompression time after 1 hour dives to 100 and 150 fsw (4). (Breathing gas: 0.7 ATM oxygen in nitrogen).

	Decompression Workload			
	Rest		Light Exercise	
Dive Depth (fsw)	Decompression Time (min)	DCS/ Dives	Decompression Time (min)	DCS/ Dives
100	80	1/5	60	0/26
100	90	0/29	--	--
150	195	1/1	155	1/28

Why should exercise during decompression reduce risk and exercise after decompression increase risk? The objective of decompression is to limit or avoid bubble formation so that inert gas can be eliminated as it was absorbed at depth, in the dissolved state. Exercise either at depth or during decompression, therefore, should accelerate the exchange of dissolved gas. If decompression progresses too far, however, bubbles form and isolate inert gas from the circulation. This decreases the difference between the tissue and arterial blood gas tensions and reduces the rate of inert gas elimination.

Tobias illustrated this effect (Fig. 6) during measurements of krypton elimination from the hand of a subject who had breathed krypton for several hours before decompression to 38,000 feet (13). The rate of krypton elimination was reduced during exercise at altitude where bubble formation occurs. Krypton elimination increased, however, upon recompression to sea level where bubbles resolve.

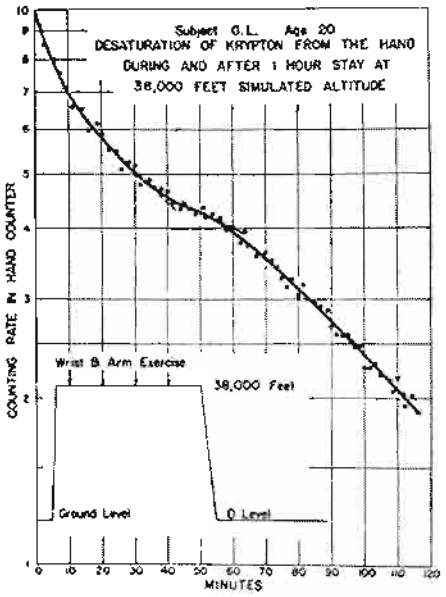


Figure 6

In Vitro Bubble Formation

Exercise affects DCS risk through its influence on bubble formation as well as on inert gas exchange. Bubble formation, or cavitation, occurs when the dissolved gas tension and water vapor pressure exceed the local absolute pressure, a condition known as supersaturation. Gaseous supersaturation, the presence of excess dissolved gas, is often thought of as the sole prerequsite to bubble formation. Bubbles can form in the absence of dissolved gas, however, if the absolute pressure becomes negative.

Hydrostatic compression raises the absolute pressure at the bottom of a standing water column. Hydrostatic tension, on the other hand, reduces the absolute pressure at the top of a hanging water column. The resulting negative pressure causes cavitation and limits the height to which a suction pump can lift water (14). The pressure decrease in water flowing through a constriction in a tube causes Reynolds' cavitation (15). The negative pressure phase of a sound wave causes acoustic cavitation (16). Negative pressure and cavitation develop as a result of viscous tension in lubricants between journals and bearings (17). Negative pressure occurs in the viscous adhesive of Scotch tape when the tape is pulled from a surface (18). This pressure is directly proportional to the liquid viscosity and separation velocity and indirectly proportional to the cube of the distance between the surfaces. Its magnitude can reach hundreds of negative atmospheres or more (19,20), and Hayward called the resulting cavitation tribonucleation (21).

In Vivo Bubble Formation

The available evidence indicates that tribonucleation is a continous source of short-lived, gas-filled bubble nucleation sites in animals and humans. The creation and elimination of these sites are in dynamic equilibrium. If the equilibrium shifts towards creation, bubble formation and DCS risk increase. Fewer bubbles form and the risk decreases, however, if the equilibrium shifts towards elimination.

Let's review the evidence suggesting this hypothesis. McDonough and Hemmingsen showed that bubble formation in marine animals occurred at gaseous supersaturations of 2 ATM when the animals moved voluntarily or were mechanically stimulated (22-25). When immobilized, however, supersaturations of up to 50 atmospheres were tolerated without bubble formation.

Bubble nucleation sites can be dissolved and eliminated by the application of hydrostatic pressure. Evans and Walder used hydrostatic pressure to test for nucleation sites in transparant shrimp (26). When shrimp were pressurized to 389 ATA before altitude decompression, there was a marked reduction of bubble formation compared to unpressurized shrimp. Bubble formation increased, however, when the shrimp were exercised after pressure treatment but before decompression.

Daniels also used hydrostatic pressure to dissolve nucleation sites in shrimp (27). Two hundred atmospheres of hydrostatic pressure reduced bubble formation at 53,000 feet from 3.5 to 0.5 bubbles/shrimp. A 24 hour

interval between pressure treatment and altitude decompression in which the shrimp could move about freely, however, increased bubble formation to 3.2 bubbles/shrimp.

The experiments of McDonough and Hemmingsen, Evans and Walder, and Daniels indicate that visible bubbles in living organisms originate from nucleation sites which are created by tribonucleation during exercise and are eliminated by hydrostatic pressure. To study the involvement of nucleation sites in decompression sickness, we applied hydrostatic pressure to rats before a 2 hour dive to 240 fsw on air (28). With no pressure treatment, there was an 83% incidence of fatal DCS. With a brief 600 fsw pressurization before the dive, the DCS incidence fell to 74%. A 1000 fsw pressurization reduced the incidence to 64%.

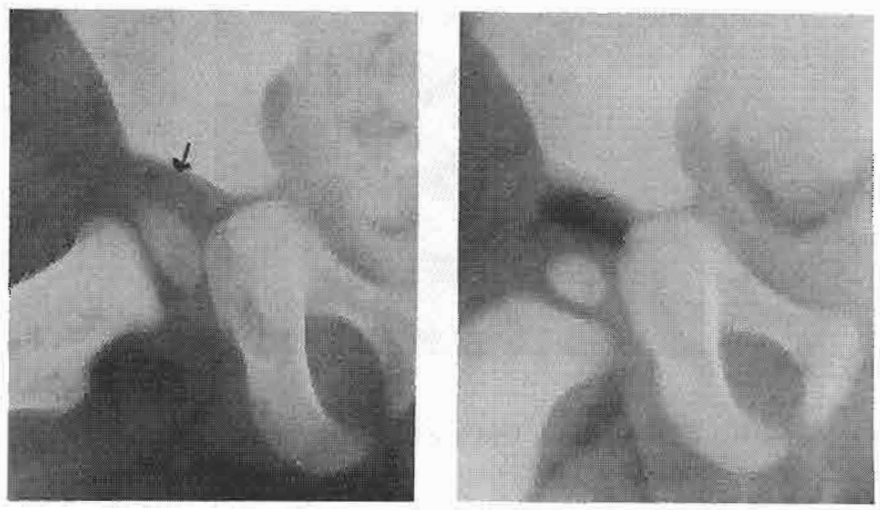
Vacuum Phenomena

There is evidence of nucleation sites in humans. This evidence, known as vacuum phenomena, was first seen in 1910 by Fick in X-rays of cadaver joints (29). Vacuum phenomena have since been found by radiograph and CT-scan in most of the major synovial and cartilagenous joints of living subjects.

A vacuum phenomenon is a gas and vapor-filled void in a joint that is placed in traction. If traction is maintained for 10 to 20 minutes, the void will usually fill with fluid and disappear demonstrating that it is indeed under a partial vacuum (30-32). Analysis of gas aspirated from a vacuum phenomenon showed that it contained 91-92% nitrogen (33).

Vacuum phenomena are a result of tribonucleation which occurs when structures in and around joints undergo relative motion. Tribonucleation can result in either vaporous or gaseous cavitation. Vaporous cavitation typically occurs in cracking knuckles and, as in acoustic cavitation (16), produces a vapor-filled bubble which collapses with a noise when the negative pressure phase passes (34,35). When nitrogen is eliminated from the tissues by oxygen breathing, vaporous cavitation and joint cracking become more pronounced and painful (36). Gaseous cavitation, on the other hand, results in a gas-filled bubble which can persist for some time before dissolving. The nucleation sites from which bubbles develop after decompression are probably produced by gaseous cavitation.

Vacuum phenomena are widely described in the radiological literature and have been observed in the fingers, wrists, elbows, shoulders, spine, sacroilliac joint, illium, symphis pubis, hips, and knees. An annotated bibliography of pertinent references can be found in these proceedings (37). Figure 7 shows a typical vacuum phenomenon in a synovial joint (38). In Fig. 7a, a spontaneous vacuum phenomenon of the hip is visible. When traction is applied in Fig. 7b, the gas volume increases and outlines the articular cartilage. The subject in Fig. 7 is a one year old girl indicating that vacuum phenomena occur at all ages.



(a) (b)

Figure 7. A spontaneous vacuum phenomenon (38) in the hip joint of a 1 year old girl (7a). The void expands when the right leg is placed in traction (7b).

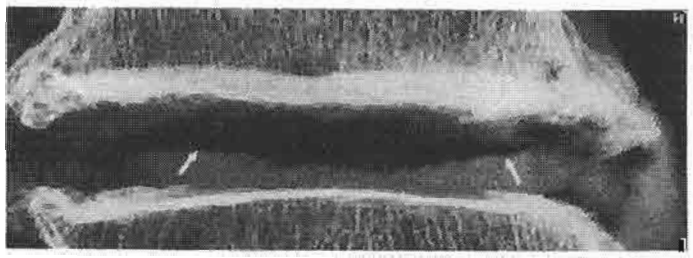


Figure 8. Radiolucent areas characteristic of vacuum phenomena in the discal clefts of the spine (9).

Vacuum phenomena of the spine are found within disks, facet joints, vertebrae, and the spinal canal itself. Figure 8 is a radiograph of a typical vacuum disk that can occur when the nucleus pulposus dries out (39). The radiolucent areas are initially circular but later progress to linear shadows. The pathologic abnormalities appear as cracks or crevices at first but enlarge to fissures which eventually involve the nucleus pulposus fibrosus. Extension of the spine opens these cracks by forming or expanding nucleation sites. Upon flexion, the cracks close, and the gas dissapears. Spinal vacuum phenomena become more common with advancing age and are diagnostic of degenerative processes (40). This suggests an explanation for the increased DCS risk which occurs with age and raises the question of whether spinal injury pre-disposes to spinal decompression sickness.

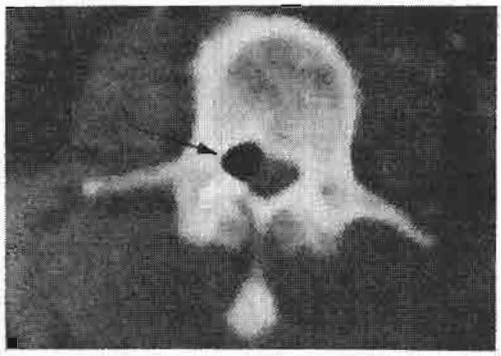
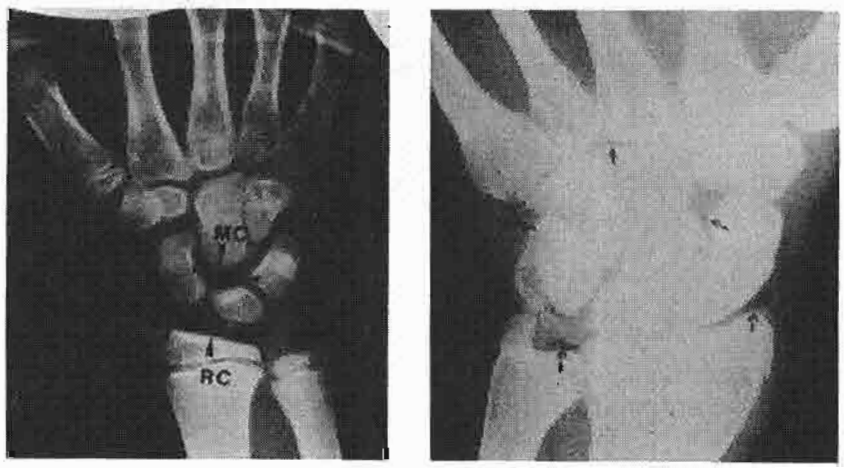


Figure 9. Gas within the spinal canal at the L3 level (42).

Gas which forms in the disks, facet joints, or vertebrae can apparently migrate into the epidural space of the spinal canal (41,42). Figure 9 is a CT-scan of a 52 year old man with chronic back pain and gas in the L2-L3 disk space (42). Gas can be seen within the spinal canal at the L3 level. Gas also has been observed in the cervical canal and can persist rather than be absorbed or replaced by fluid (43).

Vacuum phenomena are seen in bone necrosis (44). While the etiological significance of such observations is uncertain, they prompt the question of whether viscous adhesion could generate sufficient tensile force to separate articular cartilage from underlying bone. This effect might be exacerbated by gaseous supersaturation after decompression from diving or compressed air exposure.



(a) (b)

Figure 10. (a) Vacum phenomena of the wrist produced by traction (45). (b) Gas voids in the wrist produced by altitude decompression (46).

Bubbles and Decompression Sickness

The involvement of vacuum phenomena in decompression is suggested by the radiographs of Fig. 10. Figure 10a shows vacuum phenomena produced by traction of the wrist (45). Figure 10b shows similar voids produced by decompression to altitude (46). Gas in a joint space, however, be it a vacuum phenomenon or the result of decompression is usually asymptomatic. The 1944 altitude study of Thomas and Williams found decompression pain to be most frequently associated with gas streaks along fascial planes and tendons such as those in Fig. 11 (46). The knee in Fig. 11 had moderately severe pain after 3 sets of deep-knee bends during 10 minutes at 35,000 feet. In 74 observations of gas streaking, pain was present on 47 occasions.

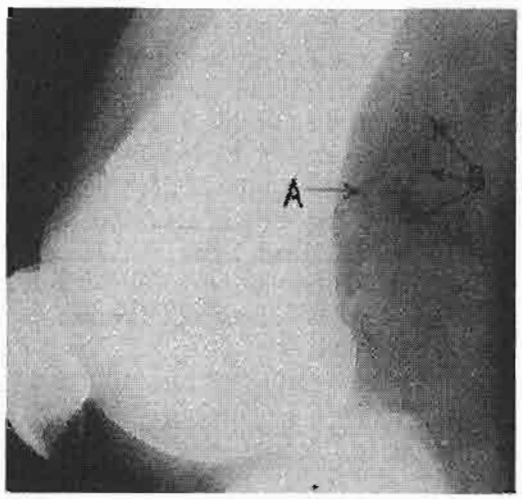


Figure 11. Discrete and irregular bubbles at location A. The wavy gas streak at location B is probably along a fascial plane or tendon (46).

Gas along fascia and tendon probably originates from nucleation sites generated by tribonucleation. Exercise would exacerbate this effect, and the resulting bubbles would expand after decompression by the inward diffusion of nitrogen from supersaturated tissue. Heavy anaerobic exercise before diving appears to increase the generation of nucleation sites just as exercise before altitude decompression increased bubble formation in Evans and Walder's shrimp (26). We have observed 4 cases in which heavy weight training within 24 hours before diving was associated with DCS and/or high precordial Doppler bubble grades. Nishi reported two similar cases at DCIEM (47).

Adaptation

While weight training may generate nucleation sites, these sites seem to be eliminated by frequent exposure to pressure (48). Haldane recognized this effect, now known as adaptation, and recommended limited exposures for new compressed air workers until adaptation had occurred (49). Figure 12 illustrates Walder's observations during construction of the Tyne tun-

nel (50). The DCS incidence fell from 12 to 3% during 10 daily exposures and to 1-2% in subsequent exposures. Adaptation was specific for each working pressure and re-occurred when the pressure increased suggesting that a different population of nucleation sites was eliminated (48). After 10 days without pressure exposure, the DCS incidence returned to its initial level.

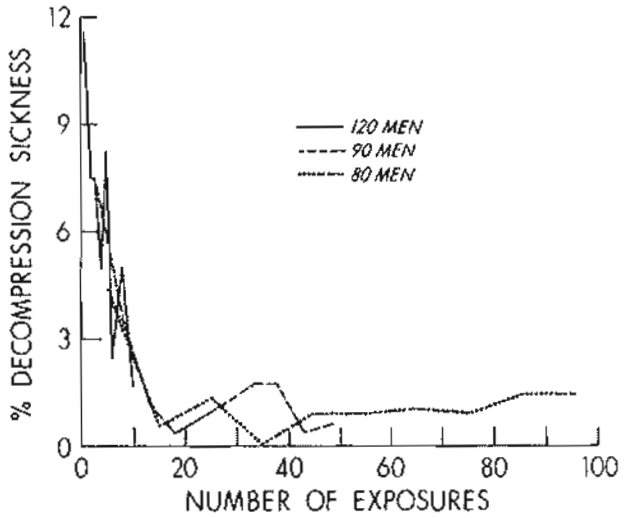


Figure 12. Adaptation in compressed air workers. The DCS incidence decreases during repeated hyperbaric exposure (50).

To determine if the mechanism responsible for adaptation might also decrease intravascular bubbling, we evaluated 7 divers for precordial Doppler bubbles after 20 min helium-oxygen exposures at 120 fsw (51). The oxygen partial pressure was 0.7 ATM, and the divers were seated at rest in a dry chamber. We used helium instead of nitrogen because our earlier studies showed that helium produced more intravascular bubbles than nitrogen (51). The results of 3 dives separated by 5 day intervals are shown in Fig. 13. The mean Doppler score decreased with each dive. The difference in mean scores between the first and third dive was statistically significant at $p=0.02$.

It has been postulated that adaptation and hydrostatic pressure reduce bubble formation and DCS risk in animals and humans by eliminating gas-filled nucleation sites. It is also known that pressure and oxygen together are more effective than pressure alone in eliminating the bubbles which cause decompression sickness. Hyperbaric oxygen therapy, therefore, might be as effective as repeated pressure exposure in producing adaptation and reducing DCS risk in humans.

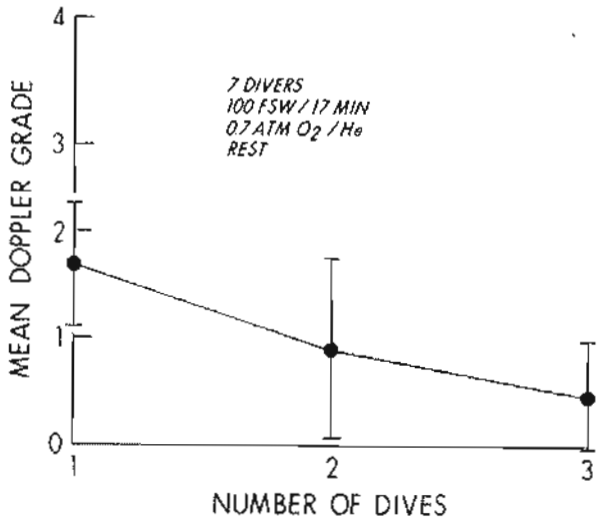


Figure 13. A decrease in precordial Doppler bubbles during repeated hyperbaric exposure (51).

References

1. Dick AP, Vann RD, Mebane, GY and Feezor, MD. Decompression induced nitrogen elimination. Undersea Biomed Res 1984; 11(4):369-380.

2. Van Der Aue OE, Kellar RJ, Brinton ES, Barron G, Gilliam HD and Jones RJ. Calculation and testing of decompression tables for air dives employing the procedure of surface decompression and the use of oxygen. U.S.Navy Experimental Diving Unit Report 13-51.

3. Schibli RA and Buhlmann AA. The influence of physical work upon decompression time after simulated oxy-helium dives. Helv. Med. Acta 1972; 36:327-342.

4. Vann RD. Decompression theory and application. In: Bennett PB and Elliott DH, eds. The physiology of diving and compressed air work, 3rd ed. London: Bailliere Tindall, 1982:352-382.

5. Gerth WA, Vann RD, Leatherman, NE and Feezor, MD. Effects of microgravity on tissue perfusion and the efficacy of astronaut denitrogenation for EVA. In: Physiologic adaptation of man in space. Av Space Environ. Med 1987; 58(9, Sect. II): A100-A105.

6. Gerth WA, Vann, RD and Leatherman, NE. Whole-body nitrogen elimination during oxygen prebreathing and altitude decompression sickness risk. In: Vann RD, ed. The physiological basis of decompression. Symposium proceedings. Nov. 16-18, 1987. Duke University.

7. Waligora JM, Horrigan, DJ and Conkin J. The effect of extended O2 prebreathing on altitude decompression sickness and venous gas bubbles. Av. Space Environ Med 1987; 58(9, Sect. II):A110-A112.

8. Bahr R, Inges I, Vaage O, Sejersted OM and Newsholme EA. Effect of duration of exercise on excess postexercise O2 consumption. J Appl Physiol 1987; 62(2):485-490.

9. Boycott AE, Damant GCC and Haldane JS. The prevention of compressed air illness. J Hyg, Camb. 1908; 8:342-443.

10. Ellsberg E. On the Bottom. New York: Dodd, Mead, 1929.

11. Cook SF. Environmental factors affecting decompression sickness. Part II. Role of exercise, temperature, drugs and water balance in decompression sickness. In: Fulton JF, ed. Decompression sickness. Ed. Philadelphia: Saunders, 1951; 223-241.

12. Van Der Aue OE, Kellar RJ and Brinton ES. The effect of exercise during decompression from increased barometric pressures on the incidence of decompression sickness in man. U.S.Navy Experimental Diving Unit Report 1949; 8-49.

13. Tobias CA, Jones HB, Lawrence JH and Hamilton JG. The uptake and elimination of krypton and other inert gases by the human body. J Clin Invest 1949; 1375-1385.

14. Derry TK and Williams, TI. A short history of technology. Oxford University Press, 1960.

15. Harvey EN. On cavity formation in water. J Appl Physics 1947; 18(2):162-172.

16. Strasberg M. Onset of ultrasonic cavitation in tap water. J Acoustic Soc Am 1959; 31(2):163-176.

17. Floberg L. Cavitation in lubricating oil films. In: Davies R, ed. Cavitation in real liquids. New York: Elsevier, 1964; 138-146.

18. Cottrell AH. The mechanical properties of matter. New York: Wiley, 1964.

19. Campbell J. The tribonucleation of bubbles. Brit J Appl Phys (J Phys D) 1968; Ser 2, 1:1085-1088.

20. Dowson D, Unsworth A and Wright V. The cracking of human joints - a study of 'cavitation' in the metacarpo-phalangeal joint. In: Proc Tribology Convention 1971. Tribology Group, Douglas, Isle of Man, Engl. May 12-15, 1971. Instn of Mech Engrs, London: 120-127.

21. Hayward ATJ. Tribonucleation of bubbles. Brit J Appl Phys 1967; 18: 641-644.

22. McDonough PM and Hemmingsen, EV. Bubble formation in crustaceans following decompression from hyperbaric gas exposures. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 56(2):513-519.

23. McDonough PM and Hemmingsen EV. Bubble formation in crabs induced by limb motions after decompression. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 57(1):117-122.

24. McDonough PM and Hemmingsen EV. A direct test for the survival of gaseous nuclei in vivo. Aviat Sp Environ Med 1985; 56:54-56.

25. McDonough PM and Hemmingsen EV. Swimming movements initiate bubble formation in fish decompressed from elevated gas pressures. Comp Biochem Physiol 1985; 81A(1):209-212.

26. Evans A and DN Walder. Significance of gas micronuclei in the aetiology of decompression sickness. Nature, Lond. 1969; 222:251-252.

27. Daniels S, Eastaugh KC, Paton WDM and Smith EB. Micronuclei and bubble formation: a quantitative study using the common shrimp, crangon cragnon. In: Bachrach AJ and Matzen MM, eds. Underwater Physiol VIII. Undersea Med Soc, Bethesda, 1984; 147-157.

28. Vann RD, Grimstad J, and Nielsen CH. Evidence for gas nuclei in decompressed rats. Undersea Biomed Res 1980; 7(2):107-112.

29. Fick R. Handbuch der anatomie und mechanik der gelenke. II. G Fischer, Jena 1910.

30. Rubin EL. The delineation of articular cartilage by x-rays without the aid of contrast media. Br J Rad 1939; 12(144):649-657.

31. Martel W and Pozananski AK. The effect of traction on the hip in osteonecrosis. A comment on the "radiolucent crescent line". Rad 1970; 94:505-508.

32. Gershon-Cohen J. Internal derangements of the knee joint. The diagnostic scope of the soft tissue. Roentgen examinations and the vacuum technique demonstration of the menisci. AJR 1945; 54:338-347.

33. Ford LT, Gilula LA, Murphy WA, and Gado M. Analysis of gas in vacuum lumbar disc. Am J Roentgenol 1077; 128:1056-1057.

34. Roston JB and Haines RW. Cracking in the metacarpo-phalangeal joint. J Anat 1947; 81:165-173.

35. Unsworth A, Dowson and Wright V. "Cracking joints," a bioengineering study of cavitation in the metacarpophalangeal joint. Ann Rheum Dis 1971; 30:348-357.

36. Comroe JH. Oxygen toxicity. The effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. JAMA 1945; 128(10):710-717.

37. Vann RD. An annotated bibliography of vacuum phenomena literature. In: Vann RD, ed. The physiological basis of decompression. Symposium proceedings. Nov. 16-18, 1987. Duke University.

38. Fuiks DM and Grayson CE. Vacuum pneumarthrography and the spontaneous occurrence of gas in the joint spaces. J Bone & Joint Surgery 1950; 32A(4):933-938.

39. Resnick D and Niwayama G. Diagnosis of bone and joint disorder. W.B. Saunders; Philadelphia. V. 2, 1981; 1373

40. Knutsson F. The vacuum phenomenon in the intervertebral discs. Acta Radiologica 1942; 23:173-179.

41. Gulati AN and Weinstein ZR. Gas in the spinal canal in association with the lumbosacral vacuum phenomenon: CT findings. Neuroradiology 1980; 20:191-192.

42. Austin RM, Bankoff MS, and Carter BL. Gas collections in the spinal canal on computed tomography. J Comp Asst Tomog 1981; 5(4):522-524.

43. Elster AD and Jensen KM. Vacuum phenomenon within the cervical spinal canal: CT demonstration of a herniated disc. J Comput Assist Tomogr 1984; 8(3):533-535.

44. Norman A and Bullough P. The radiolucent crescent line - an early diagnostic sign of avascular necrosis of the femoral head. Bull Hosp Joint Dis 1963; 24:99-104.

45. Yousefzadeh DK. The value of traction during roentgenography of the wrist and metacarpophalangeal joints. Skel Radiol 1979; 4:29-33.

46. Thomas SF and Williams OL. High altitude joint pains (bends): their roentgenographic aspects. Radiology 1945; 44:259-261.

47. Nishi RY, Eatock BC, Buckingham IP and Ridgewell BA. Assessment of decompression profiles by ultrasonic monitoring. Phase III: no-decompression diving. DCIEM Report No. 82-R-38, 1982.

48. Walder DN. The prevention of decompression sickness. In: Bennett PB and Elliott DH, eds. The physiology and medicine of diving and compressed air work, 2nd ed, London: Bailliere Tindall, 1975; 456-470.

49. Rubenstein CJ. Role of decompression conditioning in the incidence of decompression sickness in deep diving. NEDU Report No. 12-68, 1968.

50. Walder DN. Adaptation to decompression sickness in caisson work. In: Proc 3rd Int Biometerology Congress, Oxford, 1968; 350-359.

51. Vann RD. MK XV UBA Decompression trials at Duke: A summary report. F.G. Hall Laboratory Report, 1982.

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DUSCUSSION

DR. MASUREL: Circulating and stationary bubbles play very different roles in etiology of decompression sickness. Circulating bubbles are responsible for neurological symptoms, and stationary bubbles are responsible for articular pain. Figure 1 shows the principle of a pressure cuff which has been used around a knee to test the possibility to act on a knee bend. Figure 2 shows the effect of placing a pressure-cuff around a knee with decompression pain. When the cuff pressure was increased to 120 mbar, the pain disappeared. When the pressure was released, the pain reappeared. What is the hypothesis to explain such a reaction? When a diver moves or swims during bottom time, the effective perfusion is increased by the pumping action of muscles, which increases the uptake of inert gas. During decompression, however, divers generally are at rest, which reduces the rate of inert gas elimination at a time when bubble formation can occur, so the probability for some bubbles to develop increases. Figure 3 shows an intra- or extravascular bubble between the anisotropic fibers of the periarticular tissue. Pain receptors are shown surrounding the bubble. When the pressure cuff is inflated, the bubble does not disappear but becomes smaller, and the pain is alleviated because the pain receptors are no longer stimulated. This hypothesis suggests that it is important for divers to do light exercise during decompression to increase inert gas elimination by keeping the tissue warm and by augmenting perfusion with the muscle-pump effect.

DR. VANN: Exercise during saturation decompression merits a special comment. Intravascular evidence of bubble formation is common during saturation decompression. Once bubbles have formed, exercise becomes less effective at increasing inert gas elimination and can promote further bubble growth. Thus, as practical experience has taught us, exercise should be avoided during saturation decompression.

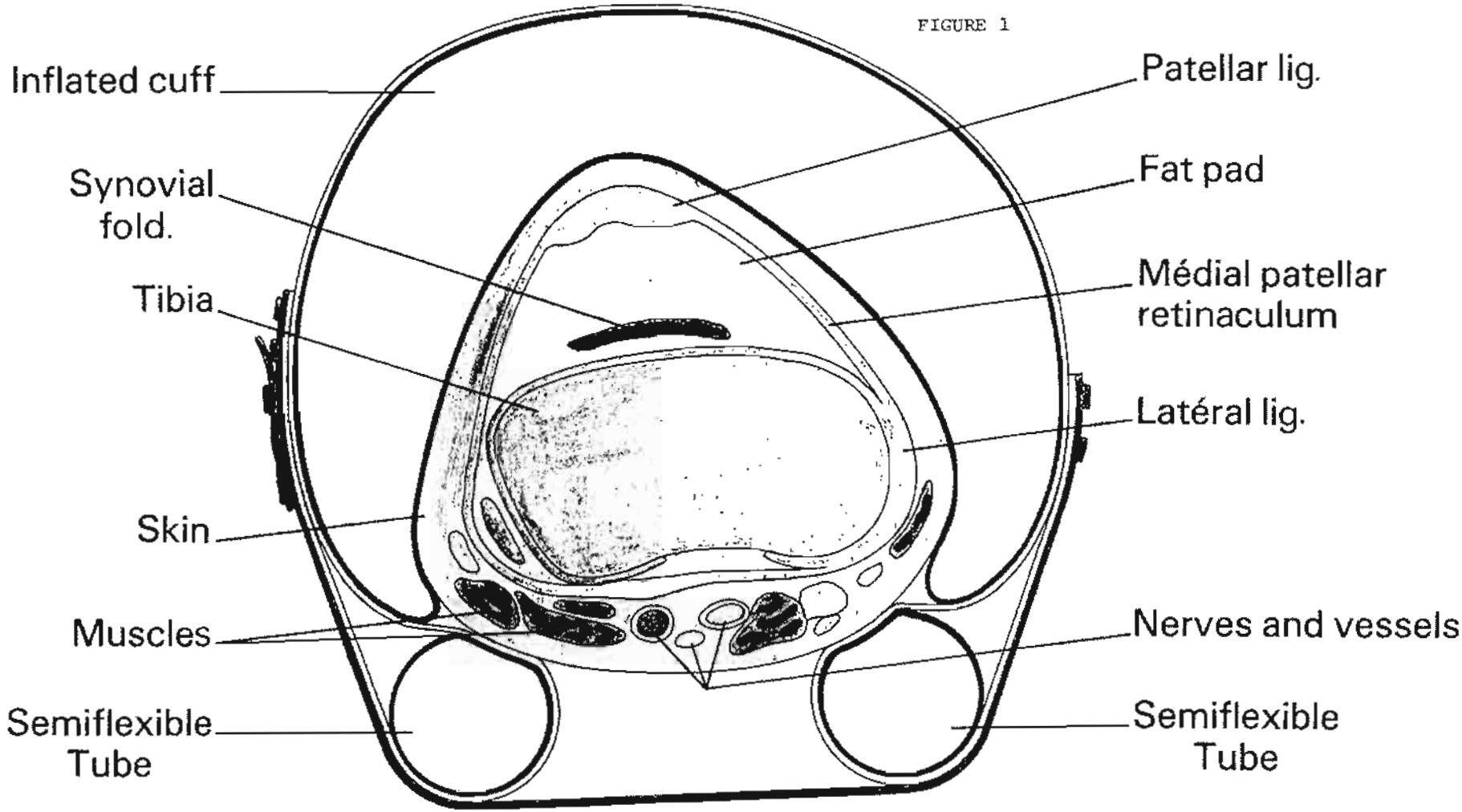
DR. BENNETT: I'm having trouble relating adaptation to multiday scuba diving and diving accidents reported to the Divers Alert Network. We've had some decompression incidents in recreational divers which usually occur on the weekend, after week of repetitive diving to 40, 60, or 100 feet.

I've always felt this was due to a continual loading of tissue gas eventually reaching sufficient tension to generate bubbles. How does this fit with adaptation and complement activation when we're getting decompression accidents occurring on Friday or Saturday after adaptation should have occurred? Is it more related to bubbles and inert gas buildup perhaps? If so, what is adaptation and why do we have sensitization?

DR. VANN: Your observation that multiday recreational diving leads to increased decompression risk appears contrary to adaptation where risk decreases with daily pressure exposure. This contradiction may be due to repetitive diving. Adaptation was best documented in caisson workers who were exposed to relatively low pressure single dives for up to 8 hours (1). Recreational diver, on the other hand, are deeper, shorter, and repetitive. After a single dive, a bubble may have time to resolve. With repetitive diving, however, a bubble which formed during an earlier dive may absorb additional nitrogen and become even larger.

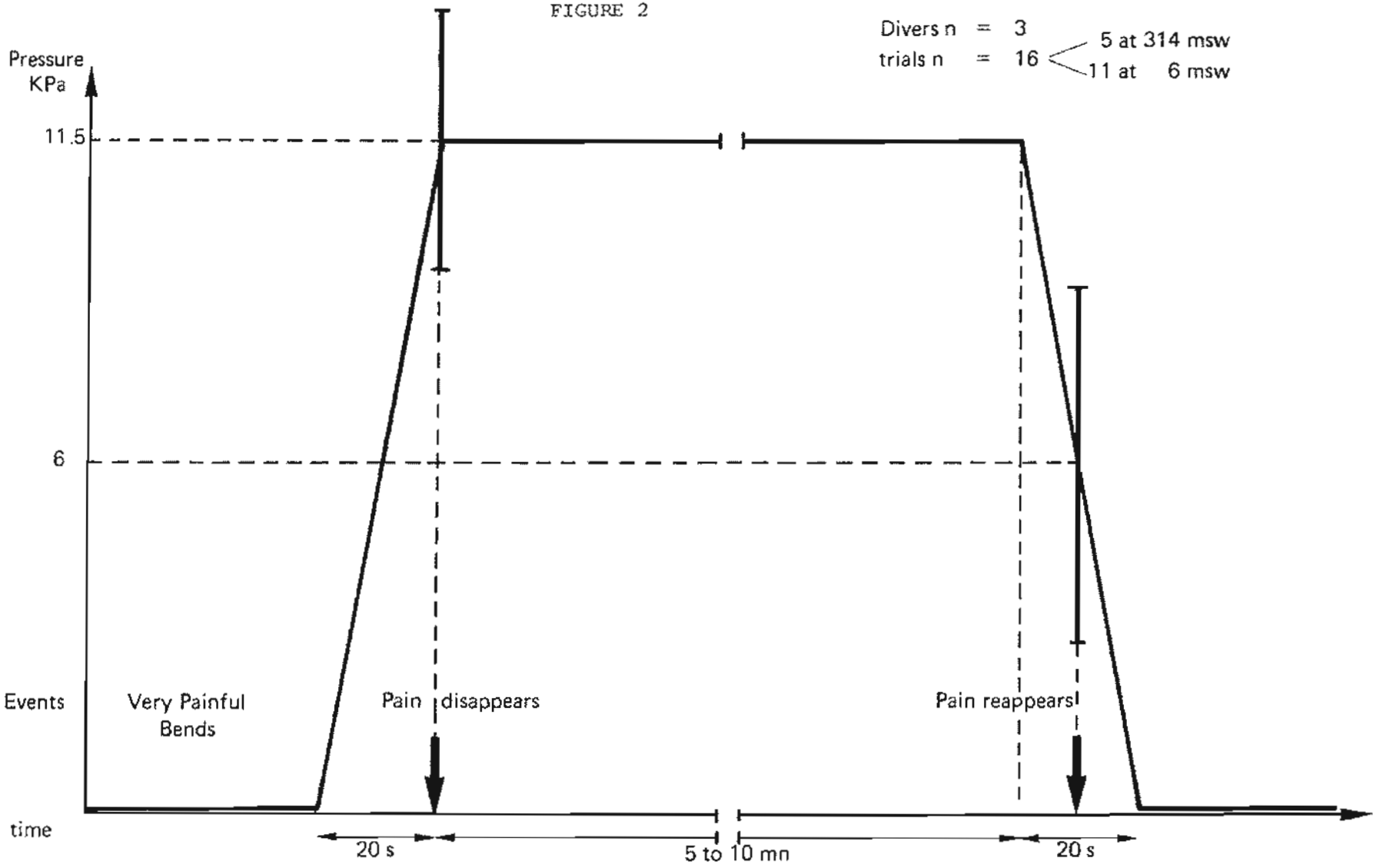
DR. KINDWALL: Dr. Vann, you showed a radiolucent line fracture in the hip which is a sign of aseptic necrosis. We see this in tunnel workers. Did you feel that was a gas-filled space?

FIGURE 1



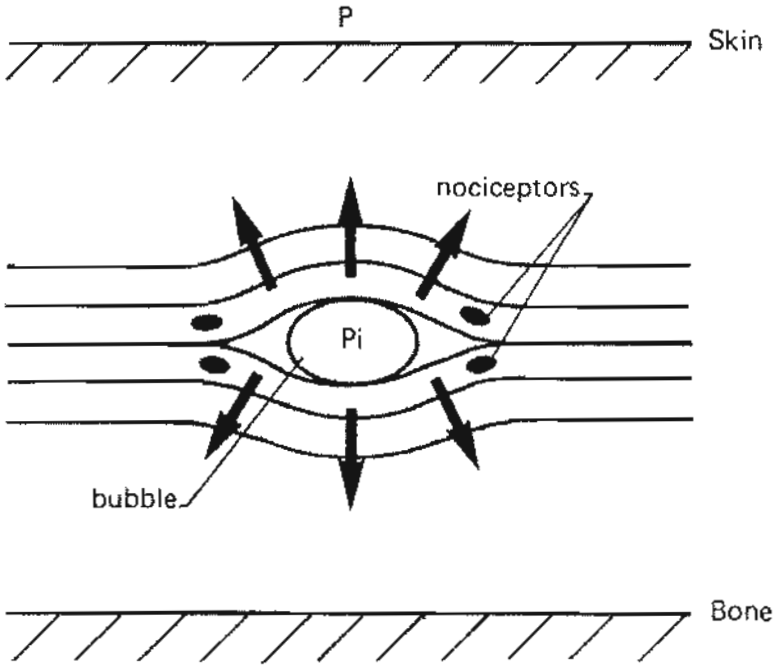
TRANSVERSE SECTION OF THE LEFT KNEE JOINT
WITH THE INFLATED CUFF

FIGURE 2



EFFECT OF LOCAL PRESSURE ON KNEE PAIN DURING SATURATION DIVE DECOMPRESSION

FIGURE 3



When Pi > P + Pc pain occur by nociceptors stimulation

Pi = Pressure inside the bubble

P = Ambiant pressure

Pc = Pressure of fluid necessary to overcome tissue cohesion forces

HYPOTHESIS ON MECANISM OF LIMB BEND

From Proceedings of the EUBS Annual Meeting, Cambridge, England, 1981.

DR. VANN: That's how it's reported in the literature. An annotated bibliography of the literature will be included in the symposium proceedings.

DR. KINDWALL: It's been our feeling that this probably represents a fracture, maybe fluid filled, with the potential for becoming gas filled. Our radiologists, have not considered gas to be found in a man who's not been diving or exposed to compressed air.

DR. VANN: I was also surprised to see that interpretation. Viscous adhesion between articular surfaces can exert very high mechanical tensions, however, and might rip the cartilage away from the bone, causing a bubble to form. This is observed in the cervical spine in whiplash injury.

DR. KINDWALL: I guess MRI will give us the answer on this one. On another subject, I was firmly convinced that any kind of exercise was bad, like shaking up a bottle of warm Coca-Cola, because you get bubbles everywhere, but you pointed out and have demonstrated that it's fine during decompression.

Mild exercise during decompression, however, may form gas nuclei and bubbles. Perhaps just 2% of the inert gas into bubbles, you double the gas carrying capacity of the blood. Thus, a little bit of bubbling may result in more effective gas transport and maybe that's why exercise is good for decompression.

DR. VANN: Well, I don't know. While there's no causal relationship between intravascular bubbles and bends, there seems to be a statistical relationship. The more intravascular bubbling you have, the more gas corpuscles there are in effect, the higher is the risk of bends.

DR. KINDWALL: Beyond a certain point, no question.

DR. BALLDIN: A comment to Dr. Bennett concerning the persistance of gas in the body. I exposed subjects to a no-stop dive of 39 meters for 10 minutes, and 15 meters for 100 minutes. Twelve hours later, I exposed them to an altitude of 9000 meters or a third of an atmosphere. Half of these breathed oxygen for 1 hour before the altitude exposure to decrease the decompression risk. This couldn't eliminate rapid appearing bubbles at altitude, indicating that there must be some silent bubbles present at least 12 hours after a short, 39-meter dive.

DR. GERTH: The nitrogen elimination profiles that we measure show that exercise enhances elimination from those compartments that are involved in bends. As Dr. Pendergast says, there is a redistribution of blood flow during exercise, so it isn't the overall volume that's coming out but where it's coming from that's important. When you focus on the slow compartments that Dr. Homer called our attention to, those are affected by exercise. Remember, our measurements were made before decompression and before there were any bubbles in the subjects.

DR. KINDWALL: During World War II, I believe they did some denitrogenation studies at altitude of 20,000 feet and found out that less nitrogen was eliminated than on the ground.

DR. GERTH: That's correct. Franklin Henry and coworkers showed that in-flight denitrogenation, once you got above about 15,000 feet, was not as effective as it was on the ground. They recommended that high-altitude bombing missions not do in-flight denitrogenations above 15,000 feet.

DR. WARD: Dr. Vann, you showed a reduction in the Doppler score with repeated dives, and you implied that was an explanation for acclimatization.

DR. VANN: That's not the classical definition of adaptation, which is a reduction in susceptibility to decompression sickness, but it did seem to produce a reduction in Doppler bubble score.

DR. WARD: I don't believe there's a correlation between adaptation and Doppler scores.

DR. VANN: It's similar to looking for visible bubbles in shrimp. These bubbles don't necessarily cause decompression sickness, but they are an effect of decompression.

DR. WARD: Let me comment on adaptation with regard to the complement hypothesis. To reduce the complement protein, you must have bubbles. The first few dives that lead to adaptation have got to be severe enough to produce bubbles.

DR. VANN: I don't believe the biochemical and mechanical mechanisms of decompression sickness are necessarily incompatible. As a matter of fact, both may be true at different times.

DR. WARD: I did not intend to imply that it was one or the other. I'm just saying that for the complement to be activated, you have to have the bubbles, and if they do activate the complement system there is a reduction in concentration of complement proteins. According to the complement hypothesis, that reduction leads to acclimatization or adaptation of the diver.

DR. YOUNGBLOOD: In the early attempts at regulation of the commercial diving industry, some of the less sophisticated operators thought that repetitive no-decompression diving would allow them to escape having to have an on-site chamber. It's my observation that diving day after day in this manner leads to an accumulation of nitrogen. Indeed, the U.S. Navy no-stop exposure limits are less conservative than any other limits currently in use. Incidently, I prefer the British term "no-stop" dive to the term "no-decompression" dive, which is inaccurate.

DR. VANN: That's true, but there is abundant evidence to indicate that the Navy no-stop limits are reasonably safe at depths greater than 50 feet for single dives. A greater risk, however, appears to exist for no-stop repetitive diving, but we have little data on this type of diving. I think Dr. Thalmann has data to that effect.

CAPTAIN THALMANN: When the depth and bottom time are accurately controlled to the Navy limits, no-stop dives as they are published are quite safe.

DR. YOUNGBLOOD: On a repetitive basis?

CAPTAIN THALMANN: When you start repetitive diving, using 12 hour surface intervals, no-stop diving may not be safe.

DR. YOUNGBLOOD: But, that's what the sport divers contend the commercial divers are doing.

DR. KINDWALL: I don't use the U.S. Navy no stop tables in clinical hyperbaric work because I've given people vestibular hits, spinal cord hits, and pain-only hits. We have experienced multiple hits at 50 feet on 100-minute dives. The Navy no-decompression limits are just not usable. However, we're decompressing in a dry chamber. It may be that we're not eliminating as much nitrogen coming up, although we're probably absorbing less too, because we're not immersed at any time. Dr. Balldin, has anyone tried denitrogenating not at 6500 meters but at 2000 meters to determine whether nitrogen removal is augmented? A modest decrease in pressure just to 7000 feet might be effective whereas a big one like 20,000 feet would not be effective.

DR. BALLDIN: I did a study with 15 meter and 39 meter dives followed about 3 hours afterward by decompression to 1000, 2000 and 3000 meters altitude without any pre-oxygenation. But even at 1000 meters and especially at 3000 meters, I had bubbles (at 3000 meters) in 90% of the cases.

DR. KINDWALL: Well, you started with additional nitrogen from a dive. I'm thinking of a sea-level resident who ascends about 2000 meters and denitrogenates. How does denitrogenation at 2000 meters compare with denitrogenation at sea level?

DR. BALLDIN: Maybe the people from NASA have done work in this area.

MR. WALIGORA: We haven't, but you're thinking of the bubbles going to the lung, aren't you?

DR. KINDWALL: Yes, the pulmonary filter tolerates an enormous embolic load very well.

DR. GERTH: The in-flight denitrogenation procedure was adopted for operational expediency to reduce the amount of oxygen that had to be carried. In-flight denitrogenation for enhancing elimination by bubble formation will cause bubbles to form in tissues which will develop DCS. If they do not quickly enter the venous circulation and get filtered out in the lungs, they are going to impair gas washout.

DR. KINDWALL: I think it's a matter of degree. Too much bubble formation will block the circulation. Behnke demonstrated more nitrogen elimination after decompression from 100 to 50 feet as opposed to decompression from 100 to 10 feet. Would the same effect occur with altitude compression? Would denitrogenation be enhanced at low altitudes but be reduced at higher altitudes?

DR. ECKENHOFF: I'd like to a comment on acclimatization and on exercise and temperature effects. We found no correlation with acclimatization and Doppler scores in a double-blind study. We're developing a new set of helium tables using dry resting, wet working, and standby divers. There have been no bubbles or decompression sickness in divers working on the bottom on viscohydrometers, wearing hot water suits, and staying underwater during decompression. We have more bubbles and decompression sickness in standby divers who are relatively sedentary while submerged in the water wearing dry suits.

DR. VANN: The ideal thermal profile would be to be cold on the bottom and warm during decompression. When a diver becomes chilled on the bottom, he doesn't take up as much gas, but during decompression he eliminates inert gas poorly. If you could warm the standby divers up during decompression, they probably would have less trouble.

DR. ECKENHOFF: We also found that active standby divers who moved around a bit had less problems.

DR. LAEK: I think in terms of caisson workers, and our experiences with our last construction site might be of interest. We've just finished a 2-year project in which there were 12 incidents of type I DCS in the first 4 months. All the cases occurred on Thursday, Friday, and Saturday, and we found that tunnel workers didn't follow the right decompression tables. Because all of them had pain during the week, they often went to the next shift 1 hour early to treat themselves without missing work. After we made them use the right table, there was not one DCS incident for the last 18 months.

DR. DANIELS: Dr. Kindwall, the idea that you can accelerate gas elimination with mobile bubbles has been around for quite a long time. We

did some calculations based on our imaging work after making assumptions that would be most favorable to the process. We couldn't get more than 5% of gas transport in the bubbles and that was on the brink of massive stationery embolization which would have greatly slowed transport. I just don't think the idea is practical.

DR. KINDWALL: How would you explain our findings that nitrogen elimination increased from a 1000 cc in an isobaric experiment at 30 meters to 1800 cc with a drop in pressure from 30 to 15 meters? We found identical numbers in repeated studies.

DR. DANIELS: I offer no explanation for it.

DR. JAMES: Maybe part of the explanation is that you're taking up the initial slack of the inherent unsaturation under those conditions. In other words, you don't have so much gas formation and perhaps Behnke didn't actually measure the gas formation under those circumstances.

DR. GERTH: Dr. Kindwall, yet another explanation of Behnke's results is that the augmented nitrogen elimination might have come from tissues not involved in bends. Perhaps from fat. Our experiments show there can be large differences in the total nitrogen eliminated under different conditions from the same person. That gas might be coming out as bubbles in a nonprovocative decompression but not influence protection from decompression sickness.

DR. LAMBERTSEN: Dr. Masurel, you feel that the sheep and goats you studied at high pressures developed bubbles, possibly by cardiac effects. These animals were presumably at rest. What do you think would happen if you repeated the studies with exercising animals.

DR. MASUREL: That would be very interesting; the deep chamber is presently unavailable.

MR. GALERNE: We have had more trouble with the tenders in the bell than with the divers after our deep dives. We think this is because the tenders were surrounded by gas and were absorbing more gas through the skin than the divers, who were submerged in water. We also have the divers and tenders totally relax for 1 minute at the end of each dive. We do this because Behnke reported that 80% of the excess CO_2 that accumulates during exercise can be removed in 1 minute. We feel CO_2 may provoke bubble formation and lead to decompression sickness.

REFERENCES

1. Walder DN. Adaptation to DCS in caisson workers. In: Proceedings of the third international biometeorology congress. Oxford; 1968:351-359.

WHOLE-BODY NITROGEN ELIMINATION DURING OXYGEN PREBREATHING AND ALTITUDE DECOMPRESSION SICKNESS RISK

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Introduction

Breathing 100% oxygen before rapid ascent to high altitudes reduces the amount of dissolved nitrogen in the body and can minimize the risk of decompression sickness or DCS. In order to learn how factors that affect tissue perfusion impact the levels of DCS protection that are afforded by these preflight denitrogenations, we have been studying whole-body denitrogenation profiles and their relation to the incidence of central venous bubbles (VGE) and DCS symptoms during subsequent hypobaric exposure.

Methods

In each experiment, the whole-body nitrogen elimination profile was measured from a human subject breathing 100% oxygen for 3.0 hr under each of three different conditions which effected different "whole-body tissue perfusion states" and correspondingly different nitrogen elimination profiles. Each profile was measured in real time using an open circuit, breath-by-breath system which was developed specifically for this work [1]. Three and one half hr after starting each denitrogenation, the subject was decompressed in about 9 min from sea level to 4.3 psia where, continuing to breathe 100% oxygen, the subject performed an upper body exercise protocol (approx. 180 kcal/hr) [2] with periodic ultrasonic monitoring of the precordium for bubbles [3] during the ensuing 4.0 hr or until DCS developed. Six to 27 days separated successive runs by a given subject, a period within which we have found that a given subject closely reproduces a given nitrogen elimination profile under otherwise practically identical conditions.

Parameters describing the kinetics of whole-body washout were found by fitting a summed series of semi-exponential decay equations to each measured profile using nonlinear least squares [4]. The model which proved most widely applicable, and upon which the present results are based, is a 6-parameter model with two semi-exponential compartments and one linear compartment:

$$A_T = \left[\sum_{i=1}^{2} A_i[1-\exp(-k_i(t-L))]\right] + m(t-L), \qquad (1)$$

where; A_T is the cumulative total volume of nitrogen eliminated at each end-expiratory elapsed time, t; A_i is the nitrogen content of compartment i at t=0; k_i is the corresponding compartmental time constant (=0.693/compartmen-

tal half-time), and; L is the system response latency. A linear compartment with nitrogen washout rate m accounts for transcutaneous diffusion of atmospheric nitrogen and includes contributions from other semi-exponential compartments which, in possessing excessively long half-times, could not be resolved from 3 hr or less of data. The fastest of the two semi-exponential compartments in each profile, usually with a half-time of from 0.2 to 0.4 min, consisted principally of nitrogen washed from the pulmonary residual volume to which the subject expired immediately before run start. The breath-by-breath solution for this compartment, as determined directly from the measured profile, was subtracted from each profile to facilitate graphical comparisons of different profiles. Nitrogen volumes are reported at standard temperature and pressure.

Results and Discussion

Three profiles from one subject are shown in Figure 1, labeled according to the three different conditions under which the denitrogenations were performed: "SR" for seated, feet on floor rest; "HDR" for supine, six degrees head-down rest, and; "SE" for seated, continuous light upper and lower body exercise on a cycle ergometer (approx. 120 kcal/hr) commenced 10 min after run start. The profiles graduate upwards indicating that the overall volume of nitrogen eliminated increased as the conditions during denitrogenation changed from SR to HDR to SE. In parallel with this graduation, the figures in parentheses after each profile label show that the approximate onset times in minutes at altitude for both VGE of Grade 2 or higher (on the left) and DCS (on the right) more than doubled after HDR denitrogenation compared to those after SR denitrogenation. The dashes indicate that neither VGE nor DCS occurred at altitude after the SE denitrogenation. Thus, the DCS protection acquired during the respective denitrogenations in this subject in-

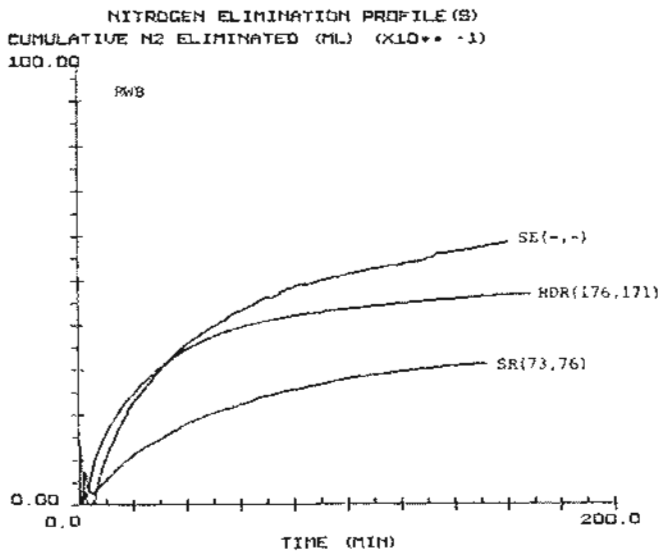

Figure 1.

creased with the overall amount of nitrogen eliminated.

However, this simple indication is not always applicable, as exemplified by results from another subject shown in Figure 2. Although, the three profiles are rather closely clustered, this subject developed DCS after each of the SR and HDR denitrogenations. Moreover, DCS developed somewhat earlier in the altitude exposure after the HDR denitrogenation than after the SR denitrogenation, even though more nitrogen was eliminated during the HDR prebreathe. Observe, however, that the SE denitrogenation, after which no VGE or DCS occurred, exhibits a profile with a greater end-section slope than evident in the other profiles. This indicates that nitrogen elimination from slow tissue compartments was hastened during SE denitrogenation, presumably by exercise-induced perfusion enhancements, and recruited into faster compartments that were resolvable still in only the slowest, linear feature of a 3 hr elimination profile.

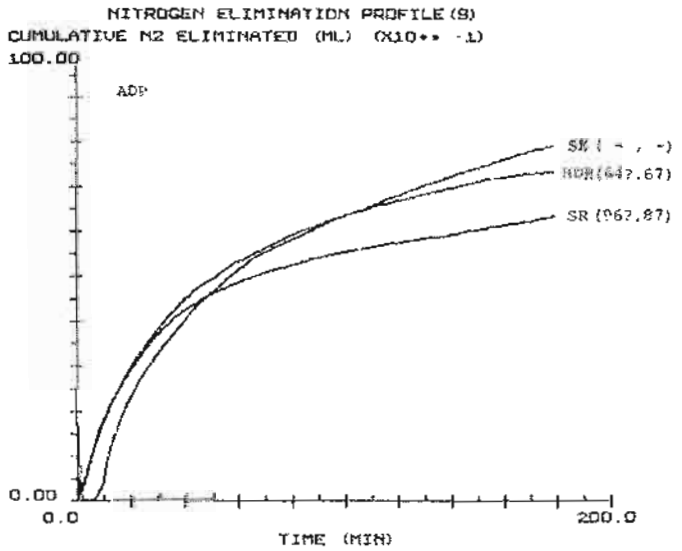

Figure 2.

The importance of these slow tissue compartments clearly emerges if each subject is treated as his own control and a ratio of the linear compartment rates relative to that for the SR denitrogenation for each subject is calculated and compared to the incidence of DCS, as shown in Figure 3. Under this analysis, our subject population naturally divides into two groups: four subjects on the left in the figure that developed DCS at altitude after SR denitrogenation and two subjects on the right that completed all exposures DCS-free. The lability of the slow compartment behavior between the different conditions in the first group contrasts sharply with the nearly constant behavior of this compartment in the second group. In the first group, the relative linear compartment rates tended to increase as conditions during denitrogenation changed from SR to HDR to SE. DCS in this group occurred following denitrogenation only when the relative rate was

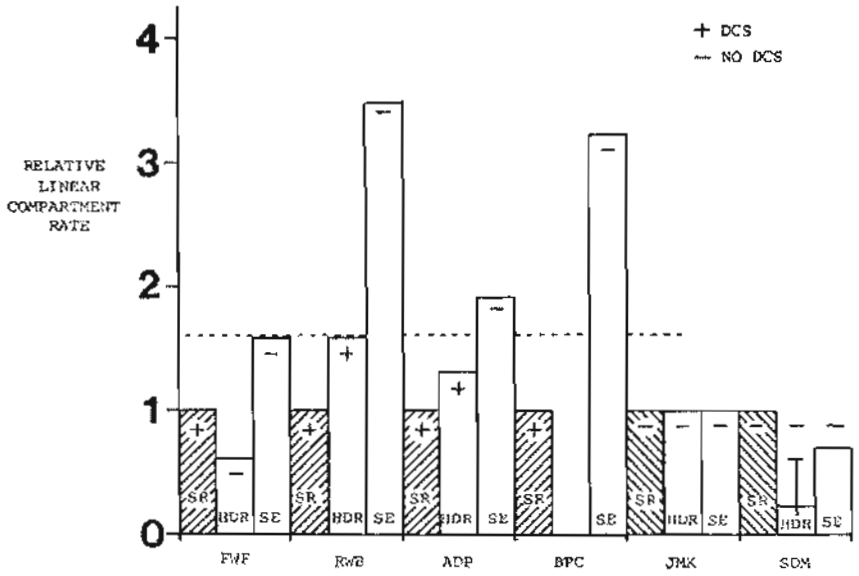

Figure 3.

less than about 1.6. The one subject excepting this observation, FWF, responded to HDR with an unusually large nitrogen elimination enhancement in the semi-exponential "tissular" compartment compared to that in response to SE; a feature excluded from consideration in this simple analysis. It should also be noted that Grade 2 VGE were detected in this subject late in the altitude exposure after the HDR denitrogenation, even though DCS did not develop. Additionally, the relative linear compartment rate shown for subject ADP during HDR denitrogenation appears overvalued when end-section tangents to the appropriate profiles in Figure 2 are visually assessed and compared. This analytic outcome was unusual, but suggests that the simple whole-body nitrogen washout model embodied in equation (1) may require further refinement. Interestingly, the two subjects in the second group were the only subjects in this small population to be highly conditioned endurance runners. These subjects are as clearly distinguished by their nitrogen elimination profiles as by their resistances to VGE and DCS in the altitude exposures.

Conclusion

It is becoming clear that whole-body nitrogen elimination profiles spanning 2.5 to 3.0 hr periods of oxygen breathing exhibit quantitative features that can be related to the efficacy of denitrogenation for DCS prevention during altitude exposures of the type used in this study. These features include the overall amount of nitrogen eliminated and, of equal importance, the nitrogen washout rates from the slowest tissue compartments. The augmentations of nitrogen elimination that provide enhanced protection from the Type I DCS risked by subjects in this study may be reflected largely in the

slowest, practically linear features of 3 hr whole-body nitrogen elimination profiles.

References

1) Gerth WA, Vann RD, Leatherman NE, Feezor MD. Effects of microgravity on tissue perfusion and the efficacy of astronaut denitrogenation for EVA. Aviat Space Environ Med 1987; 58(9, Suppl): A100-A105.

2) Waligora JM, Horrigan D, Jr, Conkin J, Hadley AT III. Verification of an altitude decompression sickness prevention protocol for Shuttle operations utilizing a 10.2-psi pressure stage. Houston, TX: Lyndon B. Johnson Space Center, 1984; NASA Tech. Memo. 58259.

3) Dixon GA, Adams JD and Harvey WT. Decompression sickness and intravenous bubble formation using a 7.8 psia simulated pressure-suit environment. Aviat Space Environ Med 1986; 57:223-228.

4) Marquart DW. An algorithm for least-squares estimation of nonlinear parameters. J Soc Indust Appl Math 1963; 11: 431-441.

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BUBBLE FORMATION MECHANISMS

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ABSTRACT

Bubbles may form spontaneously in aqueous media by several mechanisms, or may evolve from gaseous micronuclei. Homogeneous nucleation of bubbles by dissolved argon or nitrogen in water, determined experimentally, occurs with supersaturations of 155 or 200 atm, respectively. These values are an order of magnitude less than those predicted by nucleation theories. The process is not markedly affected by most surfactants or other solutes. Homogeneous nucleation induced by dissolved gas is not likely to play a role *in vivo*, unless augmented by other processes. Investigations on crustaceans and fish show that bubbles form spontaneously even with gas supersaturations of 5 atm, or less, with modest limb motions or activity. Tribonucleation in the liquid between rubbing or parting surfaces, which is known to be the cause of bubble formation *in vitro*, is the apparent underlying mechanism. While forces sufficient to overcome the tensile strength of water theoretically are possible with smooth hydrophilic surfaces in close proximity, water rupture would occur at hydrophobic ones with less force. Because the bubble formation thresholds are unaffected by hydrostatic pressurization in these organisms, gaseous nuclei are not a significant factor in the bubble formation. Although such nuclei may exist in higher animals, their presence has not been confirmed, and their role seems to be overestimated. It is likely that bubble formation here is caused by spontaneous mechanisms as well; among these, tribonucleation may be particularly important if the surfaces are not limited to those of skeletal structures. The degree to which one mechanism predominates over others probably depends on activity and other factors.

It is generally accepted that most of the medical problems associated with decompression sickness are directly or indirectly related to the development of gas bubbles in the body during conditions of gas supersaturation. There is far less consensus with regard to where and how the bubbles form. Although bubbles often are found within the circulatory system, it is uncertain whether their origin is intra- or extravascular, or even intra- or extracellular. The complexity of the mammalian organism, the lack of methods for detection of bubbles in their early stages of formation, the variability in gas supersaturation tolerances, and the limited understanding of the physical phenomena associated with bubble formation are the main reasons for the existing uncertainties. Because medically relevant gas supersaturations *per se* do not cause bubbles to form, several different mechanisms that could lead to bubbles in organisms have been suggested (e.g.,1-6); however, none has been shown to be unequivocally responsible. The purpose of this paper is to examine some of the physical processes which appear to be involved in initiating the bubbles.

Bubble Formation In Vitro

A number of different processes can cause bubbles to form in liquids; once a gas phase has become established, the Laplace equation describes the conditions for a stable bubble to exist in a liquid. For a spherical body of gas within a liquid, the equation gives the relationship between surface tension of the liquid, the size of the bubble, and the internal gas pressure which at equilibrium opposes the inward force generated by surface tension:

$$P_g - P_h = 2\gamma/R$$

where, with convenient units, P_g is the internal pressure of gas plus vapor (dynes/cm^2), P_h is the hydrostatic pressure (dynes/cm^2), γ is the surface tension (dynes/cm), and R is the bubble radius (cm). The gas phase can be made to expand either by increasing the internal gas and/or vapor pressure, by decreasing the hydrostatic pressure, or by decreasing the surface tension. The various mechanisms which exist for the creation of the initial gas phase depend on at least one of these parameters being accentuated in order to produce the required metastability.

These mechanisms may be classified into two categories: those which cause dissolved gas to be separated spontaneously from the liquid during the state of metastability, and those where the "seed" nucleus merely is derived from a gas phase which already exists prior to the metastable state. The spontaneous processes may be divided into homogeneous nucleation and heterogeneous nucleation.

In all cases of homogeneous nucleation, the water structure is ruptured to create a vapor and/or gas cavity. Subsequent diffusion of dissolved gas into the cavity provides initial stabilization and often allows continued growth even when the conditions responsible for the creation of the original cavity are changed. Homogeneous nucleation induced solely by dissolved gas does not occur readily in water or aqueous solutions. In fact, it is only in relatively recent years that this process has been dealt with under controlled experimental conditions (7-9). Because of the lack of information which has existed both with respect to the actual levels of gas supersaturations required for nucleation, and the factors which affect it, many erroneous assumptions have been made over the years. This process will be considered further in the next section.

Tensile forces, or negative hydrostatic pressures sufficient to rupture water in a nuclei-free environment may be generated by mechanical tension. Water has been subjected experimentally to -270 atm by centrifugation without rupturing (10); theoretical considerations indicate that even larger forces must be used for true structural rupture. Such rupture may occur in a flowing liquid when there is a local increase in flow velocity in a constriction; this Bernouilli effect is usually referred to as Reynolds' cavitation (11). Other examples of nucleation induced by tensile forces are cavitation by shock waves and acoustic waves. Such conditions may be encountered in organisms when ultrasound is used for detection of bubbles.

Heat will also generate vapor cavities but this is of little interest for biological systems except in cases where frictional heat may develop very

locally. Water boils at 100°C because of the presence of gaseous nuclei; in their absence, water can be heated to about 280°C at baric pressure without vapor cavity formation (10). Bubbles generated by ionizing radiation and high energy particles (e.g., cosmic radiation) represent a special case of cavity formation by heat. Such particles traveling through a liquid may cause brief, local thermal spikes along the track, creating superheated points (12). Although this may happen in organisms, it is probably not important because particles of sufficient energy level are relatively rare.

Tribonucleation of bubbles has been demonstrated to occur *in vitro* when two submerged surfaces are brought in contact with each other and then parted. The bubbles form spontaneously, presumably in the liquid layer between the surfaces. Hayward (13) showed that rubbing of the surfaces against each other could produce bubbles. He dismissed the notion that frictional heat flashes leading to localized vaporization were the cause because even substances with a low melting point produced bubbles, but he proposed no specific mechanism. Campbell (14) developed the idea that nucleation is caused by tensile forces generated in the liquid between the surfaces due to its viscous adhesion to the surfaces. Ikels' (3) observations of bubble production in viscous fluids by rolling steel balls support this idea.

Spontaneous heterogeneous nucleation requires that there is an effect from the presence of a surface *per se*, either by its geometrical shape (1,6) or by the discontinuity in cohesive forces between the liquid and the solid (15). By this definition, tribonucleation based on tensile rupture of water is not a heterogeneous nucleation while, for example, nucleation at a surface resulting from a decreased liquid adhesion is, as is the gas phase separation that has been deemed feasible to occur in the tip of a crevice. Whether or not the presence of a smooth planar surface *per se* substantially increases the probability for nucleation in an otherwise homogeneous medium has not been settled (e.g.,16-18). When essentially only the dispersion forces are present at the liquid-solid interface, such as is the case with strongly hydrophobic, non-polar solids, the condition for nucleation would be more favorable at the interface than in the bulk liquid. But it remains to be shown that modest concentrations of dissolved gas alone are sufficient to induce nucleation. When tensile forces, for example, also are imposed on the system, the presence of hydrophobic surfaces could have major consequences for the stability of the system.

Another example of heterogeneous nucleation is the formation of bubbles on surfaces of potassium nitrate and succinic acid crystals precipitated in solute- and gas-saturated solutions prior to decompression (19). The gas supersaturations (less than 10 atm) are low enough to be of interest for biological systems. Although it is difficult to delineate the underlying events of this phenomenon, it is not a transient effect generated by the brief and possibly significant elevation of gas content in the liquid immediately adjacent to the advancing surfaces during crystallization. However, the surface geometry of the crystals and entrapment of gas in the crystalline structure could contribute to the effect.

Non-spontaneous bubble formation processes, primarily those originating with gaseous micronuclei, are the most common cause for bubbles we observe in our daily life. The bubbles in carbonated beverages, for example, evolve from

such nuclei. Broadly characterized, they may be either individual gas entities each completely surrounded by some form of a "shell" or "skin", which protects them against surface tension and collapse (20,21), or they may be trapped gas in cracks and crevices in the container wall or in suspended particles (1,22).

The concept of nuclei shells is forced on us if a gas phase is to remain stable in an aqueous medium; without them, gas dissolution would occur. Such shells or skins may form from macromolecules present in solution; they must be sufficiently rigid to protect against inward forces, and be elastic enough to allow easy outward expansion. Such nuclei exist, for example, in gelatin preparations (23) and in sea water (24), but they cannot be prevalent in pure liquids which lack the necessary solute molecules.

Crevice nuclei, contained in hydrophobic solids, theoretically can have almost any stability we choose by selecting the appropriate geometrical configuration. Those which have been considered in the literature are conical with straight or elliptically curved walls. Such gas-filled shapes can generate bubbles continuously even when the system is only slightly metastable. The essential element is that the gas phase has a negative, concave curvature at the liquid interface; this tends to always enlarge the gas phase. With acute angled cone cavities, the initial gas phase may be spontaneously generated in the tip of the cavity by statistical fluctuations in the thermal motion behavior of the dissolved gas molecules (1,6,25,26).

Adsorption of gas to solid surfaces and quasi-dissolution of gas into intermolecular spaces in a solid structure may be included here as potential nonspontaneous mechanisms. It is commonly observed that under metastable conditions, bubbles tend to form on submerged hydrophobic surfaces which were exposed previously to a gas phase. When such surfaces are subjected to high hydrostatic pressures, their ability to promote bubbles usually is greatly reduced because of nuclei collapse. If any gas is superficially trapped in micropores on the surface, pressurization would affect it too. However, it is improbable that a non-polar gas such as nitrogen would accumulate at or adsorb to any type of surface submerged in a liquid, because only dispersion forces would be acting between the dissolved gas and the surface. No process or mechanism which would lead to preferential adsorption of dissolved gas to strongly hydrophobic surfaces appears to exist. Experiments with suspensions of hydrophobic particles (B.B. Hemmingsen and E.A. Hemmingsen, unpublished observations) indicate that some are effective "bubble nucleators" even after being subjected to hydrostatic pressures in excess of 500 atm, possibly because of gas trapped in intermolecular spaces within the solids. Investigations to test this possibility are now in progress.

Spontaneous Nucleation Of Bubbles By Dissolved Gas

Because of the exceptionally high cohesive strength of water due to its unique internal hydrogen bonding, very large forces must be overcome in order to create a cavity within it. Spontaneous nucleation by dissolved gas will be considered here in more detail as an example. The internal pressure of a very small bubble may be calculated by means of the Laplace equation. With an arbitrarily chosen bubble radius of 10^{-6} cm, a size through which

bubbles must pass from birth to visibility, the critical internal equilibrium gas pressure for air in water at 25°C would be 1.45×10^8 dynes/cm^2, or 143 atm. This value represents the dissolved gas supersaturation pressure (or gas tension) required just to maintain a bubble of this size. Extended to the smaller dimensions appropriate for the initial bubble nucleus, the internal pressure would be substantially higher. These estimates are based on the assumptions that the surface tension (72.8 dynes/cm) is constant down to molecular dimensions, with no fluctuations around its mean value, that no interaction occurs between the internal gas and the liquid surface, and that the surface curvature has no effect on the surface tension (27). These assumptions are not all tenable. Surface tensions measured under high gas pressures (27), for example, are substantially affected by the gas itself; for most gases, the surface tension decreases with increasing pressure.

Attempts to predict homogeneous bubble nucleation in solutions of gases in water on the basis of classical nucleation theories for liquids (29) have not led to satisfactory results. No theory has been developed that allows quantitative prediction of the nucleation induced by any dissolved gas and, as a consequence, the gas supersaturation threshold values obtained by theoretical approaches have ranged anywhere from several hundred to nearly 4000 atm (25,30,31). Because it was important to know these thresholds quantitatively in order to study bubble formation in cells (e.g.,32-34), they were determined experimentally (Figure 1).

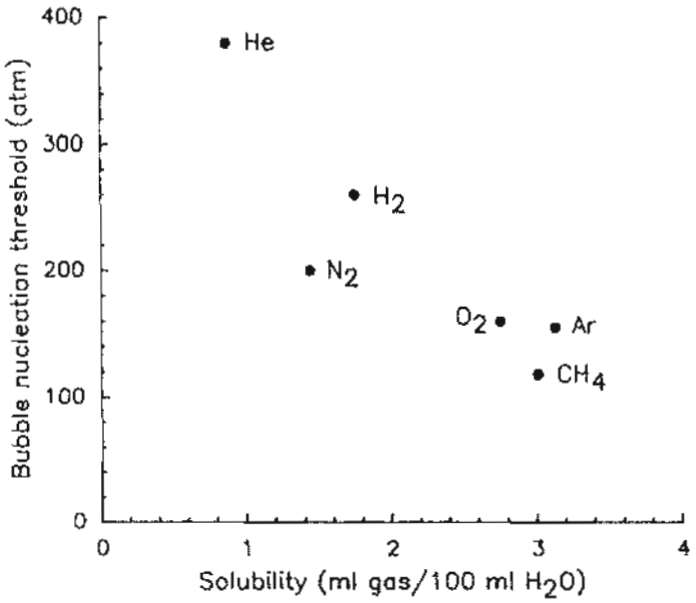

Fig. 1. Homogeneous nucleation thresholds for various gases in water.

The thresholds were derived from extensive series of determinations made on gas-saturated water, contained in 1 mm inner diameter glass tubes, during rapid decompression to baric pressure (7,8,35). Determinations by others (9), using a different experimental approach, are in satisfactory agreement.

Gas supersaturations are defined here as the gas equilibration gauge pressure in excess of ambient, baric pressure. Although gas solubility and hence, the gas tension, is affected by hydrostatic pressure (36), no correction is made here for this effect. The thresholds are plotted against the Bunsen solubility coefficients determined at 1 atm pressure. The threshold decreases with increasing solubility of the gas, but not in a simple relationship; other factors, as yet undetermined, are clearly involved.

When the solubility of the gas is altered by the addition of solutes to the water, the nucleation thresholds are changed very little (Table 1). Whereas all of the solutes produce substantial changes in the gas solubility coefficients in the solutions, little or no effect is apparent in the nucleation thresholds. A noticeable effect is obtained with 4 M of $MgCl_2$ but, even here, the degree of the change is very small compared with the nearly 8-fold difference in solubilities between the solution and pure water. The effect on the threshold may be due to such factors as an increased ordering of the water structure by the magnesium ions and changes in cohesive forces rather than decreases in the number of gas molecules in solution (37).

TABLE 1

Homogeneous bubble nucleation thresholds for argon in aqueous solutions

Solution	Argon solubility[a]	Threshold[b]
Water	3.77	155
4M $MgCl_2$	0.49	170
2M $MgSO_4$	0.97	155
2M $MgCl_2$	1.37	150
1M $MgSO_4$	1.89	150
4M NaCl	1.06	155
1M Na_2SO_4	1.62	150
2M NaCl	1.94	150
2M KCl	2.02	145
1M KCl	2.69	150

[a] in ml gas (STP)/ml solution, at 150 atm, 25°C.
[b] in atm supersaturation (±5 atm) at baric pressure.

The addition of most surfactants to water has little effect on the nucleation thresholds, even though the resultant surface tension change in the solutions is considerable (Table 2). Only with moderately low molecular weight surfactants (less than 365 daltons) is there a clear decrease in the threshold values, either for onset of bubble formation at the glass-water interface or within the bulk water (37).

TABLE 2

Bubble nucleation thresholds for argon
in 1% solutions of surfactants

Surfactant	Molecular weight	Surface tension[b]	Threshold[a]	
			Glass-water interface	Bulk water
Water		72	130	155
Na decyl sulfate	260	38	75	110
Na dodecyl sulfate	288	34	90	125
Na oleate	304	25	105	135
Cetyltrimethyl-NH_4Br	365	-	130	155
Alfonic 1012-60	378	25	125	155
Alfonic 1412-60	524	-	125	160
Triton X-100	628	-	125	150
Plurafac C-17	770	32	125	155
Priminox R-15	832	30	130	155
Triton X-165	950	-	130	155
Pluronic L64	2900	32	130	155

[a] in atm supersaturation (±5 atm) at baric pressure.
[b] in dynes/cm.

These results are not surprising in view of the dynamic nature of the nucleation process. The reduction in surface tension by surfactants is an equilibrium effect, which affects the stability of an existing gas bubble. When no free surface exists in the liquid, the surfactants are distributed randomly throughout it. As is found with the inorganic solutes, the presence of surfactant molecules *per se* is not likely to influence the initial cavity formation. Only after a free surface forms do the surfactant molecules decrease the surface tension. Therefore, in order to affect any newly formed vapor/gas cavity of subcritical size, the surfactant molecules must have sufficient time to aggregate, to align and to form an orderly structure around this nucleus to prevent its collapse. It is at this step that the molecular weight is a determinant factor. The smaller surfactant molecules, because of their higher diffusion rates, are able to aggregate around some of the unstable cavities, decrease the interfacial surface tension, and allow expansion with lower pressure of dissolved gas. Surface tension no doubt is an important factor in setting the nucleation threshold in liquids in general, but only if it is an inherent property of the liquid itself.

Bubble Formation In Vivo

Bubbles occur *in vivo* at quite low gas supersaturations. Haldane's classical supersaturation limit ratio of 2:1 for acceptable gas saturation relative to ambient decompression pressure has proved to be useful guide for avoiding serious bubble formation and subsequent decompression sickness, but many studies have indicated or confirmed that even lower levels of gas supersaturation may cause bubbles to appear (38). Although a number of different bubble formation mechanisms have been suggested over the years, none has

been shown to operate in animals, or has satisfactorily explained bubble occurrence in the wide variety of situations in which it is observed. We still do not know which mechanisms are involved, nor can we decide if non-spontaneous or spontaneous one are important. But some experimental data that have a direct bearing on this problem have become available.

Bubble formation from pre-existing nuclei has often been assumed to be the predominant source for the *in vivo* bubbles, either because no other explanation is readily apparent, or because the bubbles occur at such low gas supersaturations that the existence of pre-existing nuclei seems to be the only reasonable explanation. The convenient and often uncritical invocation of nuclei not only has circumvented the problem of nucleation, but may have detracted attention from issues more relevant to the early etiology of decompression sickness. Nevertheless, nuclei do appear to play a role in the initiation of bubbles in many circumstances. In the extensive experimental investigations of bubble formation in physical systems and in animals conducted by Harvey and colleagues (39,40), considerable evidence was obtained supporting the idea that nuclei chronically exist *in vivo* as well as *in vitro*. Bubbles developed on hyperbaric decompressions in tissues of anesthetized rats and cats, as well as in such quiescent bodies of liquid as vitreous humor and cerebrospinal and amniotic fluid. Yet, other results obtained by them, and by Blinks and colleagues (41), clearly indicate that nuclei are of lesser importance and are overpowered by different bubble formation mechanisms under certain physiological conditions. Tests performed on freshly drawn blood showed that no nuclei were present, and frog tissues did not develop bubbles unless exercised or disturbed mechanically.

Later investigations on various organisms have yielded additional, albeit still very indirect support for the existence of nuclei. For example, Evans and Walder (2) and Daniels et al. (42) have shown that hydrostatic pressurization of shrimp prior to subjecting them to hypobaric decompression resulted in a decrease in the number of bubbles formed in the animals, and Vann et al. (43) showed that the incidence of decompression sickness in rats was significantly reduced when the animals were subjected to a brief pressure pulse before decompression. The observed effects in shrimp and rats were ascribed to the collapse of nuclei during the pressurizations. Even though this type of evidence is favorable to the nuclei hypothesis, a direct link does not exist. The effects obtained conceivably could have other causes. Thus, the application of pressure may affect blood flow and muscle activity, overall or locally, or it may cause cell damage and release substances which in turn may influence the properties of surfaces involved in the bubble formation process. But assuming that nuclei are the underlying cause of some of the bubble formation *in vivo*, the question of whether the gas is contained in shells or crevices still must be resolved.

Recent studies have dealt with the role of shell-type nuclei in bubble formation in gelatin preparations (e.g.,21) apparently with the purpose of establishing model systems for the development of bubbles in animals. Bubble growth in gelatin is compared with the development of decompression sickness for various situations of compression/decompression, and certain similarities are recognized. However, in these comparisons it has been necessary to assign certain properties to the nuclei, for example, that the shells have a highly variable gas permeability dependent on hydrostatic pressure. With

radii below some critical dimension, the shells are assumed to be impermeable. Since such gas impermeability is a novel concept for organic membranes, further physical, theoretical basis and empirical work seems necessary to support the suggestion that this type of nucleus exists *in vivo* and that it exhibits properties similar to those in gelatin.

Crevice nuclei have been associated with the existence of stable nuclei on solid hydrophobic surfaces *in vitro* (1,22), and various cone-shaped models have been developed to explain the occurrence of bubbles in shrimp (26,42), and their presumed occurrence in bones (25). Some congruence has been obtained between the predictions of the hypothetical models and the observed development of bubbles. As is the case with the shell nuclei, the existence of crevice nuclei in animals has not been confirmed, and their location is highly uncertain. It has been suggested that the "ruffled" border in the resorption area of osteoclasts (25), intra- and extracellular lipid membrane surfaces and points of contact between lipid membrane surfaces (6) can meet the specific dimensions, shape, and surface properties that must be satisfied in order for the crevices to allows heterogeneous nucleation and bubble emergence. A hydrophobic surface is a particularly important requirement and it is difficult to reconcile this with the typical biological membrane composed of a phospholipid bilayer in which the exposed surfaces are hydrophilic with the hydrophobic part in the interior. Apart from the problem of whether or not crevices exist *in vivo*, it is questionable if any internal surface, in contact with the surfactant-containing aqueous fluids, has a high degree of hydrophobicity.

Spontaneous bubble formation is generally perceived as requiring higher gas supersaturations than does the growth of bubbles from existing nuclei. This is clearly the case with respect to homogeneous nucleation within biological fluids. Yet, since an organism is not a static body of liquid, it is possible that under favorable conditions of local negative hydrostatic pressure, homogeneous nucleation by dissolved gas could indeed be the triggering process. Some information, mostly based on circumstantial evidence, has accumulated to indicate that bubbles develop spontaneously in association with such factors as mechanical disturbances, muscle activity, or limb motion (39-41). But in many of these earlier studies it has been difficult to pinpoint the basic events, partly because of the complexity of the organisms investigated and partly because bubble occurrence was not monitored in sufficient detail to determine where the bubbles first form, or when they form in relation to other physical events.

These problems prompted us to examine bubble formation in various unicellular organisms and in some relatively simple animals during and after hyperbaric decompressions. Our purpose was two-fold: to establish if nuclei are common in organisms, and to establish if spontaneous nucleation of bubbles occurs *in vivo* at modest gas supersaturations. We selected organisms which could be monitored from the early embryological development stages to juvenile or adult stages, and which were translucent and suitable for microscopic observations. Most of the experiments were performed on small crustaceans, but other invertebrates, fish and amphibians were included (44-46).

In summary, these investigations reveal some important characteristics of the intracellular environment and of the organism as a whole. All unicel-

lular organisms and eggs are extremely tolerant to gas supersaturations. Usually, even supersaturations in excess of those causing spontaneous homogeneous nucleation of bubbles in pure water or aqueous solutions do not lead to internal bubble formation (32-34). This elevated resistance to nucleation probably is due to an increased ordering of the cell water. In multicellular organisms, the threshold for bubble formation decreases only modestly in the earliest stages of the development, with the threshold becoming similar to that of homogeneous nucleation in water (44,46). During the juvenile stages of development, the susceptibility to bubble formation decreases markedly, sometimes suddenly by as much as 50-100 atm during a period of a few days. In advanced stages, supersaturations of 5 atm or less often produced systemic bubble formation (42,43). Bubble formation at lower gas supersaturations often appears to be associated with activity or limb motions several minutes after decompression. Hydrostatic pressurizations (100-300 atm) prior to gas equilibration and decompression have no effect on either the number of animals that develop bubbles, or the number of bubbles that develop in each animal. Very slow, stepwise compressions with gas equilibration at each step, which would have tended to preserve nuclei that may have been present in the animals, have no detectable effect on the bubble occurrence when compared with fast compressions.

The tendency of bubbles to form with activity was explored further with the megalopal stage of the shore crab Pachygrapsus crassipes (47). One group had a small portion of their legs immobilized in a patch of epoxy thereby stopping major movements. Another group was free to move. In the latter group, bubbles often developed in the joints at the base of their legs at gas supersaturations of less than 5 atm with any of the 3 gases used (Figure 2).

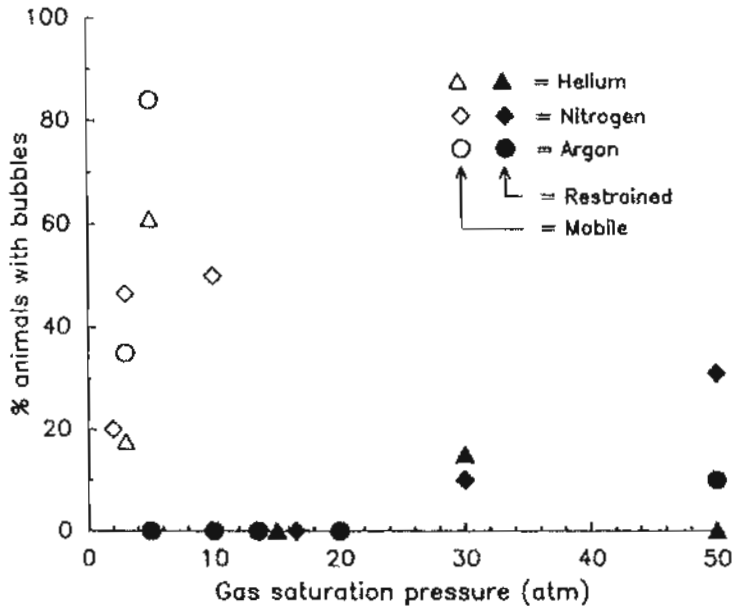

Fig. 2. Bubble formation in joints of mobile or immobile crabs (Pachygrapsus crassipes megalopa) after decompression from elevated nitrogen pressures (Replotted from 47).

The true gas supersaturations at the time the bubbles form are less than the values shown on the abscissa, because the bubbles usually form some time after decompression, when an unknown amount of the dissolved gas has dissipated. In the restrained animals, no bubbles were ever observed at supersaturations of 20 atm, or less. Even after decompressions from 50 atm, only a few of the animals developed bubbles.

The bubbles that form in free-moving crabs after decompression always redissolve in the hemolymph, usually 10-20 minutes after the animals are placed in aerated water. Crabs which had been decompressed from 5 atm and developed bubbles were allowed to redissolve them, and then were immobilized with epoxy as before, equilibrated with 15-50 atm nitrogen and decompressed. In no case did bubbles develop again (48). Clearly, nuclei are not present in these animals normally, and even when bubbles form and redissolve, no residual nuclei are left behind. Because the hemolymph into which the bubbles dissolve has proteins and other organic constituents in it, favorable conditions exist for the creation of shell-type nuclei from an existing gas phase. Yet, it does not happen. Therefore, nuclei stabilization is not an intrinsic property of these biological fluids.

Bubble formation frequently occurs at modest gas supersaturation in decompressed fish, often in the fins (45). Bubble formation in normal or lightly anesthetized (with MS222 or Quinaldine) sculpin and catfish is shown in Figure 3.

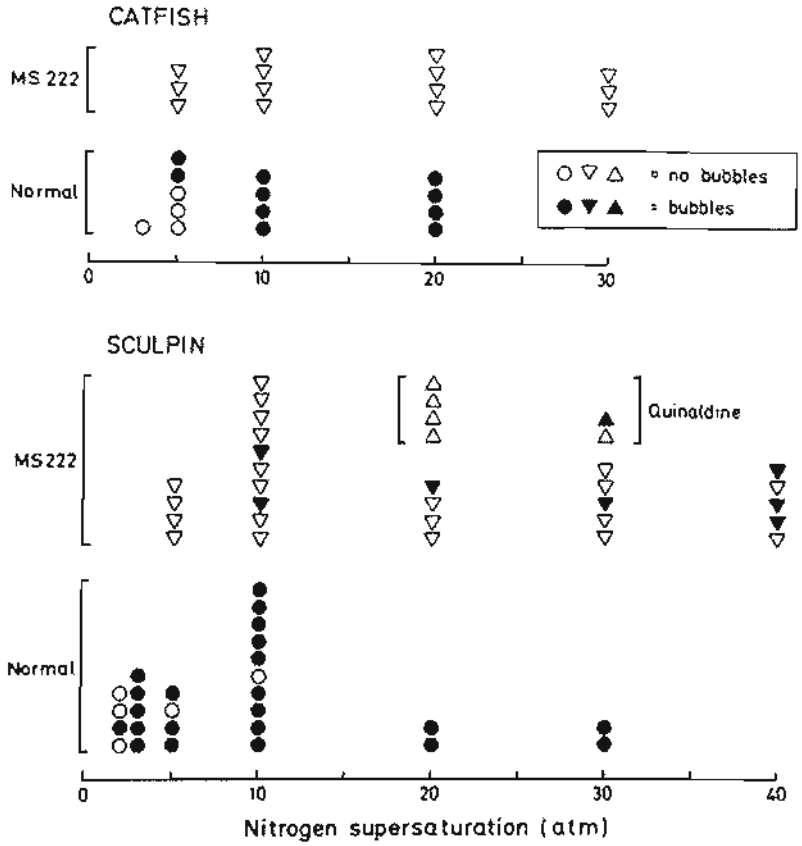

Fig. 3. Bubble formation in fins of normal and anesthetized fish after decompression from elevated nitrogen pressures (Replotted from 45).

In normal fish, bubbles usually appear in the caudal fins with nitrogen supersaturations of 10 atm, or less. In the anesthetized specimens, much higher gas supersaturations are required to induce any bubble formation; bubbles formed only rarely below 30 atm, and then probably only because the fish were not completely immobilized.

These investigations on crabs and fish demonstrate that even relatively gentle motion may nucleate bubbles. In the crabs, bubble formation appears to be localized where skeletal structures meet and rub against each other during flexing of the limbs. Either the surfaces may be making contact and then parting, somewhat like a rolling-ball motion, or they may be sliding laterally on each other. In the fins of the fish, the possibilities for rubbing or contacting surfaces is less obvious. The flexing of the rays, particularly at their base, is an essential element of the action of the fins and it seems reasonable to assume that these joint motions or the relative motion between the half rays, modest as they may be, are the triggering factor for the bubbles.

For tribonucleation to appear in either animal, the forces generated on the macroscopic level need not be exceptional. If the forces are transmitted to a small area of contact between two solid bodies, very large positive or, through viscous adhesion (49), negative forces can develop at the area of contact. When two solid, smooth surfaces are separated by a thin layer of liquid, and these surfaces are pulled apart, the tensile force generated in the center of the liquid is (in the absence of any hydrostatic pressure):

$$P_t = 3\eta VR^2/L^3$$

where P_t is liquid tension (dynes/cm^2), η is viscosity (dynes-sec/cm^2), V is velocity of separation (cm/sec), R is radius of the surfaces (cm), L is separating distance (cm). Viscosity for water at 20°C is 0.01 dynes/cm^2. If V = 0.1 cm/sec and R = 0.1 cm, then for $L = 10^{-4}$ cm, $P_t = 3 \times 10^{4}$ dynes/cm^2, or 29.6 atm. For $L = 10^{-5}$cm, $P_t = 3 \times 10^{5}$ dynes/cm^2, 2.96×10^{4} atm. The latter value is larger than any conceivable tensile strength of water (12). Although the area of the contacting surfaces is important in this type of estimate, their separation distance is the most crucial factor. This implies that the surfaces at the point of closest contact must be very smooth. If the surfaces are hydrophobic and therefore cannot provide the necessary adhesion, the cavitation will occur at the solid interface rather than in the body of the liquid. The resultant decrease in the stability of the system can only be crudely estimated; Campbell (16) calculated it to be factor of 20 for nearly perfectly hydrophobic surfaces. In the crabs and the fish where the dimensions severely limit the size of the separating surfaces, nucleation at the surfaces rather than in the center of the separating liquid may be the primary event.

Because the bubbles always were first observed close to the skeletal structures, it is unlikely that they were "seeded" from the adjacent tissues. But it cannot be excluded that mechanical action in the musculature associated with the bending and straightening of the skeletal structures may create large tensile forces at non-skeletal surfaces. Any aqueous phase confined in stretched cells and fibers potentially could be subjected to such actions. But no clear evidence for this type of process has been found.

These investigations have provided some compelling evidence for spontaneous nucleation of bubbles in organisms at very modest gas supersaturation. The mechanisms involved are more uncertain, although the direct dependence of bubble formation on joint motion strongly suggests that tribonucleation is an important one. The degree to which these conclusions have a universal applicability and may be extended to include higher organisms cannot yet be ascertained. Even though the differences in size, morphological design, physiological function, fluid composition and other factors are vast between the organisms examined here and mammals, the latter may be partitioned functionally into smaller entities with similarities to the simpler systems. Conditions suitable for tribonucleation, for example, may be very common in the mammals. It could occur in the joints, where muscles and tendons slide across bones, or each other, and in capillaries and other blood vessels subjected to collapse and expansion by action of the surrounding musculature. Two problems which should be addressed in the future are: What types of surfaces are sufficiently non-deformable to allow viscous adhesion to generate substantial negative hydrostatic pressure in the liquid or at the liquid-surface interface and, hence, lead to nucleation of bubbles? Is it possible that surfaces which are not part of skeletal structures could create conditions in the interface liquid favorable for the nucleation process to proceed? If so, nearly endless sources for spontaneous formation of bubbles may exist.

In retrospect, it appears that the role of gaseous micronuclei in organisms has been overestimated, and that the tendency to ascribe the formation of bubbles to a single mechanism or source is an oversimplification of the problem. The large body of experimental evidence indicates that different mechanisms may operate simultaneously, perhaps even with synergistic effects. Predominance of one over the others likely depends on a number of external or internal factors, among which mechanical forces may be particularly important. In our laboratory we are continuing to explore the various processes which are likely to influence the metastability of the internal fluids and tissues, using relatively simple biological systems. We expect that these investigations, together with those of others, will give us a better understanding of the spontaneous nucleation processes and help shed light on some of the unresolved problems I have touched upon here.

REFERENCES

1. Harvey EN. Physical factors in bubble formation. In: Fulton JF, ed. Decompression sickness. Philadelphia, PA: Saunders, 1951:90-411.

2. Evans A, Walder DN. Significance of gas micronuclei in the aetiology of decompression sickness. Nature 1969; 222:251-252.

3. Ikels KG. Production of gas bubbles in fluids by tribonucleation. J Appl Physiol 1970; 28:524-527.

4. Vann RD, Clark HG. Bubble growth and mechanical properties of tissue on decompression. Undersea Biomed Res 1975; 2:185-194.

5. Hills BA. Decompression sickness, Vol. 1, The biophysical basis of prevention and treatment. New York, NY: John Wiley and Sons, 1977.

6. Tikuisis P, Johnson WR. Conditions for heterogeneous nucleation in the physiological environment. In: Bachrach AJ, Matzen MM, eds. Underwater physiology VIII. Proceedings of the eighth symposium on underwater physiology. Bethesda, MD: Undersea Medical Society, Inc., 1984:107-118.

7. Hemmingsen EA. Cavitation in gas-supersaturated solutions. J Appl Phys 1975; 46:213-218.

8. Hemmingsen EA. Spontaneous formation of bubbles in gas-supersaturated water. Nature 1977; 267:141-142.

9. Finkelstein Y, Tamir A. Formation of gas bubbles in supersaturated solutions of gases in water. AIChE J 1985; 31:1409-1419.

10. Reid RC. Superheated liquids. Am Scient 1976; 64:146-156.

11. Dean RB. The formation of bubbles. J Appl Phys 1944; 15:446-451.

12. Sette D, Wanderlingh F. Thermodynamic theory of bubble nucleation induced in liquids by high-energy particles. J Acoust Soc Am 1967; 41:1074-1082.

13. Hayward ATJ. Tribonucleation of bubbles. Brit J Appl Phys 1967; 18:641-644.

14. Campbell J. The tribonucleation of bubbles. Brit J Appl Phys (J Phys D) Ser 2 1968; 1:1085-1088.

15. Pease DC, Blinks LR. Cavitation from solid surfaces in the absence of gas nuclei. J phys coll Chem 1947; 51:556-567.

16. Fürth R. On the theory of the liquid state. II. Application of the hole theory to superheated liquids and supersaturated solutions of gases in liquids. Proc Cambr Phil Soc 1941; 37:276-280.

17. Fisher JC. The fracture of liquids. J Appl Phys 1948; 19:1062-1067.

18. Cotton DJ. A theory of cavity formation at solid-liquid interfaces. Phil Mag 1972; 25:77-85.

19. Gerth WA, Hemmingsen EA. Heterogeneous nucleation of bubbles at solid surfaces in gas-supersaturated aqueous solutions. J Coll Interface Sci 1980; 74:80-89.

20. Fox FE, Herzfeld KF. Gas bubbles with organic skin as cavitation nuclei. J Acoust Soc Am 1954; 26:984-989.

21. Yount DE. Skins of varying permeability: A stabilization mechanism for gas cavitation nuclei. J Acoust Soc Am 1979; 65:1429-1439.

22. Knapp RT. Cavitation and nuclei. Trans Am Sec Mech Eng 1958; 80:1315-1324.

23. Yount DE, Gillary EW, Hoffman DC. Microscopic study of bubble formation nuclei. In: Underwater physiology VIII. Proceedings of the eighth symposium on underwater physiology. Bethesda, MD: Undersea Medical Society, Inc., 1984:119-130.

24. Johnson BD, Cooke RC. Generation of stabilized microbubbles in seawater. Science 1981; 213:209-211.

25. Ward CA, Johnson WR, Venter RD, HO S, Forest TW, Fraser WD. Heterogeneous bubble nucleation and conditions for growth in a liquid-gas system of constant mass and volume. J Appl Phys 1983; 54:1833-1843.

26. Tikuisis P. Modeling the observations of in vivo bubble formation with hydrophobic crevices. Undersea Biomed Res 1986; 13:165-180.

27. Tolman RC. The effect of droplet size on surface tension. J Chem Phys 1949; 17:333-337.

28. Eriksson JC. On the thermodynamic theory for the effect of pressure on surface tension. Acta Chem Scand 1962; 16:2199-2211.

29. Blander M, Katz JL. Bubble nucleation in liquids. AIChE J 1975; 21:833-848.

30. Harvey EN, Barnes DK. McElroy WD, Whiteley AH, Pease DC, Cooper KW. Bubble formation in animals. I. Physical factors. J Cell Comp Physiol 1944; 24:1-22.

31. Weathersby PK, Homer LD, Flynn ET. Homeogeneous nucleation of gas bubbles in vivo. J Appl Physiol 1982; 53:940-946.

32. Hemmingsen BB, Hemmingsen EA. Intracellular bubble formation: Differences in gas supersaturation tolerances between Tetrahymena and Euglena. J Protozool 1983; 30:608-612.

33. Hemmingsen BB, Steinberg NA, Hemmingsen EA. Intracellular gas supersaturation tolerances of erythrocytes and resealed ghosts. Biophys J 1985; 47:491-496.

34. Hemmingsen EA, Hemmingsen BB, Owe JO, Andersen HT. Lack of bubble formation in hypobarically decompressed cells. Aviat Space Environ Med 1987; 58:742-746.

35. Gerth WA, Hemmingsen EA. Gas supersaturation thresholds for spontaneous cavitation in water with gas equilibration pressures up to 570 atm. Z Naturforsch 1976; 31a:1711-1716.

36. Wiebe R, Gaddy VL, Heins C. The solubility of nitrogen in water at 50°, 75°and 100°from 25 to 1000 atmospheres. J Am Chem Soc 1933; 55: 947-953.

37. Hemmingsen EA. Effects of surfactants and electrolytes on the nucleation of bubbles in gas-supersaturated solutions. Z Naturforsch 1978; 33a:164-171.

38. Daniels S. Bubble formation in animals during decompression. In: Brubakk AO, Kanwisher JW, Sundnes G, eds. Diving in animals and man. Trondheim, Norway: The Royal Norwegian Society of Sciences and Letters, 1986: 229-258.

39. Harvey EN, Whiteley AH, McElroy WD, Pease DC, Barnes DK. Bubble formation in animals. II. Gas nuclei and their distribution in blood and tissues. J Cell Comp Physiol 1944; 24:23-34.

40. Harvey EN, McElroy WD, Whiteley AH, Warren GH, Pease DC. Bubble formation in animals. III. An analysis of gas tension and hydrostatic pressure in cats. J Cell Comp Physiol 1944; 24:117-132.

41. Blinks LR, Twitty VC, Whitaker DM. Part II. Bubble formations in frogs and rats. In: Fulton JF, ed. Decompression sickness. Philadelphia, PA: Saunders 1951:145-164.

42. Daniels S, Eastaugh KC, Paton WDM, Smith EB. Micronuclei and bubble formation: A quantitative study using the common shrimp, Crangon crangon. In: Bachrach AJ, Matzen MM, eds. Underwater physiology. VIII. Proceedings of the eighth symposium on underwater physiology. Bethesda, MD: Undersea Medical Society, Inc., 1984:147-157.

43. Vann RD, Grimstad J, Nielsen CH. Evidence for gas nuclei in decompressed rats. Undersea Biomed Res 1980; 7:107-112.

44. McDonough PM, Hemmingsen EA. Bubble formation in crustaceans following decompression from hyperbaric gas exposures. J Appl Physiol 1984; 56:513-519.

45. McDonough PM, Hemmingsen EA. Swimming movements initiate bubble formation in fish decompressed from elevated gas pressures. Comp Biochem Physiol 1985; 81A:209-212.

46. Ryan WL, Hemmingsen EA. Gas supersaturation thresholds for bubble formation in and damage to sea urchin embryos. Biol Bull 1988; in the press.

47. McDonough PM, Hemmingsen EA. Bubble formation in crabs induced by limb motions after decompression. J Appl Physiol 1984; 57:117-122.

48. McDonough PM, Hemmingsen EA. A direct test for the survival of gaseous nuclei *in vivo*. Aviat Space Environ Med 1985; 56:54-56.

49. Banks WH, Mill CC. Tacky adhesion - A preliminary study. J Coll Sci 1953; 8:54-56.

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DISCUSSION

DR. MASUREL: I want to describe some experiments conducted at CERTSM in Toulon with goats exposed at 1000 msw. We detected intravascular bubbles during compression and on the bottom. When the animal reached approximately 800 msw (Figure 1) we noted some bubbles that continued until 1000 meters. This was very strange because we hadn't changed the gases. Figure 2 shows bubbles that appeared in the largest goat (50 kg) at 1000 msw. The first bubbles appeared after more than 100 hours and increased after about 200 hours. Bubbles continued during decompression until the surface. The number of bubbles rose as the speed of decompression increased. We don't know how to explain the appearance of bubbles after such a long time at stable pressure. Perhaps turbulence caused cavitation at the heart valves. The gas concentration at 1000 msw is so high that dissolved gases may diffuse very rapidly into cavitation nuclei and grow into bubbles.

DR. HAMILTON: Dr. Masurel, did you decompress your animals successfully after bubbles were formed at that high pressure?

DR. MASUREL: Yes, absolutely.

DR. LUNDGREN: Dr. Masurel, you showed us these slides of bubbles in goats that were at a stable depth. Can you convince us that what you saw were bubbles. You saw echoes, yes, but can you help us to believe that this animal is just spontaneously bubbling at a 1000 meters? For instance, if you tried a compression at the time when there was supposed bubbling, could you make those signals disappear?

DR. MASUREL: We wanted to compress the animals to see if the bubbles would decrease or disappear, but at 1000 msw it was not possible to increase the pressure.

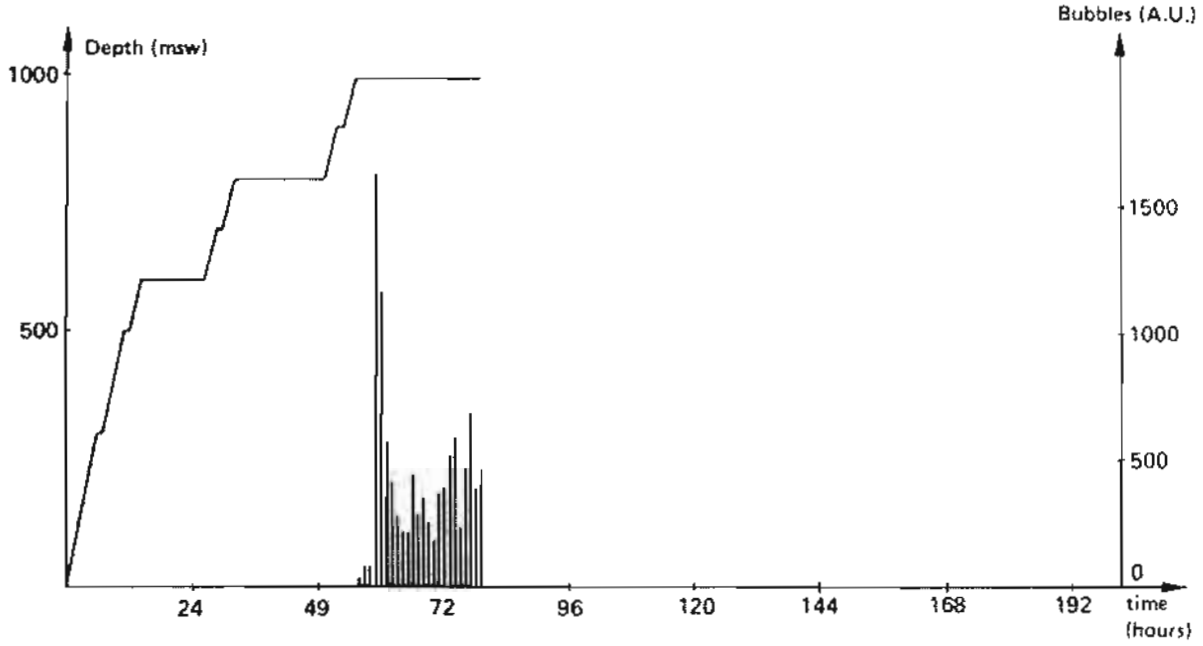
DR. LUNDGREN: What convinced you that what you saw were signals emanating from bubbles and nothing else?

DR. MASUREL: Because we have more than 15 such experiments, and the signals we observed had exactly the same characteristics as bubble signals. We have practiced bubble detection for more than 15 years, and I think we have good experience.

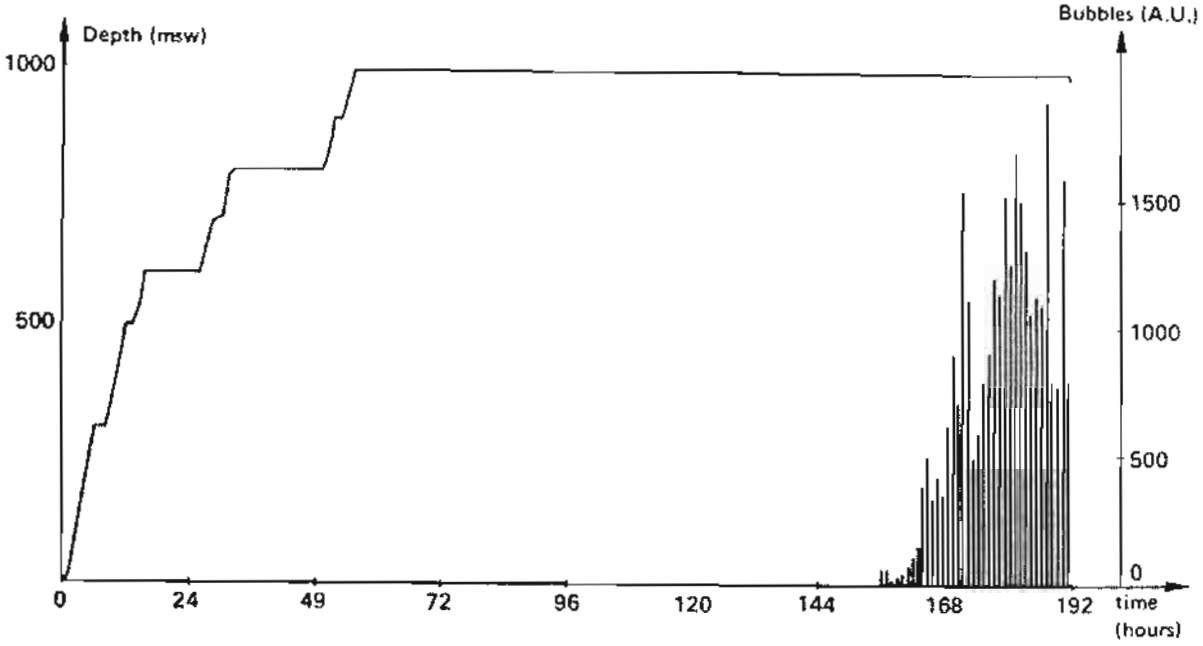
CAPTAIN THALMANN: You compressed the crabs, decompressed them, and observed the bubble formation and resolution of bubbles. Then you subjected them to the second exposure, and bubbles did not re-appear upon decompression. With a longer surface interval between dives, do you think bubbles would have re-appeared after the second dive? If so, would this represent a regeneration phenomenon? How do you reconcile your data with Evans and Walder's work with shrimp (1).

DR. HEMMINGSEN: During the first gas saturation, the animals were free to move and, presumably, this motion was the cause of the bubbles that formed upon decompression. The bubbles dissolved during the 10- to 30-minute interval between saturations. During the second saturation the animals were immobilized, and no bubbles were noted upon decompression. This supports the hypothesis that motion induces bubble formation. No external pressure was applied to dissolve the bubbles between saturations, and hence no regeneration of nuclei would have been required if they had been present.

DR. MILLER: Dr. Hemmingsen, I didn't realize either that the animals were immobilized between the two dives, I think it's quite extraordinary as this reproducibly produces decompression sickness in a mammal. You dive an animal, absorb some inert gas, and then decompress with or without



ULTRASONIC DETECTION OF CIRCULATING BUBBLES
AT THE 1000-MSW STOP
(WITH THE EWE CALLED "CLY.")
FIGURE 1



ULTRASONIC DETECTION OF CIRCULATING BUBBLES
AT THE 1000-MSW STOP
(WITH THE EWE CALLED "CLO.")
FIGURE 2

From Proceedings of EUBS Annual Meeting, Goteburg, Sweden, 1985.

bubbles. After a surface interval, you have a deeper dive with a rapid decompression, and this invariably causes decompression sickness. In your experiments, however, the absolute opposite seems to occur.

DR. HEMMINGSEN: Yes, that's true, though I cannot draw the conclusion that our observations are applicable.

DR. KUNKLE: Dave Yount examined tribonucleation 7 or 8 years ago to determine theoretically whether it could occur in humans (2). The pressure differentials that develop during tribonucleation depend very strongly on the separation between surfaces. As you pointed out, at 1 micron separation you could theoretically get a tribonucleation pressure of around 30 atmospheres. This pressure would vary as the third power of the separation. We looked at that same equation and came to the conclusion that in any living body surface the separations must be nearly the size of the cells, a couple of microns. Surface roughness, however, would limit the tribonucleation pressure to 10 bars, which would contribute to the tendency to form bubbles, but by itself doesn't explain why supersaturations of 150 atmospheres are necessary to get bubble formation in water. I think this can be demonstrated if we put on a Doppler but do not have bubbles. There seems to be a supersaturation threshold of about half an atmosphere in humans to cause gas nuclei to grow into bubbles. Do you believe that tribonucleation is a direct cause of bubbles in humans?

DR. HEMMINGSEN: I don't know if tribonucleation occurs in humans, but it seems to occur in crabs. Another point concerning tribonucleation is that it does not necessarily have to occur in joints. It could occur with very small solid surfaces on the cellular level as well. The tendency has been to look at tribonucleation only as a joint phenomenon.

DR. VANN: I refer Dr. Kunkle to a paper by Unsworth and colleagues on cracking knuckles. They demonstrated during the cracking of human joints that a vaporous bubble forms and collapses with an audible pop. Joints with eccentric articular surfaces generate the highest negative pressure and crack most easily.

DR. DANIELS: Dr. Hemmingsen, I think that perhaps your most important comment was that you shouldn't get sidetracked into thinking of a single mechanism for bubble formation. There are a number of possibilities and we must consider all of them, because in different experimental systems they might have a different relative importance. We mustn't start searching for the one mechanism which governs bubble formation under all conditions. I was puzzled that you couldn't find any substantial influence of ionic concentration in your experiments. We've been looking at the effect of different ions on bubble formation thresholds recently, and a number of other groups have done so also over the last 10 years. We find the bubble formation threshold is very markedly dependent on the ionic composition. The problem is that the effect of the concentration of the ions is highly non-monotonic. If you have the wrong concentration, you get a totally erroneous result, so you have to be very careful at looking at a range of concentrations of different ions. Did you study different concentrations with your experiments.

DR. HEMMINGSEN: Yes, but what type of bubble formation are you concerned with?

DR. DANIELS: We're studying ultrasonically generated bubbles.

DR. HEMMINGSEN: I was referring to bubbles that are induced by dissolved gas spontaneously separating from the liquid. I do not know what effect solutes have on the tensile strength of water. We studied a large variety of solutes at various concentrations and in no case did the

solutes have any effect on the bubble formation thresholds. I feel very confident about these results.

DR. VANN: I believe Dr. Hemmingsen was referring to de novo nucleation, whereas Dr. Daniels was speaking about nucleation from gas nuclei. When gas nuclei are present, additives have a significant effect, but without nuclei (de novo nucleation) additives have little effect.

DR. DANIELS: Dr. Hemmingsen, I'd like to make a comment in defense of gels, as one who's used them a lot. You remarked that extrapolating from gels to animals is difficult. I do agree. On the other hand, all our work shows that the gels have the same threshold as animals for bubble formation. We've looked at the effect of temperature on bubble formation with gel, it bears out the results with animals. We've also looked at the effect of hydrostatic compression, and it mirrors what we see in animals. As a model system, gel does not seem too bad, although it doesn't have a circulation. I was very puzzled by your observation of 10 to 15 minutes for the bubbles to disappear. In our shrimp, typically it would have been 3 or 4 hours at the shortest for bubbles to disappear, and in mammals, it's at least an hour. Ten to fifteen minutes just struck me as amazing.

DR. HEMMINGSEN: Perhaps I can shed some light on that. When a bubble appears in a joint of a crab it is because the joint surfaces separate and produce a negative pressure. Conversely, a positive pressure can be generated, and this may help to dissolve the bubble. The fact is that the bubbles dissolved as stated and did not reappear.

DR. DANIELS: Did the bubbles disappear before you immobilized them or afterwards?

DR. HEMMINGSEN: They had not completely disappeared by the time the animals were immobilized.

DR. DANIELS: Once you'd immobilized them, there shouldn't be a positive pressure to accelerate solution.

DR. HEMMINGSEN: Movement does not stop completely during immobilization. The animal could perform a swaying motion. This motion was insufficient to generate the negative hydrostatic pressure necessary for bubble formation, but may be sufficient to help dissolve the bubbles.

DR. KINDWALL: I'd like to relate Dr. Hemmingsen's fascinating work to a clinical situation. A man who had been exposed at a 2-bar gauge pressure for some hours went into shock after decompression and delivered a hematocrit of 60. We treated him at 3 ATA on oxygen for 4 hours. Subsequently, in the intensive care unit, we did a phlebotomy, and upon withdrawing the blood into a vacuum bottle noticed massive bubbles all the way up through the vacuum line. We had never seen this before in any other patient. Now, we've been moving toward treating decompression sickness at 2.8 ATA rather than at higher pressures, as we have been led to believe that oxygen at 2.8 ATA gives us better statistical results. I wonder if it might not be a more effective treatment to compress a patient to 6 or 8 ATA for a few seconds to remove gas nuclei before oxygen exposure at 2.8 ATA. Perhaps an animal trial of this procedure would be interesting.

DR. HEMMINGSEN: I believe that it would result in dissolution of some of the bubbles. It is an interesting possibility.

DR. HAMILTON: I would like to mention a situation where very much lower pressures can cause bubble formation. Fish swimming below dams where nitrogen is entrained at slight supersaturation by falling water develop bubbles in their gills after several hours. These bubbles are ultimately fatal. This gas bubble or gas lesion disease has been well

studied. The solution was to redesign the dams so that they do not entrain so much nitrogen. In this situation, you have very low supersaturation for a long time in an active creature, and it does generate bubbles. Can you comment on that?

DR. HEMMINGSEN: I'm aware of this fish bubble disease problem. As you state, it takes long exposure periods before bubbles develop. How long it would take for other animals to develop bubbles under similar conditions, I don't know. The gas supersaturations in our animals may be lower than indicated. The animal is saturated at a certain pressure, decompressed, and then observed for bubble formation after some time. During this period, some of the gas in the animal has dissipated, and we really do not know at which pressure bubble formation occurred. I have always been intrigued by the fact that prolonged exposure of fish to very low gas supersaturation leads to bubble formation. I wish I knew why. It is a problem that should be studied.

DR. VAN LIEW: We've heard some remarkable observations this morning: bubbles form without any decompression and then don't form when there was a strong decompression. Perhaps these are part of a big picture that we don't see clearly. Tribonucleation must play a role in those animals in which you can stop bubble formation by immobilizing the joints, but I doubt that tribonucleation can explain all bubbles in all animals.

I've been carrying around in my mind a puzzle for many years. Fetuses that die in utero have observable gas in the large blood vessels. If the fetus is dead, it's not tribonucleating or moving anymore, but perhaps he did just before he died. It certainly doesn't have large supersaturation, although there probably is a great deal of carbon dioxide available in the dead tissue. It is additional evidence that bubbles are probably possible most any place and time.

DR. GILBERT: Dr. Hemmingsen, several years ago we decompressed astronauts after a considerable oxygen prebreathe to 10.2 psi and then to 4.3 psi, where they exercised to simulate extravehicular activity. We then recompressed them to 10.2 psi for about 2 hours followed by decompression to 4.3 psi for about 3 hours of exercise. This protocol was repeated for 3 days. While at 4.3 psi, we used precordial Doppler to monitor bubbles in the pulmonary artery. During the first decompression on the first day, we saw significant bubble formation. On each succeeding day there were fewer bubbles during the first decompression. On all days few or no bubbles were detected during the second decompression. This tends to support your findings in the crab that bubble nuclei decrease or disappear. However, it is interesting to note that during the second decompression of each day there were few or no bubbles, although each astronaut exercised at the same level as during the first decompression of that day. I offer no explanation for this.

DR. WARD: Dr. Hemmingsen, may I see if I can state your results in my terms. The tribonucleation problem is not nucleation of bubbles in the conventional sense where the bubble is formed ab initio. Tribonucleation is a mechanism by which the nuclei existing in the body can be replenished with time. It's very important for us to consider the La Place equation which can only be derived under equilibrium conditions. For a bubble to grow, it would have to be greater than that equilibrium size. The large pressures that are produced by tribonucleation are not necessarily valid if we accept the fact that the nuclei that are being produced are subcritical in size. Now, if this equilibrium does not exist, then gas is being transferred from the nuclei back into the fluid from which it came.

Thus, decompression of the animal would give rise to the supercritical bubble and its subsequent growth. Would you agree with that summary?

DR. HEMMINGSEN: Yes, if nuclei were present, they would simply expand into bubbles when subjected to negative pressures generated by tribonucleation. The fact that a second decompression did not generate nuclei while the first one did raises the question of why would nuclei during the second decompression have a smaller critical size than nuclei during the first one?

DR. WARD: If you had more gas, then the nuclei would be smaller.

DR. HEMMINGSEN: I do not understand why the nuclei in the second case would have a smaller size than in the first case. I must be missing a point here.

DR. WARD: Are the gas concentrations higher in the second case?

DR. HEMMINGSEN: Sometimes they are higher, sometimes they are the same, and sometimes they are lower, depending on the experiment.

DR. WARD: How much time did you give the system to reform the nuclei?

DR. HEMMINGSEN: From 10 to 30 minutes.

DR. WARD: Could that be the explanation for why the nuclei weren't there in the second case?

DR. HEMMINGSEN: If nuclei were the origin of the bubbles, why would these nuclei change during the procedure, and why would they become so small that they would not be effective in the second decompression?

DR. WARD: Let's suppose that tribonucleation does form the nuclei. Then if there were adequate time, why wouldn't the nuclei form again as a result of tribonucleation of subcritical nuclei, not nuclei that would grow to a macroscopic size?

DR. HEMMINGSEN: I assume that there are no preformed nuclei because hydrostatic pressurization of the animals just before the gas equilibrations had no effect on the bubble formation.

DR. JAMES: Spontaneous bubble formation has been observed with ultrasound in both the right and left sides of the heart in patients with valve disease. I'd just like to ask Dr. Hemmingsen and Dr. Masurel whether they think that the sound pressure levels being used in these ultrasound techniques are sufficient to influence bubble nucleation?

DR. MASUREL: We have tried to induce bubbles with a 1000 more energy than we use during bubble detection. No bubbles were generated.

DR. HEMMINGSEN: If there is a certain degree of meta stability in the system and another stress is imposed on it, something may happen. The ultrasonic energy levels alone may not be enough to create bubbles, but if they add to an existing meta stability, the bubble formation threshold may be exceeded.

REFERENCES

1. Evans A, Walder DN. Significance of gas micronuclei in the aetiology of decompression sickness. Nature 1969; 222(190):251-252.
2. Yount DE. The physics of bubble formation. In: Hong SK, ed. Proceedings of the international symposium on man in the sea Undersea Medical Society, 1975:V144-V166.

BUBBLE FORMATION IN BLOOD AND URINE

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Bubbles are believed to be the cause of symptoms associated with inadequate decompression to altitude or from pressure. Whether these bubbles form intravascularly or extravascularly is uncertain. In 1774, Erasmus Darwin published the results of experiments addressing this question (1). Benjamin Franklin communicated this work to the Royal Society. We have repeated Darwin's experiments.

Darwin's purpose was to test the current theory that an elastic vapor in the blood expands upon exposure to sub-atmospheric pressure and causes the symptoms of decompression sickness. He withdrew about four ounces of blood from an attendant's arm and placed it under the vacuum receiver of an air pump. Many bubbles were observed. In a second experiment, a blood-filled jugular vein secured at both ends with ligatures was removed from a sheep. This method prevented the blood from contacting atmospheric air. The gall bladder and urinary bladder were obtained in a similar manner. Upon subjecting these specimens to reduced pressure, no internal bubbles were observed. Similar experiments with a swine produced the same results. Darwin concluded that exposure of his attendant's blood to atmospheric air promoted bubble formation. If such exposures were prevented, intact animal bodies could withstand large pressure reductions.

Methods

We repeated Darwin's experiments with 17 rats, 8 rabbits and 6 dogs. The animals were anesthesized with pentobarbital before specimens were obtained. Blood-filled sections of inferior vena cava contained between two sutures were removed from all animals. In addition, urinary bladders were removed from the rabbits. Sections of blood vessels filled with a dilute mixture of blood and saline served as controls.

Experimental and control specimens were placed in separate beakers of saline and decompressed to altitudes of 60-75,000 feet (<0.06 ATA) in 30 minutes where they were held for five hours while being observed through a window. The specimens floated when bubbles formed. This was confirmed after descent to sea level by dissection under water. Residual bubbles were always found in specimens which had floated but not in those which had not floated.

Results

Table 1 shows the results of bubble formation in the inferior vena cavae of rats, rabbits, and dogs. No bubbles formed in any of the experimental specimens, but bubbles developed in all control vessels. No bubbles were

observed in the urinary bladders of eight rabbits under similar conditions.

Table 1. Bubble formation in inferior vena cavae at 60-75,000 feet.

	Experimental		Control	
	Bubbles	No Bubbles	Bubbles	No Bubbles
Rats	0	17	17	0
Rabbits	0	8	8	0
Dogs	0	6	3	0

Discussion

Our results show that bubbles do not form in stagnant blood at 60-75,000 feet (<0.06 ATA) and suggest that bubbles in blood do not originate *in situ*. This is in opposition to the observation (2) of intravascular bubbles in humans at altitudes above 10,000 feet (0.69 ATA), but in agreement with the work of Harvey (3) and Ikels (4) who found blood to be resistant to bubble formation.

References

1. Darwin E. Experiments on animal fluids in the exhausted receiver. Philos Trans 1774; 64:344-349.

2. Conkin J, Edwards BF, Waligora JM, Horrigan DJ. Empirical models for use in designing decompression procedures for space operations. Springfield: NTIS, NASA TM-100456, 1987.

3. Harvey EN, Barnes DK, McElroy WD, Whiteley AH, Pease DC, Cooper KW. Bubble formation in animals. I. Physical factors. J Cellular Comp Physiol 1944; 24(1):1-22.

4. Ikels KG. Production of gas bubbles in fluids by tribonucleation. J Appl Physiol 1970; 28:524-527.

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VACUUM PHENOMENA: AN ANNOTATED BIBLIOGRAPHY

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The following bibliography describes much of the vacuum phenomenon literature. It is divided into the categories by anatomical region: spine, disks, vertebral body, spinal canal, limbs, hip, osteonecrosis, symphysis pubis, sacroilliac joint, infection and cracking joints, but there is considerable overlap between categories. Each category lists references alphabetically by first author and last two digits of the date. References are followed by descriptive comments underlined for emphasis. Vacuum phenomenon are referred to as VP.

SPINE

Bohrer (86). The vacuum sign is an indication of a separated annulus. The anteroinferior margin of a cervical interspace annulus fibrous separates from adjacent bone in hyperextension injury (whiplash). This was noted in 11 patients (4% of adult cervical spine injury seen in ER). Vacuum sign may be due to old injury or an acute injury.

Carrera (80). Describes lumbar facet joints seen on CT-scan. VP are defined by tissue absorption of ≤100 Hounsfield Units (HU) in joint spaces. May be due to lax joint capsule, uneven apposition of joint surfaces, or distractive forces in normal joint.

Hilton (84). A vertebral rim lesion (avulsed annulus) can be recognized by a small radiographic translucency (VP). Annulus is detached from the vertebral body.

Isu (83). VP defined ≤ 0 HU on CT-scan. Had 0.5 x 0.5 mm pixel resolution with 2-4 mm tissue slices. 30% of 37 patients with cervical disk disease had VP defined as -20 ≤ HU ≤ -925. Air is -1000 HU. Larger volumes are closer to true air. VP volumes were 9 to 240 ml with a mean of 41 ml. VP may be associated with osteomyelitis, Schmorl node formation, spondylosis and vertebral collapse. CT finds VP better than x-ray. CT revealed VP in 30% of cases whereas x-ray revealed no VP.

Lefkowitz (82). Vacuum facet phenomenon is gas in lumbar facet joint. Caused by traction between opposing articular facets. A useful sign indicating the presence of degenerative spondylosis.

Resnick (81). The appearance of VP does not uniformly indicate "degenerative" disk disease (primarily intervertebral osteochrondrosis) and may accompany other processes (vertebral osteomyelitis, Schmorl node formation, spondylosis deformans, vertebral collapse with osteonecrosis). Location and appearance of VP are diagnostically helpful. The "crescent" sign related to a radiolucent region at a linear or semi-circular fraction through subchrondral necrotic bone is virtually

pathognomonic of bone necrosis and is reminiscent of osteonecrosis of the femoral or humeral head and to VP in vertebrae.

Reymond (72). Three cases show small, smooth, lucent clefts (VP) adjacent to the cervical vertebral body end-plate anteriorly after moderate to severe neck injury. Disc is grossly intact but has partially torn away from vertebral body end-plate. VP is only radiographic sign. With the injured cervical spine in extension, the potential space where the disc is partially avulsed from the cartilaginous end-plate is pulled apart. The lucent clefts were noted within hours of the acute trauma and persisted unchanged for 2 months and up to 5 years. There are no potential spaces (VP) within a normal disc nor at its junction with the endplate. Therefore normal volunteers show no lucent cleft. VPs seen only in extension, disappears in flexion.

Schabel (79). Vertebral VP disc and vertebrae in 12/42 (28%) women with breast cancer metastatic to bone. No significance other than diagnostic.

Tash (86). Acute intervertebral gas following vertebral fracture demonstrated by CT. Compression fracture with VP in adjacent disks. Back pain in 47 year old man after trip and fall. No gas by x-ray, but gas was present by CT 4 days later. Knutsson (42) thought disk material dries up and irregular cracks appear with disk degeneration.

Yetkin (86). Gas in spinal articulations, lumbar facet joints, disks and sacroiliac joint. Synovial cysts (Spencer 83, Schulz 84) result from degeneration of facet joint particularly at L4-5 leading to synovium-lined cystic structures that communicate with joint space. Sequential CT studies show synovial cysts filled alternatively with fluid or gas suggesting communication of cyst with a facet joint where VP exists. VP is of little clinical significance in disc or sacroiliac joint.

DISKS

Beers (84). VP also called Knutsson sign. Found in lumbar disk and retroperitoneal soft tissues.

Daffner (81). Pseudo vacuum phenomenon of cervical disc. Mach band due to overlapping shadows. Differentiate between true and pseudo VP sign. 65% in 78 adults, 50% in 36 children.

Deeb (76). Two brothers with ochronosis. Multiple vacuum discs as earliest sign of degenerative ochronotic vertebral disc. Deeb thinks it may be collection of lipid material after Forrester's (78) opinion.

Ford (66). 3% of 1,614 x-ray studies of lumbrosacral spine had intradiscal gas. Seen best when standing under stress by extension.

Ford (77). Gas from lumbar disc 90-92% N_2 by gas chromatograph.

Forrester (78). Believes vacuum disk is a misnomer because it persists rather than disappears as in hip. Believes vac. disc more likely collections of lipid material within degenerative disk.

Fries (82). Epidural fat is abundant in spinal canal, particular lumbar. CT scans used 5 mm slice thickness and 0.75 mm pixel size. Gas was seen in herniated sacral-lumbar nucleus pulposus (HNP). Extended HNP can compress spinal nerves.

Frymoyer (84). 5.8% (17 subjects) had vacuum sign or disk (lumbar or lumbo-sacral) but was not correlated with pain or symptoms in legs.

Gentry (85). Chymopapin chemonucleolysis (CC) is used to treat disk herniation and to reduce pressure on spinal nerves by reducing the water-binding capacity of the nucleus pulposus. It is an alternative to diskectomy. 7 of 22 patients developed VP by 6 months after CC. CC results in interspace narrowing.

Gershon-Cohen (54). VP in 27 of 130 aged (75 mean age) spines. Extension accentuates, flexion may cause disappearance. Usually phantom nucleus (VP) found in lumbar interspace. Intervertebral spaces always narrowed when VP existed. A possible explanation is the drying out of the disk substance either as a degenerative change after trauma or as a normal aging process.

Hendry (58). Disability correlates with disc desication which occurs with injury and advancing age.

Knutsson (42). VP is a result of the generation negative pressure in joints such that synovial fluid vaporizes and gas in solution in synovial fluids changes to the vaporous form. Knutsson introduced the term vacuum phenomenon. Magnusson (37) observed disk VP in spondylitis deformans and symphysis publis in pregnancy. In osteochrondrosis (disc degeneration), the disk substance dries up and irregular cracks appear. Disc may finally disintegrate. Annulus fibrosis remains intact. VP are pathognomonic of disc degeneration. In spondylitis deformans, the annulus fibrosus cracks and falls away from peripheral attachment to the limbus vertebra. As a result, the disc may protrude and its inner parts prolapse. VP appears in lordosis when walls of cracks separate and disappears when the walls close. VP remains for at least 15 min if traction is maintained indicating that substitution of gas for fluid is slow. Describes mechanism of vacuum formation between opposing articular surfaces.

Lagier (74). Vertebral changes in ochronosis. Disc splits which explains VP and suggests diagnosis of ochronosis.

Larde (82). Spinal VP may occur in disk degeneration or injury, vertebral metastases, ischemic vertebral collapse, Schmorl's nodes (intravertebral disk herniation), and infection. CT is better than conventional radiography at detecting VP. VP disk is common in degenerative pathology. Vacuum disk seen in almost 1/2 the lumbar CT studies of patients over 40.

Age	N	# by CT	# by x-ray
40-50	12	2 (16%)	0
50-60	12	2 (16%)	1
60-70	12	6 (50%)	2
70-80	14	13 (93%)	3
	50	23 (46%)	6(12%)

Marr (53). 2,419 x-ray studies of lumbo-sacral spine. 49 (2%) had gas in at least 1 disc. Age range 19-72, mean 50.5. 57 (49-67) mean age of patients with VP. Extension was not used in this study.

Miller (78). Cervical spine trauma (isolated disk injury) rare but accompanied by VP.

Orrison (82). CT in 5 mm slice thickness. Gas in herniated nucleus pulposus. Consistently negative pressures are unnecessary to maintain a gas collection within an intervertebral disk. -200 HU in 38 year old woman with L5-S1 disk herniation.

Raines (53). Intervertebral disc fissures. Radiolucencies due to disc degeneration which produces a cracking or fissuring of disc substance. Fissure appeared with extension (cracks open) and disappeared with flexion (cracks close). 30 VP in 3,500 studies of spine.

Samuel (48). Vacuum intervertebral discs. Joint space of young children with lax joint ligaments conducive to VP. Osteoarthritic joints prone to show gas. Gas formation is pathognomonic of intervertebral disc degeneration. Gas can show as a linear streak in disc center or as small pin-point globules beneath anterior longitudinal ligament. VP often has a previous history of injury, but the air itself does not cause symptoms.

Sauser (78). In 44 cases of discogenic vertebral sclerosis, 44% had VP. Schmorl node is an intravertebral herneation of nucleus pulposus. VP commonest in the L4-5 space, then L5-S1 space. Presence of VP supports diagnosis of disogenic vertebral sclerosis.

VERTEBRAL BODY

Bretz (81). VP seen in fracture of thoracic vertebral body. Size was 5 x 40 mm.

Brower (81). In Kummell disease, post-traumatic collapse of vertebral body can be delayed weeks to months. Thoracic vertebral body with VP by CT. Bone ischemia occurs due to trauma or vasomotor spasm.

Maldague (78). Intravertebral vacuum cleft is a sign of ischemic vertebral collapse. Gas density lucency. Appears in extension (stereo views), disappears in flexion in vertebral body. Appeared in 10 cases (55-83 years, mean 68) at the thoraco-lumbar junction. In some cases gas was replaced by a water density within 1 month but the cleft persisted. Gas existed within distracted cracks in subchondral bone.

Suggests possible mechanism for bone necrosis. "Since absence of synovial effusion is prerequisite to formation of intra-articular vacuum cleft, bone ischemia might be primary cause of cleft and could also explain the intraepiphyseal gas which sometimes enhances the radiolucent cresent line characteristic of epiphyseal bone necrosis." Predisposing factors to bone necrosis are diabetes, hyperadreno-corticism, radiotherapy, alcoholism, and arterial sclerosis.

SPINAL CANAL

Austin (81). One case of lumbar VP by CT scan (-664 Hounsfield units on -1,000 scale) with rectal carcinoma and metastases. No change after 10 weeks. Second case lumbar VP (-605 HU). History of chronic low back pain. Suggests vacuum disk is origin of gas via diseased annulus. VP also observed in spinal canal.

Elster (84). CT scan. Gas in cervical spinal canal in association with herniated disc. Automobile accident 11 m earlier. X-ray showed vacuum cleft and degeneration. CT showed gas in canal (-380 HV). Only such example in 1,000 CT's. Gas not reabsorbed or replaced by fluid because the degenerating disc is avascular. "Thus gas within a nucleus pulposus may persist even when it herniates into the spinal canal".

Gulati (80). 22/70 patients had lumbar VP by CT scan. Three of these had free gas in spinal canal (epidural space). VP appears due to creation of gas space in a degenerative intervertebral or apophyseal joint as a result of motion, especially extension. Flexion causes the gas space to disappear. The CT absorption coefficient of free gas is equivalent to air. Gas in canal assumed to be due to leakage from disk space or joint secondary to a tear in the adjacent ligaments of the apophyseal joint or annulus fibrosus.

Larde (82). Gas in lumbar spinal canal.

Spencer (83). Dissection of gas into intraspinal synovial cyst from contiguous vacuum facet. Gas within cyst demonstrated by CT. Postulates that gas source is adjacent diseased lumbar facet joint which has a vacuum cleft with consequent dissection of gas into cyst. Gas in spinal canal believed to be leakage from disk or joint space after tearing of annulus fibrosus or ligaments.

Teplick (82). Gas bubbles in spinal canals of 7 out of 2,500 patients. In each case, a vacuum disk was present at the interspace suggesting that the bubbles in canal originated from vacuum disk. In one case, a bubble appeared to be partially in the canal and partly within the annulus which contained a vacuum disk. In no case was extradural gas apparently related to symptoms. 10 vacuum facet joints/2,500 CT scan. Suspects this has been overlooked. Probably of no clinical significance. Due to joint traction. Iatrogenic creation of vacuum disk at site of discectomy (2 of 7 patients). Found vacuum disk a high proportion of patients who have history of diskectomy. There are many cases of small vacuum changes (gas) on CT without a detectable cor

responding shadow on the radiographs. Schmorl node is a piece of fibrocartilage that has herniated (or grown) into adjacent vertebral border and is surrounded by dense bone.

LIMBS

Daffner (82). Pneumatosis. In total knee arthroplasty (artificial joint), air is sometimes trapped but resolves within a few days. Gas noted in 5 patients in the intramedullary cavity of the distal femur. Resolved after 48 hours.

Deffrenne (75). "In cases of severe sprain where the articular surfaces spontaneously return to their normal relationship, a few cm^3 of air are projected into the periarticular soft tissues where they remain shortly. This indicates a ligamentous rupture." Observed in knee. Shows 1 film and a line drawing.

Evans (40). Demonstration of true articular space by forcible abduction or traction. Vacuum provides a contrast which outlines the cartilage as shadows. Joint space and internal semilunar cartilage shown in 70% of normal knees. Also seen in shoulders and hips.

Fick (10). Earliest description of gas in joints. Seen in cadavers. In German.

Gershon-Cohen (45). Internal meniscus may be demonstrated by VP in 80% of cases by traction or abduction of the leg. Joint space soon fills with fluid if traction is maintained. Loose bodies may come from direct or indirect trauma. Detachments from articular surface more frequent in males of 15-25. They arise from under surface of inner femoral condyle or posterior surface of patella. Some loose bodies may be due to separation of portions of articular surface as in osteochrondritis dissecans. The many bursae about the knee are not normally seen but may be visualized, when the knee is filled with fluid due to bursitis.

Kay (85). Patient with osteoarthritis subsequent to knee injury 14 years earlier. Recently jumped off a bus and developed intra-articular gas which communicated by a narrow tract with a medial juxtan-articular cavity. Persisted for at least 5 weeks. Gas lesion 3 cm long inferomedial to tibial plateau and parallel to tibia. 1 ml gas was aspirated after 5 weeks. Analysis showed 78% N_2, 22% O_2 but specimen may have been contaminated by air. Distraction of opposing articular surfaces converts a potential space into a real one. Gas probably originated in a joint and escaped through damaged tissue. Appeared to be a meniscal cyst.

Magnusson (37). Shoulder, hip, spine, fingers, symphisis. Can be seen in children. Due to development of gas in joint (Fick's explanation). Spondylosis deformans leads to disc VP. "That any considerable practical importance should attach to the problem is hardly to be supposed".

Moore (76). VP produced in 36% of knees of patients.

Resnick (81). Review of VP in sacroiliac joint, symp. pubis, disk, vertebra.

Rubin (39). VP seen in knee, humerus, metacarpal and symphisis pubis. Joints filled with fluid do not produce VP. VP delineates articular cartilage. Cartilage is radio-translucent, but its translucency is relative and contrasts sharply with that of air. In knee, air translucency persists momentarily after abduction is discontinued, but returns when traction reapplied. With continuous abduction translucency disappears as gradual effusion occurs. No similar translucencies are seen except in sinuses, bowel, lungs. Translucencies are sometimes circular and have the appearance of bubbles not yet coalesced in synovial fluid. VP will rarely (but sometimes) occur in joints without any manipulation (knee, shoulder, subastragaloid joint). "It is difficult not to conceive that a joint may find itself momentarily placed in such a position as to increase negative pressure within it with a resulting slight and transient gaseous exudation."

Widmann (36). VP provides a radiological demonstration of true articular space. Joint may be divided by an articular disc or meniscus the periphery of which is continuous with fibrous capsule. VP seen in shoulder and knee.

Yousefzadeh (79). VP of wrist and metacarpophalangeal joints produced by traction. Resultant pneumoarthrogram clearly portrays the articular cartilage. Useful to detect joint effusion, evaluate carpal bones, differentiate arthralgia from arthritis and study joint cartilage. Radiocarpal compartment is outlined.

HIP

Fuiks (50). VP seen in hip, shoulder, knee, spine, wrist. VP not particularly unusual and generally considered of little or no significance. Gas is replaced by fluid within 10 min in knee if constant traction is applied.

Martel (70). 45 of 51 normal hips showed VP upon traction. The resulting pneumoarthrogram shows the joint space and articular cartilate and may provide important diagnostic information. Cartilage and joint effusion are difficult to observe non-invasively. With excessive joint fluid, no VP occurs. 8 of 24 abnormal hips had VP. VP is instantaneous with traction and disappear upon release. Radiolucent crescent line occurs with osteonecrosis of femoral head. Even with no VP in joint space, crescent line became more intensely lucent having the appearance of gas within the bone. The interosseous space widens with traction. VP easier to show in infants and children than in young adults due to less muscular development. Smooth joint surfaces which fit snugly resist distraction because they are held together by fluid pressure with a vacuum between opposing joint surfaces. Continuous abduction for several minutes causes gas to disappear.

Martel (71). "In hips without an effusion a 'radiolucent crescent' usually forms in the joint space which delineates articular cartilage. However, if the joint contains fluid, traction will cause widening of interosseous space without such a crescent."

Martel (81). Subchondral lucencies like a string of beads on distal femoral and hip margin of knee. Collapse of articular surface could be related to pre-existing subchondral cavities. VP in sacroiliac joint. VP in symphysis pubis which is composed of fibrocartilage and is structurally similar to the disk-vertebral joints. VP occurs in calcium pyrophosphate crystal deposition disease (CPPD).

Middleton (86). Three year old boy with hip joint fluid and VP. Unusual occurrence of both.

Van den Brock (83). Traction radiography normally creates VP between femoral head and acetabulum where there is fluid in joint and provides a non-invasive method for detecting fluid and evaluating thickness and outline of articular cartilage. Hip joint has a physiologically lax capsule. Patients studied were a 3 m old baby, 4 yr old boy, 15, 16 year olds. Gaseous line in the femoral head indicates that part of epiphysis lies loose in osteochrondrosis dissecans. Femoral head necrosis described with gas in head. Subchondrial vacuum effect indicates that dissected cartilage lies loose. No vacuum is seen when insufficient diastasis is achieved especially in muscular males. A muscle relaxant allowed good diastasis with traction.

Vegter (83). Preliminary report for Van den Brock (83). No age limit to traction investigation of joints. Even can be used in infants.

Waldenstrom (38). First stages of coxa plana described (also known as Perthes disease, osteochrondritis deformans). Flattened epiphysis is the principal sign of pathology at early stage. The pathologic process is a primary necrosis followed by resorption then new bone and cartilage. Bright zone underneath cartilage. (Waldenstrom didn't recognize this as gas.) Most cases heal with deformity only slightly troublesome.

OSTEONECROSIS

Martel (69). Aseptic osteonecrosis without apparent relationship to trauma is not rare. 33 cases were studied. Coxa plana (Legg-Calve-Perthric disease) was excluded. "Rim sign" is a subchrondral bone fragment slightly separated from rest of bone. "Bite sign" is a large defect in end of bone as though it had been bitten. Both metadiaphyseal and epiphyseal lesions occur in bends. The metadiaphyseal lesions are thought to be due to intramedullary fat necrosis. "The osteonecrotic area within a joint almost always involves the subchrondral zone. In the hip it is usually in the outer, anterior portion of the femoral head . . . The characteristic narrow, crescent-shaped line, first described by Waldenstrom (38) and more recently by Norman (63). This line which may also be observed in Legge-Calve-Perthes disease represents a frac

ture through the necrotic subchondral bone."

Martel (70). A VP is reponsible for clarity of "radiolucent crescent line" or rim sign in necrosis of femoral head. This indicates the release of gas in the zone of subchrondral separation with the induction of vacuum by traction. May be of value in early diagnosis of osteonecrosis. Three cases of gas in fracture cap are reported. The subchrondral lucent line occasionally seen in osteonecrotic joints other than the hip may have a similar derivation. In osteonecrotic joints, gas not released in articular space. Postulates that excessive joint fluid prevents VP but the fracture or subchondral separation within the femoral head need not always communicate with joint space.

Norman (63). Radiolucent crescent line (RCL) is an early diagnostic sign of avascular necrosis of femoral head. RCL parallels subchondral surface of femoral head. It is an area of subchondral separation and not resorption of necrotic bone as Waldenstrom (38) stated. Should the zone of separation from the articular cartilage be complete without leaving behind a strip of bone, the radiolucent line is not seen. Jacobs (70) and Pugh have pointed out similarity on x-ray between osteochrondritis dessicans (OD) of the femoral head and coxa plana. However, in OD the line of separation is convex toward interior of femoral head whereas in Legg-Calve-Perthes syndrome, the zone of subchrondral separation parallels the articular surface (convex toward joint space).

Caffey (68). Coxa plana. Intra-epiphyseal gas image. Gas in narrow space between bone and cartilage of femoral head. Intra-epiphyseal gas (5 cases) seen gas inside the living epiphysis seen only in "frog leg" position when stress increases the volume. Believes that local direct compression prevents inflow of arterial blood rather than as a result of injury and blockage of arterior outside the epiphysis. Local effect occurs on intraepi-physeal arteries rather than in retinocular arteries as in the hypothesis of ischemia or avascular necrosis. 80-90% of all coxa plana cases occur in young boys where muscular activity, strength, and hip stresses are greater. Virtual absence of coxa plana in negroes who have greater cortical bone thickness and strength.

Jacobs (70). Intra-epiphyseal gas in osteochrondritis. Occurs in hip and elbow. Gas within epiphysis. Six such cases were seen. Gas occupies a cleft between margin of calcified nucleus and surrounding uncalcified cartilage. Occurs early in course of disease, not in fragmentation or recovery phases. Gas appears in broken periphery of ossific nucleus not in surrounding non-calcified cartilage of femoral head. This would suggest that the surrounding cartilage is intact and has not undergone fissure formation or fibrillation.

Liebman (40). Osteochondritis dissecans is a separation of articular cartilage from bone (with or without subjacent bone). Loose bodies in the joints originate from the articular surface without injury. Not a rare condition. Common during adolescence and early adulthood in males in hip, ankle, and metatarsal articulation. Knee and elbow most common. Possibly same etiology as coxa plana (Legg-Perthes). Possible

etiologyies: (1) small emboli of end arteries resulting in infarction and aseptic necrosis of bone and cartilage deprived of blood supply. All investigators believe trauma is predisposing; (2) fat embolism; (3) low grade arthritis. Disease process begins at point of greatest contact in knee joint. Separation is gradual and may take months or years. History is usually of several years duration. VP is not discussed.

SYMPHYSIS PUBIS

Camiel (56). "Each opposing surface of the pubic bone is covered by a thin layer of hyaline cartilage joined to the bone by a series of nipple-like processes" unlined by synovial membrane. This is a potential space. 30 of 100 random sample of x-ray cases showed VP. A rare case showed small bony particles at the joint which were apparently torn away from the surface. VP seen in infant hip joints during forcible abduction. VP disappears when force is relieved. VP in symphysis is not a troublesome problem.

Camiel (86). Gas phenomenon. "Relaxion activity during pregnancy is associated with loosening, widening, and increased flexibility of the symphysis pubis."

Mayall (64). Describes Fick (1910) studies. In symphysis pubis, opposing pubic bones covered with layer of hyaline cartilage and are connected by a fibro-cartilaginous disc and superior and inferior ligaments. No synovial membrane. Sudden pain in pubic region of one patient after delivery VP present in SP. Patient was unable to lean weight on right leg but recovered with bed rest.

Scott (84). Two cases in which vacuum sign at symphtsis pubis was present after falls. VP normally occurs during pregnancy. Gas disappears with manual pressure on both greater trochanter.

Williams (55). VP occurs in symphysis pubis during pregnancy as a consequence of the normal relaxation of the pelvic joints. VP observed in 42% of 232 cases. Gas disappears when hips are pressed together.

SACROILIAC JOINT

Hart (86). Intraosseous pneumatocysts (VP) in sacroiliac joint caused pain on descent during diving and occasionally during ascent. No other pathology present. Problem diminished and diving career was unaffected.

Ramirez (84). Intraosseous pneumatocysts of the illium. CT scan of 5 patients. Gas adjacent to normal sacroiliac joint. Gas within a bone cyst adjacent to sacroiliac joint (5 cases). VP involving non-communicating juxto-articular benign bone cysts have not been described before. CT numbers derived from current scanners appear accurate in detection of gas collections and are much more sensitive than conventional radiography. Etiology of gas-filled subchrondrial bone cysts is uncertain, but they appear to be acquired lesions.

Russell (65). Gas in sacroiliac joint in pregnancy. 1% incidence in 200 patients with no apparent symptoms. Articular surfaces of sacroiliac joint are irregular and fit closely. Ligamentous laxity during pregnancy.

Shorter (84). Gas in sacroiliac joint is not associated with chondrocalcinosis. 7/44 with CPPD had vacuum sign. 44/274 normal controls had VP. Gas in sacroiliac joints can be associated with sufficient morbidity of sacroiliac articulation without any clinical symptoms.

INFECTION

Bielecki (86). Intra-discal and intra-osseous gas by CT. Radiolucent gas collections.

Phillippe (85). Anaerobic osteomyelitis with oat cell carcinoma and gas in spinal canal seen on CT. A rare complication.

Porter (61). Gas surrounding and within kidney on radiological examination. Patient had diabetes. B. coli was causative agent. Non-clostridial.

Ram (81). CT detection of intraosseous gas is a new sign of osteomyelitis. Multiple bubbles within medullary cavity of tibial graft.

CRACKING JOINTS

Lancet (71). Formation of cavities is unstable and associated with energy release and crack when bubble collapses. Clinical significance uncertain.

Roston (47). Refractory phase during which joint won't crack can be prolonged indefinitely by continuous or intermittent tension. If undisturbed, joint can crack again in approximately 20 min. Estimates about 2.5 ATM negative pressure in joint when crack occurs. Refractory phase due to resolution of residual gas. Joints which do not crack usually cannot relax muscles.

Swezey (75). Describes the consequences of habitual knuckle cracking. 28 patients (78.5 mean age) who had been knuckle crackers. No correlation beween knuckle cracking and degenerative joint disease.

Unsworth (71). Cavitation bubbles were observed radiographically in the metacarpophalangeal joint of a finger placed in tension. The cracking sound occurred when the transient bubble collapsed.

References

Austin RM, Bankoff MS, Carter BL. Gas collections in the spinal canal on computed tomography. J Comp Asst Tomog 1981; 5(4):522-524.

Beers GJ, Carter AP, Leiter B, Shapiro JH. CT detection of retroperitoneal gas associated with gas in intervertebral disks. J Comput Assist Tomogr 1984; 8(2):232-6.

Bielecki DK, Sartoris D, Resnick D, Van Lom K, Fierer J Hashishi P. Intraosseous and intradiscal gas in association with spinal infection: report of three cases. AJR 1986; 147(1):83-6.

Bohrer SP. The annulus vacuum sign. Skeletal Radiol 1986; 15:233-235.

Bretz GW, Jenkins RG. Gas density in an ununited fracture of a vertebral body. J Jone & Joint Surg 1981; 63-A(7):1183-1184.

Broden Bror. On the occurrence of gas in gallstones. Acta Rad 1942; 23:413-419.

Brower A,C Downey EF, Jr. Kummell disease: report of a case with serial radiographs. Rad 1981; 141:363-364.

Caffey J. The early roentgenographic changes in essential coxa plana; their significance in pathogenesis. Am J Radiol 1968; 103:620-634.

Camiel MR Aaron JB. The gas or vacuum phenomenon in the pubic symphysis during pregnancy. Rad 1956; 66:548-551.

Camiel MR. Relaxin and the radiolucent fissure in the symphysis pubis during pregnancy: the gas phenomenon. Am J Obstet Gynecol 1956; 154(5): 1104-1105.

Carrera GF, Haughton VM, Syvertsen A, Williams AL. Computed tomography of the lumbar facet joints. Rad 1980; 134(1):145-148.

Daffner RH, Gehweiler JA, Jr. Intraosseous pneumatosis after total knee arthrography: a "normal" variant. AJR 1982; 139:179-180.

Daffner RH, Gehweiler JA, Jr. Pseudovacuum of the cervical intervertebral disc: a normal variant. AJR 1981; 137(4):737-739.

Deeb Z, Frayha RA. Multiple vacuum discs, and early sign of ochronosis. Radiologic findings in two brothers. J Rheumatol 1976; 3(1):82-87.

Deffrenne P, Berand C. Intraarticular vacuum effect. Ann Radiol 1975; 18(4):401-406.

Elster AD, Jensen KM. Vacuum phenomenon within the cervical spinal canal: CT demonstration of a herniated disc. J Comput Assist Tomogr 1984; 8(3):533-535.

Evans WA Jr. The roentgenological demonstration of the true articular space: with particular reference to the knee joint and the internal semilunar cartilage. AJR 1940; 43(6):860-864.

Fick R. Handbuch der anatomie und mechanik der gelenke unter veruck-sichtigung der bewegenden muskeln. 1910; Vol 2. Jena, G. Fischer.

Ford LT, Gilula LA, Murphy WA, Gado M. Analysis of gas in vacuum lumbar disc. Am J Roentgenol 1977; 128:1056-1057.

Ford LT Goodman FG. X-ray studies of the lumbosacral spine. Southern Medical J 1966; 59:1123-1128.

Forrester DM, Brown JC, Nesson JW. The Radiology of Joint Disease, 2nd ed. W.B. Saunders. 1978:317, 319-320; 514-515, 522-523.

Fries JW, Abodeely DA, Vijungco JG, Yeager VL, Gaffey WR. Computed tomography of herniated and extruded nucleus pulposus. J Comp Asst Tomog 1982; 6(5):874-887.

Frymoyer JW, Newberg A, Pope MH, Wilder DG, Clements J, MacPherson B. Spine radiographs in patients with low-back pain. An epidemiological study in men. J Bone Joint Surg (Am) 1984; 66(7):1048-1055.

Fuiks DM, Grayson CE. Vacuum pneumarthrography and the spontaneous occurrence of gas in the joint spaces. J Bone & Joint Surg 1950; 32A(4): 933-938.

Gentry LR, Turski PA, Strother CM, Javid MJ, Sackett JF. Chymopapain chemonucleolysis: CT changes after treatment. AJR 1985;145(2):361-369.

Gershon-Cohen J. Internal derangements of the knee joint. The diagnostic scope of the soft tissue. Roentgen examinations and the vacuum technique demonstration of the menisci. AJR 1945; 54:338-347.

Gershon-Cohen J, Schraer H, Splaroff DM, Blumbert N. Dissolution of the intervertebral disk in the aged normal. Rad 1954; 62:383-387.

Gulati AN, Weinstein ZR. Gas in the spinal canal in association with the lumbosacral vacuum phenomenon: CT findings. Neurorad 1980 20:191-192.

Hendry NGC. The hydration of the nucleus pulposus and its relation to intervertebral disc derangement. J Bone & Joint Surg (Br) 1958;40:132-144.

Hilton RC, Ball J. Vertebral rim lesions in the dorsolumbar spine. Ann Rheum Dis 1984; 43(2):302-307.

Isu T, Miyasaka K, Swasaki Y, Ito T, Tsuru M, Takei H, Abe S. Computed tomographic findings of vacuum phenomenon in cervical intervertebral disks. Surg Neurol 1983; 19:528-531.

Jacobs P. Intra-epiphyseal gas in osteochronditis. Clin Radiol 1970; 21:318-319.

Kay SP, Gold RH, Bassett LW. Meniscal pneumatocele. A case report of spontaneous, persistent intra-articular and juxta-articular gas. J Bone Joint Surg (Am.) 1985; 67(7):1117-1119.

Knutsson F. The vacuum phenomenon in the intervertebral discs. Acta Radiologica 1942; 23:173-179.

Lagier R, Sit'aj S. Vertebral changes in ochronosis. Ann Rhem Dis 1974; 33:86-92.

Cracking joints. Lancet 1971; 18(2):649.

Larde D, Mathieu D, Frija J, Gaston A, Vasile N. Spinal vacuum phenomenon: CT diagnosis and significance. J Comput Assist Tomogr 1982; 6(4):671-676.

Lefkowitz DM, Quencer RM. Vacuum facet phenomenon: a computed tomographic sign of degenerative spondylolisthesis. Radiology 1982 144(3):562.

Liebman C, Iseman RM. Osteochondritis dissecans. AJR 1940; 43(6):865-870.

Magnusson W. Uber die bedingungen des hervortretens der wirklichen gelenkspolte auf dem rontgenbilole. Acta Radiologica 1937; 18:733-741.

Maldague BE, Noel HM, Malghem JJ. The intravertebral vacuum cleft: a sign of ischemic vertebral collapse. Rad 1978; 129:23-29.

Marr JT. Gas in intervertebral discs. Am J Roentgenology 1953; 70: 804-809.

Martel W, McCarter DK, Solsky MA, et al. Further observations on the arthropathy of calcium pyrophosphate crystal deposition disease. Rad 1981; 14:1-15.

Martel W, Pozananski AK. The effect of traction on the hip in osteonecrosis. A comment on the "radiolucent crescent line". Rad 1970; 94:505-508.

Martel W, Poznanski AK. The value of traction during roentgenography of the hip. Rad 1970; 94:497-503.

Martel W, Sitterley BH. Roentgenologic manifestations of osteonecrosis. Rad 1969; 106(3):509-522.

Martel W, Poznanski AK, Kuhns LR. Further observations on the value of traction during roentgenography of the hip. Invest Rad 1971; 6:1-8.

Mayall GF. The vacuum phenomenon as evidence of degeneration in the pubic symphysis. Br J Radiol 1964; 37:608-609.

Middleton WD, McAlister WH. Hip joint fluid in the presence of the vacuum phenomenon. Pediatr Radiol 1986; 16:171-172.

Miller MD, Gehweiler JA, Martinez S, Charlton OP, Daffner RH. Significant new observations on cervical spine trauma. AJR 1978; 130(4): 659-663.

Moore TM, Meyers MH, Harvard JP, Jr. Collateral ligament laxity of the knee. Long-term comparison between plateau fractures and normal. J Bone Joint Surg (Am) 1976; 58(5):594-598.

Norman A, Bullough P. The radiolucent crescent line - an early diagnostic sign of avascular necrosis of the femoral head. Bull Hosp Joint Dis 1963; 24:99-104.

Norman A, Steiner GC. Radiographic and morphological features of cyst formation in idiopathic bone infarction. Rad 1963; 146:335-338.

Orrison WW, Lilleas FG. Case report. CT demonstration of gas in a herniated nucleus pulposus. J Compt Asst Tomog 1982; 6(4):807-808.

Philippe J, Sheybani E, Hirschel B, Ody B. Air in the bones: multifocal anaerobic osteomyelitis associated with oat cell carcinoma. Br Med J 1985; 290:969.

Porter R, Wright FW. Intracapsular perinephric gas-forming infection in a patient with diabetic coma. Br J Rad 1961; 34:201-202.

Raines JR. Intervertebral disc fissures (vacuum intervertebral disc). AJR 1953; 70(6):964-966.

Ram PC, Martinez S, Korobkin M, Breiman RS, Gallis HR, Harrelson JM. CT detection of intraosseous gas: a new sign of osteomyelitis. AJR 1981; 137:721-723.

Ramirez H Jr, Blatt ES, Cable HF, McComb BL, Zornoza J, Hibri NS. Radiology 1984; 150(2):503-505.

Resnick D, Niwayama G, Guerro J Jr, Vint V, Usselman J. Spinal vacuum phenomena: anatomical study and review. Rad 1981; 139:341-348.

Resnick D, Niwayama G. Diagnosis of bone and joint disorder. W.B. Saunders; Philadelphia, 1981.

Reymond RD, Wheeler PS, Perovic M, Block B. The lucent cleft, a new radiographic sign of cervical disc injury or disease. Clin Radiol 1972; 23:188-192.

Roston JB, Haines RW. Cracking in the metacarpo-phalangeal joint. J. Anst 1947; 81:165-173.

Rubin EL. The delineation of articular cartilage by x-rays without the aid of contrast media. Br J Rad 1939; 12(144):649-657.

Russell JG. Gas in the sacro-iliac joint in pregnancy. J Obstet Gynaecol Br Commonw 1965; 72(5):797-798.

Samuel E. Vacuum intervertebral discs. Br J Rad 1948; 21:337-339.

Sauser DD, Goldman AB, Kaye JJ. Discogenic vertebral sclerosis. J Can Assoc Radiol 1978; 29(1):44-50.

Schabel SI, Moore TE, Rittenberg GM, Stanley JH, Javid LH. Vertebral vacuum phenomenon. A radiological manifestation of metastatic malignancy. Skel Radiol 1979; 4:154-156.

Scott ST, Watt I. 1984. Gas at the symphysis pubis: a sign of occult pelvic trauma. Br J Radiol 1984; 57(674):173-176.

Shorter AM, Burrows DA, Cockshott WP. Is the vacuum sign in the sacro-iliac joint a useful radiological sign of chondrocalcinosis? Diagn Imag Clin Med 1984; 53(3):141-143.

Spencer RR, Jahnke RW, Hardy TL. Dissection of gas into an intraspinal synovial cyst from contiguous vacuum facet. J Comput Assist Tomogr 1983; 7(5):886-888.

Swezey RL, Swezey SE. The consequences of habitual knuckle cracking. West J Med 1975; 122:377-397.

Tash RR, Weitzner I Jr. Case report. Acute intervertebral gas following vertebral fracture: CT demonstration. J Comp Asst Tomog 1986; 10(4):707-708.

Teplick JG, Teplick SK, Goodman L, Haskin ME. Pitfalls and unusual findings in computed tomography of the lumbar spine. J Comp Asst Tom 1982; 6(5):888-893.

Unsworth A, Dowson D, Wright V. 'Cracking joints'. A bioengineering study of cavitation in the metacarpophalangeal joint. Am Rheum Dis 1971; 30:348-358.

Van den Broek HA, Vester J. Traction radiography of the hip and fluid in the hip joint. Diagn Imaging 52(2-3): 76-84.

Vegter J, Van den Broek JA. The diagnostic value of traction during radigraphy in diseases of the hip. A preliminary report. J Bone Joint Surg (Br.) 1983; 65(4):428-432.

Waldenstrom H. The first stages of coxa plana. J Bone & Joint Surg 1938; 20(3):559-566.

Widmann BP, Stecher WR. Roentgenographic demonstration of the true articular space. Rad 1936; 27:541-544.

Williams JL. Gas in the symphysis pubis during and following pregnancy. AJR 1955; 73(3):403-409.

Yetkin Z, Chintapalli K, Daniels DL, Haughton VM. Gas in spinal articulations. Neuroradiology 1986; 28:150-153.

Yousefzadeh DK. The value of traction during roentgenography of the wrist and metacarpophalangeal joints. Skel Radiol 1979; 4:29-33.

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THE EFFECT OF PRESSURE PROFILE ON BUBBLE FORMATION

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Despite intensive investigation the origin, development and fate of bubbles generated by decompression in diving animals are little understood. However, the general features of bubble formation can be identified: i) Bubbles first appear in peripheral veins. ii) Excessive numbers of bubbles in the lungs will lead to arterial bubbles. iii) There is no especially susceptible site for bubble formation. iv) The gas supersaturation necessary for bubble formation in vivo is 50-70kPa in all species. v) The critical threshold is independent of exposure pressure, but once exceeded, the number of bubbles becomes pressure dependent. vi) Mild, continuous exercise does not increase bubble formation, but intermittent or violent exercise does. vii) A sequence of repeat dives may reduce the number of bubbles as nuclei are consumed. viii) Incorrect interdive intervals may produce sudden, acute symptoms because vascular redistribution of bubbles renders cardiac and respiratory functions vulnerable.

Introduction.

Gas bubbles, in blood and tissues, after decompression from raised ambient pressures are generally held to be the cause of decompression sickness. Although decompression sickness is dose related, an asymptomatic phase being followed by symptoms of increasing severity as the number of bubbles increases, the precise nature of the link between bubbles and symptoms remains to be elucidated. Undoubtedly the greatest problem in attempting to relate the likelihood of symptoms to the appearance of bubbles is the extreme variability associated with bubble formation. Whilst familiar to all those who have studied this phenomenon one example illustrates the extent of this variability. In an experiment in which hamster litter mates, prepared in an identical manner, were subjected to the same pressurisation-depressurisation regime, one had massive fatal embolisation the other none (1). However, since the introduction of non-invasive ultrasonic techniques for the detection of bubble formation in vivo, attempts have been made to quantify the link between the number of bubbles formed and the likelihood of symptoms (2-9). Few of these have met with any measure of success. A first step in approaching this problem systematically is to consider the effect on bubble formation of the parameters which characterise the pressure profile. It is convenient to approach this question in two parts, (a) bubble nucleation and (b) macroscopic bubbles.

[100 kPa = 1 bar = 0.987 ATA = 14.504 psi = 10 msw = 33 fsw]

The Effect of Pressure Profile on Bubble Nucleation.

Theories to account for the nucleation of bubbles have ranged from the entrappment of pockets of gas (10) to the effect of cosmic rays (11). The fact that a simple application of hydrostatic pressure will effectively prevent bubble formation, both *in vitro* and *in vivo*, suggests that in some way a microscopic pocket of gas must be involved (10,12-14). Although there is at present no technique to observe micronuclei directly, the effects of various pressure profiles have been recorded.

The effect of exposing marine shrimps, *Crangon crangon*, to various pressures, hydrostatically, prior to a pneumatic sub-atmospheric decompression has been investigated (14; Figure 1). The effect of pressure on the nuclei is clearly time dependent, with pre-treatment at 10MPa producing the same effect as that at 20MPa when the pre-treatment time was increased from 2min to 10min. Unexpectedly, pre-treatment with 1MPa was found to reduce the extent of subsequent bubble formation when applied for 60min. Further experiments revealed that the nuclei were regenerated with a half-time of approximately 10hr (Figure 2). The minimum decompression sufficient to cause bubble formation in the shrimps was found to be 70kPa.

That similarly pressure sensitive nuclei exist in mammals has been suggested by experiments in which a reduction in the incidence of decompression sickness in the rat after a 2hr exposure to 700kPa was observed when a short exposure to high pressure was given at the beginning of the experiment (15). The pressure pre-treatments were at 1.9MPa and 3.1MPa, with the pressure applied for 1min. A 20% reduction in sickness was observed when the pressure pre-treatment was 3.1MPa. In comparison with the shrimp experiments this result is quite remarkable, given the relatively low pressure treatment, the short time for which it was applied, and the 2hr interval between the pressure treatment and the final decompression.

Alternative mechanisms to those invoking pre-existing gas nuclei for the formation of bubbles have been suggested (16,17). The decompression necessary to induce bubbles in fish is decreased, from approximately 10MPa to less than 0.5MPa, as the fish develop from the larval stage to adults (18). The majority of bubbles in the adult fish were associated with their fins and it was speculated that movement was the cause of the bubbles. This suggestion was supported by experiments in which anaesthetised fish were decompressed where it was found that far larger decompressions were necessary to induce bubble formation in anaesthetised fish compared to controls (18). Whilst tribonucleation mechanisms (16) may well facilitate bubble formation it is hard to reconcile the effect of hydrostatic compression with such a mechanism.

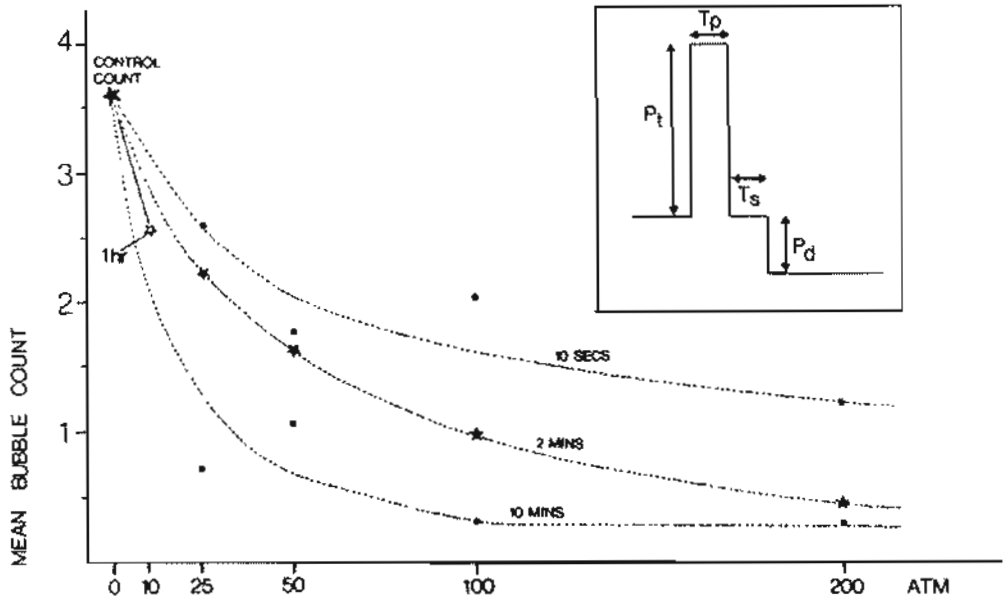

Figure 1: Mean bubble counts from groups of 20 marine shrimps, Crangon crangon, after decompression from atmosheric pressure to 0.1bar following hydrostatic pressure pretreatments from 10bar to 200bar for: a) 10s; circles b) 2min; stars c) 10min; squares. Inset: pressure pretreatment profile. P_T; hydrostatic pressure, T_p; time pre-treatment, T_s; surface interval between pretreatment and decompression, P_d; sub-atmospheric decompression. Time interval between pre-treatment decompression 5min. Bubbles were detected microscopically. The lines were drawn by eye. Average standard errors, as a percentage of the mean, were: controls 22%, 10s exposure 34%, 2min exposures 42%, 10min exposures 46%. Significant reductions (Wilcoxon Ranking test; $p<0.5$) in the number of bubbles occured after: 200bar for 10s exposures, 100bar for 2min exposures, 25bar for 10min exposures. [Taken from Daniels et.al. (8)]

The Effect of Pressure Profile on Macroscopic Bubbles.

The distribution of bubbles.

In general, post-mortem examination has shown that bubbles occur in most major veins, in fatty areas subcutaneously and around the kidneys, but only rarely in arteries, muscle or liver. Highly perfused tissues, such as the brain, appear to be quite resistant to bubble formation (19) and the passage of bubbles through the pulmonary capillaries into the arterial circulation is rare, even with extensive bubble formation in the right side of the heart

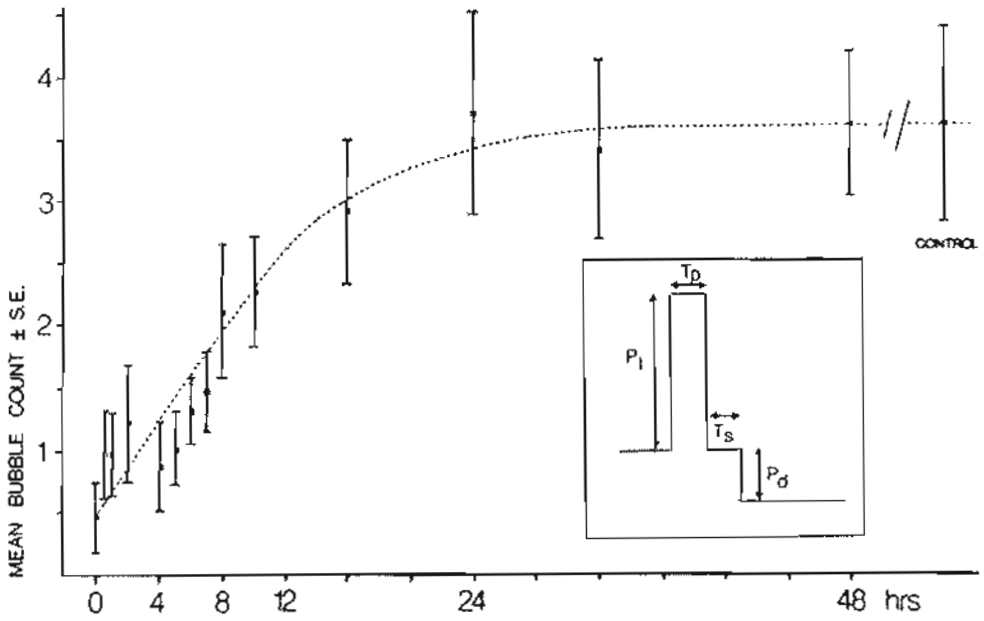

Figure 2: Mean bubble counts from groups of 20 marine shrimps, Crangon crangon, following decompression from atmospheric pressure to 0.1bar after exposure to hydrostatic pressure of 200bar for 2min with various time intervals between the pressure pre-treatment and decompression. Bars show the standard error of the mean. The line was drawn by eye. No significant (Wilcoxon Ranking test; $p>0.5$) reduction in bubble count exists if the interval between pressure pre-treatment and decompression exceeds 8hrs. Inset: Pressure pretreatment profile: P_T, hydrostatic pressure; T_p, pre-treatment time; T_s, surface interval between pretreatment and decompression; P_d, sub-atmospheric decompression. [Taken from Daniels et.al. (8)]

and in the pulmonary artery (19-21). However, with extensive, fatal embolism bubbles have been consistently observed in the left side of the heart (1). The upper body does not appear to be a significant source of bubbles (22). The distribution of peripheral bubbles has been investigated after decompression from saturation exposures ranging from 170kPa to 300kPa (23). No obvious anatomical correlations were found (Figure 3) with the severity of the decompression. However, analysis of the temporal behaviour of the bubbles indicated that the first bubbles appear in the vascular system. Furthermore, over 50% of all the bubbles observed during the 15min post-decompression observation period were intravascular. Increased severity of decompression not only increased the number of bubbles formed but also

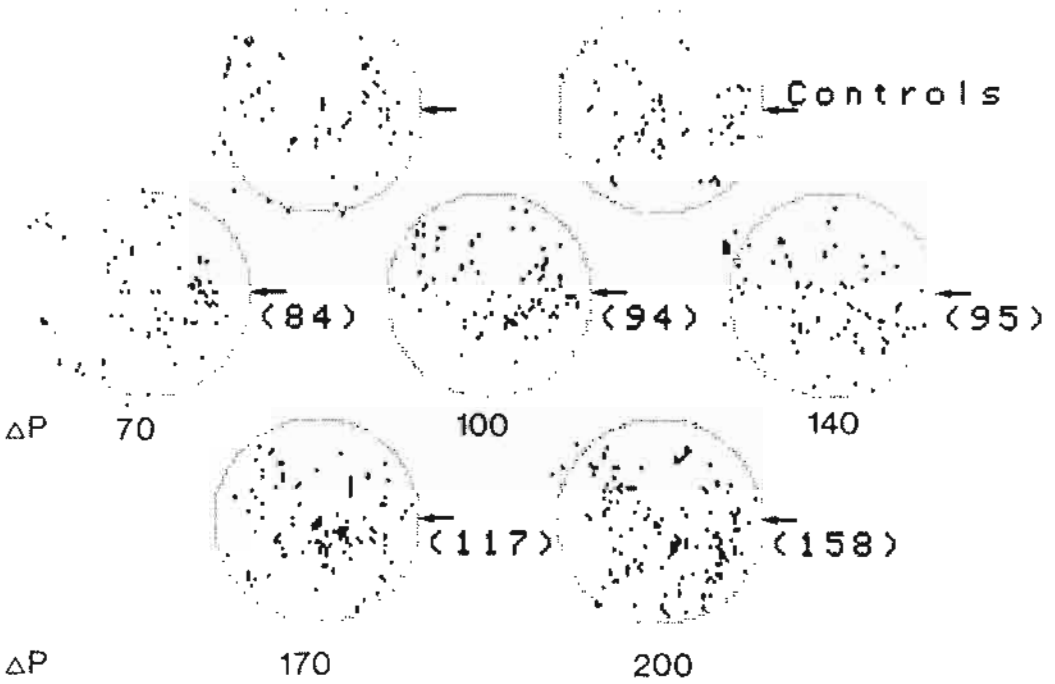

Figure 3: The distribution of sites of bubble formation, within a cross-section through the hind limb of anaesthetised guinea pigs, for 15min periods after decompression to atmospheric pressure from saturation exposures to pressures of air ranging from 170 to 300kPa. Each plot shows the total number of echo sites recorded from 10 experiments. The normal angle of incidence of the ultrasound is shown arrowed. Numbers in brackets are the total number of sites. "Sites" on the control plots represent intermuscular locations which produce transient echoes during experiments.
[Taken from Daniels (23)]

increased the proportion of stationary bubbles, which may be either intra- or extra-vascular (23-25). In peripheral areas marked differences in the sequence of appearance of bubbles have been reported (1).

The arterial paradox.

A remarkable finding from early experiments was that under some circumstances arterial bubbles were seen before venous ones (26,27). These observations provoked considerable controversy since arterial blood was considered the least gas-saturated tissue, redistribution of bubbles through the lungs or via pulmonary arterial-venous shunts was unlikely (28,29) and post-mortem examinations had not normally revealed bubbles in the left side

of the heart. The observation of arterial bubbles became known as the 'Arterial Paradox' and was generally held to arise only after severe decompressions.

Recent evidence indicates that arterial bubbles may be more common than hitherto supposed. In the course of a research dive at Duke University, a continuous stream of bubbles was observed, using ultrasound imaging, in the right ventricle and then bubbles were seen moving through the left ventricle towards the aortic outflow (30). Doppler detection methods failed to reveal these arterial bubbles. Subsequent clinical examination of this diver revealed no ventricular or arterial defects and it was concluded, therefore, that pulmonary shunting of the bubbles had occured. Arterial bubbles, mainly in the aorta and carotid artery, have been reported in 10 out of 12 divers during excursion procedures allowed by the USN Diving Table (22). Since, in these experiments, bubbles were more numerous in the venous than in the arterial circulation it was suggested that the arterial bubbles came from the venous side. The data of Lynch et.al. (1) also support the concept of vascular redistribution, since in the femoral vessels venous bubbles were always seen first but in the cheek-pouch arterial bubbles appeared first. Although the lungs are superb filters of micro-bubbles, it is clear that they may be overloaded and under these conditions allow bubbles to pass from the venous to the arterial circulation.

The effects of exercise.

Harvey conducted an extensive series of investigations on the effects on bubble formation of body fat, muscle stimulation, tissue injury and pre oxygenation on the development of bubbles in the abdominal cavity of cats (31-34). In resting animals there was a strong correlation between the fat content and the extent of bubble formation. However, when the muscles were stimulated this correlation was absent. Tissue injury was found to greatly enhance bubble formation, whereas pre-oxygenation greatly reduced it.

The effect of exercise during decompression on the extent of bubble formation is unclear. In general terms, exercise during the exposure to pressure will increase the amount of gas dissolved through increased cardiac and respiratory function. This may lead to bubbles during the subsequent decompression when few had been expected. Exercise during the decompression should increase the rate of gas elimination, for the same reasons. However, it may also lead to an increase in the number of bubbles arriving centrally. It is an accepted part of pre-cordial doppler monitoring for bubble formation to include some muscular movement during the examination, usually deep knee bends. This movement frequently gives rise to a shower of bubbles appearing in the pulmonary artery. Indeed, in the course of 150 decompression experiments, it was reported that any movement (eg. standing) during decompression produced a short burst of bubbles whilst none were detected when the divers remained quiescent (35). It was, however, noted that sustained movements produced no persistent increase in the number of bubbles when compared to motionless subjects. Thus, it may be that mild, continuous exercise would be beneficial, in the sense of increasing the

elimination of gas without inducing an excessive number of bubbles, whilst intermittent exercise should be avoided, since it may produce a shower of bubbles sufficiently large to compromise the cardiac or pulmonary system. It should also be noted that violent exercise may lead to an increase in the number of bubbles through facilitation mechanisms akin to those described for fish (18).

Vascular redistribution

Experiments involving multiple compression/decompression cycles revealed a phenomenon with potentially grave consequences (36,37). The incidence of decompression sickness after double dive experiments was compared to that after a single dive, in which the total exposure time equalled that of the two dives plus the interdive period. Despite the reduced gas supersaturation after the double dive, in comparison to the single dive, the incidence of decompression sickness was greater after the double dives. It was further shown that the interdive period which produced the greatest increase in sickness was species dependent (Figure 4). To explain these findings it was proposed that peripheral bubbles moved centrally in response to the second compression and, on the following decompression, rapidly expanded causing sudden, acute decompression sickness. Direct observation of the vena cava and aorta of guinea pigs throughout such experiments revealed showers of bubbles ascending the inferior vena cava during the compression phase of the second dive. Bubbles were also observed in the aorta during the second decompression. Bubbles have also been observed in the femoral artery of dogs after the third of a series of repeat dives (38).

More recently, in experiments using human subjects exposed to multiple excursions from saturation pressure exposures, bubbles were found to be more numerous during the first than the second ascent (22). This it was suggested may be due to nuclei being used up and insufficient time for them to regenerate. It was also noted that recompression sufficient to aleviate clinical symptoms did not remove intravascular bubbles.

Thus , illjudged repeat dives may not only give rise to an increase in the likelihood of decompression sickness but may also result in far more severe symptoms than might be expected by simple extrapolation from the effect of single dives. However, if a carefully controlled regime of repetative dives is constructed, using an appropriate interdive interval, then some benefit, in terms of a reduction in the number of bubbles on the later dives, may accrue.

The time course of bubble formation.

The initial mobile, intravascular bubble formation, after saturation exposures to pressure, in the periphery of the guinea pig occurs within the first 5min after decompression and frequently within the first minute (23-25; Figure 5). The recruitment of sites of bubble formation is dependent on the magnitude of the decompression (Figure 6). As the severity of the

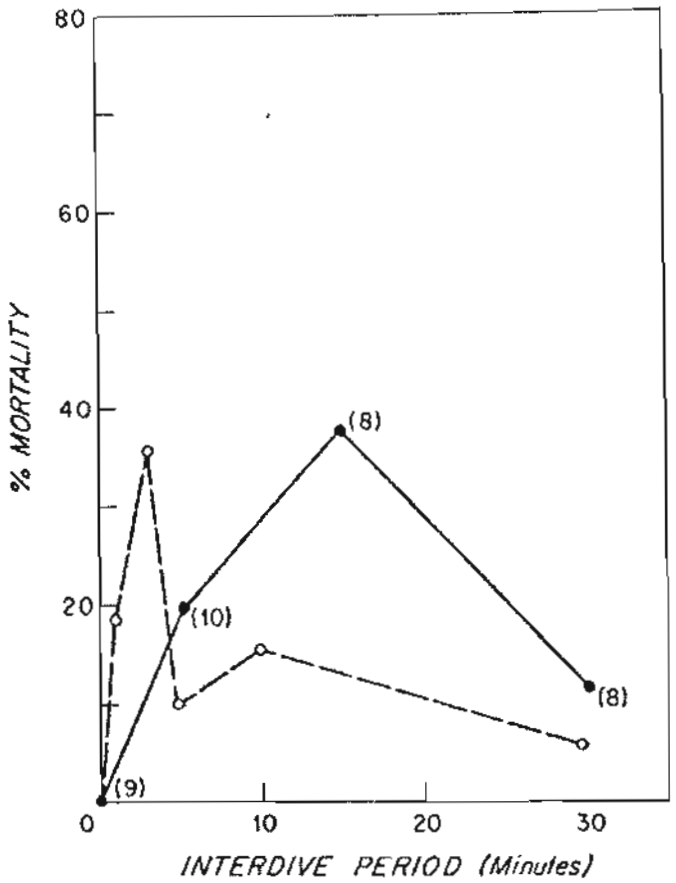

Figure 4: Mortality in guinea pigs (solid line) after exposure to 6.9atm N_2 for 15min, a variable interdive period, and a second exposure to 5.5atm N_2 for 15min. Animals breathed 1atm O_2 throughout. Numbers against each point are sample size. Mortality in mice (dashed line) exposed to two 5min dives to 10.2atm N_2 with a variable interdive period as before. [Taken from Gait et.al. (37)].

decompression is increased a further recruitment of sites of bubble formation occurs, and these bubbles tend to be stationary (23-25). The accumulation of stationary bubbles appears to be associated with the subsequent appearance of signs of decompression sickness. The latent period before the appearance of this stationary bubble phase is dependent on the severity of the decompression (Figure 7).

There is a further latent period associated with the appearance of symtoms;

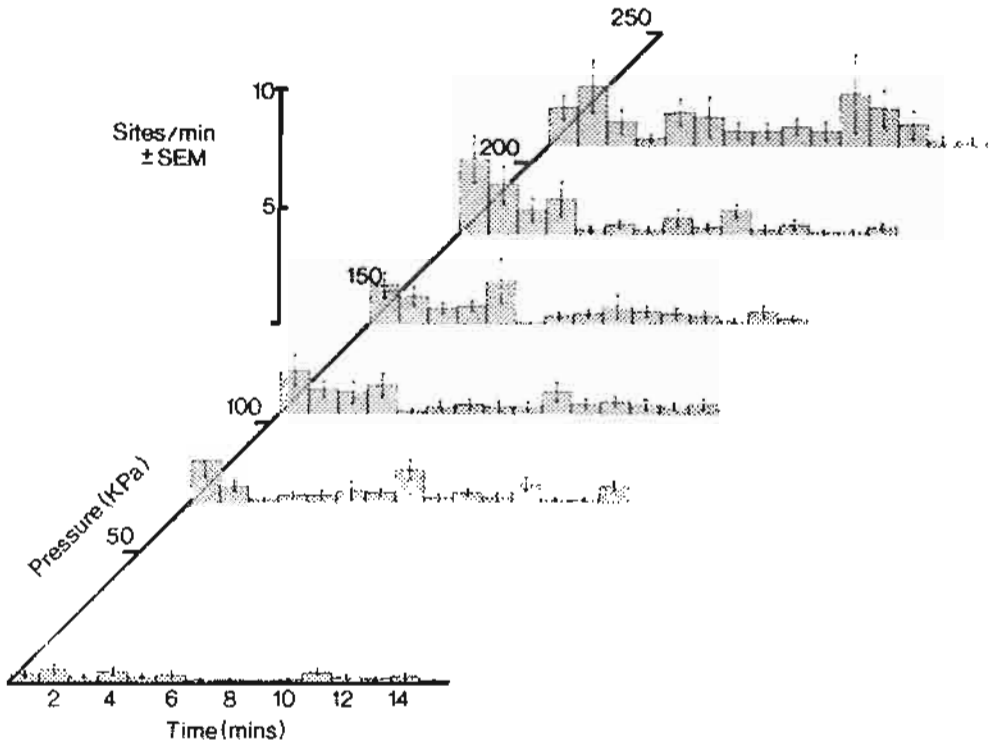

Figure 5: Mean number of sites of bubble formation in the guinea pig hind limb as a function of the magnitude of decompression. Pressure is shown relative to atmospheric pressure. 10 experiments, all asymptomatic, at each pressure. Bars show standard error of the mean. Sites shown after the control experiments represent echoes from intermuscular junctions falsely identified as due to bubbles. [Taken from Daniels (23)].

this ranges from 1min for the 0.83MPa decompressions to 15min for the 0.41MPa decompressions (8). The time for bubbles to disappear was followed for asymptommatic decompressions from 0.41 and 0.28MPa, and was found to be approximately 40min in both cases (8).

Bubbles were found to appear in the femoral vein of hamsters within 1-3min of decompression, but up to 30min elapsed before bubbles appeared in the cheek-pouch arteries (1). In animals that did not exhibit cheek-pouch bubbles and survived for 1hr post-decompression the number of bubbles in the femoral vessels gradually decreased over the first 40min. No bubbles were observed after that time. A series of experiments were made to test the effect on bubble numbers of exposure time (Table 1). No appreciable difference in numbers was seen for exposure times from 68min to 10min. However, when the exposure time was reduced to 5min no bubbles were seen.

The time course of onset and disappearance of bubbles in the pulmonary

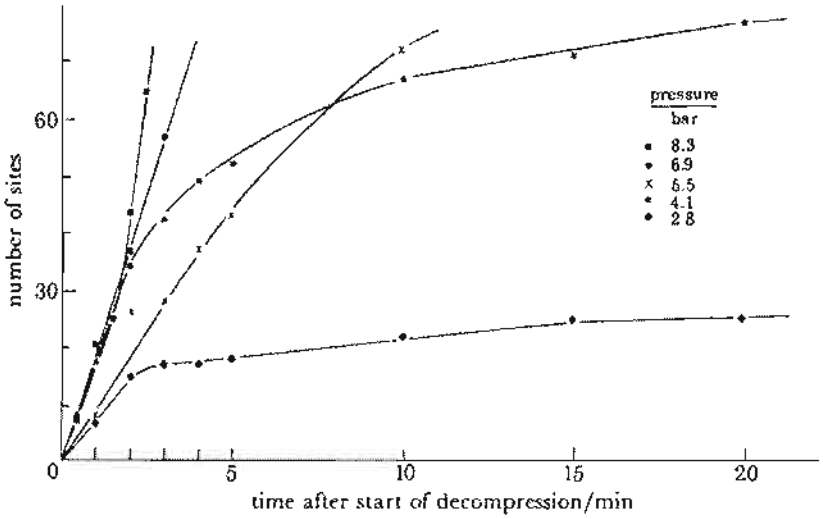

Figure 6: Recruitment of sites of bubble formation in the hind limb of anaesthetised guinea pigs after saturation air dives. The lines merely join the points which represent the average over a number of decompressions. [Taken from Daniels (24)].

artery of divers after air dives has been also investigated. During a series of excursions from saturation exposures, latent periods for the appearance of bubbles in the pulmonary artery, similar to those in the guinea pig for the appearance of stationary bubbles, were observed (39; Figure 8). As in the guinea pig experiments, a further latent period, after the appearance of bubbles, was observed before the onset of symptoms. These ranged from about 2min for the most severe to 10min for the mildest decompressions. In a subsequent series of experiments, with shallower saturation dives, the mean latency for bubbles in the pulmonary artery after decompression, was 1hr with an exposure pressure of 189kPa and 2hr with an exposure pressure of 177kPa (40; Figure 9). In these experiments the additional time elapsed before symptoms amounting to 1hr after the 189kPa decompressions and 4hrs after the 177kPa decompressions (40; Figure 9). In these experiments bubbles had essentially disappeared after approximately 8hrs (Figure 9). The difference in the latent periods between the human experiments and the guinea pig and hamster experiments appears broadly in line with the relative sizes, circulation and respiration rates.

Threshold pressures for bubbles.

The possible strategies for decompression procedures will be determined largely by the degree of supersaturation necessary for the initiation of bubble formation; and, how it depends on the absolute pressure.

The decompression necessary to produce bubbles detected by doppler techniques in the pulmonary artery has been investigated in a number of

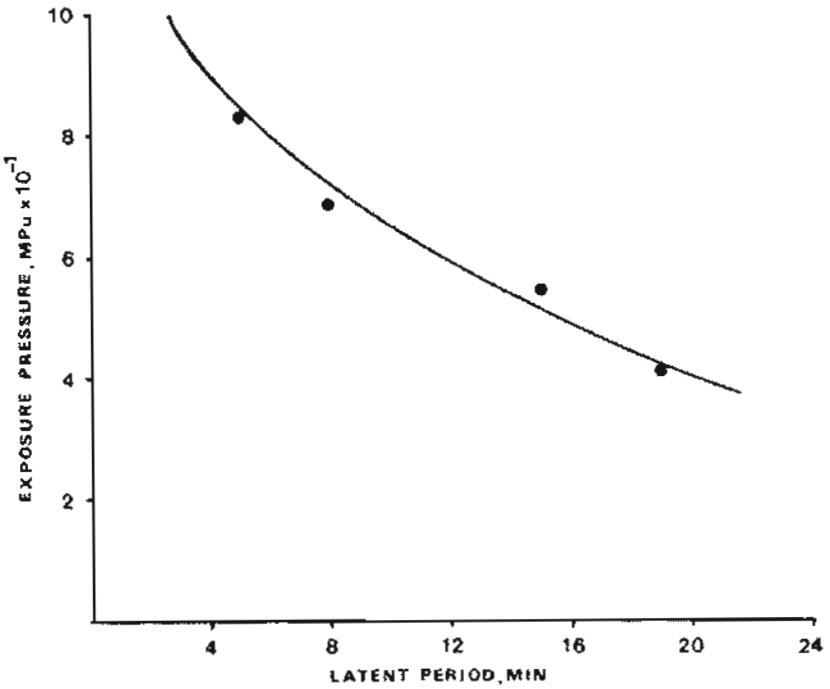

Figure 7: The latent period before the onset of a stationary bubble phase in the guinea pig after decompression from air saturation exposures. The points represent the average latent period over a number of decompressions. [Taken from Daniels et.al. (8)].

Table 1. The number and distribution of peripheral bubbles in the hamster after decompression from exposure to 0.7MPa air for various times. The data are taken from Lynch et.al. (1).

Number of Animals	Bottom time min	%age Venous bubbles	%age Arterial bubbles
40	68	90	50
10	40	90	40
10	30	90	40
10	20	90	40
10	10	80	10
10	5	0	0

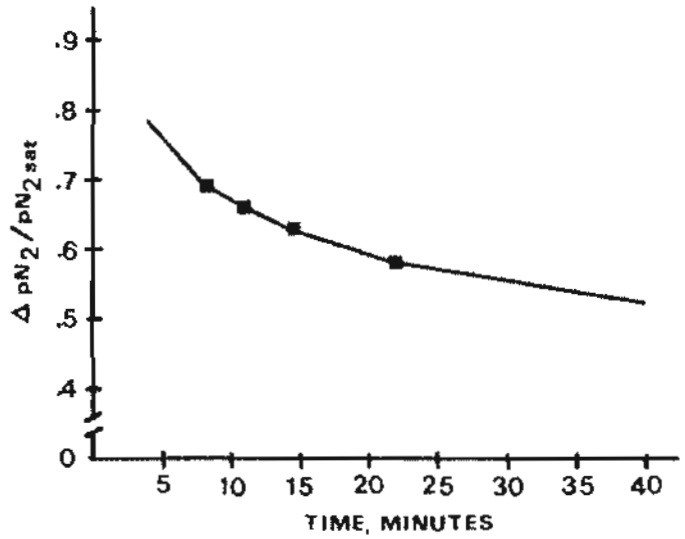

Figure 8: Mean times of appearance, in man, for gas emboli in the pulmonary artery plotted against nitrogen partial pressure reduction ratio for a variety of excursions from saturation exposure to air. [Taken from Eckenhoff & Parker (39)].

species (41) and under a variety of conditions (42). The maximum pressure drop (after exposure to saturation pressures) before the appearance of bubbles in rats is shown in figure 10 as a function of exposure pressure. As has long been recognised for the appearance of symptoms, the bubble free decompression ratio (initial/final pressure) apparently decreases with increasing depth. This result was found in all species studied; rat, cat and dog. The critical supersaturation for decompression to atmospheric pressure was found to be the same, 90kPa, in these three species. Brief exposure to 500kPa over the exposure pressure, whether applied at the beginning or the end of the saturation period had no effect on the bubble threshold. Changes in the ambient temperature, between 15 and 35°C, had little effect on the threshold; increasing or decreasing the temperature from the normal ambient temperature of 24°C reduced the threshold. Repeated exposures to pressure after a 24hr period increased the bubble threshold, allowing a greater decompression to be carried out without bubbles than was the case for the equivalent first exposure.

The critical threshold supersaturation for bubble formation in the periphery of guinea pigs has also been investigated (23,24). The extent of bubble

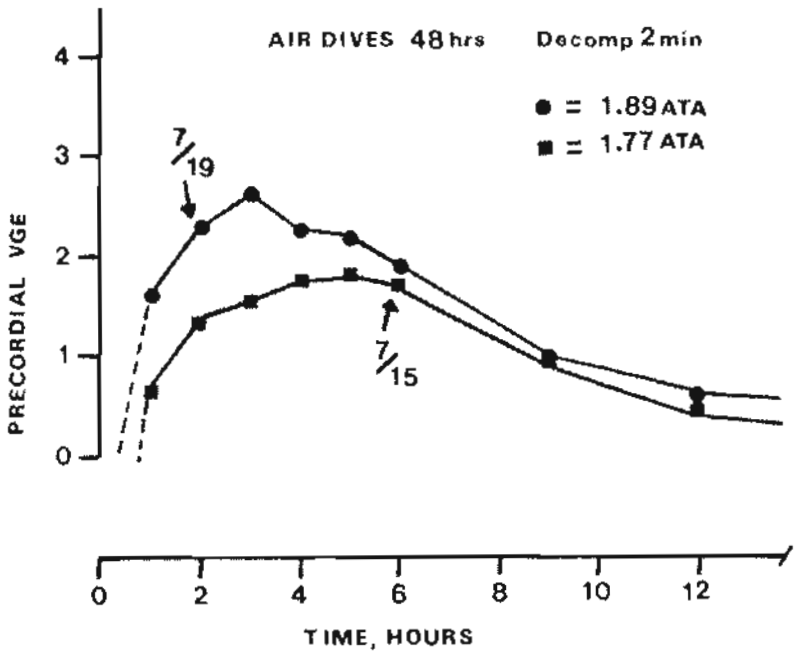

Figure 9: Mean number of bubbles in the pulmonary artery of men (scored according to the method of Kisman et.al. 1978 Undersea Biomed. Res. 5, pp28) as a function of time after decompression from saturation exposures to air. The arrows denote the mean time of appearance of symptoms of decompression sickness and the proportion of subjects exhibiting symptoms. [Taken from Eckenhoff et.al. (40)].

formation was analysed after two separate series of saturation exposures; one in which decompresion was to atmospheric pressure and the second, from higher exposure pressures, in which decompression was to 800kPa. The results of these experiments are shown in figure 11. Analysis of the number of bubbles, detected by ultrasound imaging, after these decompressions suggested a critical supersaturation equivalent to a decompression of 70kPa. Furthermore, in contrast to the critical threshold for bubbles in the pulmonary artery, that for bubble formation in the periphery was independent of the exposure pressure. However, once the threshold was exceeded, there was a clear effect of pressure on the number of bubbles produced by a given decompression. To produce a given number of bubbles approximately 5 times the decompression was required when the final pressure was 800kPa as compared to atmospheric pressure. Therefore, since most evidence indicates that peripheral bubble formation occurs first and that a certain number of bubbles have to be produced before they can be detected by doppler techniques in the pooled venous return, then the apparent reduction in the

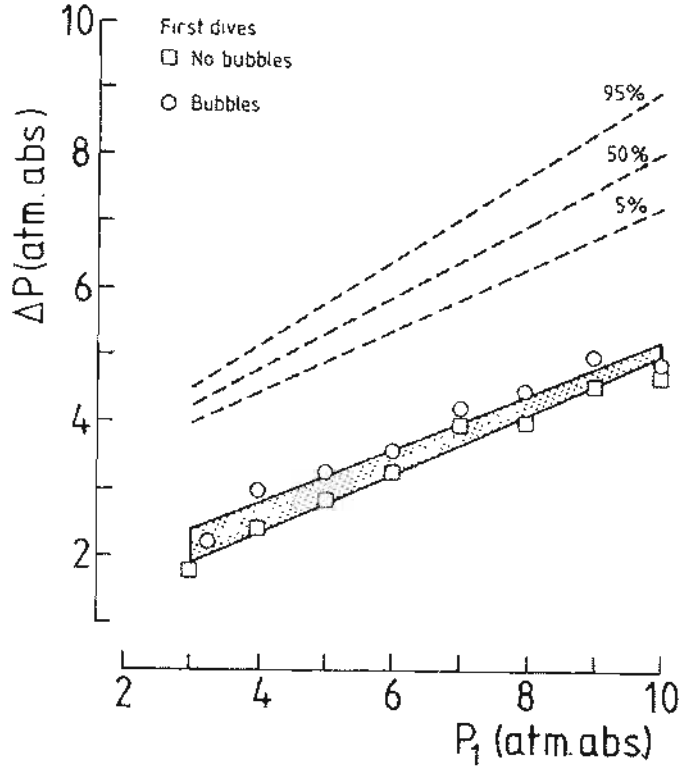

Figure 10: Doppler-determined thresholds for venous gas emboli in the rat after a step decompression from saturation exposures to pressure of air from 3 to 10ATA (300-1000kPa). Circles represent the minimum pressure reduction from saturation that produced intravascular bubbles. Squares represent the maximum pressure reduction from saturation that produces no intravascular bubbles. The true decompression-induced bubble threshold can be considered to lie between the bubble and no-bubble regression lines. P_1 is the saturation pressure, ΔP the pressure reduction from P_1 to a predetermined lower pressure P_2. Upper dashed lines indicate incidence levels for symptoms of decompression sickness. [Taken from Lin, (41)].

critical threshold with increasing pressure, as measured by doppler techniques, might be expected.

Confirmation for a critical threshold, in the guinea pig, was sought by testing the effect of conditioning saturation dives on the number of bubbles after a 15min test dive. When the exposure pressure of the conditioning dive was equivalent to the critical threshold pressure no difference was found between the number of bubbles after the test dive compared to the test dive alone. However, when the exposure pressure of the conditioning dive was greater than the critical threshold pressure a significant reduction,

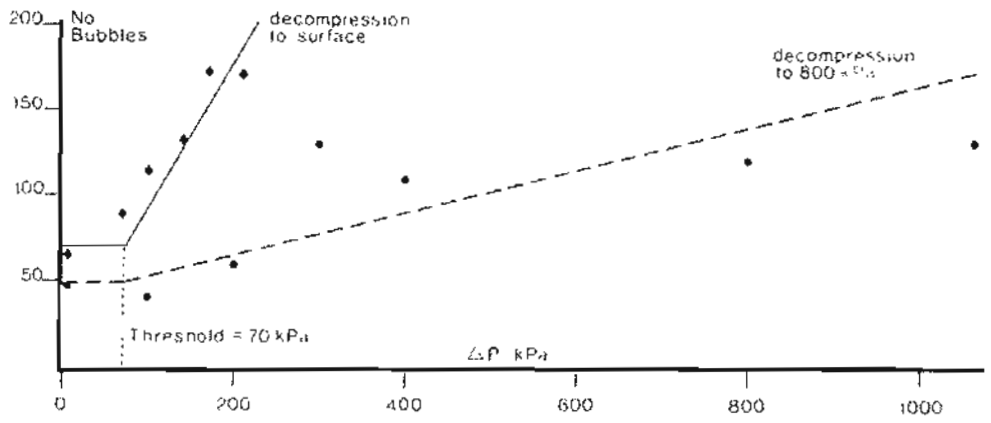

Figure 11: Number of bubbles over a 15min period, identified by the analysis of ultrasound images from cross-sections through the hind limbs of anaesthetisd guinea pigs, after decompression from saturation exposures to raised pressure of air. Solid line: results after decompression to atmospheric pressure (100kPa) from exposure pressures ranging from 170 to 300kPa, mean experimental determinations (from 10 experiments for each point) given by diamonds. Dashed line: results after decompression to 800kPa from exposure pressures ranging from 870kPA to 1870kPa, mean experimental determinations (from 10 experiments for each point) given by circles. The lines represent the best fit determined by a maximum likelihood method computed using GLIM (Generalised Linear Interactive Modelling; Numerical Algorithms Group, Oxford) running on the Oxford University VAX 11/780. The number of "bubbles" shown for the control experiments (20 for the series of experiments involving decompression to 100kPa and 10 for the series of experiments involving decompression to 800kPa) in which no decompression took place, represent transient echoes from intermuscular junctions falsely identified as being due to bubbles. For both series of experiments a threshold for bubble formation was estimated at a supersaturation equivalent to a decompression of 70kPa.

compared to the test dive alone, was observed in the number of bubbles after the test dive (24). The reduction in the number of bubbles after the test dive, when preceded by a supra-thresold conditioning dive, suggests that the number of available bubble nuclei has been reduced. This reduction in the number of bubbles is consistent with the finding that threshold for the

doppler detection of bubbles increased for second decompressions (42).

Recent experiments (39,40,43,44) in which the critical threshold for bubble formation in man has been investigated all indicate that a pressure reduction of approximately 70kPa, for decompression to the surface, is sufficient to produce doppler detectable bubbles in the pulmonary artery. Indeed, Eckenhoff et.al. (39) have suggested that the threshold may be as low as 40kPa and in experiments involving subatmospheric decompressions Dixon et.al. (43) showed that a sub-atmospheric pressure reduction, of approximately 50kPa, induced pulmonary arterial bubbles in 73% of their subjects. Bell et.al. (44) have shown that the addition of carbon dioxide to the breathing mixture (2kPa) reduced the number of pulmonary arterial bubbles.

Summary.

It is possible to identify a number of the general features of bubble formation: The first bubbles to appear are in the peripheral venous circulation. If the number of bubbles arriving at the lungs is excessive then arterial bubbles will appear. There does not appear to be any especially susceptible site for bubble formation. The level of gas supersaturation necessary for bubble formation *in vivo* is of the order of 50-70kPa. The critical bubble threshold found in all species studied (shrimp, rat, guinea pig, cat, dog and man) has been found to be similar. The critical bubble formation threshold is independent of exposure pressure, but once it has been exceeded, the number of bubbles becomes pressure dependent. Mild, continuous exercise may be helpful in increasing the rate of gas elimination, without an increase in bubble formation, but intermittent or violent exercise will increase the number of bubbles with a concomitant increase in the likelihood of decompression sickness. A carefully planned sequence of repeat dives may have a lower than expected incidence of symptoms because as nuclei are consumed the number of bubbles decreases. In this context, it would be important, to gain the maximum benefit, that the dives were conducted in order of decreasing severity. However, it must be borne in mind that incorrectly chosen interdive intervals may result in the unexpected appearance of sudden, acute symptoms as a result of vascular redistribution of bubbles rendering cardiac and respiratory functions vulnerable.

The low supersaturation necessary to initiate bubble formation would explain the empirical finding that most currently used decompression shedules result in bubble formation. As a consequence of this low threshold bubble free decompressions would require unacceptably long decompression times. It is, therefore, vital to elucidate the quantitative relationship between the number of bubbles and symptoms of decompression sickness. Experiments with doppler detection have given, by and large, a poor correlation between the number of pulmonary arterial bubbles and the likelihood of decompression sickness. To date ultrasonic imaging techniques give a clearer correlation between the overall peripheral bubble density and the likelihood of

symptoms. Developments in ultrasound imaging should allow further progress toward the quantification of the relationship between the number of bubbles and the likelihood of decompression sickness as well as the relationship between their rate of accumulation and the time before the onset of decompression sickness.

With a clear understanding of the link between bubbles and symptoms, of the effects of environmental factors (rate of change of pressure, physical properties of the gas mixture, temperature, exercise) and of the reasons underlying the variability in bubble formation, decompressions schedules will be designed which will not only prevent acute decompression sickness but also the long-term effects, which (with the exception of oesteonecrosis) are only now becoming known.

References.

[1] Lynch P.R., Brigham M., Tuma R. & Wiedeman M.P. **1985** Origin and time course of gas bubbles following rapid decompression in the hamster. Undersea Biomed. Res. 12, 105-114.

[2] Spencer M.P. & Clarke J.F. **1972** Precordial monitoring of pulmonary gas embolism and decompression bubbles. Aerospace Med. 43, 762-767.

[3] Spencer M.P., Johanson D.C. & Campbell S.D. **1972** Safe decompressions with the doppler ultrasonic blood bubble detector. In "The Proceedings of the Fifth Symposium on Underwater Physiology". (ed. C.J. Lambertsen) FASEB Bethesda, Maryland 311-325.

[4] Nishi R.Y., Kisman K.E., Eatock B.C., Buckingham I.P. & Masurel G. **1981** Assessment of decompression profiles and divers by doppler ultrasonic monitoring. In "The Proceedings of the Seventh Symposium on Underwater Physiology". (ed. A.J. Bachrach & M.M. Matzen) Undersea Medical Society, Inc. Bethesda, Maryland 717-727.

[5] Gardette B. **1979** Correlation between decompression sickness and circulating bubbles in 232 divers. Undersea Biomedical Research 6, 99-107.

[6] Nashimoto I. & Gotoh Y. **1977** Ultrasonic doppler detection of blood bubbles in caisson work. In "Early Diagnosis of Decompression Sickness". 12th Undersea Medical Society Workshop (ed. R.Pearson) Undersea Medical Society, Inc, Bethesda, Maryland 171-183.

[7] Daniels S. **1978** Improvements in or relating to decompression bubble detectors. UK Patent GB 2034037B.

[8] Daniels S., Davies J.M., Eastaugh K.C., Paton W.D.M. & Smith E.B. **1981** Monitoring bubble formation with an integrating pulse-echo ultrasonic method. In "The Proceedings of the Seventh Symposium on Underwater Physiology". (ed. A.J. Bachrach & M.M. Matzen) Undersea Medical Society, Inc. Bethesda, Maryland 729-741.

[9] Daniels S., Davies J.M., Paton W.D.M. & Smith E.B. **1984** Recent experiments using ultrasonic imaging to monitor bubble formation in divers. In "The Proceedings of the Eighth Symposium on Underwater Physiology". (ed. A.J. Bachrach & M.M. Matzen) Undersea Medical Society, Inc. Bethesda, Maryland 259-269.

[10] Harvey E.N., Barnes D.K., McElroy W.D., Whiteley A.H. & Pease D.C. **1945** Removal of gas nuclei from liquids and surfaces. J.Amer.Chem.Soc. 67, 156.

[11] Evans A. **1984** Evidence for bulk nucleation in the Berthelot tube at ground level. J.Phys.D:Appl.Phys. 17, L97-L100.

[12] Harvey E.N. **1951** Physical factors in bubble formation. In "Decompression Sickness". (ed. J.F. Fulton) W.B. Saunders Co., Philadelphia & London, 90-114.

[13] Evans A. & Walder D.N. **1969** Significance of gas micronuclei in the aetiology of decompression sickness. Nature, Lond. 222, 251-252

[14] Daniels S., Eastaugh K.C., Paton W.D.M. & Smith E.B. **1984** Micronuclei and bubble formation: A quantitative study using the common shrimp, Crangon crangon. In "The Proceedings of the Eighth Symposium on Underwater Physiology". (ed. A.J. Bachrach & M.M. Matzen) Undersea Medical Society, Inc. Bethesda, Maryland 147-159.

[15] Vann R.D., Grimstead J. & Nielsen C.H. **1980** Evidence for gas nuclei in decompressed rats. Undersea Biomedical Research 7, 107-112.

[16] Ikels K.G. **1970** Production of gas bubbles in fluids by tribonucleation. J.Appl.Physiol. 28, 524-527.

[17] Evans A. & Walder D.N. **1974** In vivo nuclear fission in the aetiology of decompression sickness. Nature, Lond., 252, 696-697.

[18] McDonough P.M. & Hemmingsen E.A. **1985** Swimming movements initiate bubble formation in fish decompressed from elevated ga pressures. Comp. Biochem. Physiol. 81A, 209-212.

[19] Spencer M.P. & Powell M.R. **1977** The etiology of convulsions after hyperbaric exposures. Undersea Biomedical Research 4, A23.

[20] Butler B.D. & Hills B.A. **1979** The lung as a filter for microbubbles. J.Appl.Physiol. 47, 537-543.

[21] Powell M.R. & Spencer M.P. **1980** The pathophysiology of decompression sickness and the effects of doppler detectable bubbles. Final report O.N.R. N00014-73-C-0094. Seattle, Washington.

[22] Brubakk A.O., Peterson R., Grip A., Holand B., Onarheim J., Segadal K., Kunkle T.D. & Tonjum S. **1985** Gas bubbles in the circulation of divers after ascending excursions from 300 to 250msw. J.Appl.Physiol. 60, 45-51.

[23] Daniels S. **1984** Ultrasonic monitoring of decompression procedures. Phil.Trans.R.Soc.Lond.B. 304, 153-175.

[24] Daniels S. **1986** Bubble formation in animals during decompression. In "Diving in animals and man" (ed. A.O. Brubakk, J.W. Kanwischer & G. Sundnes). Tapir, Trondheim, 229-264.

[25] Daniels S., Davies J.M., Paton W.D.M. & Smith E.B. **1980** The detection of gas bubbles in guinea pigs after decompression from air saturation dives, using ultrasonic imaging. J.Physiol. 308, 369-385.

[26] Wagner C.E. **1945** Observations of gas bubbles in pial vessels of cats following rapid decompression from high pressure atmospheres. J.Neurophysiol. 8, 29-32.

[27] Lever M.J., Miller K.W., Paton W.D.M. & Smith E.B. **1966** Experiments on the genesis of bubbles as a result of rapid decompression. J.Physiol. 184, 964-970.

[28] Ring G.S., Blum A.S., Kurbator T., Moss W.G. & Smith W. **1961** The size of microspheres passing through the pulmonary circuit in the dog. Am.J.Physiol. 200, 1191-1196.

[29] Emerson L.V., Hempleman H.V. & Lentle R.G. **1967** The passage of gaseous emboli through the pulmonary circulation. Resp.Physiol. 3, 213-219.

[30] Powell M.R., Spencer M.P. & von Ramm O.T. **1982** Ultrasonic surveillance of decompression. In "The Physiology and Medicine of Diving, 3rd edition". (ed. P.B. Bennett & D.H. Elliott) Bailliere Tindall, London 404-435.

[31] Harvey E.N., Barnes D.K., McElroy W.D., Whiteley A.H., Pease D.C. & Cooper K.W. **1944** Bubble formation in animals I. Physical factors. J.Cell.Comp.Physiol. 24, 1-22.

[32] Harvey E.N., Whiteley A.H., McElroy W.D., Pease D.C. & Barnes D.K. **1944** Bubble formation in animals II. Gas nuclei and their distribution in blood and tissue. J.Cell.Comp.Physiol. 24, 23-34.

[33] Harvey E.N., McElroy W.D., Whiteley A.H., Warren G.H. & Pease D.C. **1944** Bubble formation in animals III. An analysis of gas tension and hydrostatic pressure in cats. J.Cell.Comp.Physiol. 24, 117-132.

[34] Harvey E.N. **1951** Animal experiments on bubble formation: Part I. Bubble formation in cats. In "Decompression Sickness". (ed. J.F. Fulton) W.B. Saunders Co., Philadelphia & London 115-144.

[35] Powell M.R., Thoma W., Fust H.D. & Cabarrou P **1983** Gas phase formation and doppler monitoring during decompression with elevated oxygen. Undersea Biomed. Res. 10, 217-224.

[36] Giffiths H.B., Miller K.W., Paton W.D.M. & Smith E.B. **1971** On the role of separated gas in decompression procedures. Proc.Roy.Soc.Lond.B 178, 389-406.

[37] Gait D.J., Miller K.W., Paton W.D.M., Smith E.B. & Welch B. **1975** The redistribution of vascular bubbles in multiple dives. Undersea Biomedical Research 2, 42-49.

[38] Christman C.L., Catron P.W., Flynn E.T. & Weathersby P.K. **1986** In vivo microbubble detection using a second harmonic resonant bubble detector. Undersea Biomed. Res. 13, 1-18.

[39] Eckenhoff R.G. & Parker J.W. **1984** Latency in onset of decompression sickness on direct ascent from air saturation. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 56, 1070-1075.

[40] Eckenhoff R.G., Osborne S.F., Parker J.W. & Bondi K.R. **1986** Direct ascent from shallow air saturation exposures. Undersea Biomed. Res. 13, 305-316.

[41] Lin Y.C. **1981** Species independent maximum no-bubble pressure reduction from saturation dive. In "The Proceedings of the Seventh Symposium on Underwater Physiology". (ed. A.J. Bachrach & M.M. Matzen) Undersea Medical Society, Inc. Bethesda, Maryland 699-707.

[42] Lin Y.C., Mack G.W., Watanabe D.K. & Shida K.K. **1984** Experimental attempts to influence the bubble threshold from saturation dives in animals. In "The Proceedings of the Eighth Symposium on Underwater Physiology". (ed. A.J. Bachrach & M.M. Maatzen) Undersea Medical Society, Inc. Bethesda, Maryland 259-269.

[43] Dixon G.A., Adams J.D. & Harvey W.T. **1986** Decompression sickness and intravenous bubble formation using a 7.8psia simulated pressure-suit environment. Aviat. Space Environ. Med. 57, 223-228.

[44] Bell P.Y., Harrison J.R., Page K. & Summerfield M. **1986** An effect of CO_2 on the maximum safe direct decompression to 1 bar from oxygen-nitrogen saturation. Undersea Biomed. Res. 13, 443-445.

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DISCUSSION

CAPTAIN THALMANN: Dr. Daniels, we presented a paper at NUTEC (1) describing adaptation in divers who had a high bends incidence after helium-oxygen decompression. These divers were then subjected to two no-stop exposures which were followed by the original helium-oxygen decompression once again. There was a marked reduction in decompression sickness incidence after the second helium-oxygen decompression. We did venous Doppler monitoring on these divers and could detect no change in the Doppler scores. We concluded that marked adaptation to decompression had occurred, but this adaptation was absolutely unrelated to the venous gas emboli we detected. We have found in thousands of Doppler bubble detections that there is no particular relationship between venous gas emboli and severity or predictability of decompression sickness. The only conclusion one can draw is that the probability of bends is higher with a high bubble score and lower with a low bubble score. However, severe decompression sickness can occur in individuals in whom bubbles were not detected. My impression from your talk was that there is a one-to-one relationship between gas emboli and bends. In people who got bends, did you say that there was a slight increase in peripheral bubbles? Do you ever observe decompression sickness when few or no bubbles are detected?

DR. DANIELS: We have never observed decompression sickness in the absence of peripheral bubbles. We've frequently observed decompression sickness in the absence of venous gas emboli in the pulmonary artery. I do not think there's a one-to-one relationship between the pulmonary arterial gas emboli and decompression sickness, but as yet, peripheral bubbles have always been present when decompression sickness occurred.

DR. KUNKLE: We did a series of experiments with dogs to study adaptation. We exposed the animals to 100 fsw, 30-minute dives 3 times a week to determine how many dives the animals could withstand before showing signs of decompression illness. We found the number of dives before decompression sickness occurred increased from an average of two or three to five or six. This was a clear indication of adaptation. We also saw a decrease in the total number of venous gas emboli passing through the heart but no decrease in the maximum Doppler score. When the total number of bubbles passing through the pulmonary artery crossed a critical score, however, the animals got decompression sickness. The only difference between our results in dogs and Dr. Thalmann's results in humans was that we saw a fairly good correlation between a reduction in the number of venous gas emboli and decompression illness.

DR. DANIELS: We've looked for adaptation in the guinea pig and couldn't find any evidence at all, either in incidence of symptoms or in bubbles.

DR. LUNDGREN: Dr. Daniels, would you amplify your statement that there is growing evidence that arterial bubbles are more commonplace than we thought and that they are the result of ill-judged decompressions.

I ask this because of the difference between the incidence of bubbles and the incidence of symptoms. This makes some people feel that bubbles are acceptable in decompression as long as they don't produce symptoms and are not arterial bubbles. Just what is an ill-judged decompression, and how can we avoid arterial bubbles?

DR. DANIELS: I can't say with great certainty because of the variability with which bubble appear. If a decompression is monitored correctly, you can tell half-way through if it is wrong for the

individual. It is very difficult, however, to say if any particular schedule will always be safe or unsafe, apart from the obvious extremes.

DR. LUNDGREN: Is a decompression that leads to arterial bubbles more ill-judged than one that leads to venous bubbles? This is important because before we say that the decompression was ill-judged, we should consider the legal implications.

DR. GILBERT: In our work we have the tentative conclusion that venous gas emboli are a necessary but not sufficient condition for decompression sickness. We have monitored people during 8 hours of exercise at altitude, followed by 12 hours at 1 ATA, and found that a large number who have grade 4 bubbles will not manifest decompression sickness symptoms. Pertaining to adaptation, the time interval between the first and second decompressions I mentioned this morning was 2 hours. Perhaps sometime after 2 hours, micronuclei are regenerated so that decompression sickness can occur again.

We have exposed both exercising subjects and resting Doppler technicians to 6.0 or 4.3 psi. We found that both groups reached the same maximum bubble grade, but the exercising subjects reached this maximum 90 minutes earlier than the resting technicians. The subjects did moderate upper-body exercise at around 200 kcal to simulate EVA. They were supine during Doppler monitoring and had few bubbles while at rest, but showers of bubbles upon flexing their limbs. Would this represent a mechanical release of bubbles that had been sequestered somewhere, as opposed to bubble formation due to exercise? The subjects had exercised continuously for 12 of 16 minutes and repeated this cycle throughout the experiment. What are your thoughts?

DR. DANIELS: Yes, I agree. The majority of bubbles seen as a result of exercise during Doppler monitoring have already formed in the periphery and have been released to move centrally because of the exercise. The exercise, per se, has not encouraged their formation.

DR. PETERSON: I'd like to add some information pertaining to the arterial bubbles detected at NUTEC and discussed earlier by Dr. Lundgren. These bubbles were detected on ascending excursions from saturation. The shallowest storage depth from which they were detected was 1000 fsw. Some of the excursions began from approximately 1600 fsw. No bubbles were detected, however, at shallower storage depths of about 70 msw. Our belief is that these bubbles were rather small and were stable at high pressure but not at low pressure. The only symptomatology noted when the arterial bubbles were detected were extremely minor feelings in the knees of three men during one ascent. They were prepared to exercise and didn't take much note of their knees, but we recompressed just to see what would happen. The feeling in their knees went away. We believe there was some minimal relationship between the bubbles and the symptoms and that they represented a minimal health risk. I agree with Dr. Lundgren, however, and I've been very uncomfortable as we don't know what size the bubbles were or if their affects would be acute or chronic. It's an area that is worth some study.

DR. DANIELS: Arterial bubbles should not be viewed as peculiar or extremely rare. There are now substantial reports in the literature concerning arterial bubbles. Therefore, we should consider the implications of their formation. I agree with Dr. Peterson and Dr. Lundgren that arterial bubbles are inherently more dangerous than venous bubbles. All the clinical evidence of years ago from injections of gas

emboli suggests that arterial bubble formation should be avoided at all cost.

DR. PETERSON: I would be quite surprised if there weren't some depth dependence for this phenomenon. The differences in decompression sickness that one sees in different types of diving might be affected by the depth, perhaps associated with bubble stability.

DR. DANIELS: Why should depth be involved? The animal experiments where arterial bubbles were observed have mostly involved decompressions to atmospheric pressure. The experiments at NUTEC were deep dives, but I don't see that the literature suggests a depth dependence yet.

DR. MASUREL: With careful monitoring of intravascular bubbles in animals, dogs, goats, sheep, and minipigs, I always detect venous bubbles before arterial bubbles. It is difficult to understand, because the cavitation phenomena are the same on both sides, how the first bubbles can appear in the arterial system where the gas saturation is lower than in the venous blood.

DR. DANIELS: The observation of arterial bubbles without venous bubbles depends on where you look. We always saw arterial bubbles before venous in the mouse skin flap. Lynch and his colleague also found that arterial bubbles always preceded venous bubbles in the hamster cheek pouch, but in the femoral vessels venous bubbles were always first. There are anatomical peculiarities such that you might see arterial bubbles with no apparent venous bubbles. If you were able to look at bubble formation throughout the body, however, my belief is that venous bubbles would always appear first in the more common peripheral regions.

DR. BALLDIN: Dr. Daniels, you said that the threshold differential pressure for bubble formation is about 70 kilo Pascals and that there is a latency period of about 5-8 minutes for the bubbles to develop in humans.

DR. DANIELS: In some experiments, yes.

DR. BALLDIN: I always had a 4-minute latent period before the bubbles developed. Bubbles could occur immediately after decompression to altitude, however, if the altitude decompressions were preceded by dives within an interval of 24 hours. Is there a latenty period for very deep dives? For a very rapid and deep dive, such as during compression for very rapid free ascent from a submarine, is there a possibility that arterial gas emboli will develop within 4-5 minutes, perhaps even with oxygen breathing?

DR. DANIELS: The latent period depends on the adequacy of the decompression. As the decompression becomes more severe, the latent period will get shorter. Ultimately there is an irreducible minimum period, perhaps only milliseconds.

DR. BALLDIN: Is this minimum period 4-6 minutes?

DR. DANIELS: No. Quite frequently we see a few bubbles within 20 seconds of relatively mild decompressions, but I don't believe the bubbles form in the arterial blood. I think they arise secondarily due to redistribution through the lung after a sufficiently large number of bubbles compromise its function, perhaps by opening shunts which allow bubbles to pass. That may not be true, but I don't think we have experimental evidence yet to support the notion that bubbles form in the arterial system itself.

DR. BALLDIN: Even for very deep with rapid decompression?

DR. DANIELS: Excluding explosive decompression, which would kill the person without a shadow of doubt.

DR. BALLDIN: I made some explosive decompressions up to 20,000 meters altitude. During the compression phase, 4-5 minutes later at 9000 meters, we detected bubbles, which suggested that the latency period was only 1-2 minutes.

DR. DANIELS: I think explosive decompression from diving that I am used to dealing with is very different from explosive decompression to altitudes that you are describing.

DR. CHRYSSANTHOU: The implication has been made that asymptomatic venous bubbles are acceptable whereas arterial bubbles are unacceptable. My feeling is that no level of gas bubbles should be acceptable. In addition to acute decompression sickness with immediate and overt manifestations, intravascular gas bubbles may have latent or silent effects, such as aseptic necrosis or changes in the blood-brain barrier permeability. The disorders can be developed even with asymptomatic gas bubbles. We and other investigators have demonstrated this in animal (2-7).

DR. DANIELS: I think you have to be very careful in saying that no level of bubble formation can be tolerated. If our experimental data are correct, the threshold to bubble formation is 70 kilo Pascals, independent of the exposure pressure. If decompression is slow enough to avoid this bubble formation, I calculate that the decompression period increases about 25 times. Thus, for a normal 1000 fsw dive with an 11-day decompression, 272 days of decompression will be required. It's impractical. We must be able to handle bubbles. We need quantitatively and precisely to know the link between bubbles and symptoms so we can estimate the likelihood of symptoms. In particular, this includes delayed symptoms such as osteonecrosis or effects on mental performance that we are only now coming to appreciate. Only then can we produce tables that are safe and reasonably economical.

REFERENCES

1. Thalmann Ed, Zumrick JL, Schwartz HJC, Butler, FK. Accomodation to depression sickness in HeO_2 divers. Undersea Biomed Res 1984; 11(suppl):11-12.
2. Chryssanthou C. Pathogenesis and treatment of decompression sickness. NYS Med 1971; 74:808-812.
3. Chryssanthou C. Dysbaric osteonecrosis in mice. Undersea Biomed Res 1976; 3:67-83.
4. Chryssanthou C, Springer M, Lipschitz, S. Blood-brain and blood-lung barrier alteration by dysbaric exposure. Undersea Biomed Res 1977; 4:117-129.
5. Chryssanthou C. Dysbaric osteonecrosis: etiological and pathogenetic concepts. Clin Orthop Relat Res 1978; 130:94-105.
6. Chryssanthou C, Graber B, Mendelson S, Goldstein G. Increased blood-brain barrier permeability to tetracycline in rabbits under dysbaric conditions. Undersea Biomed Res 1979; 6:319-328.
7. Chryssanthou C, Palaia T, Goldstein G, Stenger R. Increase in blood-brain barrier permeability by altitude decompression. Aviat Space Environ Med 1987; 58:1082-1086.

TARGET ORGANS

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Following decompression, tissues can produce a gas phase from the inert gas which is dissolved in them. This formation is, to a first order, related to the level of supersaturation and to the number of nucleation sites which are generated by mechanical stress. This gas phase can either remain in situ or move in the blood stream to embolize other systems. Those systems with a high degree of mechanical stress are good "gas-phase formers"; lung and brain can be classified as "gas-phase receivers". While the half-times of the Haldane paradigm are generally associated with specific tissues, it is suggested here that the model is wanting for analysis of decompression pathophysiology.

INTRODUCTION

Since the earliest times when man began diving, he confined his activities under water to those lengths of time to which the most minimal of equipment was needed. With the exception of the diving bell, whose earliest origins are unknown, access to high pressure environments was basically confined to short periods of time until suitable air compressors were constructed.

Relatively good pumps for the removal of air from small chambers were constructed in the late 1600s. In 1670, Robert Boyle described his famous experiments in which he placed various animals in an envacuated chamber; in one case, he noted a gas bubble in the aqueous humor of one of its eyes, an example of the first-observed "target organ"(1).

Air compressors, and the development by Augustus Siebe of the "open" diving dress in 1819, opened the way for extended periods of stay beneath the water. In 1837, Siebe modified his "open" dress into the "closed" dress

system in which the helmet and suit were attached together, thus providing to the diver a combination of a sustained air supply from the surface, assurance against drowning if he fell, and an environmental protection suit.

Air compressors were also employed in engineering work in mines, tunnels, and caissones where workers stayed for periods of time, up to several hours, at equivalent depths as much as 70 feet. It was during these periods of prolonged exposure to pressure that men first noticed the problems of decompression sickness when they left the compressed air environment. The problem was originally ascribed to rheumatism and arthralgia engendered by the cold, damp working conditions, though the workers themselves quickly recognized that their painful joints were relieved by a return to the pressurized environment.

The first major scientific investigation of the problem of decompression sickness was conducted by Paul Bert. While he devoted the majority of his activity to investigating high altitude balloon flights, his studies of the physiological consequences following exposure to compressed air environments led him to the conclusion that the pathophysiological problems were the result of bubble formation in tissues, a direct consequence of oversaturation. By chemical analysis, he determined that the major component of these bubbles was nitrogen.

To mitigate this problem of decompression sickness, Bert recommended slow decompression or ascents; in one scheme, he advocated that the linear ascent time would be equal to the amount of time spent on the bottom. This system was basically ineffective, however, when the depths exceeded 100 feet and bottom times were longer than one-half hour.

Through trial and error procedures, Greek sponge divers in the late 1800's, using hard-hats and surface supply techniques, were diving down to depths almost as deep as 200 feet. This was more than twice the depth of procedures employed by Royal Navy Divers. In response to this, J.S. Haldane, a noted respiratory physiologist, was commissioned by the Royal Navy to investigate the possibility of developing improved procedures for decompression. From a combination of contemporary physiology and empirical knowledge of diving techniques common at the turn of the century, Haldane devised his now famous procedure utilizing stage descents(2).

Part of its theoretical basis lay in the concept of varied rates of perfusion to the various organs of the body, all of which were assumed to be "target organs". Since Haldane recognized that blood flow was not equal to all portions of the body, he realized that gas uptake and elimination would proceed at different rates. He hypothesized that these followed an exponential-type equation typical of transport in a well-stirred system and, by means of a suitable spectrum of half-times, was able to reproduce the no-decompression curves which he deduced from studies of his experimental subjects which were goats.

There is a strong tendency among many researchers to assign virtually whole organ systems to these half-times. This is done primarily on the basis of

the whole-organ perfusion rate. Thus the short half-time tissues are considered to be represented by brain and spinal cord. Tissues whose half-times are on the order of 40 to 80 minutes are considered to represent skin and muscle. Further, those of 150 to 250 minutes are associated by Buhlmann with inner ear problems. The longest half-time tissues are reasonably thought to be represented by integumental tissue and bone.

If one seeks a limited anatomical description of each of the half-time tissues, however, one must consider that if a diver performs a short, deep dive with inadequate decompression, joint pain will result. A similar consequence awaits him with inadequate decompression after making a long, shallow dive. Thus a similar joint pain is the result of an oversaturation of either the 5, 10, 20, 40, 120, or even 480-minute tissue. The correlation of large anatomical regions or organ systems with specific half-times does not appear to have validity and, for this reason, many researchers have replaced the term "half-time tissue" with the more general and non-specific phase, "half-time compartment". Here compartment means a microanatomical region whose gas-loading and unloading characteristics are determined by blood flow, diffusion resistance and distance, and gas solubility in the microregion.

Table designers have long recognized the utility of the half-time system as a part of the algorithm for cataloguing gas uptake and elimination. However, those who devote their time to decompression pathophysiology recognize that gas phase formation occurs throughout the body following the return from oversaturation, at least to some degree, as can be determined either by autopsy or ultrasound methods. The problems resulting from inadequate decompression and its consequence, gas phase formation, are associated with the size, number, and location of the gas phase which is formed.

It is useful for purposes of discussion of "target organs", to divide the body into those systems which are "gas-phase formers" and those which are primarily "gas-phase receivers". A simple example of the former would be adipose tissue, and of the latter, pulmonary tissue. It is clear, though not often considered by many workers, that the major gas-phase formers would tend to be those systems with the highest total dissolved inert gas volume by virtue of their large mass and high inert gas solubility. These would in turn be the major generators of the gas bubbles detected by Doppler ultrasound flowmeters.

When analyzing the pathophysiological aspects of decompression sickness, it appears best to divest the Haldane system. It is well suited for the calculation of tables, particularly when the assumption is made that virtually all of the inert gas will remain in a dissolved state. Should a two phase system form, however, then the gas transport processes change.

Since the theoretical tensile strength of water is on the order of 1,000 atmospheres, a saturated diver could come directly to the surface from 6 miles, were he made of "defect-free" water. Since this is clearly far removed from the experimental limit of about 33 feet, some "defects" are postulated to exist; these are the gas micronuclei.

The concept of preformed gas micronuclei, discussed earlier in this symposium does not appear in the model as originally envisioned by Haldane or, indeed, is it incorporated into any table calculation algorithms which employ that system. Either preexisting gas nuclei or mechanically assisted gas phase formation via, for example, tribonucleation, passes a commonality, there is some degree of motion involved.

Gas phase formation and attendant decompression sickness is a combination of events:

(i) Uptake Elimination
(ii) Critical Tissues
(iii) Cavitation Tendency (which is strongly suspected to depend upon tissue motion).

GAS PHASE FORMERS

There are many tissues which are gas phase formers - muscle, tendons, ligaments, adipose tissue, and possibly the spinal cord. Muscle is probably the tissue most studied because easily accessible, volumetrically large, easily studied with echo and Doppler ultrasound systems. Microscopic examination can be made of rat abdominal muscle wall by placing a large microscope slide on the tissue (after having reflected it back) so the gas is not lost by diffusion. Here we observe that the gas phase is cylinderical and intravascular. When the term "bubble" is employed, we conjure up in our minds some particular geometrical form, whereas in the micro-circulatory system, the gas phase is cylinderical following the outline of the capillaries which contain it.

Doppler ultrasound devices are most commonly employed to study the gas phase formed in muscle; this is done by monitoring the veins which drain it. For the body as a whole, the Doppler probe is usually placed over the precordial region, monitoring the pulmonary artery, the confluence of all veins from all tissues(3).

Muscle and adispose tissue being volumetrically very large, dissolve large amounts of inert gas and produce the greatest number of gas bubbles. Additionally, because of the mechanical forces for cavitation which they possess because of movement, muscle tissue in particular is prone to generate a gas phase upon decompression; much of this gas phase will eventually be released into the major veins. Because one can measure a considerable number of gas bubbles coming from muscle tissue, does not necessarily imply imminent decompression sickness; in practice, there are found a considerable percentage of false positives, since divers do not get pain in muscle and adipose tissue.

An allegory lies in the story of a policeman who found a man underneath a lamp post obviously looking for something. The policeman starts helping the fellow who indicates that he lost a silver dollar. The pair search around underneath the street light for about 20 minutes and it becomes obvious that it is not there. The policeman then says, "My good man, we have looked underneath this pole for some time, exactly where did you loose

the coin?" He replies "Back there, in the alley." Amazed, the policeman asks "Why are we looking underneath this lamp post?" Whereupon he answers, "Because the light is much better out here."

This is generally what is being done with both Doppler and gas-washout studies. The problems of joint pain lie in the tendons and ligaments, but the "light is a lot better out here" and it is considerably easier to study the gas phase which emanates from muscle and adipose tissue. In most cases, the fraction does not accord with what occurs within a tendon or ligament. In spite of the many false positives, many researchers still attempt to make strong correlations between Doppler bubbles and joint pain. Experimental evidence shows the correlation is rarely there. It does appear, however, that some dive profiles with short bottom time (up to two hours) produce large numbers of bubbles, and statistically will result in decompression sickness problems if tried a sufficient number of times(4). In a similar manner, certain factors such as blood cholesterol levels, blood pressure, family history, amount of exercise, etc., will give an estimate of which individuals are more prone to stroke or heart attack, but it will not precisely indicate which individuals will experience those problems.

In Haldane's model, one has 5, 10, 20, 40-minute, etc., "tissues". It does not seem to make any difference whether you violate the 5, 10, 20, 40, 80, or 240-minute tissue. You will develop a similar pain in the joint regions. It is thus difficult to associate exact and precise anatomical regions with specific tissue half-times.

When studying decompression pathophysiology, the Haldane system, for retrospective analysis, is one that is best avoided. It is hyperbaric physiology's version of wave-particle duality. The wave theory of light works very well for defraction and refraction but it does not explain the photoelectric effect; for that it was necessary to postulate the existence of the photon. Conversely, it is very difficult to analyze defraction effects using the concept of photons. It depends upon what you are looking at as to your best system for analysis. Thus the Haldane model functions in a one-state system, but is wanting in the analysis of decompression sickness, the consequence of a two-state system.

Pain associated with decompression sickness appears to arise in tendons and ligaments. These connective tissues are both poorly perfused and contain pain and stretch receptors (Golgi receptors). Small changes in pressure, within quite narrow limits, are known to produce pain in tendons(5).

Adipose tissue, like muscle tissue, is also volumetrically large in many individuals and it is a potentially large contributor of an intravascular decompression gas phase and hence Doppler-detectable bubbles. Very fat animals, especially when dived on air, are notorious for dying, because adipose tissue contributes a volumetrically large gas phase into the venous return which is transported to the heart where it causes an airlock. We note that very often small animals are used in diving research and the number of animals which die is equated with the bends even though people do not die of the bends. The animal subjects expire from what is, in essence,

pulmonary gas embolization. Except for possible intertissue diffusion, I would not expect adipose tissue to play a role in limb pain decompression sickness.

It is interesting to note that when a cylinderical phase is compressed and the volume is reduced by one-half, the length is likewise reduced by one-half. To effect a change in a spherical bubble, one must increase the pressure by eight times in order to reduce its diameter by one half. Since the pressure must be increased only slightly to effect a rather large change for gas cylinders, if one should extend into the venual or arteriol and block the flow of blood, a small increase of pressure would cause it to retreat into the capillary. This would reinstate normal perfusion for much of the tissue and might explain why small pressure changes often effect large changes in overall results in perfusion-related decompression disorders.

The spinal cord is classified here as a gas former for two reasons. First, in accordance with our basic principle, the cord is located in a moveable structure and would be suspected of possessing nucleation sites. Second, spinal neurologic decompression sickness is often noted to occur in experimental animals in the absence of arterial bubbles (which would embolize the cord)(6). Nerve cells have a high metabolic activity in the cell body while metabolism in the axon is low; metabolic products are passed to the axon by protoplasmic streaming. Thus inert gas transport in nerve is a combination of perfusion, intra-axonal diffusion, and axon streaming. In addition, nerve axons are surrounded by lipid-rich myelin formed by the oligodendroglial cells (which to some extent also nourish the axons); this myelin could also provide a reservoir for inert gas to diffuse into the axon. The flexing and bending which occurs in the spinal cord is part of the mechanically-assisted nucleation mechanism which can contribute to gas phase formation. Because of the peculiar anatomy, cord nerves and associated myelin could possess a complex "spectrum" half-times which could range from minutes to hours.

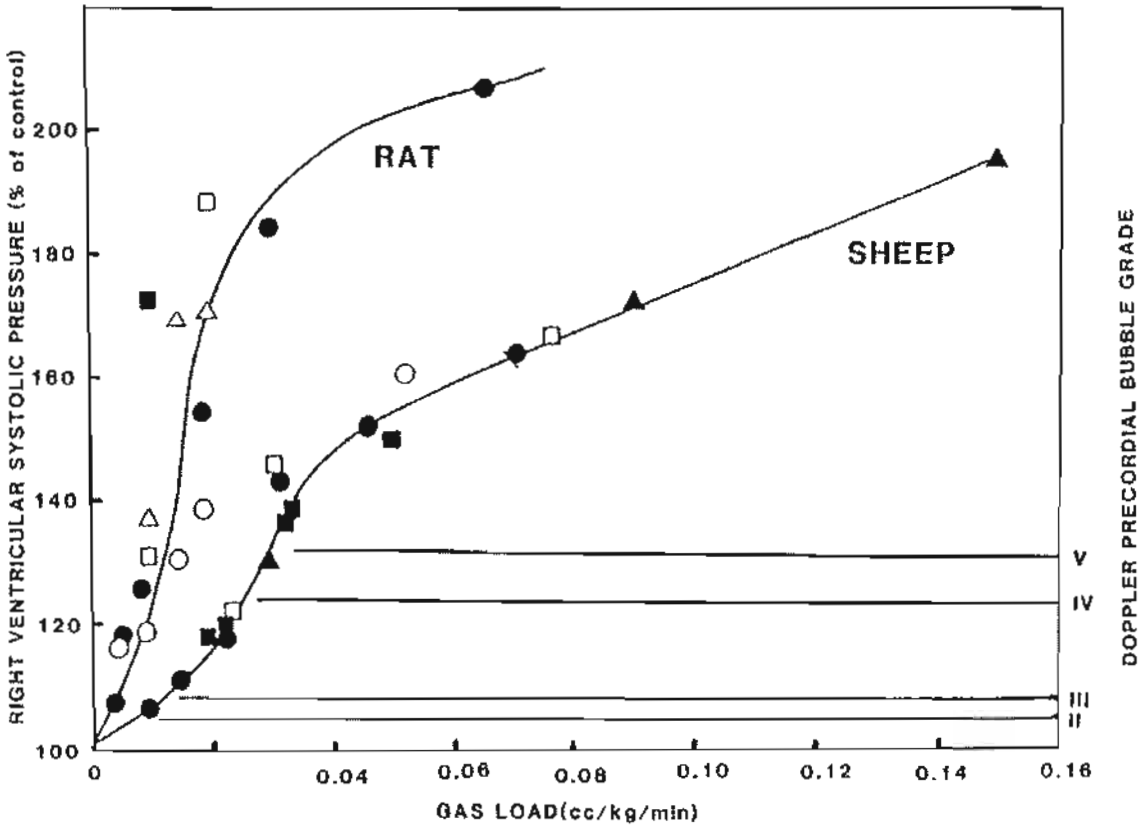
Let us now consider a system which has been studied and could be called a "minimal gas-phase former". The kidney can be studied with cuff-type Doppler probe surgically placed on the renal vein(6). While well perfused tissues such as muscle produce a large number of Doppler-detectable gas bubbles following dives of 160 feet for 20 minutes, our studies indicate that this is not true for the kidney. One possible explanation is that kidney tissues, unlike muscle tissues, are not moving structures. They are not therefore generators of the initial gas micronuclei upon which the decompression gas phase can grow.

GAS PHASE RECEIVERS

Opposite the "gas phase formers" would be the "gas phase receivers". Examples of gas phase receivers would be lung, brain and spinal cord, fetal organs, the heart, and venous blood itself. The latter is the receiver of much of the gas phase which is formed in the tissues in proportion to their volume and their solubility for inert gas. Hematologic changes noted in blood are the result primarily of gas bubbles released into it from muscle

and adipose tissue. I have never seen evidence that the venous system itself is the locus for gas phase formation following decompression.

The terminal region of reception of gas in the venous return would be the lungs. One method to study this is to generate small gas bubbles and inject them into animals(3). If you also put a catheter into the pulmonary artery, it is possible to measure the right ventricular systolic pressure (RVSP). As one increases the gas load, you occlude increasing numbers of capillaries of the pulmonary bed and produce a rise in the right ventricular systolic pressure which is indicated in the figure as percent of pre-injection control.



One can also make a simulated dive with the same animals and again measure the right ventricular systolic pressure and simultaneously note the Doppler grade. It is thus possible to relate the Doppler bubble grade to a given decompression gas load. One finds by a simplistic calculation that in dives which produce a Doppler grade of 3 or 4, about 95% of the gas is carried in solution and only 5% is actually in bubbles at least in the venous return and causing the RVSP elevation. This I have termed the "gas phase transport fraction".

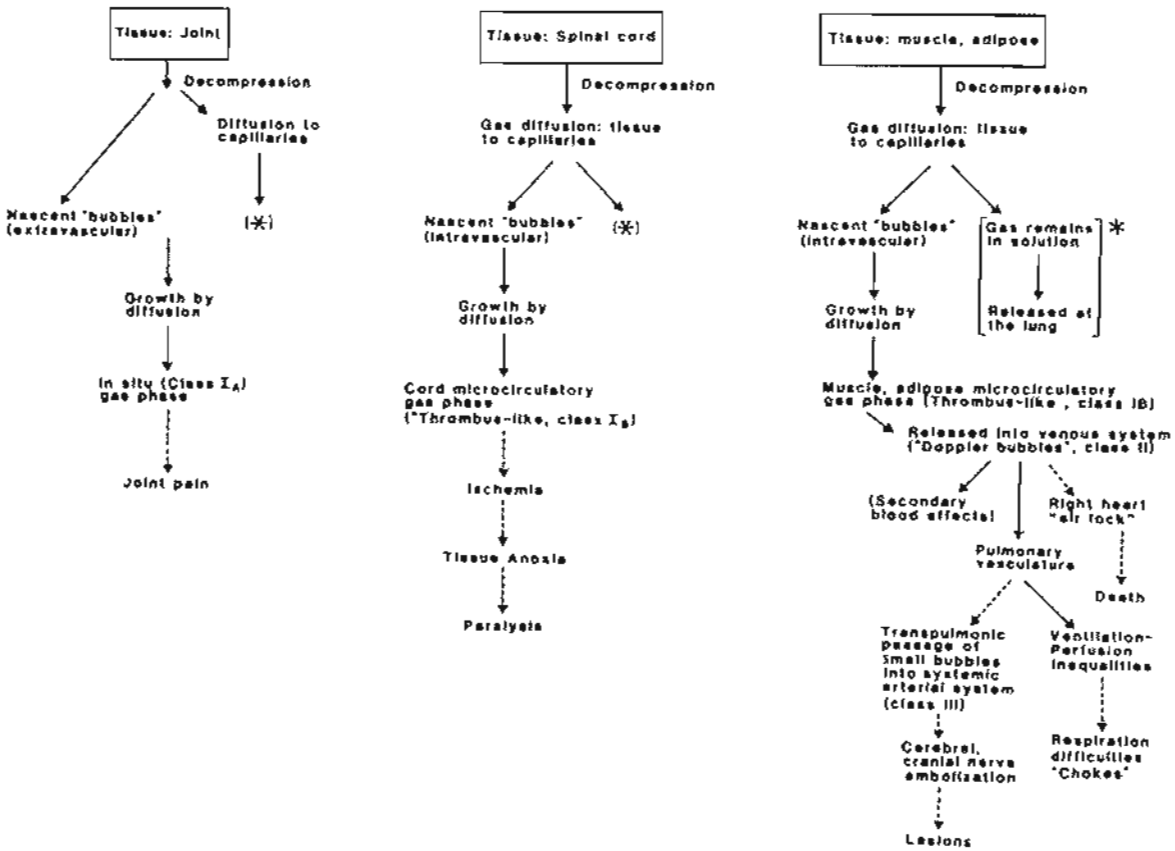
Curiously, if large gas loads are injected, you do not find any evidence of an arterial gas phase (for example, by monitoring with a Doppler cuff probe on an artery). This is true even with gas loads which produce a rise of 150% of control in RVSP. Much smaller elevations (about 120% of predive

control) in RVSP will effect transpulmonary passage, however, when the gas phase is generated in the tissue capillary beds following a dive. This can most likely be ascribed to the smaller radii of the decompression-generated gas phase.

Lastly, we can consider fetal organs. Unlike the air-breathing, post-partum animal, the fetus does not possess the filter capability of the pulmonary capillary bed. Any gas which is formed and released into the venous circulation will have the possibility of embolizing the developing brain and spinal cord. Noninvasive Doppler studies by Powell and Smith(7) have demonstrated that fetal sheep and goats are quite capable of generating a gas phase following decompression even with bottom times short enough to avoid decompression sickness in the mother. We would consider the principle that diving is contraindicated during pregnancy is a valid one.

CONCLUSION

This brief "tour" has demonstrated that decompression sickness is the result of gas phase generation that can affect all systems of the body. While some systems may remain "silent" with respect to pain or immediate disability, nevertheless, they may be the victims of hypoxia. The processes can be demonstrated in the following figure which is by no means exhaustive.



References

1. Boyle R. New pneumatical experiments about respiration. Philos Trans 1670; 5:2011-2058.

2. Boycott AE, Damant GCC, Haldane JB. The prevention of compressed air illness. J Hyg Lond 1908; 8:342-343.

3. Powell MR, Spencer MP, Ramm O. Ultrasonic surveillance of decompression. In: Bennett PB, Elliott DH, eds. Physiology and Medicine of Diving. London; Bailliere Tindall, 1982: 404-434.

4. Powell MR, Johanson DC. Ultrasound monitoring in decompression sickness. In: Shilling CW, Beckett MW, eds. Underwater Physiology VI. Proceedings of the Sixth Symposium on Underwater Physiology. Bethesda, MD: Federation of American Societies for Experimental Biology, 1978:503-510.

5. Inman VT, Saunders JB. Referred pain from skeletal structures. J Nerv Ment Dis 1944; 99:660-667.

6. Powell MR, Spencer MP. The Pathophysiology of Decompression Sickness and the Effects of Doppler Detectable Bubbles. Technical Report ONR Contract N00014-73-C-0094, 1980.

7. Powell MR, Smith MT. Fetal gas phase formation following decompression from hyperbaric environments. Undersea Biomed Res 1985; 12:59-68.

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DISCUSSION

DR. LAMBERTSEN: I think Dr. Powell's paper was a very important review that brought out aspects of decompression sickness that were not evident in some of the earlier, more specific investigations. I hope we can keep that perspective in mind for the rest of the meeting.

DR. LOEWENHERZ: The kidney receives 25 percent of the cardiac output and is very well perfused. If arterial embolization were important as a mechanism for spinal decompression sickness, certainly you would expect acute renal failure. Very minor ischemic injuries do cause clinical renal insufficiency, but it is very uncommon, except in cases of massive muscle injury, to see renal damage in decompression sickness. There's one case that I know of that had rhabdomyolysis due to bubbling, and I wonder how it correlates with the theoretical aspects of arterial bubble formation.

DR. POWELL: I think brain problems are embolic phenomena, but I'm not convinced that spinal cord ones are. I have seen sheep with a large number of gas bubbles in the arterial side and no evidence of spinal cord problems. I've seen other cases in which they did have spinal cord problems.

DR. KINDWALL: Dr. Powell, that was an excellent paper. I appreciate the perspective. I have a question concerning habituation (or adaptation) to decompression sickness in the three sheep that made 78 dives where RSVP and Doppler bubbles were measured and in other experiments where RSVP was measured after the injection of venous bubbles. Were the divers and gas injection experiments done alternately so that the results were not confused by habituation?

DR. POWELL: I do not recall.

DR. CHRYSSANTHOU: Dr. Powell, I also enjoyed your paper today very much. In our experience with mice and rabbits, we consistently found that the adrenal was a gas former with one of the highest incidences of bubbles as compared to the organs. Could the reason for these bubbles be the high lipid content in the cortical area of the adrenals? What's your experience on that with your model?

DR. POWELL: I have no experience with the adrenal, but I believe that your decompressions were more severe than ours, were they not?

DR. CHRYSSANTHOU: Yes. You mentioned that pain in the tendons could be due to stretching the stretch receptors. An alternative explanation might be, however, that bradydykinin and other pain-producing vasoactive substances may be released or activated by gas bubbles at the site of the tendons?

DR. POWELL: I suppose that's a possibility. The question is why can you get the relief of the pain so rapidly with recompression? That's why I have a tendency not to have a great deal of faith in biochemical mechanisms of decompression pain as a primary source. Maybe they are secondary effects. I cannot see how recompression would relieve pain during the treatment of decompression sickness if it were a vasoconstrictive or ischemic phenomenon alone.

DR. CHRYSSANTHOU: We know that bradykinin can be deactivated very fast by various enzymes in the tissue as well as in the blood, so without constant production of bradykinin the pain would disappear. Thus, recompression would relieve the pain, removing the activating factors of the bradykinin chain.

DR. POWELL: I suppose that's true, although I have heard also that just changing the hydrostatic pressure by raising your hand or putting on

a sphygmometer cuff will relieve pain. I find that difficult to reconcile solely with the biochemical mechanism. It's a kinetic argument rather than anything else.

DR. FARMER: Dr. Powell, some of the most fascinating work to me--being an otolaryngologist, my favorite organ is the ear--was done by colleagues in Toronto. These elegant experiments with monkeys used diving exposures of 900 feet of helium-oxygen (1-3). The fascinating and almost unique lesion is implosion of the endosteal layer of the semicircular canal into the lumen. As I understand, bubbles form in the osteoplastic cavities just in the endosteal layer causing the mediate inner layer, of the bone to implode into the canal. That is another mechanism in addition to your very elegant presentation on vascular bubbles.

DR. NASHIMOTO: Dr. Mano, your gelatin method defines a precise risk of suffering from bends. It is simple and useful for the prevention of DCS from the practical viewpoint. However, other speakers have pointed out that many factors contribute to the formation of bubbles. The risk of bends which your method predicts is not affected by these factors, however. Do you see this as a problem?

DR. MANO: If intravascular bubbles are present, the phenomenon is very different. There is a good relationship between type II bends and the number of intravascular bubbles. If we prevent type I bends, I think type II bends can also be avoided.

DR. ZANNINI: After a dive in a hyperbaric chamber to 40 meters for 30 minutes, we observed large gas pockets by radiograph in the synovial fluid of both shoulder joints in a diver with bends. The gas pockets and bends disappeared after recompression on a table 5. We calculated the volume of the gas pocket to be 1 to 2 milliliter. We believe the gas pockets to be a consequence of the relative movement of the joint, which would provoke negative pressure. We didn't find any reference to this in the decompression literature.

DR. POWELL: It's my understanding that x-ray evidence has seen gas in the synovial fluid of the joint space. This gas generally is case asymptomatic. Cracking your knuckles, for example, generally is annoying to others but doesn't produce pain in the individual doing it.

REFERENCES

1. Landolt JP, Money KE, Radomski MW, Riusech RG, Odell PC, Watson WJ. Inner ear decompression sickness in the squirrel monkey: observations, interpretations, and mechanisms. Underwater physiology VIII. Proceedings of the eighth symposium on underwater physiology. Bethesda, MD: Undersea and Hyperbaric Medical Society, 1984.
2. Fraser WD, Landolt JP, Money KE. Semicircular canal fractures in squirrel monkeys resulting from rapid decompression. Interpretation and significance. Acta Otolaryngol (Stockh) 1983; 95(1-2):95-100.
3. Venter RD, Ward CA, Ho S, Johnson WR, Fraser WD, Landolt JP. Fracture studies on a mammalian semicircular canal. Undersea Biomed Res 1983; 10:225-240.

Bubble formation and DCS

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Basic understanding of the phenomenon of bubble formation is essential for prevention of DCS. Many studies have been done on number of bubbles formed by the process of decompression. We attempted to evaluate the relationship between bubbles and DCS.

Pre-existing gas nucleus is required for bubble formation in the tissue due to decompression. Gas dissolved into the tissue under a high pressure diffuses into the nucleus through its "surface active skin", while the nucleus is being reduced to a certain size and the skin becomes impermeable to the gas. Upon beginning of decompression, it becomes permeable and the nucleus increases in size gradually.

Bubbles begin to be formed when pressure of the nucleus becomes more than a cavitation threshold (Fig.1).

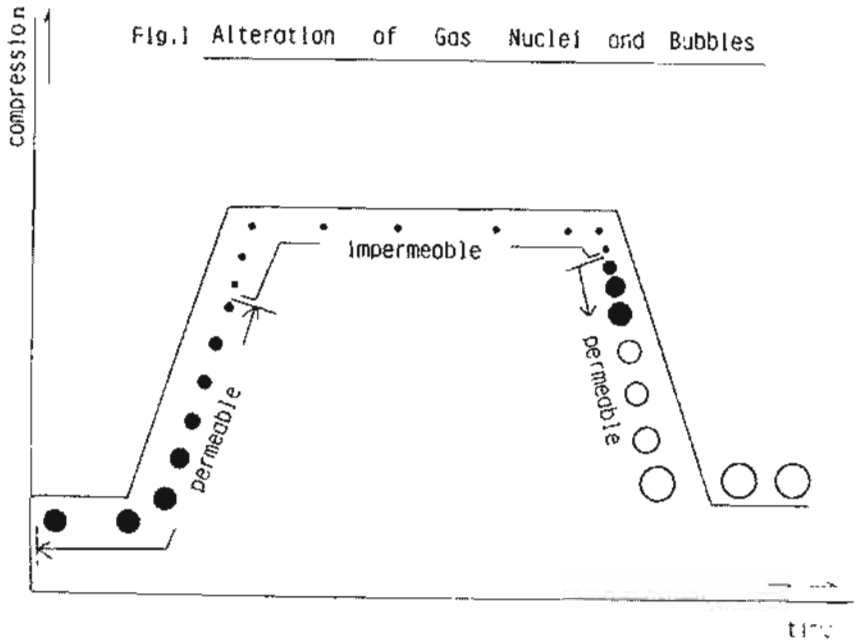
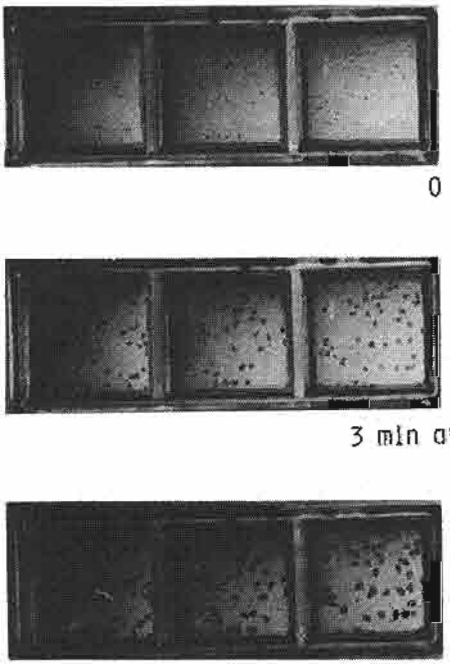


Fig.1 Alteration of Gas Nuclei and Bubbles

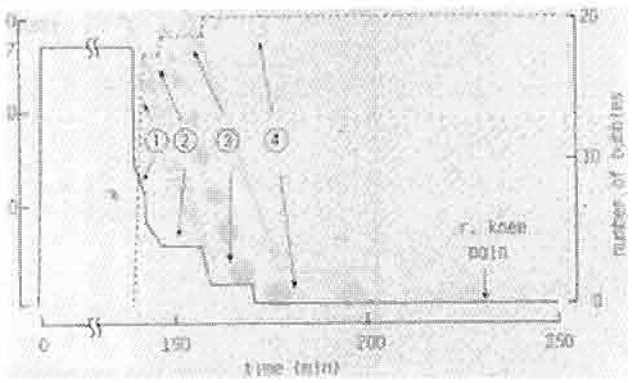
The gelatin model has contributed to clarify the etiology of DCS. Fig.2 shows the phenomenon of bubble formation. When the decompression step was kept at the same pressure, bubbles occur soon. We can number the bubbles 3 min after decompression and the size is fixed 10 min after decompression according to gel bubble technique. Fig.3 is a result of reproduction work of DCS case. Relation between bubble number and wrong decompression can easily be evaluated.

Fig.2 Bubbles Formation after Decompression from 3 ATA Exposure for 3 Hrs

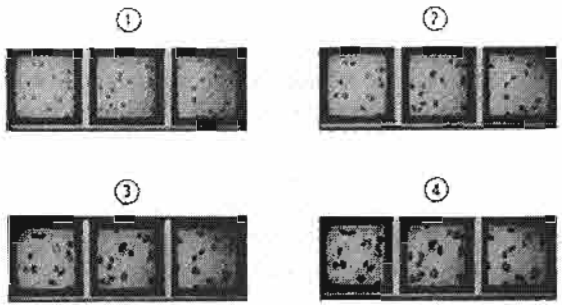


Agarose gel models of each 0.3 mℓ volume were exposed to 3 ATA for 3 hrs and decompressed to 1 ATA by the rate of 1 ATA/min.
Tiny bubbles appeared soon. It is difficult to count the number, however it becomes easy to count within eyeshot 3 min after decompression. Bubbles grow up gradually and stop the growth after 10 min if they don't unite each other. The shapes and the distributions are clear at a glance. The number of formed bubbles is influenced by the exposed pressure, the bottom time and the decompression profiles. Gas nuclei must be crushed by rapid compression rate or deeper depth. So, this bubbles counting technique is only available in cases of evaluations of decompression tables, DCS cases' reports and so forth.

Fig.3 Relation between Decompression Procedure and Bubbles Number of Bends Case #4



This type one limb bends case was evaluated by bubbles counting technique. He was suffered from DCS 65 min after decompression. Photo ① was recognized during decompression of step ① . There was considered that step 1 during decompression already predicted the onset of DCS. Number of bubbles increased gradually from step ① to ④ . Those number was stationary at 1.3 ATA. The wrong decompression schedule was already recognized and indicated at the first stop. Bubble counting technique can be used as an indicator for the prevention of DCS.



Evaluation of the decompression tables, which are now used all over the world, is mainly done by the incidence of decompression sickness. But the incidence varies so much depending on each reporter even if the same decompression table is used. In Japan, the average percentage of contracting "bends", using the Japanese Standard Decompression Schedule No.1 for compressed air work, is 0.54% (22 bends versus 4,042 trials)[1]. But Mano *et al.*[2] reported it was 1.42% (15 bends versus 1,056 trials) to 3.3% (42 bends versus 1,267 trials). Nashimoto *et al.*[3] reported it was 6.4% and Morita *et al.*[4] 4.5%. Thus, the incidence in Japan ranged from 0.54 to 6.4% and was quite different even if the same decompression table was applied. The difference in these values might be due to the fact that the Japanese workers are likely not to observe the decompression table faithfully. Walder of England[5] said that an incidence of "bends" of about 2% was inevitable. There was a report that the percentage was 0.66%, using the Washington Table[6]. Griffiths reported it was 1.5 to 2.0%[7]. Therefore, it is not recommendable to evaluate different decompression tables depending only on the incidence of the decompression sickness.

This gel bubble technique, while, shows us the relation whether the decompression rate is suitable or not according to the actual pressure exposure and decompression rate. So it gives us the indication to check the decompression profile.

Recently our colleague, Y.C.Lee finished experimental study of effects of three factors on decompression by agarose gel bubbles[8].

The influence of compression rate, initial decompression rate (IDR) and the first stop (FS) on decompression have been investigated through bubble counting technique by agarose gel, as a model of compression and/or decompression profiles. Four group experiments, on the basis of USN schedule (bottom depth and time: 30m30min), were carried out. In Group 1, six different compression rates from 90 to 7.5 m/min were tested, respectively. In Group 2, seven different IDRs from 18 to 6 m/min were tested, respectively. In Group 3, seven different first stops from 3 to 21 m were tested, respectively. In Group 4, three profiles compositely improved USN schedule (30m30min) with the best IDR (9m/min), the FS (9m) and faster compression rates. The results showed as follows:

1. The slower the compression rate, the more the bubble number.
2. The bubble numbers obviously decreased when the IDR reduced from 18 m/min. The optimum IDR was 9 m/min with the least bubble number.
3. The curve of bubble numbers was V in shape while the depths of the FS changed. The optimum depth of the FS was 9 m.
4. The bubble numbers formed in improved profiles were much less and the total decompression times were shorter.

This gel model is a single tissue of 22.5 min of half saturation time. This time is resemble to muscle tissue, and the model just simulates approximatively some human tissues on the laws of gas saturation, supersaturation, desaturation and bub-

ble formation.

Comparatively speaking, however, the less the bubble numbers formed in either gel models or tissues, the safer the decompression schedules become.

According to this concept, we actually decreased the incidence of DCS at Hong Kong Subway compressed air work of which bottom pressure was from 3.2 to 4.0 ATA (Fig.4)[9].

Fig.4 **Comparison of bends incidence in BP table and applied Model 1.**

Bottom time (hours)	BP table			Applied Model 1		
	Number of Bends cases	Number of workers	Incidence %	Number of Bends cases	Number of workers	Incidence %
0 < ≦ 4	0	2230	0	0	223	0
4 < ≦ 6	8	612	1.31	1	69	1.45
6 <	29	2313	1.25	2	366	0.55
Total	37	5158	0.72	3	658	0.46

These findings should be suggested that the actual decompression tables likes as U.S.N. or other manuals still have problems to be improved more for the prevention of DCS.

Bubble formation phenomenon gives us more detailed informations to evaluate actual decompression profiles or to attempt a future new decompression table work.

References

1) Nashimoto,I. and Mano,Y.: The effect of the Standard Decompression Schedule concerned with the prevention of bends (in Japanese). Japan J.Hyperbaric Med., 8:108-111, 1973.
2) Mano,Y. and Nashimoto,I.: Incidence of decompression sickness among caisson workers (in Japanese). Japan J.Hyperbaric Med., 8:104-107, 1973.
3) Nashimoto,I., *et al.*:Outbreak of decompression sickness in compressed air work (in Japanese). Japan J.Hyperbaric Med., 11:29-30, 1976.
4) Morita,A., *et al.*: Outbreak of decompression sickness in compressed air work #2 (in Japanese). Japan J.Hyperbaric Med., 8:39-41, 1975.
5) Walder,D.N.: The Prevention of Decompression Sickness. *In* The Physiology and Medicine of Diving and Compressed Air Work. second edit., edited by Bennett,P.B. and Elliott,D.H., 456-471, London, Bailliere, Tindall & Cassell, 1975.
6) Sealey,J.L.: Effectiveness of Washington State Decompression Standards in Seatle. *In* Decompression of Compressed Air Workers in Civil Engineering, edited by McCallum,R.I., 71-72, Newcastle upon Tyne, Oriel Press Limited, 1965.
7) Griffiths,P.D.: Decompression Sickness in Compressed Air Workers. *In* The Physiology and Medicine of Diving and Compressed Air Work, second edit., edited by Bennett,P.B. and Elliott,D.H., 496-503, London, Bailliere, Tindall & Cassell, 1975.
8) Lee,Y.C., Shi,Z.Y. and Mano,Y.: Experimental study of effects of three factors on decompression by agarose gel bubble. in contribution to J.Undersea Biomed.Re., 1987.
9) Mano,Y.: An approach to prevent DCS (in Japanese). Jpn J. Hyg., 41(6):926-937, 1987.

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A CURRENT VIEW OF THE PATHOGENESIS OF SPINAL CORD DECOMPRESSION SICKNESS IN AN HISTORICAL PERSPECTIVE

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Abstract

A review of the literature on central nervous system (CNS) decompression sickness (DCS) reveals the familiar findings that divers suffer a higher incidence than caisson workers, that involvement of the spinal cord is generally more prevalent than involvement of the cerebrum and that the distribution of CNS lesions in aviators is the reverse of that following hyperbaric exposure. A preliminary report of an extensive study of case histories of CNS DCS shows that following hyperbaric exposure, the latent interval between reaching 1 ATA and the onset of symptoms is short: 66% of spinal cord cases and 87% of cerebral cases present within 10 minutes.

Various proposed mechanisms of spinal cord DCS are reviewed and assessed with particular reference to the limited time available in the majority of cases for them to cause symptoms. Recent evidence for the existence of autochthonous bubbles in an experimental model of spinal cord DCS is presented and a case for their involvement in the pathogenesis of cases with a short latency is argued. It is concluded that pathological processes and clinical presentations triggered by inappropriately rapid decompression are so varied, that no single pathogenic mechanism for spinal cord DCS can satisfactorily explain them all.

Introduction

With the advent of the force pump in the late 18th Century, it became possible to renew continually the air in diving bells (1) and to pressurize subterranean and underwater work sites (caissons) to reduce flooding (2). This advance increased the severity of man's possible duration under pressure, and illnesses associated with hyperbaric exposure per se gradually became recognized.

Pol and Watelle (3) understood the truth of the miners' saying "on ne paie qu'en sortant" (one only pays on leaving). In other words, they observed early on that miners who became sick, usually became symptomatic after they had left the caisson. Although the picture in diving was complicated by factors such as drowning, hypothermia and CO2 retention, it was also noted that many of the medical problems became manifest only after the diver had reached the surface (4). Thus, it became apparent that decompression was a most hazardous phase of hyperbaric operations.

The first valuable record of the medical consequences of hyperbaric exposure was made by Pol and Watelle (3). They described muscular pains, cramps, numbness, dizziness, deafness, double vision, vertigo, respiratory distress, shock, coma and death that afflicted, in varying degrees, 32 out of 64 workmen employed in mining operations in Triger's caisson at Lourches. More detailed, early descriptions of this multi-system condition were made by Bauer (5) and Clark (6). Some forms of decompression sickness (DCS) became common enough to be given names such as "bends", "chokes", and "staggers", which remain part of the parlance of hyperbaric operations today.

Central nervous system DCS

One form of DCS that lacks an epithet, but is nonetheless of considerable importance, is involvement of the central nervous system (CNS). Its importance relates more to its potentially devastating consequences than to its prevalence. In fulminant form it is manifest as a rapid progression from syncope to coma and death, which may occur within minutes of returning to one atmosphere. Sub-lethal forms may involve the brain and/or the spinal cord. A typical sequence of events for a spinal cord injury is that shortly after returning to one atmosphere, the patient may notice weakness in the lower limbs that may be accompanied by paraesthesiae or a sensory deficit. There are usually no premonitory symptoms. Occasionally, dyspnea and central chest pain, suggestive of pulmonary involvement, or a painful limb bend may precede the spinal symptoms. A more common concomitant is a painful, constricting sensation that is classically in the lower abdomen or pelvis and is referred to as 'girdle' pain. However, this sensation may occasionally occur in the chest. This is a serious symptom and is often associated with a rapid progression to paraplegia and loss of control of bowel, bladder and sexual function. One curious feature of the neurological deficits seen in spinal cord DCS is that they appear to be patchy. The implication of this is that unlike most other forms of spinal injury, DCS tends not to be limited to a solitary lesion at a particular level. Father, it is a condition that generates multifocal lesions scattered throughout various tracts and levels of the cord. Two levels that clinically appear to be preferentially involved are the upper lumbar/lower thoracic and the lower cervical/upper thoracic segments. Even without recompression, it is the natural history for cases of CNS DCS, particularly less severe ones, to improve spontaneously. The speed and extent of the improvement however, can be increased by the use of recompression and oxygen (7,8).

The Epidemiology of CNS DCS

Over the years there have been a number of series that have studied the distribution of symptoms in DCS. The data pertaining to the CNS are summarized in table 1.

It will be noted that the prevalence of CNS symptoms is generally higher in divers than caisson workers and that although much more variable, spinal symptoms tend to be more common than cerebral.

A number of factors that appear to correlate with the occurrence of DCS have been noted over the years and the scant evidence available indicates

TABLE I

The distribution of CNS DCS symptoms in various published series

	Keays 1909 (9)	Levy 1922 (10)	Thorne 1938 (11)	Duffner 1946 (12)	Behnke 1947 (13)	Golding 1960 (14)	Rivera 1963 (15)	Kidd 1969 (16)	Erde 1975 (17)
Activity	C	C	C	D	D	C	D	D	D
No of Cases	3692	680	300	113	159	685	935	127	100
Total *CNS (%)	2.27	1.62	7.67	25.66	(8.80)	(2.34)	(19.1)	(12.9)	41
% Cerebral	.11	(0.74)	3.00	(12.38)	(8.18)	(1.61)	(8.0)	(4.0)	24
% Spinal	2.16	(0.88)	4.67	(13.28)	(0.62)	(0.73)	(11.1)	(8.9)	22

C = Caisson workers
D = Divers
* Does not include cases of vestibular DCS
Numbers in parentheses have been derived from the data provided and assume no cases of cerebral + spinal cord DCS.

that these seem to be as relevant to CNS DCS as to other target organs: Hyperbaric profile; breathing gas; age; obesity; previous DCS; PICO2; PIO2; alcohol intake (both chronic and acute); water balance; acclimatization; individual susceptibility and exercise - both on the bottom and during decompression. I will not labor these points as they will be addressed by other speakers.

It has also been observed that one form of DCS differs substantially in its distribution from those mentioned above, namely the DCS that afflicts aviators. The incidence of DCS is lower in aviators than hyperbaric workers (18,19) and within the CNS, the distribution of lesions is also different. In aviators, cerebral lesions overwhelmingly outnumber spinal lesions (13,20-24). Indeed, the number of reported cases of spinal cord involvement in aviators is less than 10, and an explosive decompression from 1 ATA to near vacuum is required to generate spinal cord DCS in experimental animals (25). On the other hand "chokes" or pulmonary involvement in DCS is a more frequent presentation in aviators than hyperbaric workers (19). Finally, aviators' 'bends' tend to be more amenable to treatment than those in hyperbaric workers (13,24).

The last factor with a bearing on the pathophysiology of CNS DCS that we will consider is the matter of latency. By this I mean the interval between returning to one atmosphere and the onset of symptoms of DCS. With reference to the CNS, this subject has been poorly addressed in the

past. In many of the series that have studied DCS, these data have either not been collected (26-40) or the latency of CNS DCS has been combined with those of other systems (8-15, 41-46). This has resulted in the widely held impression that the onset of CNS DCS is commonly delayed many minutes or even hours after reaching 1 ATA, as is the case in "limb bends". I am currently collecting human CNS DCS latency data. The study is incomplete, but I will present some interim results. The study is in two parts: a) A review of case reports in the literature (4-14,17,47-107), and b) The collection of CNS DCS latency data from a number of treatment centers around the World. Figure 1 shows the cumulative latency of 661 cases of CNS DCS. Of these, 376 had only the spinal cord involved, 88 had only cerebral involvement and 87 had symptoms or signs affecting both parts of the CNS. A further 110 cases (16,93,99) were defined as having "type 2" DCS, or it was not possible to separate spinal from cerebral symptoms.

It can be seen from fig 1 that CNS DCS is generally a condition with a rapid onset, with 65% of cases presenting within 10 min of returning to 1

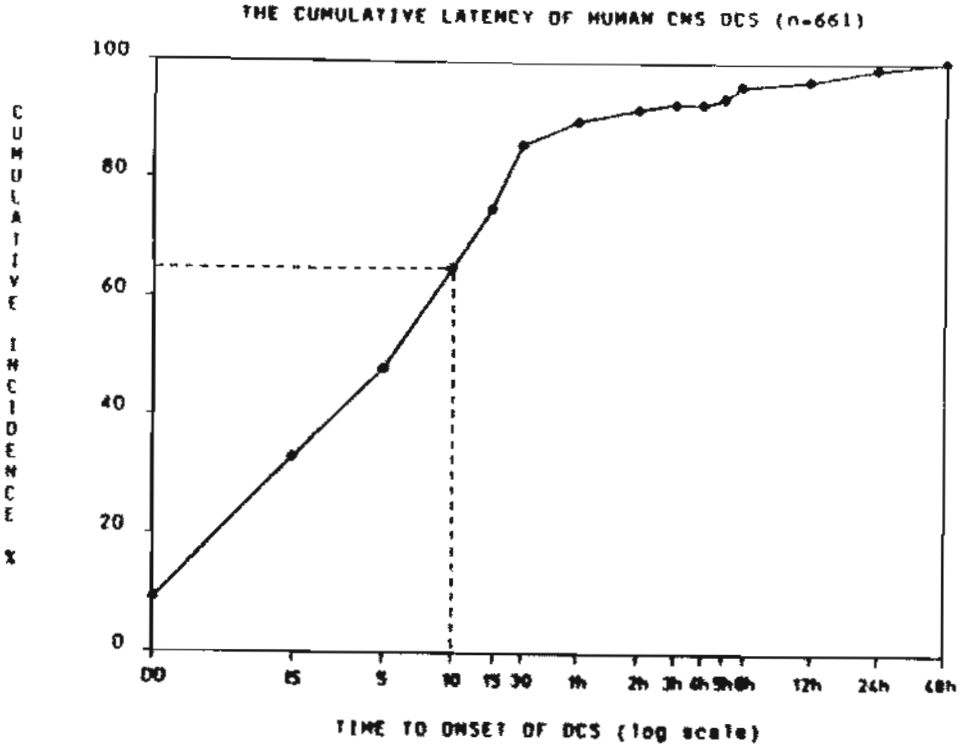

Fig 1. The latency of 661 cases of human central nervous system decompression sickness. The ordinate represents the cumulative incidence and the abscissa the interval in minutes and hours (h) between returning to 1 atmosphere and the onset of CNS DCS. DD indicates an onset during decompression and IS an onset immediately on reaching 1 ATA. The figure shows that 65% of cases presented within 10 minutes of reaching 1 ATA.

ATA. These cases have been broken down into cerebral and spinal cord DCS in fig 2.

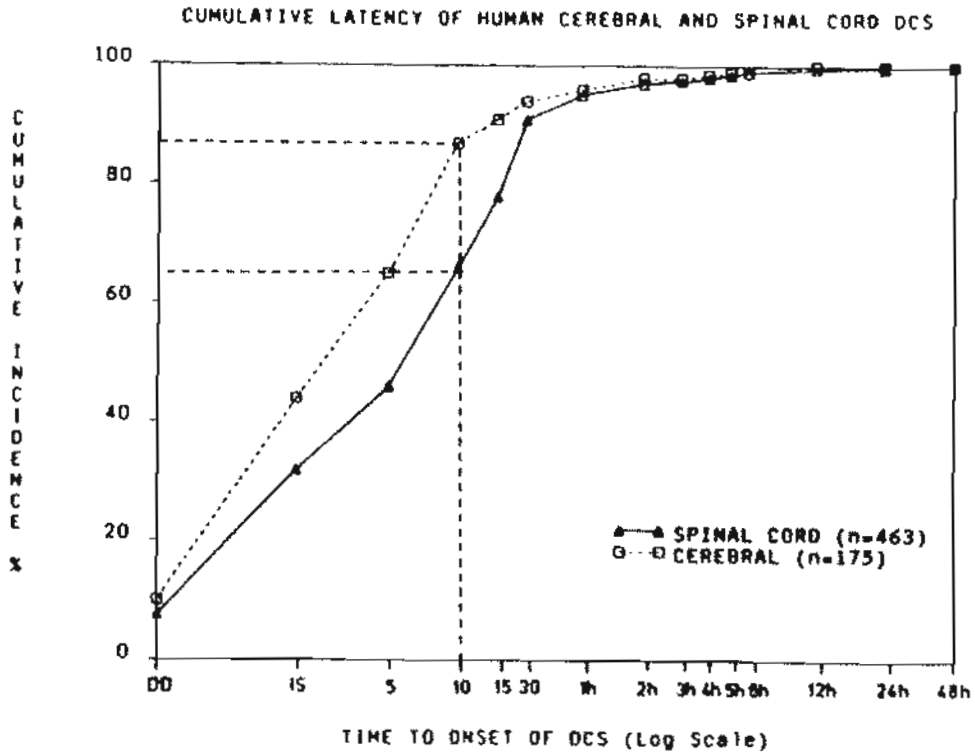

Fig 2. The latency of 463 cases of spinal cord and 175 cases of cerebral decompression sickness. The axes are labelled in a similar manner to fig 1.

Figure 2 indicates that cerebral DCS has a shorter latency than that of the spinal cord, with 87% of cerebral cases becoming manifest within 10 min compared with 66% of spinal cord cases. It should be noted that a delayed onset for either cerebral or spinal cord DCS is rare. Only 4% of cerebral and 5% of spinal cord cases present more than 1 h after returning to 1 ATA.

The Pathology of Spinal Cord DCS

In 1870, Bauer (5) described the post mortem examination of a 35-year-old caisson worker who had survived for 5 days following the onset of spinal cord DCS. The principal findings in the spinal cord were hypervascularity of the dura and arachnoid mater, an accumulation of

cerebrospinal fluid, the thrombosis of a moderately sized vein near the cauda, and some softening of the cord. Spinal cord softening in this and other cases he observed occurred in "circumscribed portions of the columns." Van Rensselaer (50) published a review of 25 post mortem examinations of cases of caisson disease. The gross findings were essentially as above with the additional observation of secondary tract degeneration in a case that had survived for 36 days. This paper contained one of the first descriptions of the microscopic findings in spinal cord DCS. He observed that it is the white rather than the gray matter of the cord that is affected and, at the late stage of the disease represented by these cases, the condition was characterized by the destruction of nerve tissue, increased neuroglia, and the loss or atrophy of axis cylinders. He considered this appearance to be degenerative or to resemble a diffuse parenchymous myelitis. He found no evidence of haemorrhage and considered that the lower dorsal cord was the region most affected. Sharples (53) made similar observations on a teraplegic diver who had died 38 days after the onset of DCS. He found lesions scattered throughout the cord, but the greatest tissue destruction was at the cervical level.

As Brooks (69) pointed out, many of the early reports on the neuropathology of DCS described cases in which death occurred many days after the onset of the condition. He described two cases in which death occurred 3 days, and 13 hours respectively after the onset of DCS. In the first case he described an abundance of CSF, patchy softening of the cord, and a single, small, H-shaped haemorrhage at the level of T8. Microscopically, there was edema and numerous "lacerations" in the firm parts of the cord and the softened areas presented the familiar appearance of "transverse myelitis". The spinal cord of the second case appeared considerably less softened, and although the spinal canal contained large amounts of blood, only tiny areas of haemorrhage were found within the spinal cord (principally located in the dorsal columns). Edema, numerous "air lacerations," and microscopic haemorrhages were demonstrated histologically in the white matter of the cord.

Since the early 20th century the pathological findings in the spinal cord described above have not been challenged, although three additional features have been described. In humans, Kitano and Hayashi (95) presented a case in which the post mortem appearance of spinal cord congestion was associated with coagulation of blood in the epidural veins. These veins contained numerous fat droplets that were thought to originate from bone marrow. Evidence of fat and bone marrow emboli has also been found in animals, particularly in the lungs, but not in cerebral or spinal cord vessels (108). Kitano et al. (109) also found, in the case of a diver that had died from cerebral DCS shortly after surfacing, several small (up to 1 mm diameter), non-staining, round spaces in the white matter of the brain and spinal cord. In animals, similar non-staining, space-occupying lesions have been described in the spinal cords of 6 out of 16 dogs subjected to a severe decompression insult (110), and in decompressed fingerling salmon (111). Gersh and Catchpole (112) however, failed to find any similar lesions in the cords of decompressed rodents. Finally, Palmer (113), reviewing his study of the spinal cords of goats with DCS, described a thin rim of sub-pial white matter that was invariably spared from involvement in even the more

peripheral lesions of white matter that he observed.

The Pathophysiology of Spinal Cord DCS

In the early years, there were almost as many theories of the mechanism of DCS as there were observers of the condition. Many of these theories were based on scant evidence and conceived in the absence of a clear understanding of physics or physiology. They were well reviewed by Van Rensselaer (50) who classified them as follows:

I. The theory of exhaustion and cold.
II. The gaseous theory.
III. The theory of congestion with sequelae:
    a. "Black blood" (i.e., blood deprived of its oxygen).
    b. Evolution of gas in the blood vessels.
    c. Haemorrhage.
    d. Acute revulsive anaemia.
    e. Comparative stasis.

He dismissed the first theory on the grounds that in winter, many of the population are exposed to greater and more prolonged cold than caisson workers during their decompression, yet they do not display the signs of caisson disease.

The second theory has its origins in the observations of Robert Boyle (114), who decompressed numerous members of the biosphere in his "exhausted receiver." One of Boyle's remarkable conclusions deserves quoting in full:

> "Whether, and how far the destructive operation of our engin upon the included animal, might be imputed to this, that upon the withdrawing of the Air, besides the removal of what the Airs presences contributes to life, little bubbles generated upon the absence of the air in the Bloud, juyces, and soft parts of the body, may by their vast number, and their conspiring distension, variously streighten in some places, and stretch in others, the vessels, especially the smaller ones, that convey the Bloud and Nourishment; and so by choaking up some passages, and vitiating the figure of others, disturb or hinder the due circulation of the Bloud? Not to mention the pains that such distensions may cause in some nerves, and membranous parts, which by irritating some of them in convulsions may hasten the death of the animals, and destroy them sooner by occasion of that irritation, than they would be destroyed by the bare absence or loss of what air is necessary to supply them with."

Another major contributor to this theory was Bert (4). He concluded at the end of a large series of experiments, conducted principally on dogs, that,

> "Sudden decompression, beginning with several atmospheres, brings on symptoms of varying severity depending upon the degree of compression, the speed of decompression, the animal

> species, the individuals, and the state of the experimental animal at the time. These symptoms must be attributed to the escape of nitrogen which had been stored up in excess in the organism, following Dalton's law. This gas changes to a free state in the blood vessels, the different organic liquids, and even the interior of the tissues; it may therefore, according to circumstances, check the pulmonary circulation, soften and cause anemia in certain regions of the nervous centers and especially the be attributed to the escape of nitrogen which had been stored up in excess in the organism, following Dalton's law. This gas changes to a free state in the blood vessels, the different organic liquids, and even the interior of the tissues; it may therefore, according to circumstances, check the pulmonary circulation, soften and cause anemia in certain regions of the nervous centers and especially the lumbar enlargement of the spinal cord, lacerate the tissues, and produce swellings or a more extensive emphysema. The severity of the symptoms depends upon both the seat and the extent of these multiple disorders."

Van Rensselaer dismissed Bert's conclusions on the grounds that findings based on animal experiments performed at higher pressures than those used in caissons cannot be extrapolated to man. He adhered to the third theory. Although these various congestive theories appeared to be supported by the pathological findings, so long as these were considered to be primary rather than reactive to other processes, their mechanisms depended upon the erroneous belief that atmospheric pressure is unevenly distributed throughout the body. Thus, it is Bert's conclusions that have formed the basis for one theory of the pathogenesis of spinal cord DCS that has proponents to this day.

The Arterial Bubble Embolus Theory

Hill and Macleod (64) observed the circulation in the vessels of a bat's wing and frog's web during and following decompression. They noticed:

> "For about a minute after rapid decompression the circulation continued unaltered, then small, dark bubbles were seen, first one, and then another, and then numbers scurrying through the vessels, and driving the corpuscles before them. In a moment or two the vessels became entirely occupied with columns of air bubbles, and the circulation was at an end."

Oliver (115) repeated this experiment and performed a number of others and declared: " My own experiments and clinical experience leave me in no doubt as to air embolism being the cause of caisson disease."

Boycott et al. (116) apart from making considerable advances in the design of safe, yet efficient decompression procedures, explored the possible pathogenic mechanisms of spinal cord DCS. They considered a number of animal models and eventually selected the goat as having a comparable decompression obligation to man.

They studied the pathology of goats that died and some that were killed

at varying intervals after decompression. Having raised the important caveat that the presence of bubbles in vivo must be inferred from their discovery post mortem with considerable caution (due to the possibility of their nucleation or introduction after death) they described a number of observations. Those pertinent to the spinal cord were as follows. First, the presence of bubbles in venous blood correlates poorly with symptoms of DCS. Bubbles were found in asymptomatic animals and no bubbles found in animals in which symptoms would have been expected had they not been killed. Arterial bubbles were occasionally seen, especially in animals that died slowly. Secondly, veins contained variable quantities of bubbles, but always more than arteries. Interestingly, they observed few bubbles in the veins of the brain and spinal cord. Finally, they found that areas of the spinal cord may be softened, as in human cases. The distribution of these areas of softening were most marked in, and usually confined to the lower dorsal and upper lumbar segments and affected only white matter.

Based on these and other observations, they concluded the following:

> "The distribution of small bubbles in the arterial stream must be universal. They probably lodge in many places: while they are rapidly pushed forward in the grey matter and in most other tissues, if they lodge among the fatty surroundings of the capillaries of the white matter, or in actual fat, they quickly increase in size to such an extent that their removal becomes impossible . . . The cause then of these areas of softening is not ordinary embolism, but embolism which becomes effective to produce infarction by reason of the effect on the size of the embolus of the local conditions of the circulation rather than from any of those peculiarities in the resistance of the different tissues to lack of oxygen, or in the freedom of collateral circulation, which determine the topography of common infarcts."

Since then, experimental work has been undertaken that appears to support the gas embolism mechanism. Behnke et al. (117) found widespread intravascular gas bubbles in dogs that had been rapidly decompressed from an exposure to 65 psig for 105 min. They concluded that spinal cord injury, which was a frequent consequence of such a dive profile, was due to these bubbles acting as emboli. The appearance of bubbles in the pial vessels of decompressed cats was studied by Wagner (118). When they were seen (in 4/14 cats) they were first observed in arteries and subsequently in veins. There was always a latent period between decompression and the appearance of bubbles. Similar findings were made by Lever et al. (119) in a mouse thoraco-abdominal skin flap preparation and by Buckles (120) in exteriorized hamster cheek pouches.

Other investigators have also observed arterial bubbles in decompressed animals (121-123). However, in these studies, arterial bubbles were only seen following their appearance in veins and were associated with severe DCS that was often fatal. These authors concluded that arterial bubbles were rare in less serious forms of DCS.

In none of the above studies was the nucleation of gas bubbles directly

observed and many of them were performed upon small rodent species that were subjected to near explosive decompression insults in order to generate DCS. As will be discussed below, it is during such a decompression that blood may have time to supersaturate and bubbles to nucleate between leaving the lungs and reaching the tissues. This could result in the appearance of arterial bubbles that may be absent in the less rapid, yet spinal cord damaging decompressions generally undertaken by man.

The pathological findings in spinal cord DCS have been described as being compatible with ischemic necrosis (96,124), which has been used to support arterial gas emboli as pathogenic mediators (124,125). We will discuss later that this need not necessarily be the case, since ischemia in DCS need not be a consequence of either bubble or other emboli.

The development of the doppler ultrasonic probe has resulted in a mass of evidence that intravascular bubbles are associated with DCS in both animals (126-129) and man (130-137). The weight of evidence is that bubbles first appear on the venous side of the circulation and that arterial bubbles are rare and only associated with severe DCS. There are, however some reservations about the use of dopplers in DCS that should be borne in mind when interpreting their results. Bubbles can only be detected if they are moving; the signal from bubbles may be confused with those from other emboli or with artefact generated by small movements of the transducer. The analysis of doppler records is not wholly objective, particularly where the observer is not "blinded" as to the outcome of the decompression. Finally, it is possible that the energy delivered to tissues by high intensity ultrasound may provoke bubble nucleation. Perhaps the most troubling aspect of the doppler evidence for the role of intravascular bubbles in DCS is the confirmation of the observation of Boycott et al. (116) that the detection of intravascular bubbles correlates poorly with the development of clinical DCS (138).

A further problem with the arterial bubble embolus theory is the question of the origin of arterial bubbles. It is widely recognized that following passage through the lungs, arterial blood gases have equilibrated with alveolar tensions. Hills (139) calculated that during an ascent of less than 20 $fsw \cdot min^{-1}$, arterial blood would not reach saturation between the lungs and tissues. He considered that it is difficult for bubbles to form in blood even with appreciable degrees of supersaturation and thus the *de novo* nucleation of bubbles in arterial blood during decompression at conventional rates is most unlikely.

Bubbles of gas may be released into pulmonary capillaries if for any reason air is trapped in the lungs and reaches an overpressure of about 80 mm Hg (140). Such pulmonary barotrauma and arterial gas embolism can result from a failure to exhale during decompression, from preexisting lung pathology (141-143), from a raised compliance or uneven distribution of ventilation (144), or idiopathically. Invariably, symptoms of cerebral embolism present within about 5 min of reaching 1 ATA. The spinal cord is very rarely involved, and the condition is unusual in caisson workers, although this mechanism has been proposed for CNS DCS in this group (14). The very rare involvement of the spinal cord makes this

an unlikely mechanism for spinal cord DCS.

It is possible for arterial bubbles to arise from the paradoxical embolism of gaseous venous emboli (145). Potential atrial septal defects are common in the adult population. It is estimated that the prevalence of valvular-competent foramen ovale is about 35% (146). However, it should be noted that under normal circumstances there is little or no shunting between the atria in these cases. This situation should be distinguished from atrial septal defects (ASD). These are far less common, being found in less than 0.1% of children surviving beyond 1 year (147). These may remain asymptomatic until the mid teens and until this time, most shunting is from left to right. With a reversal of the shunt these defects often become symptomatic. In cases of severe DCS, when pressures in the right side of the heart are increased due to the impaction of bubbles in the pulmonary vasculature, potential shunts may open and provoke arterial gas embolism (148). However, this process is likely to be time consuming and play a part only in delayed-onset CNS DCS. Since aviators, divers and caisson workers are screened for symptomatic or clinically detectable cardiac abnormalities, paradoxical embolism should not be a frequent source of arterial emboli in the early stages of DCS.

The only other way for bubbles to appear in arterial blood is as a consequence of the transpulmonary passage of venous bubbles. The lungs, however, have been shown to be a most efficient filter of beads (149) and gas emboli (150,151) in the size range of bubbles measured in the venous blood of decompressed dogs (152). Admittedly, the filtering capacity of the lungs may be exceeded when during massive intravascular bubbling (153). However, in an animal model of venous air injection, this has been shown to take more than 10 min to occur (154), which is too slow to account for the majority of cases of CNS DCS. Furthermore, intravascular bubbling sufficient to overwhelm pulmonary filtering capacity is likely to be accompanied by pulmonary symptomatology. As we have seen, this is relatively rare in divers and caisson workers.

In conclusion, the hypothesis that arterial bubble emboli are the primary pathological event in the generation of spinal cord DCS, although longstanding and with current proponents, remains based on less than conclusive evidence.

Other Embolic Theories

End (155,156) proposed that an initiating event in DCS is the agglutination of formed blood elements that loose their common revulsion by some undisclosed mechanism during decompression. He proposed that these aggregates then act as emboli. Certainly, rheological changes within blood occur in DCS. An increase in haematocrit and a loss of plasma volume are commonly found in both humans and animals with DCS (108,157-161). This tends to increase blood viscosity and reduce tissue perfusion. The aggregation of blood components such as platelets (160,162-164) and leukocytes (165), the formation of rouleaux (161), and the finding of endothelial cell (165,166), fat and bone marrow emboli (109,110,166-170) have all been described. However, all of these phenomena may be explained as being a consequence of the nucleation of

bone marrow or intravascular gas bubbles and thus not necessarily primary events in DCS. Furthermore, as Walder (171) argues, the sludging of blood occurs in other conditions without resulting in the manifestations of DCS.

The pathological findings in disseminated intravascular coagulation (DIC), in which many of these hematological events occur on a considerable scale, are at variance with the classical findings in DCS. The more common occurrences in DIC (hemorrhagic necrosis of the gastrointestinal mucosa, severe congestion of the abdominal viscera and microscopic occlusion of capillaries by thrombi, with surrounding, secondary, focal necrosis (172)) are rare in DCS. In addition, spinal cord injury is a most unusual feature of DIC.

An observation that is difficult to explain using any mechanism based upon the impaction of solid emboli as the principle pathological event, is the dramatic improvement in DCS that is often seen with recompression. If embolic phenomena are responsible for DCS, this observation would be more readily explained by invoking compressible, gaseous emboli as the causative agents.

The Venous Infarction Theory

Haymaker and Johnston (173) raised the theoretical possibility that under conditions of extreme DCS, bubbles in the Epidural Vertebral Venous Plexus (EVVP) combined with back pressure from bubble-laden lungs transmitted through venous anastamoses with the pulmonary circulation, may cause venous engorgement of the spinal cord. Haymaker (83) developed the hypothesis by noting Batson's (174,175) observation that the EVVP is a large, valveless, low-pressure system, making it a favourable site for the formation of bubbles.

Hallenbeck, Bove, and Elliott (176) went further. They reasoned that gas bubbles are not inert in the bloodstream, but, as a result of a 40-100 A layer of electrokinetic forces at the blood-gas interface, they cause structural alterations to plasma proteins. These alterations result in the activation of the coagulation, complement and fibrinolytic cascades, the release of kinins and complex alterations to haemodynamics. They demonstrated that coagulation was accelerated by the presence of bubbles in blood and cell-free plasma (177). These and other possible haematological consequences of decompression were comprehensively reviewed by Philp (178). More recently, evidence has been presented that the activation of the complement system, in particular, may be an important event in the generation of the symptoms of DCS (179,180).

Another argument developed by Hallenbeck et al. was that embolic mechanisms for spinal cord DCS could be criticized on the grounds that the distribution of CNS lesions in DCS appear to be unique. The brain is the principle target organ in other clinical, embolic conditions such as subacute bacterial endocarditis, fat embolism and mural thrombus of the left atrium. They quote Blackwood's observation (181) that arterial embolism of the cord is extremely rare. Of the 3,737 autopsies on patients dying with neurological diseases that he reviewed, he found not a single case of spinal cord embolism. If emboli are responsible for the

pathological findings in CNS DCS, it is the brain rather than the spinal cord that should be preferentially embolized as it constitutes some 98% of the mass of the human CNS and receives 75-85 times the blood flow of the spinal cord (182). Even within the spinal cord, it is the grey matter that might be expected to be impacted more frequently than the white matter, based upon the distribution of blood flow. Even if the argument of Boycott et al (116) is employed, that only bubbles that embolize the white matter of the CNS might be expected to grow and remain in situ, cerebral rather than spinal cord white matter lesions should predominate since cerebral white matter has a 60% greater blood flow than that in the cord (183) and should therefore receive more emboli.

Such arguments led Hallenbeck et al. to perform a number of elegant experiments that demonstrated many elements of the hypothesis that bubbles accumulate in the venous drainage of the cord and their presence, combined with their activation of the clotting mechanism results in a slowing and eventual cessation of venous outflow. This causes congestion and ultimately, venous infarction of the spinal cord (159,184-187). They argued that such a mechanism should result in a pathological appearance of white matter haemorrhage compatible with that found in DCS (188). A further mechanism that they considered would facilitate this process in severe DCS is central venous congestion secondary to overloading of the pulmonary circulation with bubbles. This would further reduce the already compromised venous drainage of the cord.

This theory also has its shortcomings. Firstly, there is some doubt that the characteristic lesions of spinal cord DCS are compatible with a venous infarction mechanism (189). As we have seen, the typical haemorrhages of DCS tend to be scattered, punctate and restricted to white matter (figs 3 and 4). On the other hand the haemorrhage associated with venous infarction tends to be massive and involve both grey and white matter (190,191) (fig 5). Venous infarction of the spinal cord is a very rare pathology (192). This may be because it is an extensive plexus with numerous alternative routes. If this plexus were to be completely blocked at any given level it would seem probable that the resulting venous congestion and infarction would involve an extensive proportion of the cord below that level (fig 6). Such a finding has not been described in DCS. Even obstruction of the venous drainage at the radicular level might be expected to result in one or more lesions with a segmental distribution. Again, this is not typical of the lesions of DCS.

Another problem relates to the frequent finding of 'silent', intravascular bubbles in divers and cases of pulmonary DCS ('chokes') that are apparently free of spinal cord involvement, particularly in aviators. How is it that 'silent' bubbling, that presumably provokes similar rheological changes to symptomatic bubbling, fails to compromise spinal cord drainage? Although this may be explained on the basis that such bubbling fails to exceed an arbitrary threshold, it is difficult to understand why aviators, with sufficient venous bubbling to cause chokes, should not also invariably suffer spinal cord injury.

Cerebral involvement in DCS is by no means rare (table 1, fig 2). Also, the cerebral venous drainage differs substantially from that of the spinal cord and lacks the slow flow characteristics of the EVVP. Thus

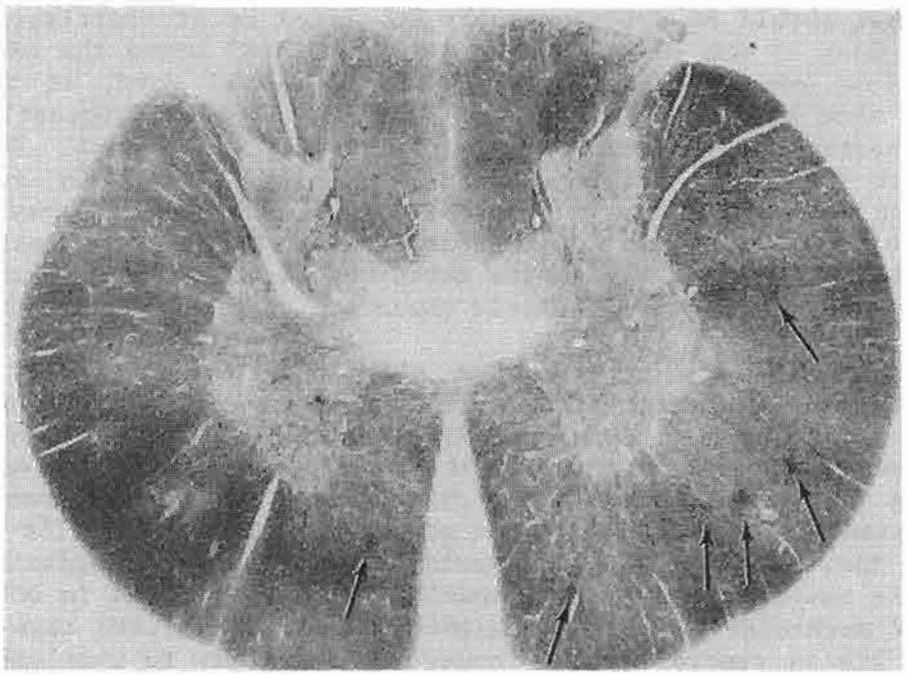

Fig 3. A low power cross section of a spinal cord with decompression sickness. Arrowed are the characteristic punctate, white matter hemorrhages.

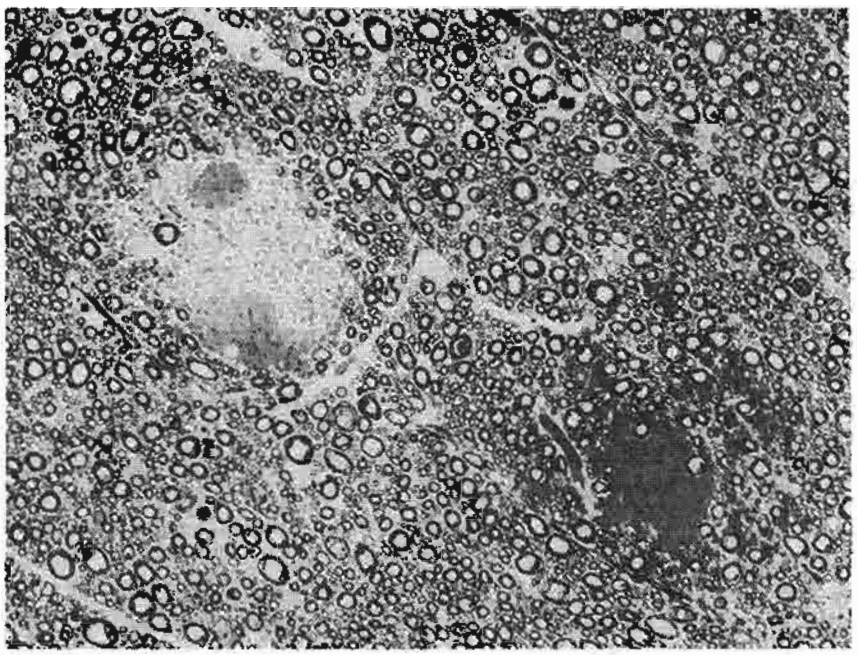

Fig 4. High power view of a punctate, white matter haemorrhage in a spinal cord with DCS.

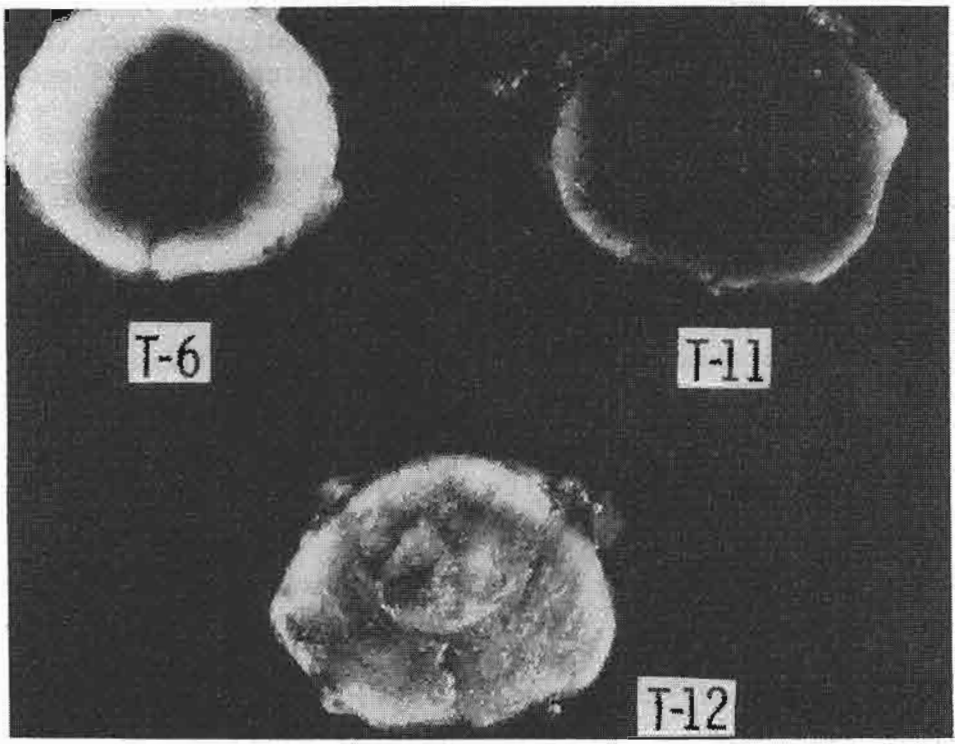

Fig 5. Low power cross section of a human spinal cord showing venous infarction. The principal lesion is a massive central hemorrhage involving both gray and white matter. From Hughes (190).

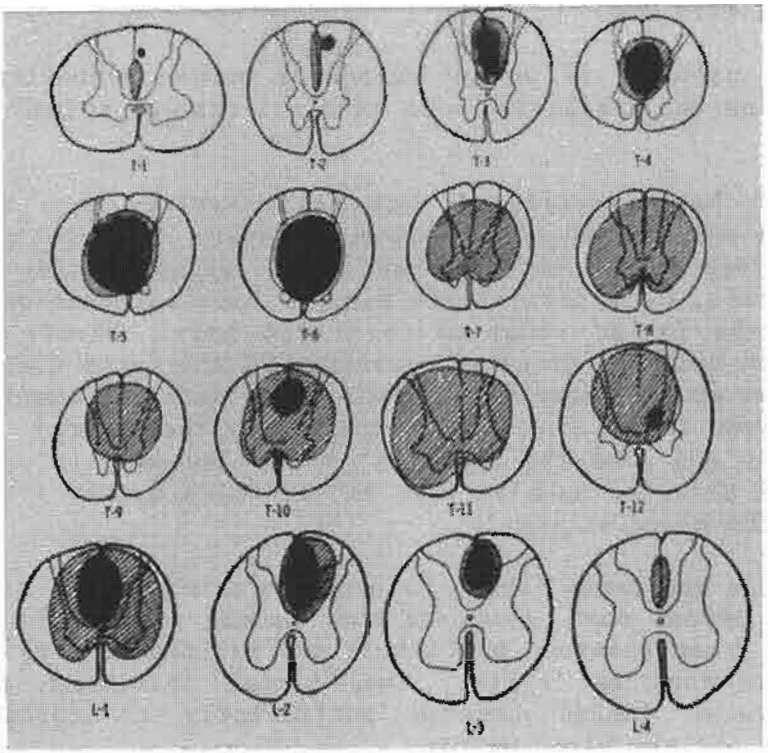

Fig 6. Diagram of the distribution of haemorrhagic infarction (shaded) and hematoma (black) in a case of venous infarction of the spinal cord. Redrawn from Hughes (190).

the cerebral venous drainage is a less plausible location than the EVVP for the venous infarction mechanism to operate optimally. Hence it would be difficult to employ venous infarction as a unifying theory of cerebral and spinal cord DCS.

Finally, there is the matter of latency. The venous infarction mechanism is likely to take a considerable period of time to develop. In the case of venous infarction from other causes, this may take many hours or days (190,192). Although the mechanism in DCS may be considerably more rapid, it took an average of 13.5 min for the venous drainage to apparently cease in Hallenbeck's canine model of severe DCS (186). There is also some question as to whether the technique of directly visualizing the blood flow in the EVVP via laminectomy (employed in this experiment) predisposed the spinal cord to circulatory embarrassment. There is evidence that an effect of laminectomy is to reduce spinal cord blood flow by as much as 45% (193). It is possible therefore, that venous bubbling may take somewhat longer to halt a more rapid blood flow in the EVVP. In consequence, venous infarction may be too slow a process to account for the rapid onset of the majority of human cases of spinal cord DCS (fig 2).

The Autochthonous Bubble Theory

It is possible to interpret the conclusions of Boyle and Bert that I quoted above (114,4) as proposing a role for autochthonous bubbles in DCS. However, this is rarely done. Even Boycott et al. (116) who published classic drawings of the spinal cord of a goat that had died from O2 toxicity during decompression from 6.4 ATA that demonstrated massive autochthonous bubble injury (fig 7), concluded, as we have seen, that arterial bubble emboli were the principle pathological mechanism involved in spinal cord DCS.

The first serious proposal of an autochthonous bubble mechanism was by Keyser (79). During the discussion of a clinical case of spinal cord DCS he reasoned,

> "Vernon (194) has demonstrated that fat dissolves more than five times as much oxygen and nitrogen as water. The myelin of the white matter of the cord belongs to the group of fats and would, therefore, be a most common site of bubble formation in common with the fat of other parts of the body. Minute gas bubbles, which would be of no significance in the fatty tissues of the omentum or abdominal wall, would cause definite symptoms if they occurred in the cord . . . From purely theoretical considerations and also the location of the lesions, it seems more probable that the bubbles form in the white matter itself rather than the blood stream."

More recently, Hills and James (195), following a study of the mechanical properties of the spinal cord, proposed that spinal cord ischemia could result if, during decompression, sufficient gas is liberated to increase the volume of the cord by 14-31%. They argued that such a volume increase would raise tissue tension sufficiently to collapse the arterioles and cut off the blood supply.

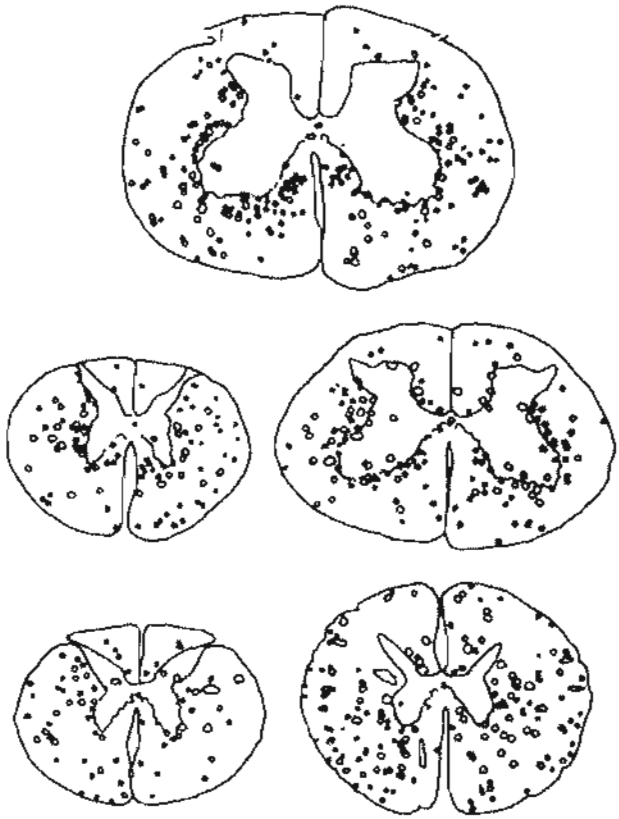

Fig 7. Camera Lucida drawings of cross sections of goat spinal cord. The animal died of oxygen poisoning during decompression from 6.51 ATA. Each drawing is a composite showing all the bubbles in a 0.4 cm length of cord. Redrawn from Boycott et al. (116).

The major problem with the autochthonous bubble theory has been that, with the exception of Boycott's goat and vague references to "air lacerations" (69) or "stippling" (196) in descriptions of the human pathology, extravascular bubbles have rarely been described in either human cases or animal models of the disease. Until quite recently, there was only scant histological evidence from animal models of DCS for the existence of autochthonous bubbles in the spinal cord (110,111). In man, non-staining, round lesions have been demonstrated in the brain and spinal cord of a diver that died shortly after surfacing from a cerebral DCS-provoking dive (109), and numerous similar lesions were described in the cerebral white matter of two SCUBA divers that had apparently died prior to decompression from 140 ft (197). Unfortunately, the spinal cord was not examined in the latter case.

The probable reason why autochthonous bubbles have so rarely been demonstrated is that their presence in the cord is apparently transitory. Unless tissues are rapidly fixed after the onset of DCS, it is very difficult to demonstrate bubbles. Sykes and Yaffe (198) perfusion fixed dogs with fully developed spinal cord DCS, and although they described

abnormalities in myelin that may have been a consequence of autochthonous bubble nucleation, overt bubbles could not be demonstrated. We recently reported a number of experiments where dogs completed a spinal cord DCS-provoking dive (300 ft for 15 min (199)); as soon as the amplitude of their spinal evoked potentials (SEP) fell to below 80% of the pre-dive control value, they were rapidly perfusion fixed (200-202). This enabled us to demonstrate numerous non-staining, space- occupying lesions in the white matter myelin of the spinal cord (figs 8-13). Such lesions have been shown to be absent in the cords of dogs subjected to the same dive profile but which failed to demonstrate any reduction in SEP amplitude, and in undived controls.

Although not yet published, we have observed that the population of these white matter lesions appears to decline as the latency for the loss of SEP amplitude increases. For example, we found that in one cord where the loss of SEP amplitude did not occur until 30 min after surfacing from the dive, there were virtually none of these space-occupying lesions to be seen.

Further work is under way to describe the distribution of these lesions within the cord and to demonstrate whether or not they are caused by the nucleation of gas bubbles.

I will conclude the discussion of the autochthonous bubble theory by attempting to outline some of the clinical and pathological features of CNS DCS that may be explicable in terms of an autochthonous bubble mechanism.

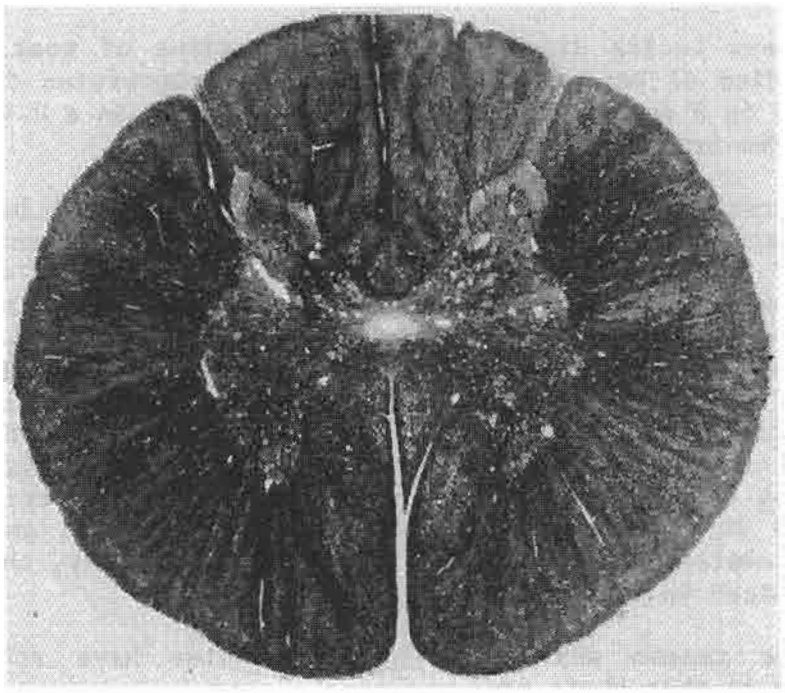

Fig 8. A low power cross section of an undived, canine spinal cord.

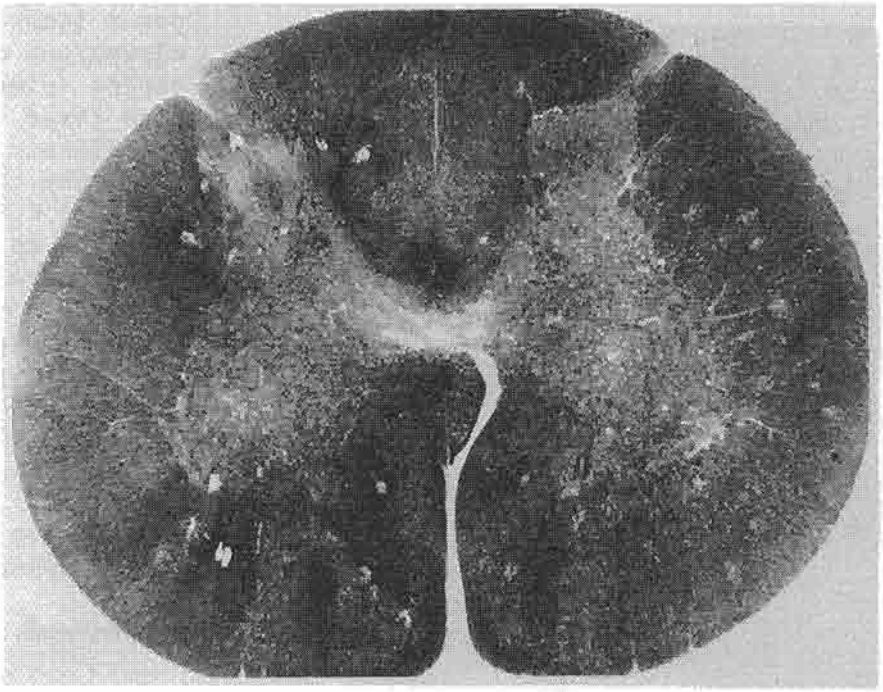

Fig 9. A low power cross section of canine spinal cord, fixed immediately following the diagnosis of spinal cord decompression sickness. Arrowed are some of the numerous non-staining, space-occupying lesions in the white matter.

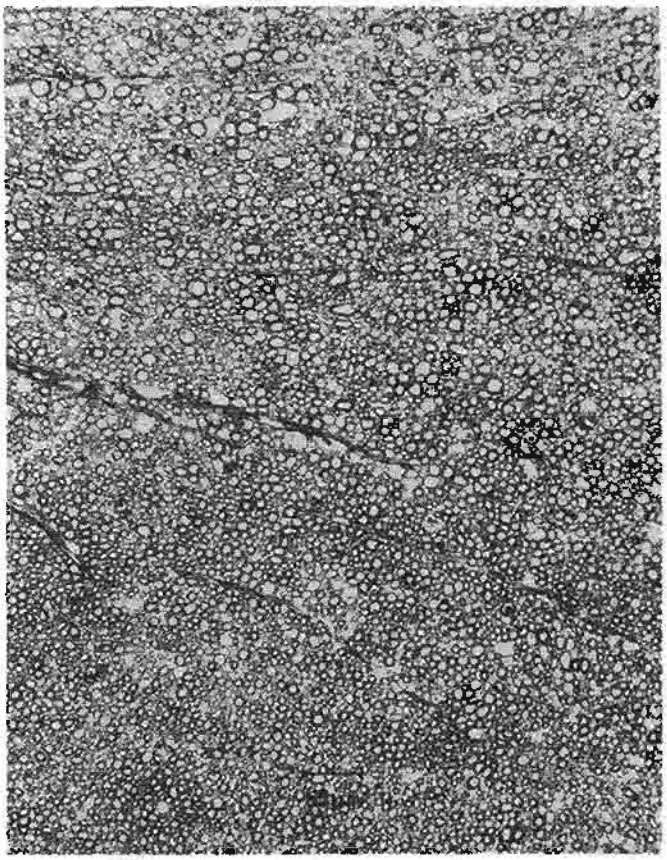

Fig 10. A high power light micrograph of normal canine spinal cord white matter. Note 50 um bar for scale.

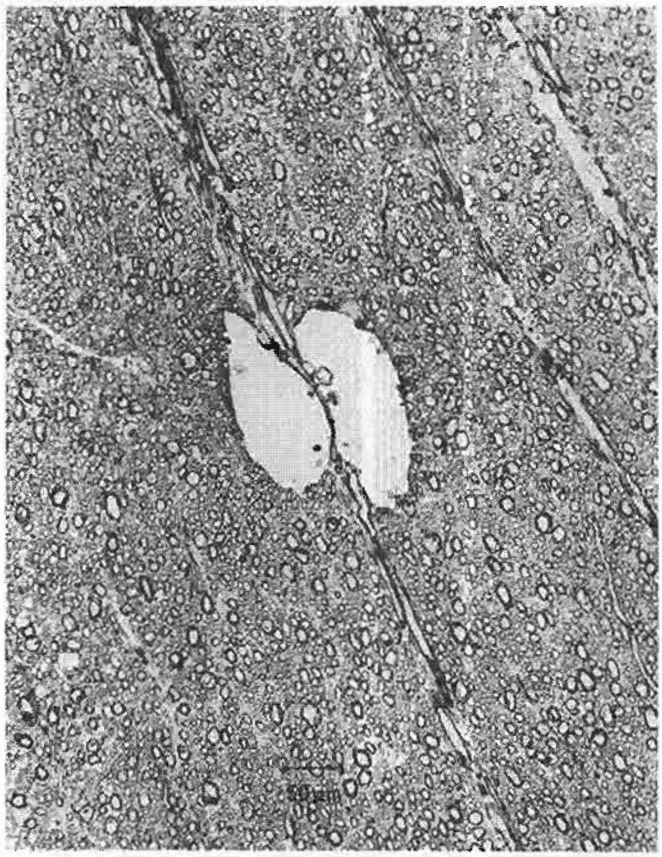

Fig 11. A high power light micrograph of canine spinal cord fixed immediately following the onset of DCS. There is an approximately 200 x 150 um non-staining, space-occupying lesion in the center of the field. Note that the surrounding tissue appears to be compressed.

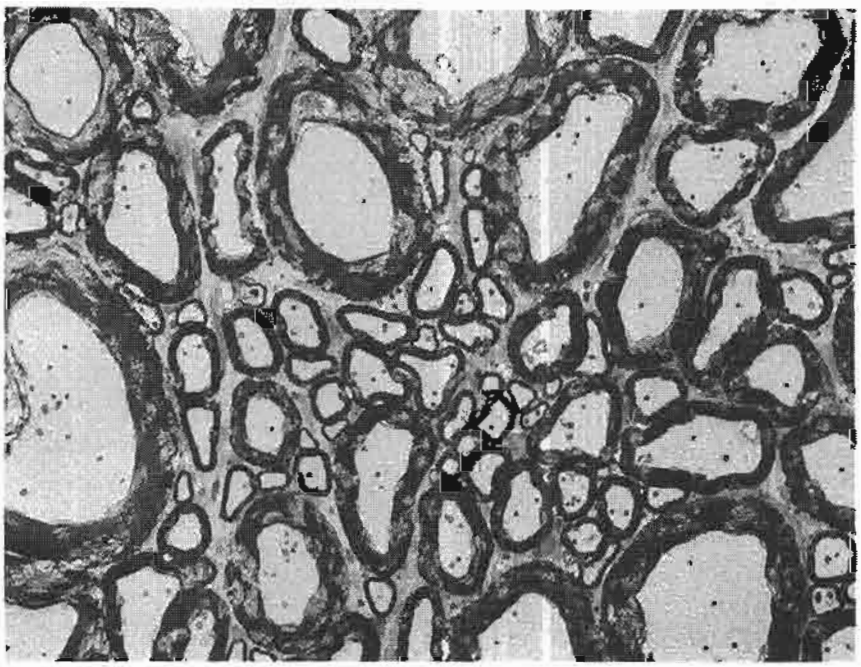

Fig 12. Transmission Electron Micrograph (TEM) of normal canine spinal cord white matter (x1,700).

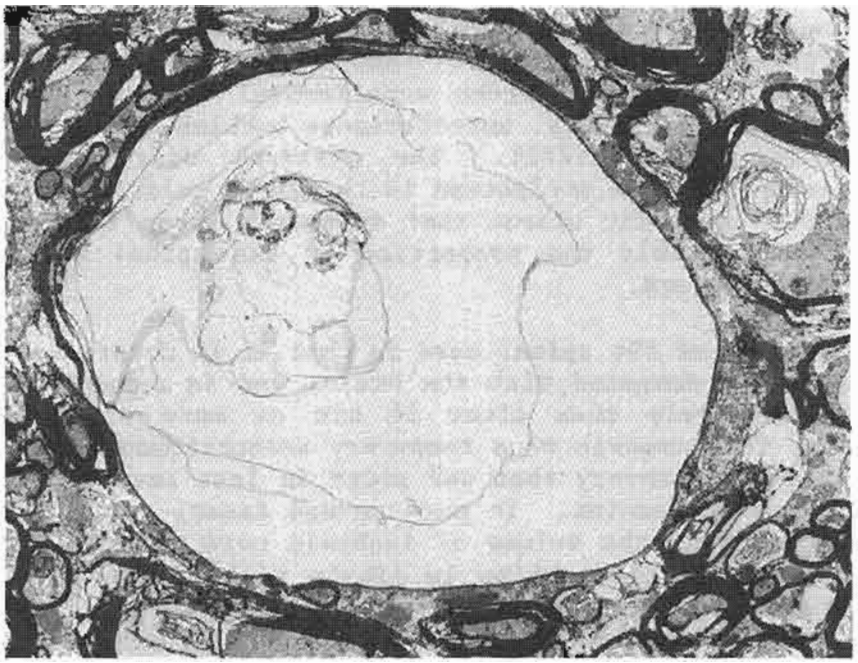

Fig 13. TEM of canine spinal cord white matter showing a small, non-staining, space-occupying lesion. Note the involvement of myelin and the compression of surrounding structures (x1,700).

1. As Keyser observed (79), because myelin has a high fat content, it is a likely site for nitrogen to accumulate during a dive. In fact, more gas is likely to accumulate in the spinal cord than the brain due to its greater lipid content (203,204). Because spinal cord white matter has a relatively low blood flow (205-207), the clearance of gas in spinal cord white matter during decompression will be slower than in other parts of the CNS. The potential, therefore, exists for the rate of gas clearance to be insufficient to maintain the nitrogen tension below the critical nucleation pressure (208). Should this occur, bubble nucleation would result, particularly in those parts of the cord with the lowest blood flow - namely the upper lumbar/lower thoracic and upper thoracic/lower cervical levels (209,210). Circulating CSF may provide a route for the most superficial white matter to "off gas" and result in Palmer's observation of subpial sparing (113). Thus, the distribution of DCS lesions may be explained by invoking this mechanism.

2. It may be envisaged that as a bubble nucleates, it generates an increase in tissue tension and shearing forces in the surrounding white matter which, containing little connective tissue, tears as a consequence. Thus, loss of function might be attributable both to physical disruption of the white matter (211), and to ischemia (212), which is secondary to the raised tissue pressure. Once it has formed however, there is no reason why a bubble should persist. As tissues distant to the bubble, such as the gray matter, continue to be perfused, gas will gradually diffuse down a tension gradient away from the bubble. As the bubble decreases in volume, the tissue tension would also reduce,

allowing blood flow to the damaged white matter to resume. At this stage, it is likely that haemorrhage would occur from capillaries that were traumatized during bubble nucleation and result in the characteristic appearance on histology of scattered, punctate haemorrhages. The most recent experimental evidence is that even in cases with a short latency, autochthonous bubbles occupy only about 1% of white matter volume (202). The physical disruption of the cord consequent upon bubble nucleation is therefore relatively minor, although the volume of ischemic tissue that surrounds these lesions is likely to increase considerably the proportion of the spinal cord that has its function compromised.

Another feature of the spinal cord is that it is notoriously resistant to ischemic injury compared with the brain, and is capable of considerable functional recovery even after 20 min or more of absolute ischemia (213-216). The scenario of a temporary autochthonous bubble may explain the spontaneous recovery that can occur in less severe cases even in the absence of recompression. In more severe cases, in which more bubbling may have occurred, the volume of ischemic cord and the distance for gas to diffuse out of the bubbles is likely to be greater. Thus, although such diffusion will eventually occur, it may not be accomplished in time for the tissue to be spared from more refractory ischemic injury.

3. Although the physics of bubble nucleation is beyond the scope of this paper, I will touch on whether autochthonous bubble nucleation more or less likely to occur in the spinal cord myelin of aviators than divers. Piccard (217) studied the weight and volume of air dissolved in and escaping from water that was subjected to comparable hyperbaric and hypobaric decompressions (table 2).

TABLE 2

Air dissolved in and escaping from 1 liter of water.

Pressure atm.	Air dissolved		Air escaping	
	Weight, mg.	Volume, cc.	Weight, mg.	Volume, cc.
↑ 0.2	4	20	16	80
↑ 1.0	20	20		
↑ 1.0	20	20	80	80
↑ 5.0	100	20		

During decompression from 5 ATA to 1 ATA, five times the weight of gas is released from the water than during a decompression from 1 ATA to 0.2 ATA, even though the volume of air that escapes is the same (80 cc) in each case. He observed that the rate at which the gas is released also differed in the two cases: with the bulk of the air escaped within 5 s

of reaching 1 ATA from 5 ATA, whereas several minutes were required for the effervescence to even approximately cease following the hypobaric decompression. He considered that this may be because the probability of bubble nucleation in the hyperbaric experiment is considerably greater than in the hypobaric experiment. He calculated that the air molecules dissolved in 12.8 μ^3 of water are required to congregate to form a stable bubble in the hyperbaric decompression whereas those from 1,606 μ^3 of water are required in the hypobaric instance - a much less likely event. Although it is a big leap to extrapolate from a beaker of water to a biological system, Piccard's observations on the rate of gas release may provide a clue as to what happens in spinal cord myelin. Bubble nucleation in a perfused, biological tissue subjected to hypobaric decompression is less likely than for a hyperbaric decompression, since the gas has a longer period of time to leave the tissue in solution via the blood stream prior to bubble nucleation.

4. The nucleation of autochthonous bubbles is likely to be a rapid occurrence during the later stages of decompression or soon after reaching 1 ATA. This is because it is at this stage of a hyperbaric exposure that the inert gas supersaturation (should it occur) is at its greatest (218). With every minute that passes on the surface, gas is cleared from the spinal cord, as it is from the rest of the body, and the likelihood of gas bubble nucleation declines. This may explain why few bubbles were seen in the spinal cord of our dog with a latency of 30 min. Autochthonous bubble nucleation, therefore, represents a plausible mechanism for short-latency spinal cord DCS. It does not, however, explain DCS with a longer latency as there would appear to be a relatively short "window of opportunity" for this pathogenic mechanism to operate. In the case of cerebral DCS, we have not yet looked for autochthonous bubbles. If they occur, one might imagine that the window of opportunity for their formation would be shorter and their occurrence less frequent than in the spinal cord, since the brain's superior perfusion and lower lipid content would permit a more rapid clearance of a smaller inert gas load than the spinal cord. In this respect it is interesting to note that cerebral DCS is less prevalent and its latency shorter than that of the spinal cord DCS (fig 2). Autochthonous bubbles, therefore, offer a plausible mechanism for CNS DCS with a short latency, which encompasses the majority of (but by no means all) cases.

5. There are few human data available, but the evidence in sheep (219) is that spinal cord blood flow decreases with age. The lipid content, on the other hand, tends to increase (202). An effect of this from the point of view of DCS would be to compromise the clearance of a greater gas load from the spinal cord. This would increase the probability of bubble nucleation, as well as lengthen its the window of opportunity. This may explain the increased prevalence of DCS in older divers and caisson workers over younger ones.

6. Hills and James (195) observed that in cases of spinal cord DCS that receive inadequate recompression, following initial recovery, the neurological deficit returns with a similar distribution to that prior to treatment. They conclude that such an sequence of events is much more likely to be due to the presence of an autochthonous bubble than intravascular gas.

Conclusion

It is clear that if an inadequate period of time is spent decompressing from a hyperbaric exposure, structural and functional abnormalities in a number of systems and organs within the body may result. It is likely that many of these are due to the nucleation of gas bubbles. In attempting to understand the pathogenesis of any particular form of DCS, it is essential to identify which of the many physiological and anatomical abnormalities that can be demonstrated to occur are relevant to the organ under study. Furthermore, it is important to arrange the various pathological events in a cogent sequence that can be shown to operate within a similar time scale to the disease process. With reference to the spinal cord, the focus of attention over the years has been to invoke a causal role for intravascular bubbles. Although there is no doubt that these bubbles occur and may eventually cause emboli or venous obstruction, it is more difficult to ascribe a principal role to these bubbles in the majority of cases of spinal cord DCS, which present in a shorter time frame that these intravascular mechanisms are likely to take to operate.

At the same time, it is clear that not all cases of spinal cord DCS have a short latency (fig 2), and autochthonous bubbles provide a plausible mechanism only for such cases. It is probable that intravascular events are responsible for longer latency presentations.

It is likely therefore, that more than one mechanism is responsible for the pathogenesis of spinal cord DCS. This is hardly a surprising conclusion when one considers the multiplicity of pathological reactions to decompression that have been demonstrated to occur. Furthermore, there is nothing wrong with invoking more than one mechanism: There is, after all, more than one way to kill a cat!

References

1. Smeaton J. Historical report on Ramsgate Harbour. London 1791.

2. Triger E. Memoir sur un appareil a air comprime pour le percement des puits de mine et autre travaux, sous les eaux et dans les sables submerges. Comp Rendus Acad des Sciences. 1841; 13:884-896.

3. Pol B, Watelle TII. Memoir sur les effets de la compression de l'air applique au creusement des puits a houille. Ann d'Hyg. Pub et Med Legale Paris. 1854; Ser 2(1): 241-279.

4. Bert P. La Pression Barometrique; recherches de physiologie experimentale. Paris: G Masson 1878. Translated from the French by MA Hitchcock and FA Hitchcock. Columbus College Book Co, 1943. Republished by the Undersea Medical Society Inc. Bethesda 1978.

5. Bauer L. The pathological effects upon brain and spinal cord of men exposed to the action of largely increased atmospheric pressure. St Louis Med Surg J 1870; 7:234-245.

6. Clark EA. Effects of increased atmospheric pressure upon the human body: with a report of 35 cases brought to City Hospital from the caisson of the St Louis and Illinois Bridge. Med Arch St Louis 1870; 5:1-30.

7. Behnke A R, Shaw L A. The use of oxygen in the treatment of compressed-air illness. Nav Med Bull 1937; 35:61-73.

8. Workman RD. The treatment of bends with oxygen at high pressure. Aerospace Med 1968; 39:1076-1083.

9. Keays FL. Compressed air illness with a report of 3692 cases. Dept of Med Publ Cornell Univ Med Coll 1909; 2:1-55.

10. Levy E. Compressed air illness and its engineering importance with a report of cases at the East River Tunnels. Dept of the Interior, Washington DC. Technical paper 285, 1922.

11. Thorne IJ. Caisson Disease. A Study based on 300 cases observed at the Queens-Midtown tunnel project, 1938. JAMA 1941; 117:585-588.

12. Duffner GJ, van Der Aue OE, Behnke AP. The treatment of decompression sickness. Analysis of 113 cases. US Naval Medical Research Institute project X-443 report No 3, 1946.

13. Behnke AR. A review of physiologic and clinical data pertaining to decompression sickness. US Naval Medical Research Institute Research Project X-443 report No 4, 1947.

14. Golding FL, Griffiths P, Hempleman HV, Paton WDM, Walder DN. Decompressipon Sickness during the construction of the Dartford Tunnel. Br J Industr Med 1960; 17:167-180.

15. Rivera JC. Decompression Sickness amongst divers: An analysis of 935 cases. Milit Med 1963; 129:314-334.

16. Kidd DJ, Elliott DH. Clinical manifestations and treatment of decompression sickness in divers. In: Bennett PB and Elliott DH, eds. The physiology and medicine of diving and compressed-air work. London: Balliere, Tindall and Cassell 1969.

17. Erde A, Edmonds C. Decompression sickness: a clinical series. J Occup Med 1975; 17:324-328.

18. Gribble MD. Comparison of high altitude and high pressure syndromes of decompression sickness. Br J Industr Med 1960; 17:181-186.

19. Hornberger W. Decompression sickness. In: German Aviation Medicine, World War II, Vol 1. Washington DC: US Govt Printing Office 1950; 354-394.

20. Behnke AR. Decompression sickness incident to deep sea diving and high altitude ascent. Medicine 1945; 24:381-402.

21. Berry CA. Severe dysbarism in airforce operations and training. US Armed Forces Med J 1958; 9:937-948.

22. Slager U. Decompression sickness (dysbarism). In: Minkler J, ed. Spinal Cord Decompressionb Sickness Pathology of the Nervous system vol. 1. New York: McGraw-Hill. 1968; 979-984.

23. Fryer DI. Subatmospheric decompression sickness in man. Slough: Technivision Services 1969.

24. Davis JC, Sheffield PJ, Schuknecht RD, Heimbach RD, Dunn JM, Douglas G, Anderson GK. Altitude decompression sickness: Hyperbaric therapy results in 145 cases. Aviat Space Environ Med 1977; 48:722-730.

25. Dunn JE, Bancroft RW, Haymaker W, Foft JW. Experimental animal decompression to less than 2mm Hg absolute (pathological effects). Aerospace Med 1965; 36:725-732.

26. Bassoe P. Compressed air disease. J Nerv Dis 1911; 38:368-369.

27. Abadir F. Caisson disease on the new Kasr El Nil bridge. J Egyp Med Assn 1933; 16:811-825.

28. Rozsahegyi I. Late consequences of neurological forms of decompression sickness. Br J Industr Med 1959; 16:311-317.

29. Rose RJ. Survey of work in compressed air during construction of the Aukland Harbour Bridge. New Zealand Dept of Health 1962.

30. Berhage TE. Summary Statistics: US Navy diving accidents. Research Report 1-66. US Navy Experimental Diving Unit, Washington DC, June 1966.

31. Akimov CA. Disorders of the nervous system in decompression sickness. Zh Nevropat Psikhiat 1969; 69:979-984. DRIC translation No. 2788.

32. Force L, Esvan J, Barthelmy L, Michaud A, Gilly R, Joly R. Aspect cliniques d'une serie d'accidents neurologiques de la plongee. Bull Medsubhyp 1972; 8:10-11.

33. Kelly PJ, Peters BH. The neurological manifestations of decompression accidents. In: Hong SK, ed. International Symposium on Man in the Sea. Bethesda: Undersea Medical Society Inc. 1975; VI:227-232.

34. Zannini D. Aspects etiopathogeniques des formes neurologiques des accidents de decompression. Analys de 47 cas, Med Aeronautique et Spatiale Med Subaquatique et Hyperbare 1977; 54:427-430.
35. Bayne CG. Acute decompression sickness: 50 cases. JACEP 1978; 10:351-354.

36. Seng TE, Balachandran N. Rehabilitation of caisson's disease with spinal cord involvement. Ann Acad Med Singapore 1978; 8:53-58.

37. Shields TG, Lee WB. The incidence of DCS arising from commercial offshore air-diving operations in the UK sector of the North Sea 1982/83.

Robert Gordon Institute of Technology, Aberdeen, Scotland. UK Department of Energy Contract No. TA 93/22/147, 1986.

38. Leitch DR, Green RD. Additional pressurisation for treating non-responding cases of serious air decompression sickness. Alverstoke: Institute of Naval Medicine report No 4/85, 1985.

39. Robertson AG. Treatment and results of thirty hyperbaric cases at the recompression facility HMAS Sterling. SPUMS J 1986; 16:141-143.

40. Lo WK, O'Kelly FJ. Health experience of compressed air workers during construction of the mass transit railway in Hong Kong. J Soc Occup Med 1987; 37:124-126.

41. Erdman S. Aeropathy or compressed-air illness among tunnel workers. JAMA 1907; 49:1665-1670.

42. Slark AG. Treatment of 137 cases of decompression sickness. J Roy Nav Med Serv 1965; 50:219-225.

43. Doll RE, Berhage TE. Interrelationships of several parameters of decompression sickness. US Naval Experimental Diving Unit Research Report No. 7-65; 1965.

44. Uretzky G, Satinger A. Decompression sickness among divers in Israel. Harefuah 1976; 91:161-157.

45. Kizer KW. Dysbarism in paradise. Hawaii Med J 1980; 39:109-116.

46. Torrey SA, Webb SC, Zwingelberg KM, Biles JB. Comparative analysis of decompression sickness: Type and time of onset. J Hyperbaric Med 1987; 2: 55-62.

47. Babington TH, Cuthbert A. Paralysis caused by working under compressed air in sinking the foundations of Londonderry New Bridge. Dublin J Med Sci 1863; 36:312-318.

48. Jaminet A. The physical effects of compressed air and the cause of pathological symptoms produced on man by increased atmospheric pressure employed for the sinking of piers in the construction of the Illinois & St Louis Bridge over the Mississippi river at St Louis, Missouri. St Louis: R&TA Ennis 1871.

49. Leyden E. Ueber die durch plotzlicke Verminderung des Barometerdrucks Entstehende Ruckenmarksaffection. Arch F Psychiatr 1879; 9:316-324.

50. van Rensenlaer H. The pathology of Caisson Disease. Med Rec New York 1891; 40:141-150.

51. Bassett-Smith PW. Diver's Paralysis. Lancet 1892; 1:309-310.

52. Watson AE. A case of diver's paralysis. Lancet 1893; 1:1063-1064.

53. Sharples CW. A contribution to the pathology of the spinal cord in

diver'spalsy. J Nerv Dis 1894; 19:636-640.

54. Smith AH. Caisson Disease. Med Rec New York 1894; 45:130-133.

55. Thompson WG. Notes on the caisson disease. Med Rec New York 1894; 45: 133-134.

56. Maidlow WH. Notes on a case of caissin disease. St Barts Hosp J 1895-96; 3:84-85.

57. Smith AH. Cases of caisson disease. Medical and Surgical Reports of the Presbyterian Hospital, New York, 1896:28-40.

58. Snell EH. Compressed air illness or so-called caisson disease. London: H K Lewis. 1896.

59. Cayley, Douglas-Powell R. Diver's paralysis. Middx Hosp Rep Reg 1898; 37-38.

60. Gaudoin GR. Spinal Paralysis due to deep sea diving. Indian Med J 1898; 14:358-359.

61. Nixon CJ. Diver's Paralysis. Trans Roy Acad Med Ireland. 1898; 7:62-67.

62. Taylor F. A lecture on diver's paralysis and lead paralysis. Clin J 1898; 12:1-6.

63. Shattuck FC. Caisson Disease. Boston Med Surg J. 1902; 146:414.

64. Hill L, Macleod JJR. Caisson Illness and diver's palsy. An experimental study. J Hyg Cambridge 1903; 3:401-445.

65. Parkin A. Caisson disease, or, compressed air illness. Univ Durham Coll Med Gaz 1904; 4:81-88.

66. Patrick HT. Caisson disease. Illinois Med J 1905; 7:13-14.

67. Oliver T. Caisson disease. Northumberland Durham Med J 1905; 13:21-22.

68. White WH, Bainbridge FA. A case of diver's paralysis with histological examination of the spinal cord. Lancet 1905; 2:1101-1102.

69. Brooks H. Caisson disease. The pathological anatomy and pathogenesis with an experimental study. Long Is Med J 1907; 1:149-158.

70. Hamilton FT, Haldane JS, Bacon RHS, Lees E. Report of a committee appointed by the Lords Commissioners of the Admiralty to consider and report upon the conditions of deep-water diving. London: HMSO CN.1549 1907.

71. Zografidi S. Contribution a l'etude des accidents de decompression chez les plongeurs a scaphandre. Rev Medecine 1907; 27:150-187.

72. McCune F E. A case of compressed-air illness or caisson disease. Br Med J 1908; 2:326.

73. Ryan LM. Compressed air disease from a clinical aspect. New York Med J 1909; 90:193-198.

74. Starr A. Caisson disease. Med Rec New York 1909; 75:1047-1049.

75. Hill L. Caisson Sickness and the physiology of work in compressed air. London: Arnold 1912.

76. Bassoe P. The late manifestationsof compressed-air disease. Amer J Med Sci 1913; 145:526-542.

77. Hoskyn DT. A case of caisson disease. J Roy Nav Med Serv 1915; 1:473-475.

78. Sewall RJ. Caisson disease on the Cuyuna Iron Range. J Lancet 1915; 35:265-269.

79. Keyser TJ. Compressed air disease, with notes on a case and discussion of etiology from the standpoint of physical laws. Cleveland Med J. 1916; 15:250-255.

80. Baske HFA. Caisson disease resulting from disregard of published instructions and established practice. Nav Med Bull Washington 1929; 27:514-518.

81. Francis WS. An unusual case of compressed-air illness. Nav Med Bull Washington 1943; 41:188-189.

82. Welham WC, Blanche JJ. An unusual case of decompression sickness. Nav Med Bull Washington 1945; 44:607-609.

83. Haymaker W. Decompression sickness. In: Lubarsch O, Henke F, Rossle R. Handbusch, eds. des speziellen pathologischen anatomie und histologie. Berlin: Springer Verlag. Vol XIII ptl. pp 1600-1672, 1957.

84. Johnson JF. Decompression sickness simulating infectious myelitis in a SCUBA diver. New Engl Med J 1957; 10:1138-1142.

85. Taylor WL, Santos GW, Behnke AR. Localisation of spinal cord injury in a deep sea diver. US Armed forces Med J 1959; 10:1223-1226.

86. Richter RW, Behnke AR. Spinal cord injury following a SCUBA dive to 360 feet. US Armed Forces Med J 1959; 10:1227-1234.

87. Gillen HW. Neurological Hazards in diving. Arch Environ Hlth 1965; 5:723-727.

88. Weeth JB. Crippling effects of decompression sickness. A report of 10 cases. Southern Med J 1965; 58:657-660.

89. Saumarez RC, Bolt JF, Gregory RJ. Neurological decompression sickness

treated without recompression. Br Med J 1973; 1:151-152.

90. Kelly PJ, Peters BH. The neurological manifestations of decompression accidents. In: Hong SK, ed. International Symposium on Man in the Sea. Bethesda: Undersea Medical Society Inc. 1975; 227-232.

91. Frankel HL. Paraplegia due to decompression sickness. Paraplegia 1977; 14:306-311.

92. Hayashi K, Kitano M, Kawashima M, Torisu T, Matsuoka S. Studies of decompression sickness in Japanese fishermen. In: Shilling CW, Beckett MW, eds. Underwater Physiology VI. Bethesda, MD: FASEB 1978; 547-554.

93. Melamed Y, Ohry A. The treatment and the neurological aspects of diving accidents in Israel. Paraplegia 1980; 18:127-132.

94. Thalman ED, Buckingham IP, Spaur WH. Testing decompression algorithms for use in the US Navy underwater decompression computer, phase 1. US Naval Experimental Diving Unit Report No. 11-80. 1980.

95. Kitano M, Hayashi K. Acute decompression sickness. Acta Pathol Jap 1981; 31:269-276.

96. Palmer AC, Calder IM, McCallum RI, Mastaglia FL. Spinal cord degeneration in a case of "recovered" spinal decompression sickness. Br Med J 1981; 283:888.

97. Halpearn P, Greenstein A, Melamed Y Marguiles JY, Robin GC. Spinal decompression sickness with delayed onset, delayed treatment and full recovery. Br Med J 1982; 284:1014.

98. Mastaglia FL, McCallum RI, Walder DN. Myelopathy associated with decompression sickness: a report of 6 cases. Clin Exper Neurol 1983; 19:54-59.

99. Dick APK, Massey EW. Neurologic presentation of decompression sickness and air embolism in sport divers. Neurology 1985; 35:667-671.

100. Hayashi K, Kitano M. Twenty six cases of complete transverse injury of the spinal cord in decompression sickness. In: Miller JN, Parmentier JL, eds. Rehabilitation of the paralysed diver. Bethesda, MD: Undersea Medical Society Inc, 1985.

101. Linaweaver PG, Greer HD. Paralysis in divers: the natural history of decompression sickness. Ibid.

102. Rugman F, Meecham J. Spinal decompression sickness at unusually shallow depth. J Soc Occup Med 1985; 35:103-104.

103. van Meter KW. Two diving accident case histories. In: Miller JN, Parmentier JL, eds. Rehabilitation of the paralyzed diver. Bethesda, MD: Undersea Medical Society Inc. 1985.

104. Hughes JS, Eckenhoff RG. Spinal cord decompression sickness after

standard US Navy air decompression. Milit Med 1986; 151:166-168.

105. Jones DN, Hirst AJ, Mizrahi NB. Spinal cord Decompression sickness: A case report. J Roy Nav Med Serv 1987; 73:105-109.

106. Milne AH, Shields TG, Johnston DD, Rae CK. Recreational wreck diving in the Orkney Islands, 1986. In: Marroni A, Oriani G, eds. Proceedings of the XIII Annual Meeting of European Undersea Biomedical Society, Palermo, Italy. 1987; 39-45.

107. Cimsit M, Aydin S. A Case of Diving Accident. Ibid.

108. Cockett ATK, Nakamura RM, Franks JJ. Recent findings in the pathogenesis of decompression sickness (dysbarism). Surgery 1965; 58:384-389.

109. Kitano M, Hayashi K, Kawashima M. Three autopsy cases of acute decompression sickness. Consideration of pathogenesis about spinal cord damage in decompression sickness. J West Jap Orthop Traumatol 1977; 26:402-408.

110. Clay JR. Histopathology of experimental decompression sickness. Aerospace Med 1963; 43:1107-1110.

111. D'Aoust BG, Smith LS. Bends in Fish. Comp Biochem and Physiol 1974; 49:311-321.

112. Gersh I, Catchpole HR. Decompression Sickness: Physical Factors and Pathological Consequences. In: Decompression Sickness Ed. Fulton J F. London: Saunders 1951; 165-181.

113. Palmer AC. The neuropathology of decompression sickness. In: Cavanagh JB, ed. Recent Advances in Neuropathology Edinburgh: Churchill Livingstone 1986; 3:141-162.

114. Boyle R. New pneumatical experiments about respiration. Philos Trans Roy Soc 1670; 5:2035-2056.

115. Oliver T. Lecture on caisson disease or compressed air illness. J Prev Med 1906; 14:1-18.

116. Boycott AE, Damant GCC, Haldane JS. Prevention of compressed air illness. J Hyg (Cambridge) 1908; 8:342-443.

117. Behnke AR, Shaw LA, Messer AC, Thomson RM, Motley EP. The circulatory and respiratory disturbances of acute compressed-air illness and the administration of oxygen as a therapeutic measure. Am J Physiol 1936; 114:526-533.

118. Wagner CE. Observations of gas bubbles in pial vessels of cats following rapid decompression from high pressure atmospheres. J Neurophysiol 1945; 8:29-32.

119. Lever MJ, Miller KW, Paton WDM, Smith EB. Experiments on the genesis

of bubbles as a result of rapid decompression. J Physiol 1966; 184:964-969.

120. Buckles RG. The physics of bubble formation and growth. Aerospace Med 1968; 39:1062-1069.

121. Heimbecker RO, Lemine G, Chen CH, Keven I, Leask D, Drucker WR. Role of gas embolism in decompression sickness. A New look at "the bends". Surgery 1968; 64:264-272.

122. Spencer MP, Campbell SD. Development of bubbles in venous and arterial blood during hyperbaric decompression. Bull of the Mason Clinic 1968; 22:26-32.

123. Lynch PR, Brigham M, Tuma R, Wiedeman MP. Origin and time course of gas bubbles following rapid decompression in the hamster. Undersea Biomed Res 1985; 12:105-114.

124. Lichtenstein BW, Zeitlin H. Caisson disease. A histologic study of late lesions. Arch Pathol (Chicago) 1936; 22:86-98.

125. Palmer AC. The pathology of spinal cord lesions in goats. In: James PB, McCallum RI, Rawlins JSP. Symposium on decompression sickness - VII Annual Congress of European Undersea Biomedical Society. Cambridge, 1981; 46-52.

126. Gillis MF, Peterson PL, Karagianes MT. In vivo detection of circulating gas emboli with decompression sickness using the doppler flowmeter. Nature 1968; 217:965-967.

127. Spencer MP, Campbell SD, Sealey JL, Henry FC, Lindbergh J. Experiments on decompression bubbles in circulation using ultrasonic and electromagnetic flowmeters. J Occup Med 1969; 11:238-244.

128. Evans A, Walder D N. Detection of circulating bubbles in the intact mammal. Ultrasonics 1970; 3:216-217.

129. Powell MR. Doppler ultrasound monitoring of venous gas bubbles in pigs following decompression from helium, neon and air. Aerospace Med 1974; 45:505-508.

130. Evans A, Barnard EEP, Walder DN. Detection of gas bubbles in man at decompression. Aerospace Med 1972; 43:1095-1096.

131. Smith KH, Johanson DC. Hyperbaric decompression by means of bubble detection. ONR Technical Report, Contr No. N000014-69-C-0402, 1970.

132. Gardette B. Correlation between decompression sickness and circulating bubbles in 232 divers. Undersea Biomed Res 1979; 6:99-107.

133. Nashimoto I, Gotoh Y. Relationship between precordial doppler ultrasound records and decompression sickness. In: Shilling CW, Beckett MW. Proceedings of 6th Symposium on Underwater Physiology. Bethesda:

FASEB, 1976; 497-502.

134. Powell MR, Johansson DC. Ultrasound monitoring and decompression sickness. ibid pp 503-510.

135. Pilmanis AA. Intravenous gas emboli in man after compressed air open ocean diving. ONR Contract No. N00014-67-A-0269-0026. Washington DC: Ofice of Naval Research, 1976.

136. Neuman TS, Hall DA, Linaweaver PG. Gas phase separation during decompression in man: Ultrasound monitoring. Undersea Biomed Res 1976 3; 121-130.

137. Eatock BC, Nishi RY. Analysis of doppler ultrasonic data for the evaluation of dive profiles. In: Bove AA, Bachrach AJ, Greenbaum LJ, eds. Underwater and Hyperbaric Physiology IX Bethesda, MD: Undersea and Hyperbaric Medical Society. 1987 (in press).

138. Bayne CG, Hunt WS, Johanson DC, Flynn ET, Weathersby PK. Doppler bubble detection and decompression sikness: a prospective clinical trial. Undersea Biomed Res 1985; 12:327-332.

139. Hills BA. Decompression Sickness. Vol 1. Chichester: John Wiley & Sons. 1977; 65.

140. Malhotra MC, Wright HC. Arterial air embolism during decompression and its prevention. Proc Roy Soc B 1960; 154:418-427.

141. Malhotra MC, Wright HC. The effect of a raised intrapulmonary pressure on the lungs of fresh, unchilled bound and unbound cadavers. Med Res Council (RNPRC) Report No. UPS 189, 1960.

142. Liebow AA, Stark JE, Vogel J, Schaeffer KE. Intrapulmonary air trapping in submarine escape casualties. US Armed Forces Med J 1959; 10:265-289.

143. Collins JJ. An unusual case of air embolism precipitated by decompression. US Naval Medical Research Laboratory Report No. 382, Bethesda MD.

144. Colebatch HJH, Smith MM, Ng CKY. Increased elastic recoil as a determinant of pulmonary barotrauma in divers. Resp Physiol 1976; 26:55-64.

145. Meister SG, Grossman W, Dexter L, Dalen JE. Paradoxical Embolism. diagnosis during life. Am J Med 1972; 53:292-296.

146. Sweeny LJ, Rosenquist CC. The normal anatomy of the atrial septum in the human heart. Am Heart J. 1979; 98:194-199.

147. Kannel WB, Thom TJ. Incidence, prevalence and mortality of cardiovascular diseases. In: Hurst J W ed. The Heart, 6th edition. New York: McGraw-Hill 1986; 557-565.

148. Haymaker W, Johnston AD, Downey VM. Fatal decompression sickness during jet aircraft flight. Aviat Med. 1956; 27:2-17.

149. Ring GC, Blum S, Kurbatov T, Moss WD, Smith W. Size of microspheres passing through the pulmonary circuit in the dog. Am J Physiol 1961; 200:1191-1196.

150. Butler BD, Hills BA. The lung as a filter for microbubbles. J Appl Physiol: Respirat Environ Exercise Physiol 1979; 47:537-543.

151. Christman CL, Catron PW, Flynn ET. Weathersby PK. In vivo microbubble detection in decompression sickness using a second harmonic resonant bubble detector. Undersea Biomed Res 1986; 13:1-18.

152. Hills BA, Butler BD. Size distribution of intravascular air emboli produced by decompression. Undersea Biomed Res 1981; 8:163-174.

153. Spencer MP, Oyama Y. Pulmonary capacity for dissipation of venous gas emboli. Aerospace Med 1971; 42:822-827.

154. Butler BD, Hills BA. Transpulmonary passage of venous air emboli. J Appl Physiol 1985; 59:543-547.

155. End E. The use of new equipment and helium gas in a world record dive. J Ind Hyg 1938; 1938; 20:511-520.

156. End E. Blood agglutination in decompression sickness. In: Lambertsen CJ, ed. Underwater Physiology IV. New York: Academic Press 1971; 325-328.

157. Mallette WC, Fitzgerald JB, Cockett ATK. Dysbarism: A review of 35 cases with suggestions for therapy. Aerospace Med 1962; 33:1132-1139.

158. Brunner FP, Frick PG, Buhlmann AA. Post decompression shock due to extravasation of plasma. Lancet 1964; 1:1071-1073.

159. Bove AA, Halenbeck JM, Elliott DH. Circulatory responses to venous air embolism and decompression sickness in dogs. Undersea Biomed Res 1974; 1:207-220.

160. Jacey MJ, Heyder E, Williamson RA, Tappan DV. Biochemistry and haematology of decompression sickness: A case report. Aviat Space Environ Med 1976; 47:657-661.

161. Wells CH, Bond TP, Guest MM, Barnhart CC. Rheologic impairment of the microcirculation during decompression sickness. Microvascular Res 1971: 3:163-169.

162. Philp RB, Gowdey CW. Platelets as an etiological factor in experimental decompression sickness. J Occup Med 1969; 11:257-258.

163. Philp RB, Schacham P, Gowdey CW. Involvement of platelets and microthrombi in experimental decompression sickness: similarities with disseminated intravascular coagulation. Aerospace Med 1971; 42:494-502.

164. Philp RB, Warren MJ, Ackles KN, Radomski MW. Effects of decompression on platelets and haemostasis in men and the influence of anti-platelet drugs (RA233 and VK744). Aerospace Med 1974; 45:231-240.

165. Philp RB, Inwood MJ, Warren A. Interactions between gas bubbles and components of the blood: implications in decompression sickness. Aerospace Med 1972; 43:946-953.

166. Smith KH, Stogall PJ, Harker LA, Slichter SJ, Richmond VL, Hall MH, Haung TW. Investigation of haematologic and other pathologic responses to decompression. US Office of Naval Research Report No. N00014-71-C-0273.

167. Cockett ATK, Nakamura RM. Newer concepts in the pathophysiology of experimental dysbarism - decompression sickness. Am Surg 1964; 30:447-451.

168. Bennison WH, Catton MJ, Fryer DJ. Fatal decompression sickness in a compressed-air worker. J Pathol Bacteriol 1965; 89:319-329.

169. Cockett ATK, Pauley SM, Saunders JC, Pirose FM. Coexistance of lipid and gas emboli in experimental decompression sickness. In: Lambertsen CJ, ed. Underwater Physiology IV. New York: Academic Press, 1971; 245-250.

170. Haymaker W, Davidson C. Fatalities resulting from exposure to simulated high altitudes in decompression chambers. A clinico-pathological study. J Neuropathol Exper Neurol 1950; 9:29-59.

171. Walder DN. The prevention of decompression sickness in compressed-air workers. In: Bennett PB, Elliott DH, eds. The Physiology and Medicine of Diving and Compressed Air Work. London: Balliere, Tindall and Cassell, 1969; 437-450.

172. Holland JA. Discussion of disseminated intravascular coagulation in decompression sickness. US Naval Submarine Medical Center, Groton CT Report No. 585. 1969.

173. Haymaker W, Johnston AD. Pathology of decompression sickness. Milit Med 1955; 117:285-306.

174. Batson OV. The function of the vertebral veins and their role in the spread of metastases. Ann Surg 1940; 112:138-149.

175. Batson OV. The valsalva maneuver and the vertebral vein system. Angiology 1960; 11:443-447.

176. Hallenbeck JM, Bove AA, Elliott DH. The bubble as a non-mechanical trigger in decompression sickness. In: Ackles KN, ed. Blood-Bubble Interaction in Decompression Sickness. DCIEM conference proceedings 73-CP-960 1973; 129-139.

177. Hallenbeck JM, Bove AA, Moquin RB, Elliott DH. Accelerated coagulation of whole blood and cell-free plasma by bubbling in vivo. Aerospace Med 1973; 44:712-714.

178. Philp RB. A review of blood changes associated with compression-decompression: relationship with decompression sickness. Undersea Biomed Res 1974; 1:117-150.

179. Ward CA, Koheil A, McCulloch D, Johnson WR, Fraser WD. Activation of complement at the plasma-air or serum-air interface of rabbits. J Appl Physiol 1986; 60:1651-1658.

180. Ward CA, Yee D, McCulloch D, Stanga D, Fraser WD. Complement proteins mediate decompression sickness in rabbits. Undersea Biomed Res 1987; 14(Suppl):16.

181. Blackwood W. Discussion on vascular disease of the spinal cord. Proc Roy Soc Med 1958; 51:543-547.

182. Hallenbeck JM, Andersen JC. Pathogenesis of the decompression disorders. In: Bennett PB, Elliott DH, eds. The Physiology and Medicine of Diving, 3rd Edition. San Pedro: Best 1982; 435-460.

183. Kety SS. The cerebral circulation. In: Field J, Magoun HW, Hall VE, eds. Handbook of Physiology, section 1; Neurophysiology. Baltimore: Williams & Wilkins 1960; 1751-1960.

184. Hallenbeck JM, Bove AA, Elliott DH. Mechanisms underlying spinal cord damage in decompression sickness. Neurology 1975; 25:308-316.

185. Hallenbeck JM, Bove AA, Elliott DH. Decompression sickness studies. In: Lambertsen CJ, ed. Underwater Physiology VI. Bethesda: FASEB, 1976; 273-286.

186. Hallenbeck JM. Cinephotomicrography of dog spinal vessels during cord-damaging decompression sickness. Neurology 1976; 26:190-199.

187. Hallenbeck JM, Sokoloff L. Blood flow studies during spinal-cord damaging decompression sickness in dogs. In: Shilling CW, Beckett MW, eds. Underwater Physiology VI. Bethesda: FASEB 1978; 579-585.

188. Henson RA, Parsons M. Ischemic lesions of the spinal cord: an illustrated review. Quart J Med 1967; 36:205-222.

189. Frankel HL. Paraplegia due to decompression sickness. Paraplegia 1977; 14:306-311.

190. Hughes JT. Venous infarction of the spinal cord. Neurology 1971; 21:794-800.

191. Taylor AR, Byrnes DP. Foramen magnum and high cervical cord compression. Brain 1974; 97:473-480.

192. Garland HJ, Greenberg J, Harriman DFF. Infarction of the spinal cord. Brain 1966; 89:645-680.

193. Anderson DK, Nicolosi GR, Means ED, Hartley LE. Effects of laminectomy on spinal cord blood flow. J Neurosurg 1978; 48:232-238.

194. Vernon HM. The solubility of air in fats and relation to caisson disease. Proc Roy Soc (London) 1907; 79:366-371.

195. Hills BA, James PB. Spinal decompression sickness: Mechanical studies and a model. Undersea Biomed Res 1982; 9:185-201.

196. Blick G. Notes on diver's paralysis. Br Med J 1909; 2:1796-1798.

197. Waller SO. Autopsy features in SCUBA diving fatalities. Med J Australia 1970; 1:1106-1108.

198. Sykes JJW, Yaffe LJ. Light and electron microscopic alterations in spinal cord myelin sheaths after decompression sickness. Undersea Biomed Res 1985; 12:251-258.

199. Leitch DR, Hallenbeck JM. A model of spinal cord dysbarism to study delayed treatment: 1. producing dysbarism. Aviat Space Environ Med. 1984; 55:584-591.

200. Francis TJR, Pezeshkpour GH, Dutka AJ, Hallenbeck JM, Flynn ET. Is there a role for the autochthonous bubble in the pathogenesis of spinal cord decompression sickness? IX International Congress on Hyperbaric Medicine Sydney, Australia 1-4 March 1987.

201. Francis TJR, Pezeshkpour GH, Dutka AJ, Hallenbeck JM, Flynn ET. Space occupying lesions in experimental spinal cord decompression sickness may be evidence of autochthonous bubble injury. Undersea Biomed Res 1987; 14(suppl); 6.

202. Francis TJR, Pezeshkpour GH, Dutka AJ, Hallenbeck JM, Flynn ET. Is there a role for the autochthonous bubble in the pathogenesis of spinal cord decompression sickness? J Neuropathol Exper Neurol (in press).

203. Brante G. Studies on lipids in the nervous system with special reference to quantitative chemical determination and topical distribution. Acta Physiol Scand. 1949; 18 (suppl 63):1-189.

204. Behnke AR, Thomson RM, Shaw LA. The rate of elimination of dissolved nitrogen in man in relation to the fat and water content of the body. Am J Physiol 1935; 114:136-146.

205. Sandler AN, Tator CH. Regional spinal cord blood flow in primates. J Neurosurg 1976; 45:647-659.

206. Tschetter TH, Klassen AC, Resch JA, Meyer MW. Blood flow in the central and peripheral nervous system of dogs using a particle distribution method. Stroke 1970; 1:370-374.

207. Smith DR, Smith HJ, Rajjoub RK. Measurement of spinal cord blood flow by the microsphere technique. Neurosurg 1978; 2:27-29.

208. Weathersby PK, Homer LD, Flynn ET. Homogeneous nucleation of gas bubbles in vivo. J Appl Physiol: Respirat Environ Exercise Physiol 1982; 53:940-946.

209. Del Maestro RF, Shosser R, Agerup B. Multiple cerebral and spinal cord blood flow measurements using the radioactive microsphere method. In: 10th Europ Conf Microcirculation, Cagliari 1978. Biblthca Anat No. 18; 201-203.

210. Marcus ML, Heistad DD, Ehrhardt JC, Abboud FM. Regulation of total and regional spinal cord blood flow. Circ Res 1977; 41:128-134.

211. Nims LF. Environmental factors affecting decompression sickness. Part 1. A physical theory of decompression sickness. In: Fulton JF, ed. Decompression Sickness. Philadelphia: WB Saunders, 1951; 192-222.

212. Leitch DR, Hallenbeck JM. Somatosensory evoked potentials and neuraxial blood flow in central nervous system decompression sickness. Brain Res 1984; 311:307-315.

213. Kobrine AI, Evans DE, Rizzoli HV. The effects of ischemia on long-tract neural conduction in the spinal cord. J Neurosurg 1979; 50:639-644.

214. Kobrine AI, Evans DE, Rizzoli HV. Effects of progressive hypoxia on long tract neural conduction in the spinal cord. Neurosurg. 1980; 7:369-375.

215. Kobrine AI, Evans DE, Rizzoli HV. Relative vulnerability of the brain and spinal cord to ischemia. J Neurol Sci 1980; 45:65-72.

216. Sato M, Pawlick C, Umbach C, Heiss WD. Comparative studies of regional CNS blood flow and evoked potentials in the cat. Stroke 1984; 15:97-101.

217. Piccard J. Aero-emphysema and the birth of gas bubbles. Proc of the Staff Meetings of the Mayo Clinic 1941; 16:700-704.

218. Weathersby PK. Engineering analysis of diver decompression sickness. Chem Eng Comm 1984; 30:183-190.

219. Hales JRS. Radioactive microsphere measurement of cardiac output and regional tissue blood flow in the sheep. Pflugers Arch 1973; 344:119-132.

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DISCUSSION

DR. JAMES: I believe that Doppler may not be detecting very small bubbles. ~~Catron~~ recently injected 50 ~~milliliters~~ at 5 milliliters per minute into ~~animals~~ and compressed them to 100 fsw. This reduced the bubble size and allowed them to pass through the lungs into the arterial blood. Presumably in these experiments, the pulmonary arterial pressure would actually be falling as a result of this recompression, but the bubbles are arterialized.

Data from ultrasonic contrast echocardiography show that bubbles can be transmitted through the lungs. A recent paper indicated an 18% incidence of right to left atrial shunting in a healthy population. These are people who haven't got cardiac murmurs or pathology. Five percent of the shunting occurs at rest.

Venous involvement is typical of decompression sickness. Dr. Francis pointed out hemorrhages, as have others. What is the mechanism of these hemorrhages? I believe very small bubbles are getting across the lungs and into the arterial blood. Bubbles introduced deliberately into the cerebral circulation, as ~~Garland~~ has shown recently, must be very large in order to stop. Brian Hills and I have recently injected 10-20 micron bubbles into the right carotid artery of guinea pigs. At 1, 2, and 3 hours, tryptan blue, an albumin binding dye, is injected to look for blood. One hour later there is a gross disturbance of the blood-brain barrier. Dr. Chryssanthou, I think, has made similar observations. At 1 hour, every one of the 220 test animals developed blood-brain barrier dysfunction, whereas none of the controls did. The blood-brain barrier remains open at 2 hours but closes during the third hour to the passage of tryptan blue. Are these very small arterial bubbles innocuous if they pass through the lungs? I don't believe so. I believe that edema occurs if the blood-brain barrier is opened. This interferes with gas transport, and a cascade of events follows. Autochthonous gas can also occur and some degree of venous blockade. Bubbles arise during the decompression, as in the case of the diver who presented during the ascent with paralysis of the legs. In a 50 meter dive, the bubbles are easily detected with Doppler at around 30 meters. This might explain the rather curious finding of hyalinization of the cerebral vessels in professional divers. In my experience, I only have two cases of spinal cord decompression sickness where the diver has not complained of cerebral symptoms--blurring of vision, slight dizziness, and so on. Thus, both spinal and cerebral decompression sickness may arise from arterialized venous bubbles.

DR. WARD: Dr. Francis, were there cells in the zones you called areas of rarefication?

DR. FRANCIS: I think you saw a certain amount of wreckage and degenerated material. The inside of a bubble is very difficult to perfusion fix.

DR. WARD: Does this mean that there's been a change in the permeability of the vessel walls?

DR. FRANCIS: Not necessarily. As the bubble nucleates within the myelin, myelin and damaged axon become trapped within the bubble. This material is very difficult to reach with a fixative. Alterations in permeability may occur, but not necessarily occur immediately. If bubbles cause the surrounding tissue pressure to rise sufficiently to cause ischemia, capillary and the blood-brain barrier permeability can be

altered. However, under an autochthonous bubble scenario this would happen after nucleation of the bubble.

DR. KINDWALL: Dr. James, how did you control the size of the emboli you injected?

DR. JAMES: We used micro bubbles, micro fat droplets, and mineral oil droplets for three entirely independent reasons. We dispersed the emboli ultrasonically and ran them through a Coulter counter to get the 10-20 micron size range that we found would break down blood vessels.

DR. ZWINGELBERG: Dr. Moon, what are the sensitivities of MRI and CT scans and what are their false-positive rates? This pertains to questions from divers, particularly medical-legal, concerning their scans.

DR. MOON: There is definitely an age-related incidence of abnormal areas on T-2 weighted images. For a given patient, one might come up with a probabilistic interpretation of such an abnormality based on his age. It's equally possible, however, that many of our divers have MRI, abnormalities from previous DCS or AGE old images. We know from studies in stroke, for example, that these areas of abnormality stick around for a long time. It would be interesting to compare diving and control populations for increased incidence of these abnormalities.

DR. ZWINGELBERG: As it stands now, can retrospective findings of lesions that might correlate loosely with the history of spinal cord decompression sickness or AGE in decompression sickness be related to that incident?

DR. MOON: We don't have the data yet to answer your question. If there is an abnormality in an area that anatomically correlates with a deficit on physical examination, I suppose one can make the intellectual link. If someone asks "I've got this area of abnormality on the MRI scan, can I still dive?", your judgment must be on the basis of the patient's age and history.

DR. JAMES: We recently had a meeting in London looking at diagnostic procedures in decompression illness and Dr. Brian Kendall presented data on what is termed the normal population, using MRI and reported that 1-2% of the normal population, aged between 21 and 35 have slight abnormalities; that is, bright areas on the tips of the horns of ventricles and bright lining around the edge of the cerebral ventricles. Some of these findings are very nonspecific. We need an adequate control population.

DR. MOON: That's right. In many ways, the MRI is too sensitive perhaps.

DR. WHIDDEN: How clinically effective would you expect CT and MRI imaging to be for treating microembolic deseases?

DR. MOON: We have used MRI to examine four patients with clinical histories compatible with air embolism. There was a discrepancy between what we saw and what we expected to see. In other embolic phenomena, such as embolic stroke, the embolism usually follows the arterial distribution of greatest flow. Most embolic strokes involve the middle cerebral circulation. We didn't see that. On the other hand, if you look at the brains of people that have subacute bacterial endocarditis, in which the emboli may be smaller, they tend to follow watershed distributions. That's essentially what we saw. It's probably the size of the bubbles that really make the difference. If one injects 5 cc of air into the carotid artery, one might expect a middle cerebral infarct. We saw that in a patient years ago before we had MRI. If you're dealing with diving-

related AGE, in which the bubbles are probably small, you probably will see a watershed distribution.

DR. BENNETT: If a diver with spinal decompression sickness is recompressed and has immediate relief of symptoms, has there been spinal cord damage, and how do you interpret this theoretically?

DR. FRANCIS: I think that as these bubbles nucleate and grow, some of them cause tearing of the white matter. The white matter is unique in that it has little in the way of connective tissue to support it, and the consequence of its tearing is that sooner or later the microvasculature is damaged and the bubbles become replaced by hemorrhage. By recompressing the individual, this process may be aborted. In some cases before and in others after hemorrhage has occurred. If left untreated, the gas in the bubble will diffuse away, the tissue tensions will return to normal levels, and where tearing has occurred, the bubble will be replaced by hemorrhage. An important consequence of hemorrhage may be that when iron is introduced into the central nervous system, perioxidation is promoted.

DR. BENNETT: In that case, one would expect that therapy wouldn't work very often if enough damage and permanent injury have occurred. That doesn't seem to happen, and in fact we get good recoveries, although it may take a time.

DR. FRANCIS: No, the question is, is recovery due to repair of the injury or is it due to the rerouting of pathways? I don't know the answer to that. I think that much of the recovery one sees, particularly over a period of weeks, is due to recruitment of alternative pathways.

DR. BENNETT: That might be the case after the initial treatment followed by further improvement over 2 years, but in terms of an immediate recovery, perhaps there is no residual damage at all.

DR. FRANCIS: There's more than one thing going on, quite clearly. One of the pathologies you can see through the microscope after maybe half an hour to an hour is considerable edema. One good treatment for edema is recompression on oxygen, which might produce an improvement in a short time.

DR. JAMES: One problem we face is the relevance of the animal model. Very few commercial divers have dived to 300 feet on air for 15 to 30 minutes, omitted all decompression, and waited around for an hour for things to develop. I'm convinced that the immediate response to recompression seen in a commercial environment is the resolution of a gas bubble. Whether or not that totally leaves the individual without damage, I'm not sure. There's been a report in the proceedings of the Palermo Conference of the European Society, by Tony Palmer, Ian Calder, and Trevor Hughes, concerning three professional divers who had no episode recorded of spinal cord or any other decompression sickness. Using a Marchi stain, these divers were found to have some early myelin degeneration in the posterior columns, which I think gives rise to concern. I'm sure we all recognize that the spinal cord, despite its relatively small size, can be injured at a level that will not be detected within its functional reserve.

DR. SYKES: Since Dr. Francis quoted me in his presentation, I might add some comments relevant to Dr. Bennett's remarks. I'm not sure whether we were down the alley with Dr. Powell and the silver dollar or under the mat in the basement, but our study was primarily designed to evoke decompression sickness and then to assess the effects of treatment, using spinal potentials to interrogate the spinal cord. This was the same model as used by Dr. Francis. We were struck by the response to treatment. It

was either a good response or it was no response at all. For that reason, we undertook our pathological studies to find out why some animals responded to treatment and others didn't, when all other factors were relatively equal. Our studies showed--these were presented in Long Beach in 1985--that the animals that did not respond to treatment had significantly more hemorrhage in the spinal cord, which we've all seen this afternoon. They also had considerably more edema and damaged axons, which perhaps sheds a little more light on the subject.

DR. FRANCIS: By and large, animals that have the shortest latency have the worst recovery, if you treat them all within 15 minutes of the onset. I think the same can be extrapolated to clinical experience. If people have their hit very quickly when they reach the surface, they tend not to do quite as well as those who have a slower onset. This may relate to the autochthonous bubble, which gives the shortest latency of any pathogenic mechanism considered. If the physical damage we have seen caused by these bubbles should occur, 100% recovery cannot be expected.

COMMANDER DEMBERT: I've spent considerable time in the Philippines treating Filipino divers. It is a common practice among Filipinos and other Asian divers to squat and talk instead of stand and talk. The divers squat in their boats both before and after a dive, and I wondered if that might play a role in spinal cord decompression sickness which occurred frequently in the Philippines. Many of the Filipino divers brought to the hyperbaric chamber at Subic Bay Naval Station didn't speak English well enough to get a really good history of circumstances surrounding the event and subsequent symptoms. However, neurological examinations usually showed well-demarcated spinal decompession sickness. My point is that the Valsalva maneuver appears to have similar physiological vascular flow changes as squatting. Two cases of my interest concerned a Coast Guard diver and a Navy diver who I treated there in the Philippines. They had just finished strenuous no-decompression dives which were on the edge of decompression limits. One had a bowel movement after getting topside and within about a minute completely lost motor ability in both legs. The other one urinated topside immediately postdive and also lost motor function within about 2 or 3 minutes. We treated them for spinal cord DCS. John Hallenbeck described to me a similar case he was aware of. Can anyone comment on the effects of squatting or the Valsalva maneuver on decompression sickness?

DR. MOON: Yes, I saw a diver recently who had the onset of symptoms after a bowel movement right after a dive.

COMMANDER DEMBERT: Dr. Francis, would that figure in any of the mechanisms you talked about relevant to short latency.

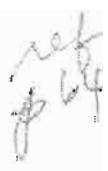
DR. FRANCIS: How quickly after reaching the surface did these people have their bowel movements?

COMMANDER DEMBERT: They had them within about 5-10 minutes.

DR. FRANCIS: Well, one thing a Valsalva maneuver does is to reduce spinal cord venous drainage. If you're looking for an autochthonous mechanism, you ought to avoid reducing blood flow so as to get rid of the gas as quickly as possible. Anything you do that alters perfusion is likely perhaps to exacerbate bubble growth. Of course, a Valsalva maneuver would also promote the venous infarction mechanism.

DR. JAMES: The Valsalva maneuver also promotes the transpulmonary passage of bubbles.

DR. MOON: And probably across the heart in people with patent foramen ovale.



COMMANDER DEMBERT: Any comments on squatting and decompression sickness?

DR. JAMES: Wouldn't it be nice to do a study of squatters and nonsquatters and see which has the highest incidence?

COMMANDER DEMBERT: It might be hard to find a control population in the Philippines.

DR. YOUNGBLOOD: Well, as an observation, it's difficult to squat and not do a Valsalva maneuver. I'm glad we've returned to that point because if there are 18% of the normal population who have a patent septal defect, and we're accepting venous bubbles and counting on the lungs to strain them out as it were, then perhaps we should screen divers and astronauts for patent septal defects. Those who have such a defect could be at an unacceptable risk of arterial bubbles. 2-D echocardiography is a relatively good means of conducting such a screen.

DR. MOON: We have routinely started looking with 2-D echo at all of our patients with decompression sickness. We have found a substantial number of them with spontaneous right-to-left shunts at the atrial level. I believe that now that we have 2-D echo, an easy, noninvasive test, that we should start looking at diving populations in this regard.

DR. GREER: There is a population of people who have neurologic lesions from squatting. There have been a number of observations published about squatting or "hunkering" which is a habit not uncommon in the Appalachians. People who "hunker" habitually develop bilateral perineal nerve lesions. This doesn't have anything to do with diving, but it does speak to the fact that there are temporary lesions of white matter from which recovery is possible. If white matter, which is already poorly perfused, loses its circulation as a result of pressure, function will also be lost. A common example occurs when you wake up after sleeping on your ulna nerve at the elbow. That's an ischemic lesion which ordinarily resolves spontaneously, but if it's badly ischemic and you treat it with hyperbaric oxygen, it ought to recover. Thus, when we see people who have neurologic lesions of the spinal cord from which they recover with treatment, they may very well have complete recovery. Dr. Francis, do you have any comment on Palmer and Calder's work (1) which seems to show that a watershed area in the dorsal horns and dorsal route entry may be arterially embolized.

DR. FRANCIS: I don't think you necessarily have to invoke arterial embolism to get decompression sickness in areas of poor perfusion. Poor perfusion would also reduce the rate at which gas is eliminated and effectively promote an autochthonous mechanism.

DR. KINDWALL: In our clinical experience with compressed air workers, people may have experienced severe bends pain for an hour or two, and then entered a hot bath and immediately become paralyzed. How would you relate this to the spinal cord mechanisms you have described today?

DR. FRANCIS: With enormous difficulty, I think. I would find that difficult to explain by any of the three mechanisms.

DR. JAMES: The hot bath has been used in the disease since 1939 to provoke neurological dysfunction in the presence of demyelination. The conventional explanation is that increased temperature blocks conduction along demyelinated axons, but sometimes the hot bath test leads to permanent neurological disability. It was postulated that vasodilatation associated with heating was a stress on the blood-brain barrier which caused acute focal edema. If you vasodilate with a hot bath in the

presence of existing focal edema and blood-brain barrier dysfunction, it could promote and accelerate the problem.

DR. KINDWALL: In the cases I've seen, it's been very sudden and dramatic.

DR. JAMES: With any lesion, edema or autochthonous gas, there's a threshold at which symptoms develop.

DR. KINDWALL: Presumably one wouldn't see this if the hot bath were applied within about 5 minutes of surfacing. It would have to wait until the cord had been damaged.

DR. MOON: Dr. Pendergast, would you have any comment on possible blood flow alterations induced by hot baths within the central nervous system?

DR. PENDERGAST: Well, the dogma is that the brain would autoregulate, and you would not see an increase in blood flow due to vasodilatation from the hot bath. There is more recent evidence that autoregulation is not perfect; however, there may be hyperperfusion relative to the metabolism of the brain, especially in the spinal cord. This is an area that hasn't been looked at very much and needs further investigation. It is also possible that immersion in very hot water elevates brain blood flow.

REFERENCE

1. Palmer AC, Calder IM, Hughes JT. Spinal cord degeneration in divers. Lancet 1987; II:1365-1366.

ARE EVOKED POTENTIALS USEFUL IN THE MANAGEMENT OF PATIENTS WITH ACUTE DYSBARIC ILLNESS?

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SUMMARY:

Sensory evoked potential testing is the recording of CNS potentials induced by peripheral nerve stimulation. Types of commonly measured evoked potential include somatosensory (SSEP) and brainstem auditory evoked response (BAER). Short-latency evoked potential monitoring has been described in animal models of AGE and DCS (1,2). Leitch and Hallenbeck have correlated loss of SSEP amplitude with neuronal ischemia in dogs with central nervous system DCS (3). We have reported the use of SSEP monitoring in human diving casualties (4,5). In this report we present a total of 14 diving casualties treated at Duke University Medical Center in whom this diagnostic modality was used, demonstrating that SSEP may improve during the course of hyperbaric treatment but is less sensitive than clinical examination in detecting neurological abnormalities in these patients.

INTRODUCTION:

SSEP monitoring responses to lower extremity (tibial nerve) electrical stimulation was performed in all patients and BAER were obtained in two patients using a Nicolet Pathfinder II connected to the patient by a through-hull penetrator. The technique was basically that recommended by the American Electroencephalographic Society (6). Latencies were classified as **normal** or **abnormal** based upon values for the general population.

CASE SUMMARIES:

WC lost consciousness in an underwater explosion at 3 msw. He fell to 25 msw but was rapidly rescued by his partner and taken to the surface. He regained consciousness and was said to be asymptomatic. He was treated with USN Table 6A near the dive site and had a seizure during decompression in the chamber. He then had 8 more generalized convulsions with focal onset involving the right side of his body. On arrival at Duke he had right arm weakness and a tendency to fall to the right while standing with his eyes closed. Tandem gait was abnormal and he had difficulty voiding. He also had unilateral hemotympanum.

LK was a 20 year old professional SCUBA instructor who had been diving daily for about a week and made two dives on the day of her accident, to 36 and 9 msw. She surfaced feeling extremely tired and subsequently developed polyarticular joint pain and numbness of her hands and legs in a patchy distribution. She was treated locally and then transferred to Duke after failing to improve. On examination she had mild unilateral deltoid weakness. Strength was otherwise normal. She had markedly decreased position sense in her toes, inability to perform tandem gait walking backwards and a Romberg sign. She had patchy areas of hypesthesia involving her arms, trunk and legs.

Clinical summaries of the other patients have been reported previously (4,5). Outlines are in the Table.

DISCUSSION:

GB, *RJ* and *WC* had clinical evidence of AGE. Twelve of the 14 patients had clinical evidence of spinal cord DCS. One patient (*RJ*), who died of a pulmonary embolus a week after his injury, had histopathological evidence of it. Clinical severity of DCS varied from very mild (*LN*) to severe (*TK*, *GB*, *LD*, *RJ* and *KD*). Mean number of treatments prior to SSEP study was 4.0 (range 0-8). Eight patients had recordings performed during hyperbaric sessions.

All 14 patients had abnormalities on neurological examination at the time of SSEP testing. SSEP were abnormal in 9 of the 14 patients. One patient (*LK*) had normal SSEP while awake but her latencies to tibial nerve stimulation were asymmetrical, although within normal limits. The absolute P_1 latencies while asleep were 36.32 msec (left) and 39.52 msec (right). While awake they were 36.80 msec (left) and 35.68 msec (right). The significance of this finding is unclear, but could be compatible with a sensory pathway abnormality on the right. One patient with pure vestibular DCS had normal SSEP and BAER. All patients with abnormal SSEP had severe DCS. Of the 9 patients with significant motor weakness, 7 had abnormal SSEP. Seven patients had bilateral leg weakness; 2 of these patients had latencies on one side that were normal for age and height.

One additional patient had bilateral leg weakness and abnormal bilateral SSEP which normalized on one side while weakness persisted. In general, however, SSEP improvement paralleled clinical improvement.

The correlation between SSEP and the clinical exam in our series of divers is similar to the findings of Greenberg and Erwin (7) in non-divers. These investigators examined carefully 50 consecutive patients referred by clinical neurologists for SSEP testing. In that series 7 patients had no neurological abnormalities and all had normal SSEP. Twenty-two of 43 patients with abnormal clinical exams had abnormal SSEP. Abnormal SSEP correlated best with clinical weakness. In the present series of divers, abnormal SSEP also correlated best with clinical weakness rather than any specific sensory abnormality.

It is possible that some of the studies which we classified as normal in fact were abnormal for those patients (e.g. latencies significantly prolonged post-injury). We had no baseline (pre-injury) studies however, with which to compare.

SSEP improved during hyperbaric oxygen treatment in 3 patients providing objective support for continuation of therapy beyond initial hyperbaric treatment. The possibility that hyperbaric oxygen may artifactually alter SSEP has been investigated (8). Tibial nerve stimulation was performed in 5 normal volunteers at 1 and 2.8 ATA breathing air and 100%

O_2. Arterial blood gases were measured to ensure that PaO_2 values were appropriately elevated. P_1 and N_2 latencies were not altered by changes in barometric pressure or inspired O_2 concentration. There were minor alterations in P_1N_2 amplitude with changes in arousal, but there was no systematic effect of the experimental conditions. We conclude that improvement in short latencies in patients with diving related neurological injury would reflect improved neural function rather than artifact due to hyperbaric O_2 or N_2.

In summary, based upon this series of patients with gas bubble disease due to SCUBA diving, SSEP testing appears less sensitive than clinical neurological examination in detecting abnormalities of the spinal cord. However, the technique may offer an additional means of monitoring patients who can not be adequately examined in the cramped conditions of a hyperbaric chamber. While current SSEP technology monitors predominently posterior column conduction newer techniques are being developed to measure conduction in descending (motor) pathways by stimulating either spinal cord (9) or cerebral cortex (10) and recording the evoked motor response.

While SSEP waveform recording requires averaging of 500-2000 responses, evoked motor responses require only a single stimulus. The combination of SSEP with measurement of evoked motor responses might conceivably be of greater sensitivity than SSEP or clinical examination alone.

References:

1. Leitch DR, Greenbaum LF and Hallenbeck JM. Cerebral Arterial Air Embolism: I. Is There Benefit in Beginning Treatment at 6 Bar? ***Undersea Biomed Res*** 1984;11:221-235.

2. Leitch DR and Hallenbeck JM. Oxygen in the Treatment of Spinal Cord Decompression Sickness. ***Undersea Biomed Res*** 1985;12:269-289.

3. Leitch DR, Hallenbeck JM. Somatosensory Evoked Potentials and Neuraxial Blood Flow in Central Nervous System Decompression Sickness. ***Brain Res*** 1984;311:307-315.

4. Moon RE, Camporesi EM, Massey EW, Erwin CW and Djang WG. Functional Imaging of the Central Nervous System (CT, MRI, Xenon-Blood Flow) and Use of Evoked Potentials During Therapy of Decompression Sickness and Arterial Gas Embolism. In: Bove AA, Bachrach AJ, Greenbaum LJ. Jr., eds. Underwater and Hyperbaric Physiology IX. Proceedings of the ***Ninth International Symposium on Underwater and Hyperbaric Physiology***, Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.

5. Moon RE, Camporesi EM and Erwin CW. Use of Evoked Potentials During Acute Dysbaric Illness. Workshop Report, ***Workshop on Diagnostic Techniques in Diving Neurology***. (April 24, 1987) London. Medical Research Council, 1987.

6. American Electroencephalographic Society. Guildelines for Clinical Evoked Potentials Studies. ***J Clin Neurophysiol*** 1984;1:3-53.

7. Greenberg J, Kaplan P, and Erwin CW. Somatosensory Evoked Potentials and the Dorsal Column Myth. ***J Clin Neurophysiol*** 1987;4:189-196.

8. Mitchell P, Erwin CW, Camporesi EM, Moon RE, Goad R, Mebane Y, Stolp B and Bennett PB. Latency and Amplitude of Somatosensory Evoked Potentials in Normal Subjects Breathing Air and Oxygen at 1 and 2.8 ATA. Proceedings of the ***Ninth International Symposium, on Underwater and Hyperbaric Physiology***, Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.

9. Merton PA, Hill DK, Morton HB and Marsden CD. Scope of a Technique for Electrical Stimulation of Human Brain, Spinal Cord and Muscle. ***Lancet*** 1982;ii:597-600.

10. Thompson PD, Dick JPR, Asselman P, Griffin GB, Day BL, Rothwell JC, Sheehy MP and Marsden CD. Examination of Motor Function in Lesions of the Spinal Cord by Stimulation of the Motor Cortex. ***Ann Neurol*** 1987;21:389-396.

LEGEND FOR TABLE

Latency of SSEP performed before or during therapeutic recompression is recorded as N (normal) or A (abnormal). "SSEP Rx#" refers to the number of the therapeutic recompression before or during which the measurements were made. Parentheses following the dive number indicate that recordings were performed *during* therapeutic recompressions: (+) indicates an improvement in latencies during treatment; (-) indicates no response. For example, patient *MM* had SSEP performed during recompression #6 and latencies improved during that treatment. SSEP were also performed before treatment #11 and #15. All 3 studies revealed abnormalities (A,A,A). Patient *MS* had both SSEP and brainstem auditory evoked response measurements (BAER) during recompression number 4. There was no change in either one during treatment. Patient *WC* had abnormal BAER on one side, compatible with the middle ear barotrauma (hemotympanum) which was evident on physical exam.

DUKE EXPERIENCE WITH SSEP IN DCS AND AGE.

July 1985- October 1987

Pt:	Age	Sex	Dive profile (msw/min)	Neurological findings	Leg Strength (++++ = N)	Diagnosis	SSEP Rx #	Results
TK	44	M	18/30	P.par., L arm w., T12	+	DCS	6 (-)	N
GB	30	M	50/ ?	P.pl., T8, confusion	+	AGE+DCS	9	A
MP	28	M	24/40	Quadrapar., C7 level	+ +	DCS	4	N
LD	49	M	50/90	P.pl., L2 level	0	DCS	7	A
RJ	42	M	18/40	Dysph., Anomia, Q.pl.	0	AGE+DCS	4 (+), 7 (+)	A,A
SS	41	M	27/27;23/29	Mild R arm, leg w., C4	+ + +	DCS	5	N
LN	21	M	21/30;21/30	Hypesth. L torso, leg	+ + + +	DCS	1 (-)	N
MS	26	M	27/15;27/17	Unil. hearing imp, +Rom.	+ + + +	DCS (vest)	4 (-) (BAER)	N
GD	16	M	34/5;21/20	P.par., T8 level	+ +	DCS	6, 9 (-)	A,A
MM	28	M	30/20	P.par., L5 level	+ +	DCS	6 (+), 11, 15	A,A,A
JSn	37	M	27/30	P.par., T7, urinary ret.	+ +	DCS	2 (+), 5 (-)	A,A
KD	43	M	37/25	P.pl., T6 level	+	DCS	3, 5 (-)	A,A
WC	40	M	23/30;14/?	Seizures; ataxia; urinary ret.	+ + +	AGE	3 (BAER)	A
LK	20	F	36/12;9/25	Ataxia; patchy hypesthesia.	+ + + +	DCS	7	A*

*: asymmetry of latencies, only while asleep (see text).

MAGNETIC RESONANCE IMAGING IN SEVERE DECOMPRESSION SICKNESS AND ARTERIAL GAS EMBOLISM

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INTRODUCTION

Neurologic symptoms in severe decompression sickness and arterial gas embolism may range from minimal dysesthesias to complete quadriplegia, encephalopathy or death. Characterization of the site, extent, and etiology of these lesions has previously relied on history and physical examination. Neuroimaging has not traditionally played a major role in the assessment of this pathology, although an objective imaging modality would clearly aid physicians in the care of these patients. Moreover a sensitive neuroimaging technique may be invaluable in investigating the epidemiology of neurological abnormality in divers. Magnetic resonance imaging (MRI) has been shown to be an extremely sensitive imaging method in detecting brain pathology in other clinical settings. Furthermore it can image the spinal cord. We describe in this communication our recent experience with MRI and computerized tomography (CT) in the course of clinical assessment of dysbaric lesions.

METHODS

MRI or CT scanning, or both, were performed on twenty patients referred to Duke University Medical Center for major diving related injuries from July, 1985 to October, 1987. Clinical management relied primarily on their history, physical exam and particularly on a careful neurological examination. Many of the cases in this series have been more fully described elsewhere [1, 2].

MRI was initally preformed on a GE prototype system operating at 1.5 Tesla. Later scans were preformed on a clinical GE Signa 1.5 Tesla system. Head images were obtained with T1 weighted (TR 500, TE 20-25 msec) and T2 weighted (TR 2000-2500, TE 40-80 msec) scans utilizing head coils. Spine images were obtained with a 5 inch circular surface coil, utilizing the the same scanning parameters. Scans were frequently limited to selected regions of the spine on the basis of clinical data in order to reduce total scan time.

CT scans of the brain were performed without intravenous contrast on a GE 9800 or 8800 scanner. The posterior fossa was evaluated with 5 mm thick contiguous slices and the remainder of the brain with 10 mm contiguous slices. Xenon-enhanced CT scans (Xe-CT) were obtained by subtracting the baseline image from one obtained while the patient was inhaling 30% non-radioactive Xenon.

All imaging studies were performed at various times after the accident, in the Radiology Department, during intervals between hyperbaric treatments, usually within four days of the accident. Neurological examinations were performed by a staff neurologist. Patients were treated with therapeutic recompression and ancillary therapy at the F.G. Hall Laboratory.

RESULTS

Data concerning the clinical status and results of neuroimaging studies in twenty patients are summarized in Table 1.

Four patients presented with clinical symptoms and signs primarily suggestive of arterial gas embolism (*GB*, *RJ*, *WC* and *DD*). Two of these patients also had severe spinal cord signs, implicating an additional component of spinal cord decompression sickness (*GB* and *RJ*). All four patients had CT scans of the brain and MRI of the brain and spinal cord. Intracranial lesions were identified in three of these four patients by MRI. CT examination was abnormal in one patient. In that patient (*GB*), MRI demonstrated two lesions while CT demonstated only one, the second lesion obscured by beam hardening artifact. In this context, therefore, MRI appears to be significantly more sensitive than CT scanning.

Fourteen patients presented with clinical symptoms and signs suggesting primarily spinal cord decompression sickness. Eleven of these patients had MRI of the brain, of which two were abnormal (*SS* and *GD*). The abnormalities consisted of small areas of increased T2 signal, indicative of regional edema. Fifteen patients, including the two who also had AGE, had MRI of the cord, which was abnormal in two patients. The abnormalities corresponded in each case to the area thought to be clinically involved. However, due to the long scanning times, several of the examinations were limited only to those regions which were thought to be abnormal on the basis of clinical examination. Although the sensitivity of MRI in spinal cord decompression sickness appears to be low, this represents the only imaging modality presently available for the spinal cord. Expected advances in resolution should increase its utility for this disease.

Two patients had symptoms which contained features of vestibular pathology (*MS* and *ES*). Patient *ES* had an area of increased T2 signal in the cerebral peduncle.

There were areas of increased T2 signal in the bodies of thoracic vertebrae overlying the areas of spinal cord abnormality in patient *KD*. The signal pattern was considered most compatible with fat. Plain radiographs and technetium scan failed to demonstrate any abnormalities. The genesis and significance of these lesions is obscure. Followup MRI scan of the same area 7 months later revealed persistence of these bony lesions.
Two patients (*TH* and *LK*) demonstrated abnormalities which predated the diving injuries. *TH* had a small syrinx. Both patients had mild cervical spinal stenosis. The relevance of these findings is unknown.

DISCUSSION

Although Kizer et al [3] have described the use of brain CT in the managment of diving-induced neurologic dysbarism syndromes, these illnesses have not in the past been investigated extensively with neuroimaging modalities. This is related to the poor sensitivity of lesion detection utilizing conventional CT scanning as documented in this series. MRI is more useful than conventional CT scanning due to its increased intrinsic sensitivity to pathologic tissue alterations and to its markedly diminished artifact. In two of our cases (*SS* & *GD*), we noted definite abnormalities in areas which did not correspond to anatomic lesions predicted by the clinical neurologic examination. Divers are typically extremely healthy individuals, such that the likelihood of concurrent non-dysbaric neurologic disease would be very low. We believe that these MRI abnormalities represent asymptomatic cerebral injury related to dysbarism.

The pathophysiology and mechanism of injury in diving accidents is still somewhat controversial and has been reviewed in detail [4,5]. Intracranial injuries are likely due to arterial gas embolization, and may be related to pulmonary barotrauma with direct rupture into the arterial system or paradoxical embolization of venous gas bubbles. Bubble formation may continually occur during decompression and is usually asymptomatic, though it may become manifest through previously unrecognized right-to-left shunts which may only open when right atrial pressure exceeds left atrial pressure. It is possible that the increase in central blood volume due to water immersion and the higher negative inspiratory intrathoracic pressure which may occur during diving might contribute to this reversal of the normal inter-atrial pressure gradient.

Far more common than cerebral gas embolism is the syndrome of spinal cord decompression sickness (77% of CNS diving insults [4]). This illness may be related to venous stasis in the large epidural venous lakes surrounding the cord. This can be related to elevated central venous pressure and/or local microbubble formation. Eventually, the coagulation cascade is activated and cord hypoxia and possible necrosis may ensue. The pathophysiology of spinal cord decompression sickness may also include bubble formation within the myelin sheath. Light and electron microscopic changes have been reported in cord myelin in experimentally dived animals [6] and humans [7]. A patchy distribution of lesions has been observed. Imaging of such small, patchy pathologic changes would be expected to be difficult. Continued progress in surface coil technology and image resolution has enabled us to improve sensitivity in this difficult area, although in this series MRI only detected abnormalities in a minority of patients with spinal cord decompression sickness. MRI appears to be more sensitive than CT scanning in detecting brain lesions.

We suggest that successful use of this modality to screen for subclinical abnormalities of the spinal cord described by Palmer [8] will have to await improvements in technology. However, MRI might be useful as a screening tool for such abnormalities in the brain.

REFERENCES

[1]. Moon, R.E., E.M. Camporesi, E.W. Massey, C.W. Erwin and W.T. Djang. Functional imaging of Central Nervous System (MRI, CT, Xenon-Blood Flow) and Use of Evoked Potentials During Therapy of Decompression Sickness and Arterial Gas Embolism. Chapter in: Bove, A.A., Bachrach, A.J. and Greenbaum, L.J. (Eds.): ***IX International Symposium on Underwater and Hyperbaric Physiology***, Bethesda, Md, The Undersea and Hyperbaric Medical Society, 1987 (in press).

[2]. E.M. Camporesi, R.E. Moon, W.T. Djang and P. Warren: Neuroimaging in severe decompression sickness and arterial gas embolism. Report of ***Workshop on Diagnostic Techniques in Diving Neurology***. London: April 24, 1987. Medical Research Council of the United Kingdom (in press).

[3]. Kizer, K.W. The role of computed tomography in the management of dysbaric diving accidents. ***Radiology*** 1981; 140: 705-707.

[4]. Leitch, D.R. and J.M. Hallenbeck A model of spinal cord dysbarism to study delayed tratment: I. Producing Dysbarism. ***Aviat Space Environ Med*** 1984: 55: 584-591.

[5]. Leitch, D.R., L.F. Greenbaum and J.M. Hallenbeck Cerebral arterial air embolism: I. Is there benefit in beginning HBO treatment at 6 bar? ***Undersea Biomed Res*** 1984; 11: 221-235.

[6]. Leitch D.R. and J.M. Hallenbeck. Oxygen in the treatment of spinal cord decompression sickness. ***Undesea Biomed Res*** 1985; 12: 269-289.

[7]. Kitano, M., K. Hayashi and M. Kawashima. Three autopsy cases of acute decompression sickness. ***J West Jap Orthop Traum*** 1977; 26: 402-408.

[8]. Palmer, A.C. and I.M. Calder. Neuropathological Evidence for Neurological Defects in Divers. Report of ***Workshop on Diagnostic Techniques in Diving Neurology***. London: April 24, 1987. Medical Research Council of the United Kingdom (in press).

DUKE EXPERIENCE WITH IMAGING IN DCS AND AGE.
July 1985-October 1987

Pt:	Age	Sex	Dive profile (msw/min)	Diagnosis	Neurological findings
TK	44	M	18/30	DCS	Paraparesis, L arm weakness, T12
GB	30	M	50/?	AGE+DCS	Paraplegia, T8, confusion
MP	28	M	24/40	DCS	Quadraparesis, C7 level
LD	49	M	50/90	DCS	Paraplegia, L2 level.
RJ	42	M	18/40	AGE+DCS	Dysphonia, anomia, quadraparesis.
SS	41	F	27/27;23/29	DCS	Mild R arm and leg weakness, C4.
MS	26	M	27/15;27/17	DCS(vestibular)	Unilat. hearing impairm.,+Romberg.
GD	16	M	34/5;21/20	DCS	Paraparesis, T8 level.
MM	28	M	30/20	DCS	Paraparesis, L5 level.
JSn	37	M	27/30	DCS	Paraparesis, T7, urinary retention.
KD	43	M	37/25	DCS	Paraplegia, T6 level.
CJ	37	M	34/24;15/22	DCS	R fool, L hand hypesthesia.
ES	40	M	28/80 (surf. d.)	DCS	R ophthalmoplegia, ataxia, vertigo
WC	40	M	23/30;14/?	AGE	Seizure, ataxia; urinary retention.
DD	24	M	27/30	AGE	LOC; headache; p.paresis; L2/3 sens. level.
TH	49	M	30/17	DCS	Epigastric and back pain; p. paresis.
MB	31	M	47/30;27/30	DCS	Shoulder pain, hypesth. hands & feet, L1 sens. level.
RL	32	M	20/30	DCS	Abdominal numbness; hypesthesia T12 & L1 dermatomes.
NK	34	M	40/20	DCS	Dizziness; abnormal tandem gait; Romberg sign.
LK	20	F	36/12;9/25	DCS	Patchy hypesthesia; Romberg sign.

Pt:	Age	Sex	CT brain	MRI-brain	MRI-cord	Xe-CT
TK	44	M	normal	Normal	Normal	-
GB	30	M	L parietal abn	L parietal-occipital/R temporal	Limited, no abnorm.	-
MP	28	M	Normal	Normal	Normal	-
LD	49	M	-	-	Limited, no abnorm.	-
RJ	42	M	Normal	Parietal subcortex bilat.	Dorsal col C4	Decreased subcortical flow
SS	41	F	-	R frontal, centrum semiovale	R ventral C3/L dorsal C5	-
MS	26	M	Normal	Normal	-	-
GD	16	M	-	R cerebellum	Limited, no abnorm.	-
MM	28	M	-	Normal	Normal	-
JSn	37	M	-	Normal	Normal	-
KD	43	M	-	-	Dorsal T9/bone lesions*	-
CJ	37	M	-	-	Normal	-
ES	40	M	-	L cerebral peduncle	-	-
WC	40	M	Normal	Normal	Normal	-
DD	24	M	Normal	R centrum semiovale	Normal	Normal
TH	49	M	-	Normal	Spinal stenosis: small syrinx	-
MB	31	M	-	Normal	Normal	-
RL	32	M	-	Normal	Normal	-
NK	34	M	Normal¶	Normal	-	-
LK	20	F	-	Normal	Mild spinal stenosis at C4-5	-

¶: with contrast

*: followup MRI study of cord 7 months post injury showed persistence of bony lesions.

INFLUENCE OF PRESSURE PROFILE ON DCS SYMPTOMS

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Abstract

Pressure profiles influence the relative frequency of decompression sickness (DCS) manifestations. Relatively few anatomical sites are commonly vulnerable to decompression injury and are responsible for symptomatic DCS manifestations. Physiological and anatomical conditions in those tissues determine the probability of DCS injury and symptomatic manifestations with decompression.

DCS in scuba divers versus tunnel workers shows a greater percentage of central nervous system decompression sickness (CNS-DCS) among divers than tunnel workers. This outcome is associated with the duration of hyperbaric exposure: rapid decompression from short exposures at higher pressures often provokes more CNS-DCS than long exposures at lower pressures. Limb bends predominate in tunnel worker DCS. Animal studies confirm this relationship between pressure profile and the form DCS takes. The incidence of severe DCS manifestations, not overall DCS incidence, predicts the risk of permanent or fatal injury. Spinal cord tissues appear more vulnerable to decompression injury from short, comparatively deep air dives with no-stop decompression than from shallower, longer dives that provoke the same overall DCS incidence. These and other findings suggest a diving safety recommendation: Decompression from "bounce" dives with an additional shallow water decompression stop or slowed ascent near the surface should reduce the risk of CNS-DCS.

Introduction

Different dive profiles have been associated with different decompression sickness (DCS) manifestations (1). Our experience with decompression in animals, and reports of human DCS indicate that the duration and pressure of hyperbaric exposure mediate the relative frequency of the major DCS manifestations (2,3). We pose the question: How do pressure profiles influence DCS manifestations?

The subject of this paper encompasses the major forms of DCS in both experimental animals and humans subjected to decompression (4). The major forms of DCS include: 1) limb bends, a pain-only manifestation, and the more serious manifestations, 2) CNS-DCS that involves many sites in the central nervous system, but primarily the spinal cord, and 3) the chokes, a respiratory form of DCS. Our animal experiments and most of the available human DCS reports provide information about these major forms of DCS after shallow dives. These DCS manifestations are the focus of this paper.

We will search for patterns in the decompression responses of large animals and humans, and relate these findings to some of the physiological processes in DCS, and to implications and safety recommendations for the scuba diver.

Awareness of Pressure Profile Effect

In our early work, we investigated the decompression responses of animals to chamber air dives. We found differences in DCS manifestations between short relatively deep and long relatively shallow hyperbaric exposures. These air dives formed the basis for examining the effect of pressure profile on DCS manifestations. This investigation initially compared animal findings in our laboratory with human responses to decompression, particularly tunnel workers and scuba divers in a retrospective survey. Much of what we report is a chronological view of our increasing awareness of the influence that dive profiles have upon the form of DCS most likely expressed.

Early animal studies at Wisconsin

Diving physiology research at the University of Wisconsin has focused on the nature of DCS with the hyperbaric exposure of pygmy goats and sheep to model the human response to decompression. Sheep and goats are near the human body mass and this scaling factor plays an important role in the suitability of these species as models of human DCS (5).

Our early work included simulated air dives with a "bounce" dive profile without decompression stops in 24 and 4 hour exposures (Fig. 1). Later, sheep and goats experienced a ½-h "bounce" dive series. Both series of hyperbaric exposures also included simulated ascents to 8000 ft altitude with pressure reduction after a 20 min stop at surface pressure.

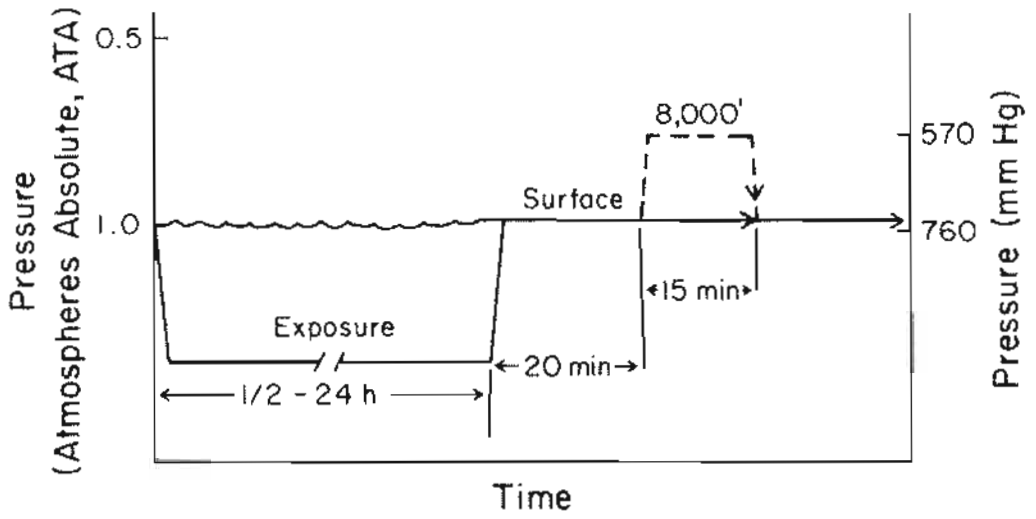

Fig. 1. Simulated "bounce" (no-stop decompression) dive profile with altitude provocation when DCS signs were not provoked at surface.

In the 24- and 4-h simulated dives of sheep and goats, we observed DCS outcomes near the often-quoted conventional frequency of limb bends versus CNS-DCS cases (6-8), with somewhat more than the usual 10:1 limb bends to CNS-DCS proportion. In these species, limb bends presents by the lifting of the affected limb as described by Boycott, Damant and Haldane in 1908 (9). CNS-DCS episodes in sheep and goats typically present with gross clinical signs of limb paralysis or loss of equilibrium. Other more subtle effects of CNS-DCS, known to occur in humans, cannot be so simply assessed in these animals. Greater than 10 times more limb bends than CNS-DCS cases were provoked in these long, shallow exposures.

During the 25th Undersea Medical Society Workshop in 1980, Dr. John Florio met with members of our research group during a tour of our laboratory. We asked him about the incidence of CNS-DCS that he observed in goat experiments at the Royal Naval Physiological Laboratory. He remarked that he saw a much higher percentage of CNS-DCS involvement in goats than we had observed in the 4- and 24-h dive series at Wisconsin. We thought this puzzling, particularly in light of the published CNS-DCS percentages. Our next series of shorter air dives with ½-h exposures began soon after Florio's visit. To our surprise, CNS-DCS cases increased in line with the RNPL experiments with decompressed goats. The contrast between the longer, shallower air dives and the shorter, deeper ½-h air dives was remarkable. In several weeks, the ½-h air dives produced more CNS-DCS cases than observed in nearly a year with longer, shallower dives with about the same DCS incidence.

We reported our findings in Tokyo and they appear as a paper in the proceedings of that meeting (1). Results of this study included responses from more than 750 animal-dives in the ½, 4 and 24-h hyperbaric exposures.

Of the DCS cases in sheep, the incidence of CNS-DCS was only 6% at 24 h and 7% at 4 h but 64% after the ½-h hyperbaric exposures. In goats, CNS-DCS represented only 0 and 6% of the cases in the 24- and 4-h dives, but 32% in the ½-h air dives.

The presence or absence of at least one CNS-DCS episode in each individual for a dive series (½, 4 and 24 h) was compiled (Table 1). These results indicated a trend for increasing CNS-DCS from long to short hyperbaric exposures. Data from the 4- and 24-h series were pooled and then compared to the ½-h dive series.

Table 1. Occurrence of CNS-DCS among individual sheep and goats at different exposure durations.

Duration:		30 min	4 h	24 h
Sheep	CNS-DCS +	3	7	3
	CNS-DCS −	0	7	8
Goats	CNS-DCS +	4	1	0
	CNS-DCS −	2	6	4

Differences between the ½-h and the combined longer exposures (4 and 24 h) in sheep were at the 0.09 level of significance. Fisher's exact test was used to test significance. In goats, the exact probability was 0.028. When both of these outcomes were combined, the significance reached $P < 0.025$. Thus, shorter hyperbaric exposures that provoke DCS have a higher probability of CNS involvement than longer exposures that also provoke DCS in sheep and pygmy goats.

Dive duration effects: near-saturation to submarine escape

The importance of the duration of hyperbaric exposure was illustrated by two papers presented at the 8th Symposium on Underwater Physiology. During this symposium, we presented a paper on 24-h compressed air exposures of sheep (10), and Bell and colleagues presented their findings on simulated submarine escapes in goats (11).

Chokes were present in sheep after near-saturation conditions on compressed air, especially at moderate altitude of 8000 ft. Limb bends were also a predominant form of DCS in these 24-h chamber dives. Twenty-four hour air exposures represented one end of the pressure profile spectrum and Bell's submarine escape profiles represented the other end with very rapid compression and decompression of goats.

Bell's group had produced results that drew our attention. Their short, deep dives produced CNS-DCS at levels that correlated with our ½-h series previously conducted with sheep and goats.

Bell et al. (11) investigated goat decompression responses to very brief pressure profiles of high maximum pressure to simulate submarine escapes. Short duration spikes of compression and decompression < 1 min were used to simulate submarine escapes with long but low presaturation pressures.

CNS-DCS incidence in the RNPL goat experiments was high. Bell and associates noticed a shift in DCS manifestations from limb bends to CNS-DCS. Brief exposures to high pressure were associated with a high incidence of CNS-DCS, reaching about 70% of the DCS cases in goats. As the maximum pressure spike increased so too did the CNS-DCS incidence, from about 20% to about 70%. These results (11) contrast with the complete absence of CNS-DCS in our 24-h sheep experiments (10) that provoked chokes and limb bends.

Further investigation: animal vs. human CNS-DCS

Animal findings in our laboratory and those from British studies, particularly Bell's group, encouraged us to explore whether the pattern of increasing relative frequencies of CNS-DCS in shorter, deeper dives also occurred in humans. This pattern of DCS manifestations suggested that "bounce" dives of short duration to greater pressure carry a higher risk of CNS-DCS than longer, shallower dives with the same DCS incidence.

Retrospective survey of human DCS

Animal responses to decompression prompted us to conduct a survey of published DCS reports of divers and tunnel workers to search for a similar pattern. We undertook a retrospective survey of human DCS reports and found that DCS reports conveniently divided into tunnel worker and diver responses to decompression from air exposures.

In Fig. 2, tunnel worker and diver DCS cases are divided into the three major DCS manifestations: CNS-DCS, chokes (respiratory DCS), and limb bends (from left to right). Human DCS reports show an operational and historical trend, with most early reports focused on compressed air work in tunnel and caisson projects (12-14). Tunnel and caisson work tends to involve relatively long hyperbaric exposures at moderate pressure as compared with shorter hyperbaric exposures at greater pressure typical of most scuba diving.

Reports of DCS in tunnel workers generally show a low percentage of CNS involvement. Most reported DCS cases are limb bends, and CNS-DCS is only high in the older Heller report (12). Chokes case reports are uncommon. Conventional percentages of CNS-DCS and limb bends, quoted in authorative decompression literature (e.g. 6-8), characteristically have been taken from early tunnel worker reports.

Divers with DCS, represented in the lower panel (Fig. 2), sustained a higher percentage of CNS-DCS (15-17) than tunnel workers (12-14). Limb

bends cases again predominate and chokes remain the least common major form of DCS whether among tunnel workers or divers.

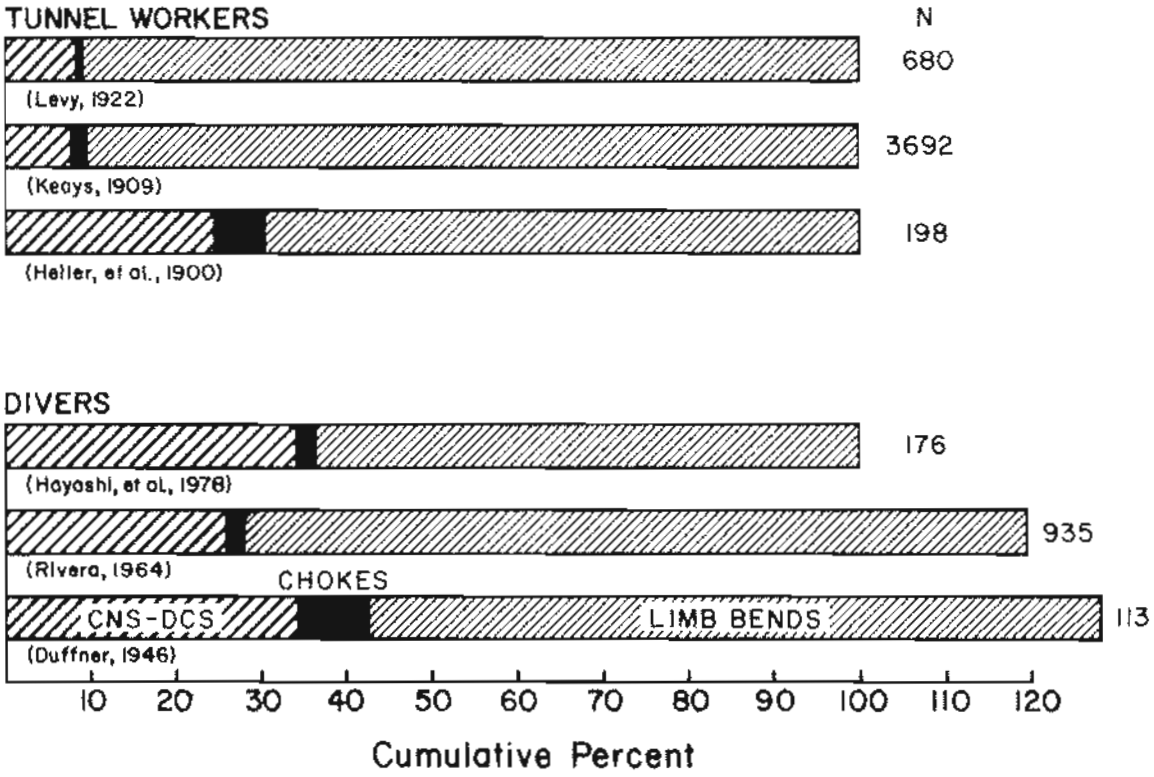

Fig. 2. Decompression sickness manifestations in tunnel workers and divers.

Scuba diving, especially as practiced by the sport diver, has often involved short "bounce" dives at much greater pressures than the usual pressure experienced by tunnel workers. In the reports of Slark (18) and Kizer (19) illustrated by panels in Fig. 3, DCS is represented by its two clinical categories (20): Type I DCS, pain-only manifestations or limb bends; and Type II DCS, the serious forms of DCS that include CNS-DCS and the chokes. Where both Type I and II occur in the same cases, there is an

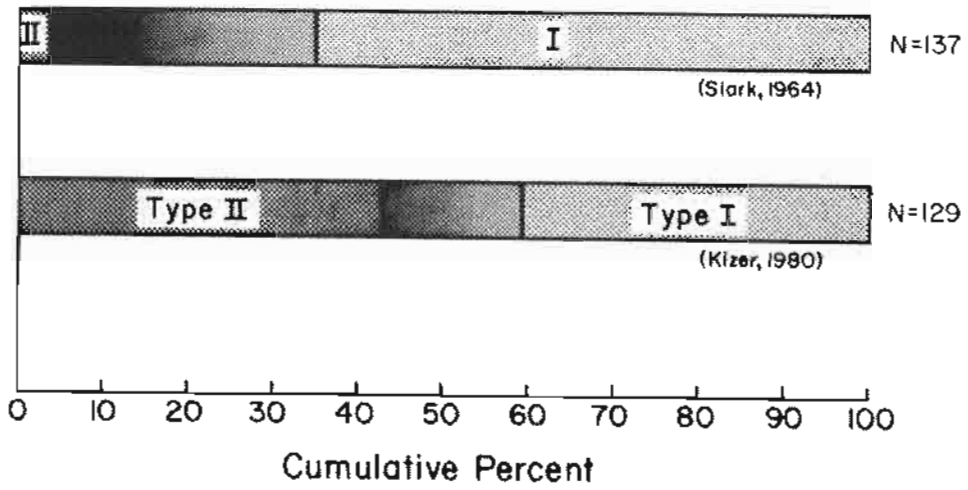

Fig. 3. Type I and II decompression sickness in divers, with both Types I and II DCS occurring in some individual cases (center section).

is an overlap (center section, Types I and II). As previously shown, divers tend to have a greater percentage of Type II or serious DCS cases. We attribute this difference of greater relative frequencies of CNS-DCS in divers to the pressure profile: Shorter hyperbaric exposures at greater pressure provoke more CNS-DCS cases than longer exposures at lower pressure with about the same probability of DCS.

Human DCS shown in Fig. 4 is represented by Type I and Type II DCS cases in tunnel workers (13,20,21) and divers (4,16,22).

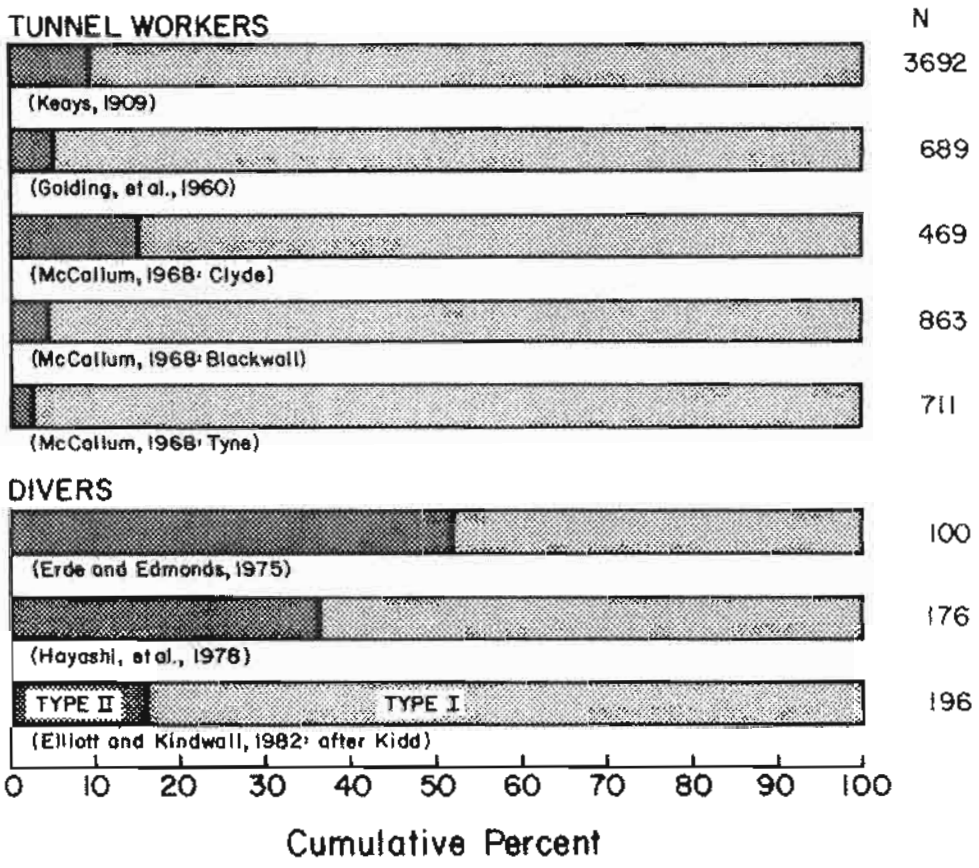

Fig. 4. Cumulative percentage of decompression sickness (Type I and II) in tunnel workers and divers.

The same pattern seen previously with DCS manifestations is repeated with proportionally more Type II DCS in divers than tunnel workers. (The often-quoted Keays report with 3692 DCS cases seen in Fig. 3 is also included for comparison.) Divers sustained a higher percentage of Type II DCS than tunnel workers in these case reports.

Torrey and colleagues (23) reported a high frequency of CNS-DCS observed in U.S. Navy divers. They also pointed out that concerns about CNS involvement in DCS and new diagnostic procedures may identify more CNS-DCS cases that otherwise went unrecognized and unreported. Reporting bias may also skew the relative frequencies of DCS manifestations in the opposite direction, particularly in mild CNS-DCS cases that quickly undergo symptomatic resolution (24) and presumably go unreported.

Modelling DCS Manifestations

DCS incidence modelling (5,25-32) offers another approach to assessing the effects of pressure or dive profile on the occurrence of DCS manifestations (2). Separate incidences of DCS manifestations, for example CNS-DCS and limb bends, as well as the overall DCS incidence can be estimated (3).

Logistic regression approach

We modelled DCS incidence provoked in no-stop dive profiles with two independent variables: log pressure change (difference between maximum pressure and observation pressure) and log duration (time spent at maximum pressure and descent time). Decompression responses were transformed by the logistic function. The model was fit by maximum likelihood with the GLIM statistical package (33), based on earlier theoretical work (34). In addition to overall DCS, individual forms of DCS, limb bends and CNS-DCS, were also modelled. The chokes (respiratory DCS or RDCS) was not included in this analysis, because the chokes is relatively uncommon and has a wide range of signs and symptoms often subject to various clinical interpretations.

DCS incidence estimation, including logistic regression modelling, becomes increasingly subject to sample size constraints when predicting low DCS incidence levels. In addition, model assumptions and extrapolations to regions outside those heavily tested also must be assessed with caution. Nevertheless, patterns and trends that develop from independent data sources can be useful for indicating the behavior of DCS and its individual manifestations over a range of pressure profiles.

Animal and human decompression responses

We evaluated the effect of dive profiles on DCS signs and symptoms with three sets of data. We compared DCS provoked in no-stop "bounce" dives with sheep in simulated air dives to human decompression responses in the Van Der Aue et al. report (35) with no-stop "bounce" dives on air and in Thalmann's report (36) containing no-stop "bounce" dives on heliox. These data are summarized in Table 2.

Table 2. Summary of human and sheep data modelled for DCS incidence estimates.

Source	Max. Pressure (range, ATA)	Duration (range, min)	No. of dives	No. of DCS cases*
Thalmann (36)	3.0 - 7.1 (heliox)	6 - 147	443	19 (6 CNS, 13 LB, 1 RDCS)
Van Der Aue et al. (35)	2.2 - 6.6 (air)	7 - 205	144	11 (1 CNS, 6 LB, 4 RDCS)
UW-Madison sheep	2.1 - 4.7 (air)	30 - 240	193	15 (5 CNS, 8 LB, 7 RDCS)

*A DCS case may involve > 1 DCS manifestation. CNS (CNS-DCS); LB (limb bends); and RDCS (respiratory DCS or chokes).

Sheep decompression responses (air)

Estimated 1, 5 and 10% DCS incidence in sheep after no-stop air dives indicate a parallel fit to the U.S. Navy "no-d" (no-decompression stop) air limits (8) shown in Fig. 5. Also, the U.S. Navy "no-d" air limits

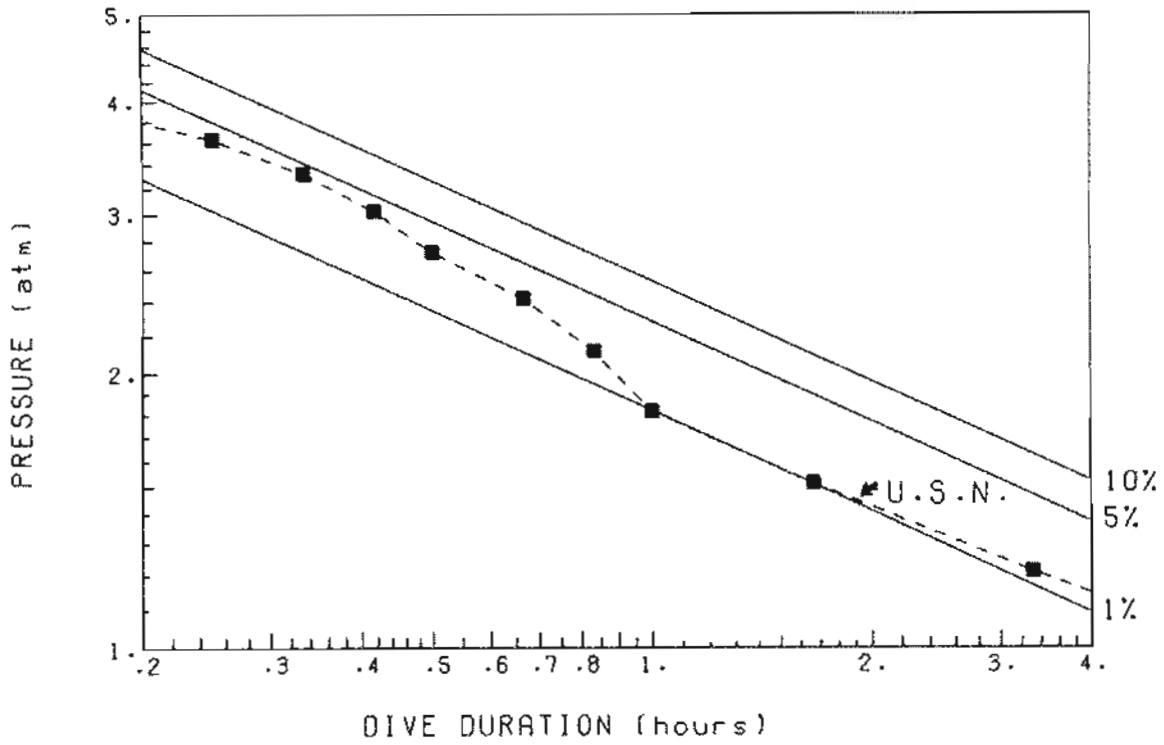

Fig. 5. Overall DCS incidence provoked in sheep versus the U.S. Navy's no-decompression stop limits for air dives.

with the maximum allowed pressure profile are thought to provoke a DCS incidence near that observed in sheep. These findings indicate an overall similarity in decompression responses elicited in sheep and humans (5). The similarity in decompression responses presumably reflects similar physiological rate functions that scale allometrically with body mass (37,38). Thus, small mammals usually have higher metabolic rates than larger mammals. With DCS, this argument suggests that animals with similar body mass (and therefore perfusion rates) will have similar decompression responses.

CNS-DCS and limb bends were also separately modelled. In sheep, these estimates indicate a distinct pattern of increased risk of CNS-DCS in the shorter, deeper dive profiles (Fig. 6).

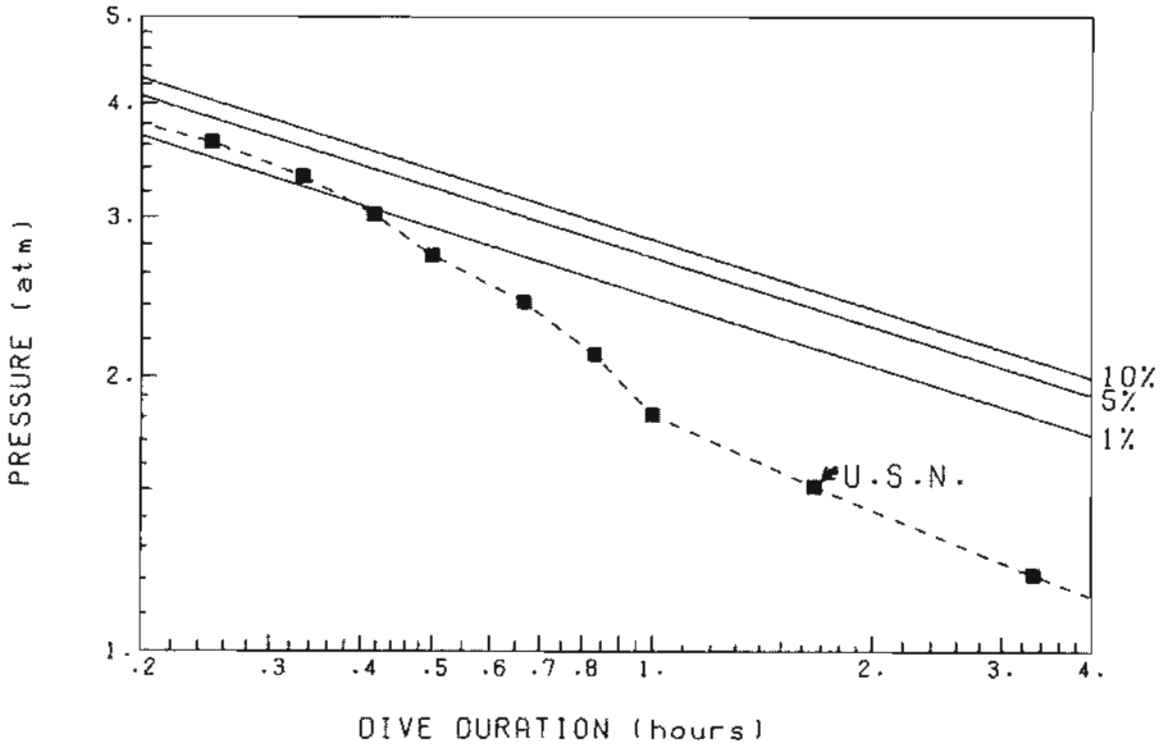

Fig. 6. Estimated CNS-DCS incidence in sheep and the U.S. Navy no-stop limits for air dives.

Conversely, much less CNS-DCS is predicted from long, shallow dives. Estimated CNS-DCS percentage isopleths intercept the U.S. Navy "no-d" limits in the region of shorter, deeper dive schedules on air. Short, relatively deep schedules provoke the most CNS-DCS as was previously demonstrated (1). Also, we speculate that the tightness of these CNS-DCS estimates indicates small deviations beyond the permitted schedules carry a high risk of spinal cord injury.

We observe that limb bends (Fig. 7) tracks the U.S. Navy "no-d" limits more closely than CNS-DCS estimates in sheep. Except for the shorter deeper exposures, limb bends in the most common form of DCS, especially in the longer, shallower dives beyond 1 h.

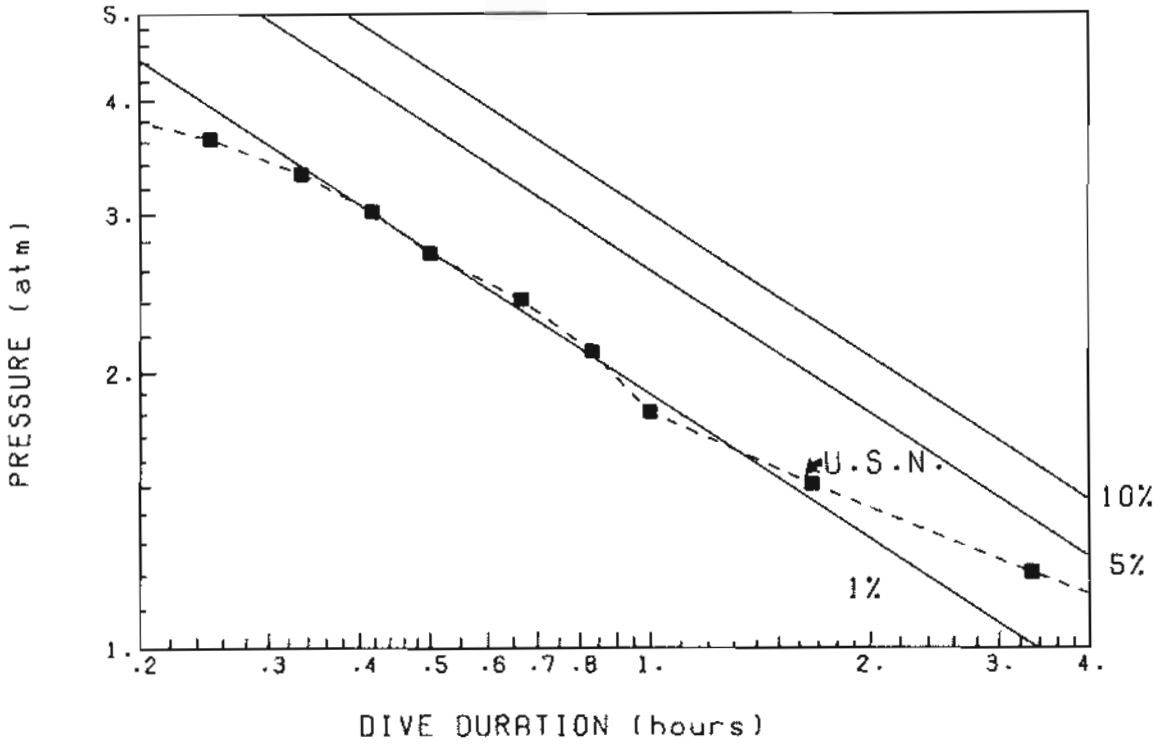

Fig. 7. Estimated limb bends incidence in sheep and the U.S. Navy no-stop limits for air dives.

When both incidence predictions appear superimposed, the effect of dive profile on DCS manifestations becomes more obvious (Fig. 8). CNS-DCS becomes increasingly common in the shorter, deeper dives, while limb bends incidence curves lie parallel to the "no-d" limits. The relative frequency of CNS-DCS rises in the shorter deeper hyperbaric exposures. Limb bends incidence tends to remain the same at the "no-d" limits. Indeed, this pattern of increased CNS-DCS in shorter dives corresponds to the overall difference between CNS-DCS and limb bends (serious Type II vs. pain-only Type I DCS) seen previously in diver and tunnel worker comparisons and in our early animal experiments (1).

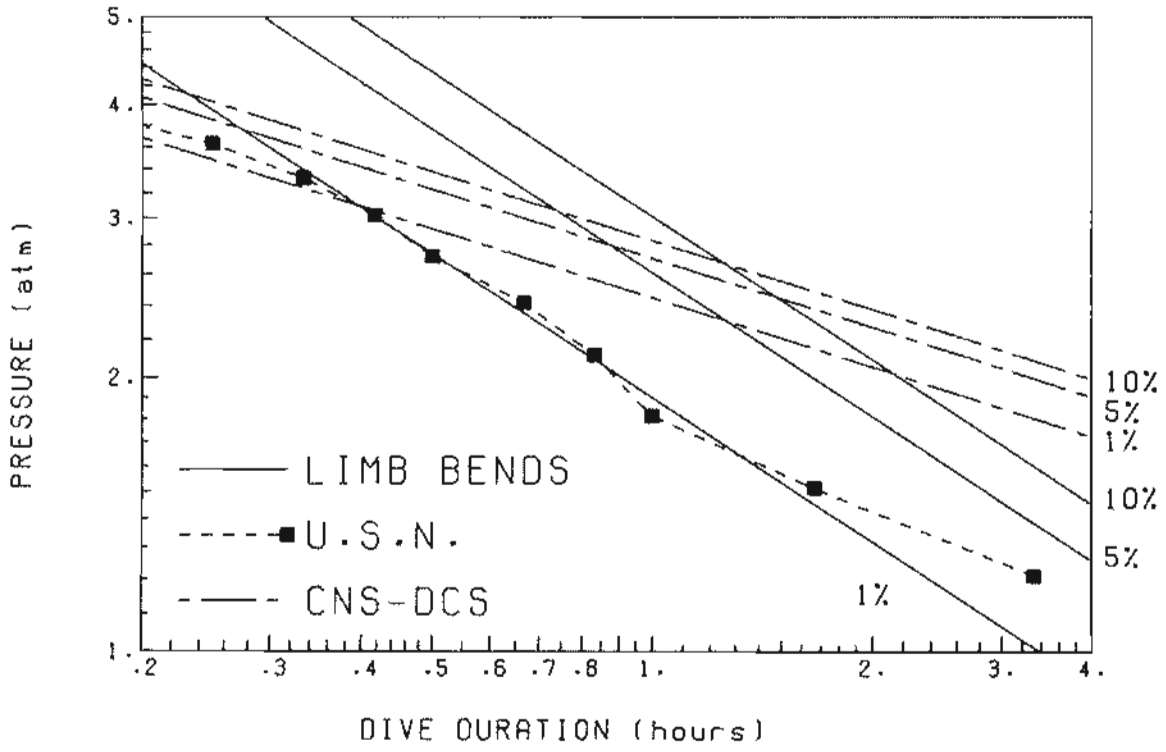

Fig. 8. Estimated incidence of CNS-DCS and limb bends in sheep versus the U.S. Navy no-stop limits for air dives.

The relationship between pressure profiles and DCS manifestation becomes apparent with the percentage of CNS-DCS versus limb bends predicted at the no-stop limits (Fig. 9). Relative frequencies of CNS-DCS and limb bends

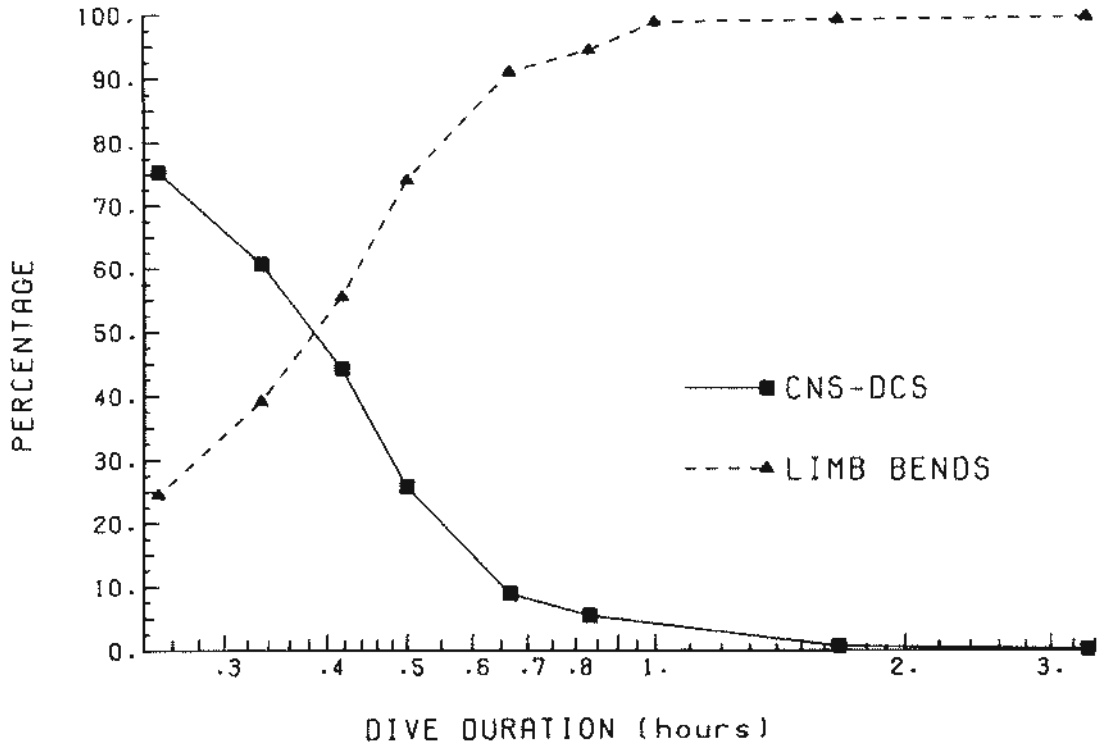

Fig. 9. Estimated percentage of CNS-DCS to limb bends at the U.S. Navy no-stop limits for air dives.

estimated for sheep along the "no-d" limits predict a low percentage of CNS-DCS in the longer dive schedules but a high percentage of CNS-DCS in the short, deep side of the "no-d" limits. This pattern of a high CNS-DCS percentage among DCS cases increases among deeper "bounce" dive profiles, with durations less than ½ h, the shortest dive profile tested with sheep.

Human decompression responses (air)

We also modelled the Van Der Aue sea trial data (35) to compare the human decompression responses with the U.S Navy "no-d" limits (Fig. 10). Most

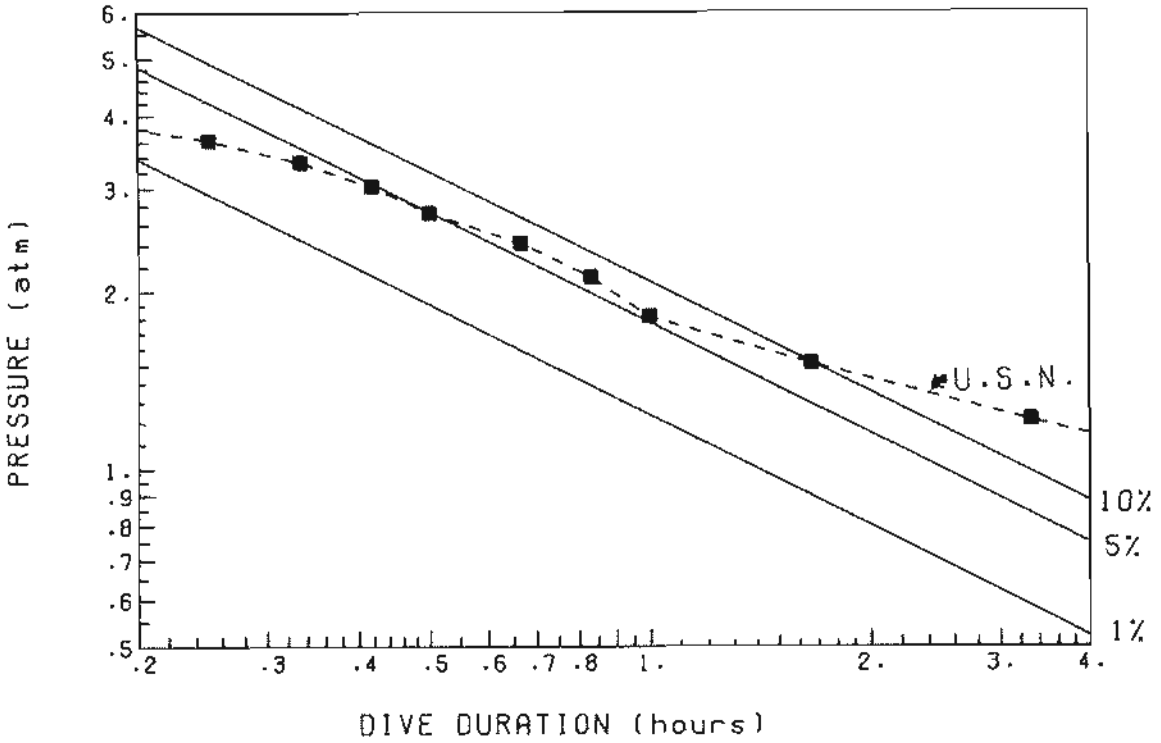

Fig. 10. Estimated human DCS incidence in the Van Der Aue et al. sea trials (35) and the U.S. Navy no-stop limits for air dives.

of the trials involved surface decompression, but 144 man-dives followed a no-stop "bounce" dive profile. These "bounce" dives provoked mostly limb bends. Unfortunately, we could not model the CNS-DCS separately as before with the sheep, because there were too few CNS-DCS events (Table 2). Overall DCS incidence in human (Fig. 10) divers closely corresponds to comparable DCS incidence estimates in sheep (Fig. 5). This offers additional evidence for the similarity in human and sheep decompression responses.

Human decompression responses (heliox)

Thalmann conducted a series of heliox (He, O_2) dives with divers at the U.S. Navy Experimental Diving Unit (36). In his heliox series, "bounce" dives provoked some DCS that we modelled as done previously with the sheep responses. Sufficient numbers of limb bends and CNS-DCS episodes permitted separate incidence modelling of these DCS manifestations. Overall DCS

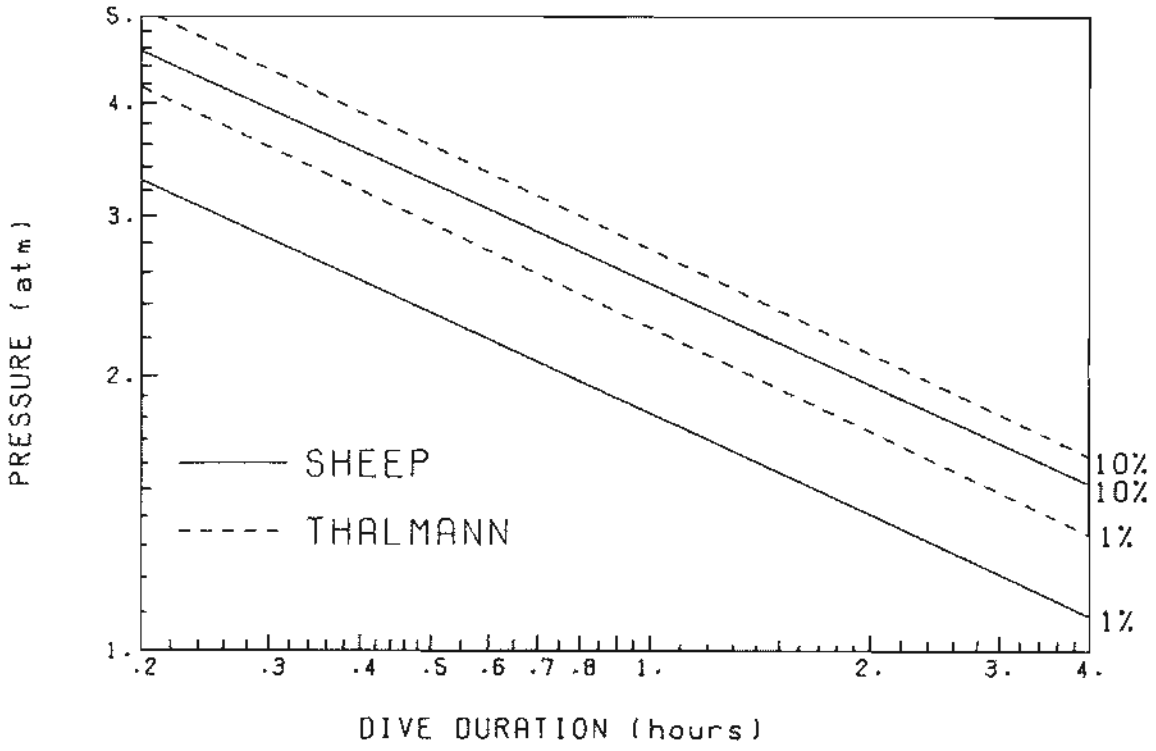

Fig. 11. Estimated DCS incidence from no-stop "bounce" dives in sheep (air) and in humans (heliox) from Thalmann's data (36).

incidence estimates (Fig. 11) suggest a protective effect in avoiding DCS that heliox affords over air as a breathing mixture. Heliox "bounce" dives in humans and air "bounce" dives in large sheep produce a similar pattern in overall DCS incidence, although both the species and gas mixtures differ.

Separate estimation of 10% CNS-DCS and limb bends in the heliox dives as compared with sheep responses reveals an interesting and distinctly new pattern (Fig. 12). While the sheep responses to air dives demonstrate a trend for an increasing percentage of CNS-DCS in the shorter deeper "bounce" dives, this pattern is not observed in the heliox dives. Limb bends and CNS-DCS appear to have similar responses over the pressure profile range tested by Thalmann. This observation suggests that heliox and air breathing mixtures may be responsible for different tissue responses under similar pressure profile conditions.

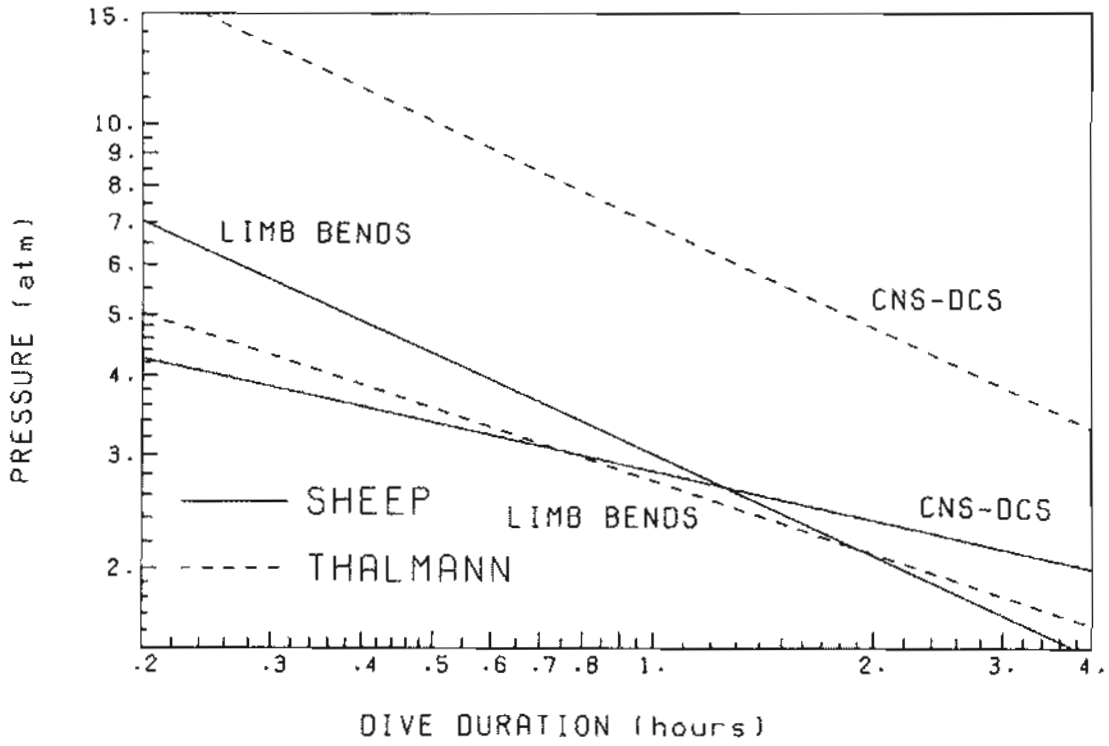

Fig. 12. Estimated 10% incidence of CNS-DCS and limb bends in sheep (air) and in humans (heliox) from Thalmann's data (36).

Thus, we observe an increasing relative frequency of CNS-DCS with deeper, shorter dives on air. Unlike air dives, dives with heliox show no trend for an increasing relative frequency of CNS-DCS in shorter, deeper bounce dives.

Physiological and Anatomical Influences on DCS

Factors influencing DCS manifestations

A relationship between pressure profile and DCS manifestations has been established by human and animal responses to decompression previously described. A brief discussion of the underlying physiological and anatomical factors that influence DCS manifestations follows.

The pattern of CNS-DCS in shorter, deeper air dives not evident in heliox dives suggests roles for both inert gas solubilities in tissues and tissue perfusion rates. Inert gas solubility differences (39), especially

between N_2 and He, may partly account for the differences observed between CNS-DCS predictions in sheep on air dives and humans on heliox dives.

Major differences in inert gas solubilities, particularly between H_2, He and N_2, and the relative fat to water tissue composition appear to be major factors in predisposing tissue sites of DCS to bubble formation. This relationship points to the vulnerability of the lipid-rich spinal cord in air dives, since N_2 is almost five times more soluble in fat than water.

Tissue perfusion is also a factor controlling the degree to which tissues load with sufficient inert gas to form bubbles in DCS.

Another factor is the anatomical architecture of organs and tissues. Complicated vascular anatomy may render a site vulnerable to bubbles, especially if bubble formation promotes the development of a compartment syndrome (40) and resulting ischemia.

Spinal cord DCS

Spinal cord injury in DCS, discussed by Dr. Francis and others at this Symposium, is associated with well-perfused tissues that have a high lipid content. We maintain that the spinal cord has important predisposing attributes that account for its vulnerability to decompression injury from short, deep "bounce" dives on air. The spinal cord has a comparatively high lipid content that allows for greater quantities of N_2 to diffuse into its tissues. Its relatively high perfusion rate make it a comparatively fast washin and washout tissue, with a rapid uptake and elimination of dissolved inert gases. In fast washin-washout tissues, bubble formation requires relatively fast decompression rates, for example "bounce" dives, for inert gas tensions to form bubbles. Its tissue architecture also predisposes it to compartment syndrome (40) that promotes ischemia in the spinal cord once bubbles form (41-43).

Pressure profiles and different DCS forms

Physiological and anatomical factors, as previously discussed, appear to control the relative frequencies of DCS signs and symptoms over a spectrum of pressure profiles. Dives with different durations and bottom pressures that provoke a constant DCS incidence can focus decompression injury at different tissue sites.

Implications

Dive profiles: short and deep vs. long and shallow

Short, relatively deep "bounce" dives will favor bubble formation in fast washin and washout tissues. The spinal cord is an example of a comparatively "fast" tissue that becomes vulnerable to decompression injury upon rapid decompression. Long shallow dives will favor bubble formation in many tissues, but particularly in those tissues with slow washouts relative to the rate of decompression. Limb bends tissues probably constitute such a group of intermediate to slow washout tissues.

Experimental DCS and dive duration

Hyperbaric exposures can be designed to elicit greater frequencies of certain DCS manifestations. Differences in the relative frequencies of DCS manifestations suggests that duration of maximum pressure exposure is a critical factor that determines which tissues will most likely form bubbles.

Sheep responses after simulated no-stop dives indicate that DCS manifestations can be differentially provoked by altering the dive duration and maximum "bottom" pressure. This titration approach allows the investigator to select dive schedules that produce the desired form of DCS. Certain dive durations in no-stop profiles selectively provoke various DCS manifestations: CNS-DCS at ½ h (1) or shorter dive times (11,43); limb bends at 4 h (1); and the chokes at 24 h (10). Another form of injury provoked by hyperbaric exposure is dysbaric osteonecrosis. It frequently occurs in large sheep following no-stop decompression from 24 h hyperbaric exposures (44).

Diving safety: acceptable risk

An understanding of pressure profile effects on DCS manifestations offers a basis for improving diver safety. If the diver is to avoid the most serious forms of DCS, then dive schedules can be altered so they are compatible with the diver's acceptable risk (45). Acceptable risk in this context is the risk or probability of DCS, particularly serious forms, that the diver is willing to accept when diving. Acceptable risk will vary between individuals and between populations of sport, commercial, scientific and military divers. Acceptable risk constrains the practice of sport and other diving to avoid DCS, especially CNS-DCS.

Diving safety: recommendations

Relative frequencies of DCS manifestations, particularly CNS-DCS, associated with different pressure profiles suggest the following diving safety recommendations:

1. To reduce the risk of CNS-DCS, avoid rapid no-stop decompression conducted at or slightly beyond the table limits permitted in deep, "bounce" air dives.

2. Decompression from "bounce" dives with an additional shallow water stop or with a slowed ascent near the surface should reduce the risk of CNS-DCS.

Conclusions

The configuration of pressure profiles has an important influence on the form of DCS that is provoked. Short, comparatively deep "bounce" dives on air probably carry a higher risk of CNS-DCS than has been previously recognized. Each DCS manifestation has a different set of underlying physiological and anatomical conditions that respond differently to pressure profiles.

References

1. Lanphier EH, Lehner CE, Lightfoot EN, Will JA. The influence of exposure time on manifestations of decompression sickness. In: Saeki M, ed. Proceedings of the seventh meeting of the United States-Japan Cooperative Program in Natural Resources (UNJR) Panel on Diving Physiology and Technology. Yokosuka, Japan: Japan Marine Science and Technology Center, 1984:218-227.

2. Lehner CE, Adler GG, Kanikula TM, Palta M, Lanphier EH. Influence of dive profile on manifestations of decompression sickness. Undersea Biomed Res 1985; 12:12 (Suppl).

3. Lehner CE, Hei DJ, Palta M, Ives TM, Lanphier EH. Dive profile selectively influences the relative frequency of decompression sickness manifestations. Undersea Biomed Res 1987; 14:17 (Suppl).

4. Elliott DH, Kindwall EP. Manifestations of the decompression disorders. In: Bennett PB ad Elliott DH, eds. The physiology and medicine of diving, 3rd ed. London: Bailliere Tindall, 1982:461-472.

5. Lehner CE, Palta M, Lanphier EH. The role of testing in animals. In: Nashimoto I, Lanphier EH, eds. Decompression in surface-based diving. Bethesda: Undersea Medical Society, 1987:125-129.

6. Hempleman HV. Decompression theory. In: Shilling CW, Carlston CB, Mathias RA, eds. The physician's guide to diving medicine. New York: Plenum Press, 1984:223-272.

7. Goad RF. Diagnosis and treatment of decompression sickness. Ibid.:283-312.

8. U.S. Navy diving manual, air diving, vol I (NAVSEA 0994-LP-001-9010). Washington, DC: U.S. Government Printing Office, 1978.

9. Boycott AE, Damant GCC, Haldane JS. Prevention of compressed air illness. J Hyg, Camb 1908; 8:342-443.

10. Lehner CE, Will JA, Lightfoot EN, Lanphier EH. Decompression sickness in sheep: fatal chokes after 24-hour dives with altitude provocation. In: Bachrach AJ, Matzen MM, McAllister ST, eds. Proceedings of the eighth symposium on underwater physiology. Bethesda, MD: Undersea Medical Society, 1984:191-200.

11. Bell PY, Burgess DW, Summerfield M, Towse EJ. The effect of presaturation on the maximum submarine escape depth of goats and the implications for human research. Ibid.:241-248.

12. Heller R, Mager W, von Schrotter H. Luftdruckerkrankungen mit besonder Berucksichtigung der sogenannten Caissonkrankheit. Vienna: Alfred Holder, 1900.

13. Keays FL. Compressed air illness, with a report of 3,692 cases. Publ Cornell Univ Med Coll 1909; 2:1-55.

14. Levy E. Compressed-air and its engineering importance, with a report of cases at the East River tunnels. Tech Paper Bur Min, Wash 1922: 285:1-46.

15. Duffner GJ, Van Der Aue OE, Behnke AR. Treatment of decompression sickness: An analysis of 113 cases. Report No. 3, Naval Medical Research Institute and Experimental Diving Unit, 1946.

16. Hayashi K, Kitano M, Kawashima M, Torisu T, Matsuoka S. Studies of decompression sickness in Japanese fisherman. In: Shilling CW, Beckett MW, eds. Proceedings of the sixth symposium on underwater physiology. Bethesda, MD: Federation of American Societies for Experimental Biology, 1978:547-554.

17. Rivera JC. Decompression sickness among divers: an analysis of 935 cases. Mil Med 1964; 129:314-334.

18. Slark AG. Treatment of 137 cases of decompression sickness. J Roy Nav Med Serv 1964; 50:219-225.

19. Kizer K. Dysbarism in paradise. Hawaii Med J 1980; 39:109-116.

20. Golding FC, Griffiths P, Hempleman HV, Paton WDM, Walder DN. Decompression sickness during the construction of the Dartford Tunnel. Brit J Indstr Med 1960; 17:167-180.

21. McCallum RI. Decompression sickness: a review. Brit J Indstr Med 1964; 25:219-225.

22. Erde A, Edmonds C. Decompression sickness: a clinical series. J Occup Med 1975; 17:324-328.

23. Torrey SA, Webb SC, Zwingelberg KM, Biles JB. Comparative analysis of decompression sickness: type and time of onset. J Hyperbaric Med 1987; 2:55-62.

24. Dick APK, Massey EW. Neurologic presentation of decompression sickness and air embolism in sport divers. Neurology 1985; 35:667-671.

25. Weathersby PK, Homer LD, Flynn ET. On the likelihood of decompression sickness. J Appl Physiol 1984; 57:815-825.

26. Lehner CE, Palta M, Adler GG, Lightfoot EN, Lanphier EH. Prediction of DCS incidence from no-stop air dives. Undersea Biomed Res 1985; 12:42 (Suppl).

27. Lillo RS, Flynn ET, Homer LD. Decompression outcome following saturation dives with multiple inert gases in rats. J Appl Physiol 1985; 59:1503-1514.

28. Weathersby PK, Survanshi SS, Homer LD, Hart BL, Nishi RY, Flynn ET, Bradley ME. Statistically based decompression tables I. Analysis of standard air dives: 1950-1970. Bethesda, MD: Naval Medical Research Institute, Report No. 85-16: March 1985.

29. Weathersby PK, Hays JR, Survanshi SS, Homer LD, Hart BL, Flynn ET, Bradley ME. Statistically based decompression tables II. Equal risk air diving decompression schedules. Bethesda, MD: Naval Medical Research Institute, Report No. 85-17: March 1985.

30. Weathersby PK, Survanshi SS, Hays JR, MacCallum ME. Statistically based decompression tables III. Comparative risk using U.S. Navy, British, and Canadian standard air schedules. Bethesda, MD: Naval Medical Research Institute, Report No. 86-50: July 1986.

31. Vann RD. The production of decompression procedures at Duke University. In: Nashimoto I, Lanphier EH, eds. Decompression in surface-based diving. Bethesda: Undersea Medical Society, 1987:70-75.

32. Lin Y. Decompression procedures for air saturation dives based on bubble threshold in animals. Ibid.:84-89.

33. Baker RJ, Nelder JA. The GLIM system, generalized interactive modelling (version 3.77, update 0). Oxford: Numerical Algorithms Group, Royal Statistical Society, 1985.

34. Nelder JA, Wedderburn RWM. Generalized linear models. J Roy Stat Soc A 1972; 135:370-384.

35. Van Der Aue OE, Kellar RJ, Brinton ES, Barron G, Gilliam HD, Jones RJ. Calculation and testing of decompression tables for air dives employing the procedure of surface decompression and the use of oxygen. Washington, DC: Experimental Diving Unit, Report No. 13-51, November 1951.

36. Thalmann ED. Development of a decompression algorithm for constant 0.7 ATA oxygen partial pressure in helium diving. Panama City, FL: Navy Experimental Diving Unit, Report 1-85, April 1985.

37. Berghage TE, David TD, Dyson CV. Species differences in decompression. Undersea Biomed Res 1979; 6:1-13.

38. Schmidt-Nielsen K. Scaling, why is animal size so important? Cambridge University Press, 1984.

39. Weathersby PK, Homer LD. Solubility of inert gases in biological fluids and tissues: a review. Undersea Biomed Res 1980; 7:277-296.

40. Mubarak SJ, Hargens AR. Compartment syndromes and Volkmann's contracture. Philadelphia: W.B. Saunders Company, 1981.

41. Elliott DH, Hallenbeck JM. The pathophysiology of decompression sickness. In: Bennett PB, Elliott DH, eds. The physiology and medicine of diving and compressed air work. London: Balliere and Tindall, 1975:435-455.

42. Hills BA, James PB. Spinal decompression sickness: mechanical studies and a model. Undersea Biomed Res 1982; 9:185-201.

43. Leitch DR, Hallenbeck JM. Somatosensory evoked potentials and neuraxial blood flow in central nervous system decompression sickness. Brain Res 1984; 311:307-315.

44. Adams WMC, Lehner CE, Dubielzig RR, Wilson JW, Palta M, Lanphier EH. Dysbaric osteonecrosis in sheep: a model of aseptic bone necrosis. The Physiologist 1985; 28:308 (Abst).

45. Fischhoff B, Lichtenstein S, Slovic P, Derby SL, Keeney RL. Acceptable risk. Cambridge: Cambridge University Press, 1981.

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DISCUSSION

CAPTAIN THALMANN: You made the statement that divers have more type II than type I DCS. Might that not be a function of the type of diving? In just about every well-controlled series of dives for decompression table development, type I DCS generally predominates over type II.

DR. LEHNER: Divers have a higher relative frequency of CNS-DCS than do tunnel workers, based on a retrospective survey of literature.

CAPTAIN THALMANN: I might offer a much simpler explanation for your observation of a higher spinal cord DCS incidence on short, deep rather than long, shallow dives. At 190 feet, the no-"D" limit is only 10 minutes, but at 60 feet, it is 60 minutes. A 1 minute error at 190 feet (11 minutes) is much more significant than a 1 minute error at 60 feet (61 minutes). The fact that a dive is deep means that no-"D" limit is short. Perhaps you're seeing more type II DCS because an error on a deep dive is much more serious than an error on a shallow dive.

DR. LEHNER: It's my recollection that we had a lower overall incidence of DCS in our half-hour dives than on the 4- or 24-hour dives but considerably higher incidence of central nervous system decompression sickness. Nevertheless, you are quite correct that a small error is more important at the greater depths.

CAPTAIN THALMANN: You used our He-O_2 dive data but didn't compare them to our air data. We found almost the same bends incidence for helium as for nitrogen, and we did not see any increase in CNS symptoms on air for the shorter, deeper dives. The biggest difference between the two series was that there were almost twice as many type II symptoms on helium as on nitrogen, but no particular relationship between type II symptoms and the dive depth.

DR. ZANNINI: Dr. Lehner, I have three comments about your observation. First, in Italy, we have about 100 cases a year of decompression sickness among sport divers. These were mainly spinal cord. These accidents are mostly due to errors such as blow-up and panic. This is different from professional divers who follow decompression procedures exactly. Second, we are studying bubble formation within the U.S. Navy tables. There is lower bubble formation after deeper and shorter dives. Maybe this is due to the need for deeper stops, as Dr. Lehner suggested. Third, we adopted an ascent rate of 10 msw/minute for professional divers many years ago instead of 18 meters/minute with U.S. Navy tables. We have followed a lot of professional divers who performed about 24,000 dives at 10-50 msw without bends. This included repetitive dives.

DR. LEHNER: Your observation is interesting and bears upon Dr. Francis' model of spinal cord decompression in dogs. I think the speed of decompression strongly influences the incidence of spinal cord decompression sickness. With animals, our decompressions have been at the conventional rate of 60 feet/minute. It will be interesting to look at the protective effect of a shallow water stop or a slow ascent near the surface upon the relative proportion of CNS-DCS versus limb bends.

MR. IMBERT: In a study we published on the French air table, we recorded a relatively small number of type II decompression incidents, 6 cases in over 60,000 dives. To our surprise, however, two or three cases were in the no-stop dives. Dr. Shields also found several cases of type II decompression sickness in the no-stop area. How would you account for these cases of type II decompression sickness for shallow and long exposure?

DR. LEHNER: I don't have an answer.

MR. IMBERT: Have you been able to differentiate between in-water decompression and surface compression?

DR. LEHNER: There simply aren't many such reports of human decompression sickness in the literature.

DR. CHAYKA: Five or six years ago, commercial scalloping in Maine was done in cold water at an average depth of 10-15 fsw. The average scallop divers were home-trained. Few had been through a basic scuba course. They used wet suits, which limited diving time to 1-2 hours. Over 5 years, two things have happened. Dry suits are used virtually without exception and the scallop beds have been cleaned out to a depth of 70 fsw. The average dive is now between 70 and 110 fsw. These divers believe that if they could dive as long as they wanted to at 10 fsw with a wet suit, they can make similar dives to 110 fsw with a dry suit. Our average DCS case has made somewhere between 15 and 20 repetitive dives over a 4-hour period to a depth of 100 fsw. They leave the Navy tables by their second repetitive dive, and I get lost between there and 15 or 20 dives. There are many cases of type I bends, and as Dr. Kindwall pointed out, many of these go unreported. It is of interest, however, that we've seen no type II bends whatsoever, and I don't think we're missing very many cases. In contrast, the only three cases of spinal cord bends we have seen have all been very serious. These occurred at relatively deep depths, 100 to 150 fsw, on a single dive, and all made rapid ascents or very rapid ascents, either after running low on air or panicking. Contrasting this to the scallop divers who don't seem to develop type II bends, the scallop diver usually works with one topside tender in a lobster boat. The lobster traps are pulled in with hydraulic haulers at a rate of 60 fsw/min or less. The scallop diver rides the bucket up and down every time he makes a dive. These observations suggest that ascent rate is an important factor in determining whether pain-only or spinal decompression sickness will occur. Has anyone studied the affect of ascent rate on the type of bends which results?

DR. LEHNER: I think the rate of decompression certainly is important. Our conclusions are that there may be strong association between the rate of decompression and the incidence of spinal cord decompression sickness.

DR. KINDWALL: Dr. Chayka, what was the surface interval between the scallop divers dives? Was it a matter of just a couple of minutes?

DR. CHAYKA: They rode the basket up, unloaded it into the boat, and went right back down. Probably less than 5 minutes.

DR. KINDWALL: Any bubble would get quickly recompressed?

DR. CHAYKA: That's true.

DR. KINDWALL: It sounds as though your divers were well habituated, and habituation can make possible almost any kind of awful exposure such as we find tunnel workers experiencing. Dr. Lehner, I presume you were careful not to habituate your animals.

DR. LEHNER: We always allowed, to my best knowledge, at least 3 days recovery time. Normally, they only dived once a week, which shouldn't produce habituation based on Ward's evidence and evidence from the literature.

DR. KINDWALL: So, even for CNS you can get habituation protection.

DR. LEHNER: We have no experimental evidence for habituation in CNS DCS.

DR. LUNDGREN: Twenty years ago, I was involved with goat experiments to determine if the type of decompression symptoms could be selected by

specifically supersaturating either the fast or slow tissues (1). To create a high supersaturation in slow tissues, the animal was exposed for a relatively long time at a desired pressure and then given a period of oxygen breathing to wash nitrogen from rapid tissues. After this, we decompressed to altitude and looked for symptoms. To supersaturate the fast tissues, we denitrogenated the animals by oxygen breathing at 1 ATA and then gave them a short exposure to high pressure air. The idea was that these different saturation profiles would generate different types of symptoms. The most impressive outcome of these studies was that the symptoms were independent of where we placed the supersaturation. Would you care to comment on our findings relative to your observations that short, deep dives seem most likely to induce CNS symptoms. I presume this invites the thought that we are dealing with high gas pressures in rapidly saturating tissue.

DR. LEHNER: That is our thinking at the moment, particularly with the spinal cord. I'm interested in the frequencies of limb bends and spinal cord bends in your animals. It sounds like an elegant way of looking at the problem.

DR. JAMES: In support of Dr. Lundgren's comments, an early paper reported on the detection of bubbles in the vena cavae of animals using implanted Doppler probes. Bubbles were detected at 100 fsw after dives to 165 fsw. If the ascent rate is too rapid, these bubbles which are generated deep may cross the pulmonary filter. If there is a high lipid content tissue in the CNS, such as spinal cord which saturates relatively fast, it might predispose to serious symptoms.

DR. VANN: Can you differentiate between short, deep dives and long, shallow dives insofar as intravascular bubbles are concerned?

DR. LEHNER: In our Doppler precordial monitoring after air diving, we have never seen symptomatic animals, with either limb or spinal cord decompression sickness (frank paraplegia or quadriplegia) without evidence of venous gas bubbles or emboli (VGE). I wouldn't want to draw a conclusion relative to VGE and spinal cord DCS or limb bends, however, without further study.

DR. JAMES: Nevertheless, the deeper the bubble arises, the more chance it has of crossing the pulmonary filter. Indeed, several people this afternoon have pointed out that serious symptoms are associated with rapid ascent in which the diver effectively omits decompression. This may generate a large number of small bubbles which pass through the pulmonary microcirculation because there isn't the time for them to grow and be trapped.

DR. LEHNER: We found the maximum Doppler bubble counts in sheep after shallow, 4-hour exposures to occur about 30 minutes after surfacing. After the 4- and 24-hour dives, there is often evidence of respiratory decompression sickness, the chokes, when spinal symptoms occur. Chokes are less common after deep, 30-minute dives when spinal symptoms occur.

DR. JAMES: Would you suggest that bubbles pass through the lungs?

DR. LEHNER: Yes, under some conditions.

DR. JAMES: Jean-Pierre Imbert raised the question of type II decompression sickness after shallow diving. This is common in commercial diving where bottom time is logged as at the maximum depth of the dive, but multiple intermediate ascents which are not logged seem to give rise to a greater likelihood of CNS-decompression sickness. The recompression which occurs during descent on the repetitive dives may shrink the bubbles and encourage their transpulmonary passage.

DR. BENNETT: The Divers Alert Network has found that spinal cord injury is more common in sports divers than type I in bends. When I bring this up, people always say, "Ah, but they don't report the type I bends." That may be the case, but the fact is that the predominant injuries are about 60 to 65% spinal cord. This frequently occurs after 20-30 minutes at 60-80 fsw, and I believe that the rapid ascent rate is a contributing factor. Glen Egstrom, for example, measured sport diver ascent rates and found the 120 fsw/minutes rather than 60 fsw/minutes was not uncommon. It must be the faster tissues that are affected by these fast rates. The computer manufacturers are reducing their ascent rates to 30 fsw/minutes or even to 15 fsw/minutes in the last 20 fsw to the surface. If there is less spinal cord injury with these computers, fast ascent rates may be implicated as a contributing mechanism.

DR. BALLDIN: We again made 39 msw dives for 10 minutes and 15 msw dives for 100 minutes. Both dives were followed by a 3 hour surface interval and then a hypobaric exposure at 3000 meters of altitude where we looked for intracardiac gas bubbles. We found about 90% of the subjects had bubbles after the shallow, long dive, but only about 30% did after deep, short dive.

DR. MILLER: There is a certain incidence of transient cerebral embolism within apparently no-stop decompression limits that appears to get better, but develops into severe spinal cord decompression sickness. It is as if the transient event, which often lasts only a few minutes and often does not require treatment, precipitates a severe spinal cord event in a diver whose inert gas load would appear to be insufficient to cause serious symptoms.

DR. FRANCIS: Dr. Lehner, what was the onset time for the spinal cord DCS of your sheep? This might provide information on the rate of gas washout from the spinal cord.

DR. LEHNER: Your mean onset time of spinal cord decompression sickness was about 10 minutes, was it not?

DR. FRANCIS: Yes, about 55% of cases presented within 10 minutes of surfacing.

DR. LEHNER: In our cases of spinal cord decompression sickness in sheep and goats, the onset time was approximately 30 minutes, somewhat longer than you observed. Your profile was deeper than ours, and you were working with the dog, a smaller animal. I would assume, based on size scaling, uptake and elimination of gases would be faster in dogs than in goats and sheep.

DR. HAMILTON: There is a type of diving practiced in Lake Erie that I would call continuation diving. The diver spends 10 minutes at 100-200 fsw, goes to the surface, and 5 or 10 minutes later makes a similar dive. He does this for up to 10 dives per day, and then jumps in the chamber where he is decompressed as if he did a dive at his deepest depth for the sum of all his bottom times. I know of some 20,000 logs of dives of this nature although I have not had a chance to go through them. They do not seem to have a decompression sickness problem, and there is certainly no unusual amount of CNS decompression sickness.

DR. VAN LIEW: Why not put a bubble trap in the arterial circulation of an experimental animal so we can find out about the possibilities of embolization in various dives? All you need is a wide space in the artery to let the bubbles float to the top.

SUSCEPTIBILITY TO DECOMPRESSION SICKNESS

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As an etiology for decompression sickness (DCS), it has been proposed that production of bubbles in the circulatory system results in activation of the complement system and that the consequences of this activation is DCS. This hypothesis accounts for the individual variation in susceptibility to DCS through the natural variation in sensitivity of individuals to complement activation. It accounts for the reductions in susceptibility of individuals undergoing repeated compression-decompression cycles (i.e. acclimatization) through the depletion of the complement proteins that results when the complement system is activated by bubbles introduced into the circulatory system when an individual undergoes compression-decompression cycles. And this hypothesis suggests that the return to normal susceptibility that results when an individual is no longer exposed to compression-decompression cycles (i.e. de-acclimatization) arises from the natural tendency of the body to restore the complement proteins to their normal concentration, once the depletion of the complement proteins by circulatory bubbles has been stopped. We examine the viability of this hypothesis by determining if these variations in susceptibility can be induced in animals by manipulation of their complement proteins. It is found that they can be reproduced.

If a group of individuals undergoes the same compression-decompression cycle, not all of them will experience any symptoms of DCS. In a study with 1,021 men in which there were 397 cases of DCS, it was noted that 4% of the men accounted for 49% of the cases of DCS (1). Further, there is evidence of an "acclimatization" when an individual undergoes repeated exposure to elevated pressures. Golding et al. (1) report an exponential decrease in the incidence of DCS with repeated exposure to elevated pressures of the same group of individuals. There is a second change in individual susceptibility that results in the loss of his acclimatization. The percentage of exposures to elevated pressure that resulted in DCS was doubled as a result of two days without experiencing a compression-decompression cycle and the percentage was four times greater when the period without exposure was greater than six days.

Doppler ultrasonic monitoring of individuals after they have undergone a compression-decompression cycle has provided evidence that indeed bubbles are present in the circulatory system; however, the presence of bubbles does not insure DCS because bubbles have been noted in the circulatory system of individuals who have no symptoms of DCS sickness (2).

Thus three characteristics of DCS that must be explained by any proposed etiology of this syndrome are: 1) the variation in susceptibility to DCS of individuals, all of whom have experienced bubbles in their circulatory system; 2) the reduction in susceptibility to DCS that results from repeated exposure to compression-decompression cycles, i.e. the acclimatization of individuals and the return to normal susceptibility of acclimatized individuals when they are no longer subjected to pressure cycles.

A hypothesis has been introduced that claims the complement proteins mediate the symptoms of DCS that occur within a few days of the exposure to elevated pressures (3,4,5). It claims that the more sensitive individuals are to complement activation, the more susceptible they are to DCS, and accounts for the variation in susceptibility of individuals to DCS through natural variation in their sensitivity to complement activation. We examine the complement hypothesis to determine if it can explain: 1) the variation in susceptibility of individuals to DCS; 2) acclimatization, and 3) de-acclimatization. We show that these characteristics can be produced in animals by manipulating their complement proteins in a manner that would be predicted from the complement hypothesis.

Complement Activation By Air Bubbles

When gas bubbles are introduced into plasma, a protein layer is formed at the plasma-gas interphase (6,7,8). If the adsorbed proteins are altered from their natural state, as could be reasonably expected (9), then the defense mechanisms of blood would be expected to respond as they would to the presence of any other foreign surface. One of the defense systems that could be expected to be mobilized by the presence of this protein surface is the complement system of blood plasma.

There are at least twenty proteins that are associated with this sequentially acting, plasma enzyme system. When the complement system is activated by a foreign surface along either of its two possible activation pathways, certain of the proteins are fragmented. One portion remains on the foreign surface and the other returns to the fluid phase. In particular, C3 and C5 are fragmented to produce the fluid phase components C3a and C5a. Because these proteins are fragmented in the process of complement activation, they are consumed and must be replaced to restore their concentration to normal.

To determine if complement activation would result from the presence of bubbles in the circulatory system and to determine if there is any relation between the degree of complement activation in an individual's plasma and his susceptibility to DCS, a series of experiments were performed with humans.

Blood was collected from each of fifteen males. After the plasma had been separated, each sample was divided into two portions. One portion was incubated at 37°C for thirty minutes and served as the control. Air bubbles were introduced into the other portion, and it was incubated with the air bubbles in the same fashion (3,5). The degree of complement activation was then assessed by measuring the concentration of C3a, C4a, and C5a in the two plasma samples. It was concluded that the air bubbles indeed activated the complement system of "certain individuals", and that the activation was along the alternative pathway (5) i.e. the activation sequence is C3, C5, C6 . . . C9. Other individuals in the group showed no signs of complement activation as a result of incubating their plasma with air bubbles. If an individual produced less than 25 ng/ml, he was classified as Insensitive to complement activation and those producing more as Sensitive. The measured concentration of C5a for the two groups of individuals is summarized in Table 1. For the Sensitive group of individuals, the complement activation (i.e. the C5a concentration) was significantly greater than the controls, but there was no significant difference between these samples for the Insensitive

group.

Table 1

Human Decompression Sickness

	Average C5a Concentration, ng/ml			Dive Series		
	Control Mean ± SE	Air Bubbles Mean ± SE	Paired t - test	Average Bubble Grade	Total P(DCS)	Observed DCS
Sensitive Individuals	25 ± 4.0	43 ± 6.0	Different P<0.01	2.8	0.504	5 of 11
Insensitive Individuals	5.5 ± 1.4	6.0 ± 1.4	Not Different	3.1	1.014	0 of 14

In the second series of experiments, the individuals were then subjected to a series of 25 air dives, and decompressed according to the DCIEM procedure for air dives (10). The dive profiles to which an individual was subjected were chosen without reference to whether an individual was Sensitive or Insensitive. All dives were severe enough to produce bubbles that could be detected with Doppler monitoring. The probability of DCS occurring on each of these profiles, P(DCS), has been assessed on the basis of historical evidence using the maximum likelihood method (5,11).

The severity of the dive profiles to which the Sensitive and Insensitive individuals were subjected may be judged by the total value of P(DCS) for each of the two dive series. As may be seen from the results shown in Table 1, according to this measure, the Insensitive individuals were subjected to the more severe dive profile. Another method of judging the severity of the dive profiles is from the average bubble grade that was assigned on the basis of ultrasonic Doppler monitoring (2,5). According to this measure as well, the Insensitive individuals were subjected to the more severe profile.

As may be seen in the last column of Table 1, the Insensitive group of individuals did not experience any cases of DCS. By contrast, the Sensitive group experienced DCS on 45% of their dive profiles, even though the dive profiles to which the Sensitive group was subjected was less severe than the dives to which the Insensitive group was subjected (3,5).

The clear implications of these results are that the complement system mediates decompression sickness. The presence of bubbles in the circulatory system of an individual is clearly not sufficient to cause DCS. If the complement system of the individual is sensitive to activation by air bubbles and bubbles are produced in the circulatory system of the individual, then the individual is susceptible to DCS and stands a high probability of becoming ill. Thus the variation in susceptibility of individuals to DCS results from their native sensitivity to complement activation.

Changes In Susceptibility To DCS - Acclimatization

Since bubbles can activate the complement system and the complement proteins are fragmented in the process, circulatory bubbles would destroy the complement proteins as

they activate the complement system. Provided it takes the body a period of time to replace the complement proteins once they have been depleted, the effect of repeated production of bubbles in the circulatory system would be to decomplement the individual. Since the results above indicate that the complement system mediates DCS, the depletion of the complement proteins by circulatory bubbles could be responsible for the acclimatization of divers. To investigate this possibility, a series of experiments has been conducted with rabbits, some of which were pharmacologically decomplemented (4) so that the concentration *in-vivo* of certain of their key complement proteins were reduced to a small fraction of their normal concentration.

A plasma sample was collected from each rabbit and each sample divided into three portions; one portion was incubated with air bubbles, another with zymosan, and a third as a control. Zymosan is obtained from the cell walls of yeast and is known to be a strong activator of the complement system by the alternative pathway. Each portion of an incubated plasma sample was assayed for complement activation using the neutrophile aggregation test (4). As with the human subjects, it was found that provided the complement system of a rabbit was sufficiently sensitive, incubation of its plasma with air bubbles resulted in complement activation. A rabbit was classified as Sensitive provided the degree of complement activation in its plasma sample incubated with zymosan was at least three times larger than that in its control sample.

The results obtained for the Sensitive and Insensitive rabbits are summarized in Table 2. The complement activation is expressed as a percentage of that found in the plasma sample incubated with 5 mg of zymosan per ml of plasma. For the Sensitive rabbits, significant complement activation was found to result from incubating their plasma samples with air bubbles; however, there was no significant complement activation measured in the plasma samples of the Insensitive rabbits incubated with air bubbles.

Table 2
Complement Activation in
Rabbit Plasma Incubated with Air Bubbles

	% Complement Activation of Sample Incubated with 5 mg Zymosan / ml plasma Mean ± SE		
Rabbit	Control (n = 5)	Air Bubbles (n = 5)	Paired t - test
Sensitive	19 ± 3.8%	41 ± 4.7%	Different (P<0.01)
Insensitive	72 ± 11%	78 ± 16%	Not Different
Decomplemented	92 ± 22%	80 ± 19.5%	Not Different

Also shown in this Table are the results obtained with decomplemented rabbits (4). Each rabbit in this group was administered a drug derived from the cobra venom factor Naja n. naja, i.e. CVF^{n}. This substance is known to be a strong convertase of both C3 and C5 (12). It has been shown with rocket immunoelectrophoresis that administering this drug three times to a rabbit at intervals of 24 hrs. reduces the concentration of C3 to a small fraction of its

normal concentration (4). If this component of the complement system were removed completely, it would not be possible to activate the complement system by either pathway.

After the rabbits had been decomplemented in this fashion, their plasma was collected and samples were incubated in the same fashion as were the samples from the normal rabbits (4). For the decomplemented rabbits, there was very little complement activation measured in the plasma samples incubated with zymosan, air bubbles, or in the control sample. The latter two produce approximately the same degree of complement activation, and samples incubated with zymosan only slightly more.

These results indicate that some rabbits have complement systems that are activated by incubation of their plasma with air bubbles, i.e. the Sensitive rabbits. Others show no signs of complement activation when their plasma is incubated with air bubbles (the Insensitive ones). Further, rabbits can be made Insensitive by decomplementing them.

Since decomplementing a rabbit *in-vivo* strongly reduces its capacity for activating complement, the next step was to determine if decomplementing the rabbits would protect them against decompression sickness (13,14). A chamber was constructed that allows a rabbit to be subjected to a pressure as high as 2 ATA, or as low as 0.2 ATA, while moving on a treadmill and breathing air or pure oxygen. Each rabbit was subjected to the pressure profile and exercise routine described in Table 3.

Table 3

Pressure Profile and Exercise Routine for Rabbits

Step 1.	With a rabbit in the chamber and breathing air, the pressure was increased to 2 ATA and maintained for 30 minutes. The rabbit was required to move on the treadmill for one minute, followed by a five minute rest. The treadmill moved at a rate of 1.3 m/min.
Step 2.	The pressure was reduced to 1 ATA and the gas changed so that the rabbit was breathing pure oxygen. It was maintained in this condition for 5 minutes.
Step 3.	The pressure of the pure oxygen was reduced to 0.2 ATA. If no signs of DCS were observed, the rabbit was maintained for a maximum of 30 minutes at this condition. The exercise cycle was changed to one minute of movement, followed by one minute of rest.

If during Step 3 of this procedure signs of DCS were observed, the animal was immediately returned to atmospheric pressure. The indications of DCS were taken to be erratic movement on the treadmill, such as dragging its rear legs or unusually lively behavior followed by loss of consciousness. All rabbits that experience DCS recovered immediately after they were returned to normal pressure.

Each rabbit in the study was subjected to the pressure and exercise routine described in Table 3 on three occasions. All rabbits in the study demonstrated symptoms of DCS on the first and the second occasion. The second occasion was at least five days after the first. One-half of the rabbits were decomplemented before they were subjected to the pressure profile and exercise routine for the third time.

The results are summarized in Table 4. Note that all of the normal rabbits (i.e. those with

their native complement system intact) demonstrated symptoms of DCS on the third occasion as they had on the previous two occasions when they were again subjected to the protocol described in Table 3. By constrast, none of the rabbits that were decomplemented showed any symptoms of DCS on the third occasion, although they had on the previous two occasions.

Table 4

Effect of Decomplementation On Decompression Sickness in Rabbits

* Rabbit Preparation	% DCS When Subjected to Pressure Profile for Third Time
None	100% (n = 3)
Decomplementation	0% (n = 3)

*All rabbits were observed to have symptoms of DCS when subjected to the same pressure profile on two previous occasions.

Five or more days after the rabbits were subjected to the pressure profile and exercise routine for the third time, their plasma was collected and their sensitivity to complement activation by zymosan and by air bubbles was established using the neutrophil aggregation test (4). All of the rabbits in this study were found to be Sensitive according to the criterion described above.

The clear implication of the above results is that decomplementing a rabbit reduces its susceptibility to decompression sickness. One question which arises is whether the decomplementing procedure changes any other basic parameter. The values of three other parameters have been investigated (14). Their values, along with the normal values of these parameters, are listed in Table 5. As may be seen there, the decomplemented animal had an approximately normal fibrinogen concentration. The white cell count was slightly elevated, as was the platelet count. The reactivities of the platelets from the decomplemented and the normal rabbits were compared to obtain the results shown in the fifth column of Table 5. A group of four rabbits was decomplemented as described above. Blood was collected from each and a platelet suspension formed in which the platelet concentration was in the range from 450 to 550 x 10^3 platelets/μl. Portions of each suspension were placed in an aggregometer and then aggregation was induced by adding ADP. The degree of platelet aggregation was measured at thirty seconds after the addition of ADP. The average value of the aggregation at this time was determined for both the normal and for the decomplemented rabbits. The measured degree of platelet aggregation for the decomplemented rabbits is expressed as a fraction of that for the normal rabbit. As may be seen in Table 5, the platelets of the decomplemented animal are approximately 45% as responsive to ADP as are the platelets of the normal animal.

Table 5

Effect on Blood Parameters of Decomplementing Rabbits *In-vivo*

Rabbit	Fibrinogen g/l Mean ± SE	10^3 White Cells per μ l Mean ± SE	10^3 Platelets per μ l Mean ± SE	ADP Induced Platelet Agg. Mean ± SE
Normal	2.6 ± 0.1 (n = 8)	10.1 ± 0.27 (n = 8)	362 ± 19 (n = 8)	100%
Decomplemented	2.84 ± 0.01 (n = 3)	11.7 ± 0.24 (n = 3)	493 ± 28 (n = 3)	45 ± 2% (n = 4)

It is doubtful that this reduction in the reactivity of the platelets could account for the absence of DCS in the rabbits that is indicated by the results listed in Table 4. For example, Philp and co-workers (15,16) have shown that inducing thrombocytopenia in rats does not protect them against DCS. There is substantial evidence to indicate that platelets are involved in the pathophysiology of DCS; however, there is no evidence to indicate that platelets mediate DCS.

The only blood parameter that we have identified as being substantially changed by the decomplementing procedure is the concentration of the plasma protein C3 (4). Others have shown that C5 is also reduced by the decomplementation procedure that we have adopted (12). With both of these proteins removed, the first two proteins in the sequence leading to complement activation by the alternative pathway are removed from the plasma of the animal *in-vivo*. Thus the complement activation by the bubbles would be prevented in the decomplemented animals, and this is seen in Table 4 to protect the rabbits against DCS. The decomplemented rabbits behave in the same manner as do the acclimatized divers in the sense that they both appear "immune" to DCS.

De-acclimatization

According to the complement hypothesis then, the de-acclimatization that was reported in Ref. 1 would be expected to occur when the individual stopped experiencing the pressure profiles because his body would replenish the complement proteins in his blood plasma. This aspect of the complement hypothesis can be examined to some degree by determining whether the time required for the body to replenish the complement proteins is consistent with the period required for the de-acclimatization.

A group of 5 rabbits was studied. On the first day, a blood sample was taken from each, the plasma separated and stored at -70°C for later examination and afterward each rabbit was given its first injection of CVF^n. Twenty-four hours later, the process was repeated a second time and 48 hours later it was repeated a third time. No further injections were given to any of the rabbits. One of the rabbits was sacrificed approximately 48 hours after the first injection, and its sensitivity to complement activation at the different times was then assessed by incubating separately each sample of its plasma, taken at the three different times, with zymosan and a control. Four of the rabbits were continued for a third day and a plasma sample collected from each of them. Three of them were then sacrificed and their sensitivity

to complement activation assessed in each of the plasma samples that had been collected from them. One additional rabbit was then continued for a fourth and a fifth day, with plasma samples taken on each of these days as well. It was then sacrificed and its sensitivity to complement activation assessed at each of the five days of the study.

These results are summarized in Fig. 1, where the average value of the ratio of complement activation in the plasma samples incubated with zymosan to that for the control samples has been plotted against time. When this ratio is greater than three for a rabbit, it has been previously shown that the complement system of the rabbit is activated by air bubbles, i.e. the rabbit is Sensitive. However, it has also been shown that for those rabbits that were decomplemented this ratio approached unity, and they did not show any symptoms of DCS when they were subjected to the pressure profile described in Table 3. As may be seen from the results shown in Fig. 1, the rabbits were Sensitive before the first injection; however, 24 hours later they would be classified as Insensitive. They were fully decomplemented after the second or third injection. In this state, the rabbits would correspond to fully acclimatized human subjects.

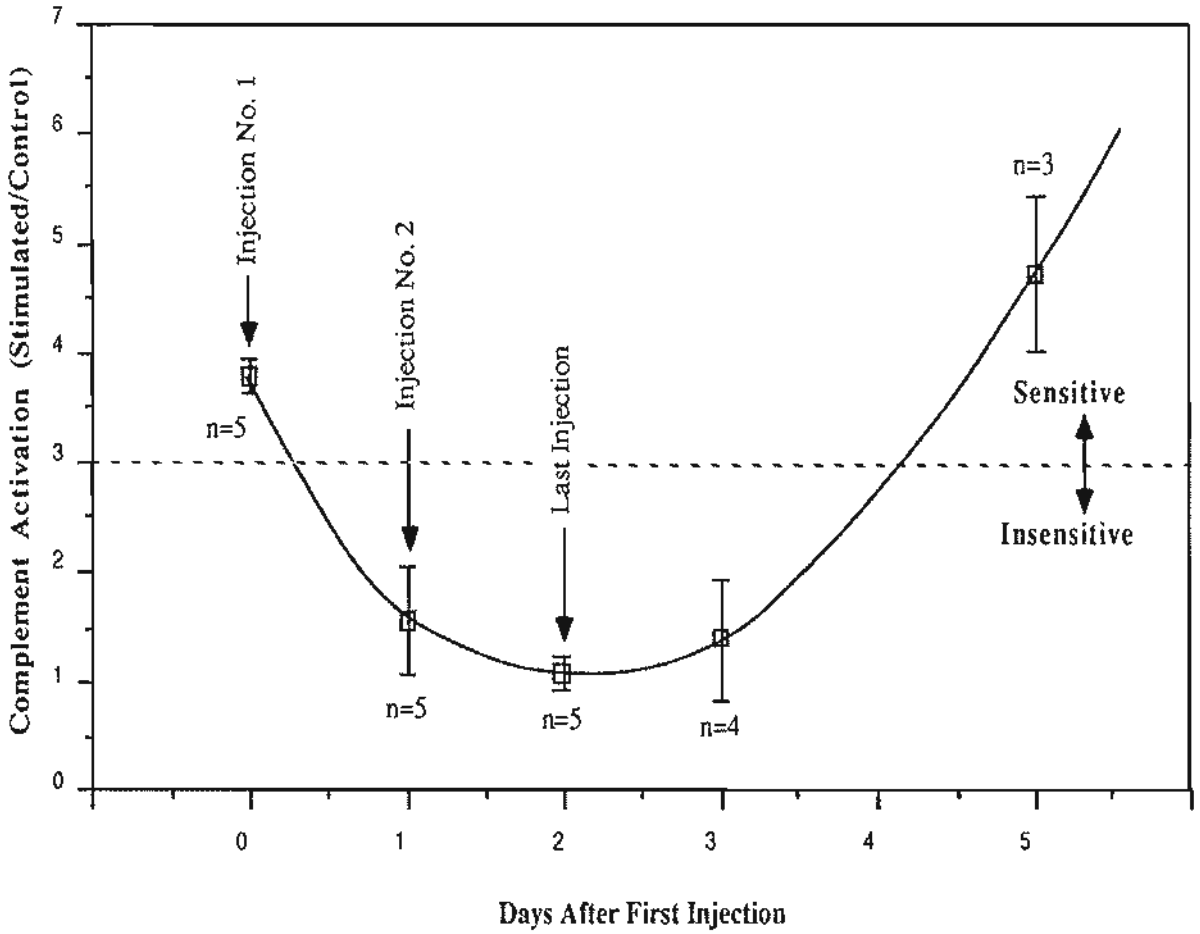

Figure 1 **The ratio of complement activation in rabbit plasma incubated with zymosan to that in the control samples. The degree of complement activation was assessed with the neutrophil aggregation test.**

After the CVF^n injections were stopped, it took approximately two days before the rabbits would be classified as being Sensitive again. This period corresponds well with that observed by Golding et al. (1) for the human subjects. After a two day interval without experiencing a pressure profile, they found a susceptibility rate for the human subjects that was approximately twice the one before the interval. For progressively longer intervals without experiencing a pressure profile, the human subjects were found to have progressively higher rates of susceptibilities.

Conclusions

1) Human subjects that are susceptible to DCS can be identified before they are subjected to a pressure profile by performing a complement activation sensitivity test on a blood sample taken from the individual. Those individuals who are sensitive to complement activation by air bubbles are susceptible to DCS. The variation in susceptibility to DCS results from the natural variation in sensitivity of an individual's complement system to activation. To-date these conclusions are only supported by a series of 25 dives with 15 individuals.

2) Rabbits can be protected against DCS by decomplementing them before they are subjected to a pressure profile.

3) Since certain of the key complement proteins are "fragmented" by the complement activation process, an animal can become "decomplemented", i.e. depleted of these proteins, as a result of repeated activation. Bubbles have been shown to activate the complement system; thus repeated exposure to pressure profiles that produce bubbles in the circulatory system would decomplement the individual and thereby reduce his susceptibility to DCS, i.e. he would become acclimatized. De-acclimatization would thus result if he were to stop his exposure to pressure profiles for a period. The period of time before an initially decomplemented rabbit returns to the Sensitive state is between one and three days. Thus the complement hypothesis provides an explanation for the decrease in susceptibility that follows repeated exposure to compression-decompression cycles and for the return to normal susceptibility that results when the exposure to compression-decompression cycles of an acclimatized individual is interrupted.

References

1. Golding FC, Griffiths PD, Paton, WDM, Walder DN, Hempleman HV. Decompression sickness during the construction of the Danford Tunnel. Br. J. Ind. Med. 1960; 17: 167-180.
2. Nishi RY, Kisman KE, Eatock BC, Buckingham IP, Masurel G. Assessment of decompression profiles and divers by Doppler ultrasonic monitoring. In: Bachrach AJ and Matzer MM, eds. Proceedings of the Seventh Symposium on Underwater Physiology, Bethesda, MD: Undersea Med. Soc., 1981: 717-728.
3. Ward CA, McCullough D, Fraser WD. Relation between complement activation and susceptibility to decompression sickness. J. Appl. Physiol. 1987; 62:1160-1166.
4. Ward CA, Koheil A, McCullough D, Johnson WR, Fraser WD. Activation of complement at plasma-air or serium-air interface of rabbits. J. Appl. Physiol. 1986; 60: 1651-1658.
5. Ward CA, Weathersby PK, McCullough D, Fraser WD. Identification of individuals susceptible to decompression sickness. To appear in the Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology.

6. Philp RB, Inwood MM, Warren BA. Interactions between gas bubbles and components of the blood: implications in decompression sickness. Aerosp. Med. 1972; 43:946-953.
7. Warren BA, Philp RB, Inwood MM. The ultrastructural morphology of air embolism: platelet adhesion to the interface and endothelial damage. Br. J. exp. Path. 1973; 54:163-172.
8. Lehto VP, Kantola I, Tervo T, Laitinen LA. Ruthenium red staining of blood-bubble interface in acute decompression sickness in rats. Undersea Biomed. Res. 1981; 8:101-111.
9. Ward CA, Stanga D. Biological activity of fibrinogen adsorbed on synthetic materials. J. Colloid and Interface Sci. 1986; 114: 323-329.
10. Lauckner GR, Nishi RY, Eatock BC. Evaluation of the 1983 decompression model for compressed air diving. Defence and Civil Institute of Environmental Medicine, Downsview Ontario, Canada, 1984; Report No. 84-R-72.
11. Weathersby PK, Homer LD, Flynn ET. On the likelihood of decompression sickness. J. Appl. Physiol.: Respirat. Environ. Excercise Physiol. 1984; 57: 815-825.
12. Zabern I, Hinsch B, Przyklenk H, Schmidt G, Vogt W. Comparison of Naja n. naja and Naja h. haje cobra-venom factors: correlation between binding affinity for the fifth component of complement and mediation of its cleavage. Immunobiology 1980; 157:499-514.
13. Ward CA, Yee D, McCullough D, Stanga D, Fraser WD. Complement proteins mediate decompression sickness (DCS) in rabbits. Undersea Biomedical Research (Supplement) 1987; 14: 16.
14. Ward CA, Yee D, McCullough D, Stanga D, Fraser WD. Factors controlling decompression sickness in rabbits. Submitted for publication.
15. Clark ML, Philp RB, Gowdey CW. Changes in platelets and lipids in experimental aeroembolism and bends. Aerospace Med. 1969; 40: 1094-1098.
16. Philp RB, Gowdey CW. Platelets as an etiological factor in experimental decompression sickness. J. Occupational Med. 1969; 11: 257-258.

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DISCUSSION

DR. **CHRYSSANTHOU:** I'm very happy that finally somebody drew attention to the fact that in decompression sickness something else is happening in addition to the physical and mechanical phenomena--something else in addition to the direct effects of gas bubbles.

I think that Dr. Ward's work has very elegantly shown that the complement system probably plays a role in the pathogenesis of decompression sickness. I would like to add that data accumulated in our laboratories in the last two decades have demonstrated that in addition to the pathway that Dr. Ward has presented to us today, there are other mechanisms that lead to the activation or release of vasoactive substances (1-7). For example, the disruption of tissue and cells releases lysosomal and other enzymes that can activate the Hageman factor leading to the activation of bradykinin.

It seems probable that bubbles trigger several chains of reactions that lead to the generation of vasoactive agents, including those derived from the complement system, histamine, bradykinin, prostaglandin, and 5-hydroxytryptamine (*see* chart). These substances could explain many of the symptoms in decompression sickness as well as the changes in susceptibility that Dr. Ward pointed out.

If you suspect a factor of being responsible for a phenomenon, the critical experiments are to produce the phenomenon by introducing this factor and prevent the phenomenon by counteracting the effect of the factor. We have done this (1, 3).

We use a dive profile which causes decompression sickness in rabbits and mice within 20 minutes of surfacing. During this time, we administer those factors we believe to play a role in the pathogenesis of decompression sickness. These include bradykinin, 5-hydroxytryptamine, histamine, prostaglandin, etc. By this technique, we can aggravate the symptoms and can produce decompression sickness in animals that are not susceptible to the disease.

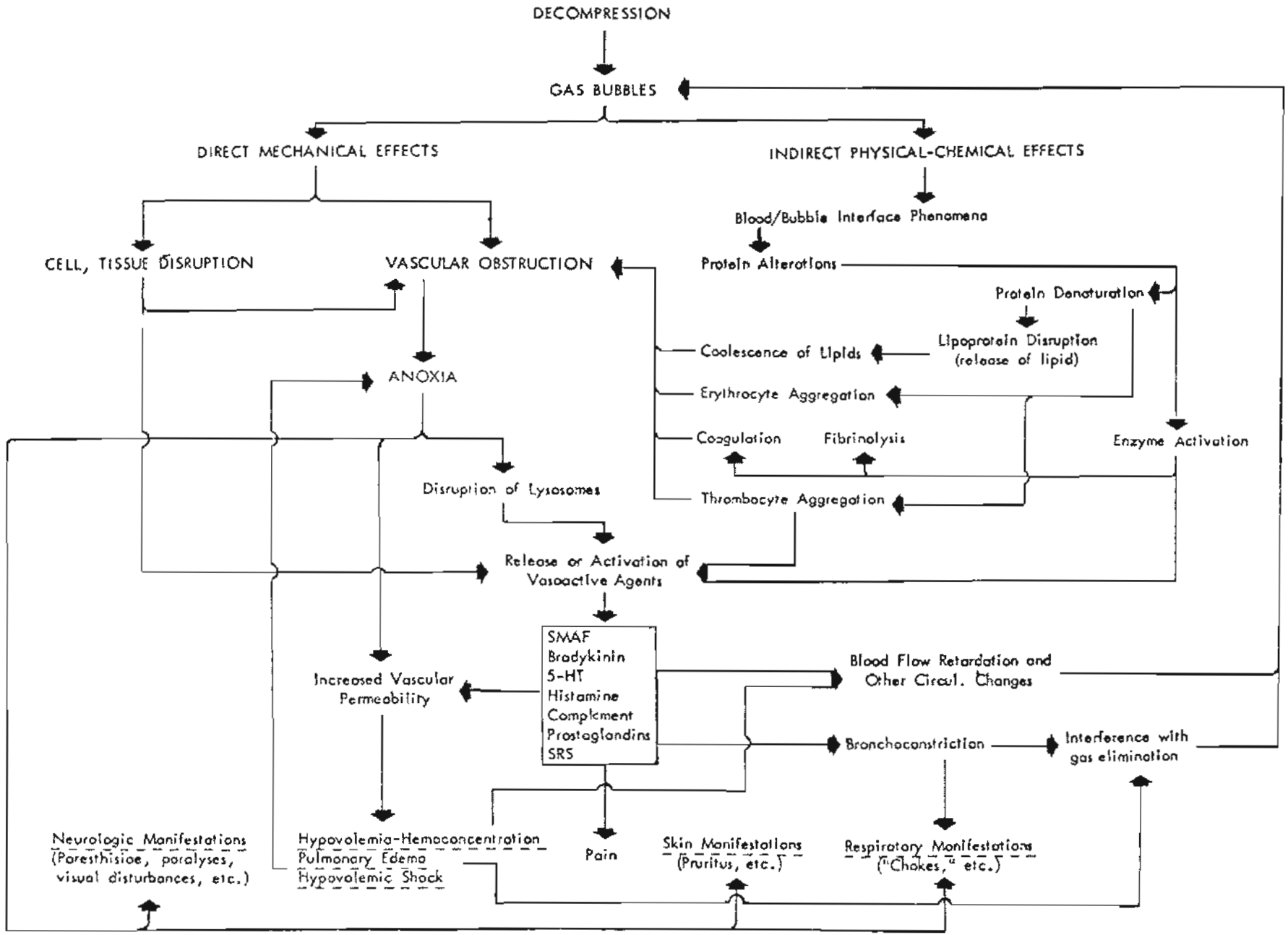
Furthermore, and more important, if before we decompress we administer antagonists or inhibitors of the substances that are produced by bubbles, not only do we prevent many of the symptoms but we have a dramatic decrease in mortality if we use a very severe dive profile. For example, with a substance such as migristene which combines activities against bradykinin, histamine, and to a certain extent, against 5-hydroxytryptamine, we can reduce mortality from 60 to 17% (5). Impressive reduction in mortality is also observed with cyproheptadine, another compound that combines activities against vasoactive agents (11).

Yesterday, Dr. Powell asked, "How does the theory of chemical mediators explain the observation that the symptoms disappear after recompression?" I offered the explanation that many of those substances are deactivated very rapidly and unless there is a constant supply they no longer cause symptoms.

Let me now reverse the question. If it is only the mechanical effects of gas bubbles that produce decompression sickness, how do you explain the observation that antagonists and inhibitors of the chemical mediators prevent or ameliorate the symptoms without recompression?

DR. **FRANCIS:** Dr. Ward, it's widely recognized that there's not only susceptibility between individuals, but actually within the individual who may be susceptible to decompression sickness on one day and not on another

PROPOSED PATHOGENETIC MECHANISMS OF DECOMPRESSION SICKNESS



day. Have you studied the activation of complement by bubbles in humans on a day-to-day basis and looked for diurnal variations?

DR. WARD: No, but we do have some anecdotal evidence. One individual had extraordinarily high complement measurement at one time. We found that he also had a secondary infection. We're aware that the sensitivity can change from day to day within the same individual. It has not been followed up but should be.

DR. FRANCIS: Dr. Ward and Dr. Chryssanthou, what is the mechanism whereby the activation of complement generates the multiplicity of symptoms of decompression sickness?

DR. WARD: That's a wonderful question to which Dr. Chryssanthou referred also. When you produce C5a, a multiplicity of effects is induced downstream. C5a immediately produces aggregation of neutrophils, which then release a series of other substances. I was struck yesterday, for example, with your photographs of the edema around, what you called, the rarefied sites. That's exactly what you would expect complement activation to produce. Local complement activation causes bleeding by causing change in the permeability of the vessel walls.

The effect on platelets and red cells also can be accounted for by the production of C5a. C5a starts a sequence of events including elevated white cells in the decomplemented rabbit, slightly higher fibrinogen levels, and an elevated level of less active platelets in decomplemented animals.

DR. CHRYSSANTHOU: I will address my response not only to the activation of the complement system, but generally to the triggering of the chain reactions that lead to the release or activation of the substances in question. An intravascular gas bubble is a foreign surface to begin with. It has been demonstrated in vitro that bubbles trigger Hageman factor and, in turn, activates the coagulation systems, kinin, and complement. Possible denaturation of proteins and lipoproteins occurs at the blood-gas interface, including the uncoiling of the protein moiety, the release of lipid from lipoproteins, and the activation of certain enzymes. These events could lead to the release or activation of vasoactive substances. Tissues damage with disruption of cells, and cellular elements, releases plasmic and lysosomal enzymes. These can trigger some of the reactions that lead to the release or activation of vasoactive substances.

So, the information we have today suggests several triggering mechanisms. There may be others that we don't even suspect. The key point is, however, that if the chain of reactions is broken at any link, you may prevent some of the effects of decompression which occur as a result of the activated substances. As for the symptoms of decompression sickness that could be attributed to the activation of complement and vasoactive substances, bear in mind that many of these substances produce pain. Furthermore, they increase vascular permeability and cause bronchoconstriction. These effects can play a role in respiratory distress and may be responsible for hypovolemia.

DR. VANN: Dr. Lambertsen stated that no important changes occurred in the coagulation properties of animals in which massive volumes of intravascular bubbles were produced by cutaneous counterdiffusion. DCS can also occur in humans with the apparent absence of bubbles, and bubbles can persist for many, many hours at altitude without absolutely no sign of decompression sickness. How are these observations reconciled with the hypothesis of biochemical mediation of DCS?

DR. WARD: It's very hard to generalize, unless we know what a person's sensitivity is to complement activation. Roughly half the people in our study did not have detectable complement activation even though we incubated their plasma with bubbles for 30 minutes. Unless we can address the question in a controlled manner, I don't think we can explain such anecdotal evidence. I do not claim we proved that complement mediates decompression sickness, but look at what happened when we decomplemented those animals? They stopped having decompression sickness. There's no reason to suppose that complement doesn't mediate the activation of the Hageman factor, for example, to produce bradykinin, etc. It may be that the complement system is the mediator of the whole sequence of events.

DR. CHRYSSANTHOU: I would like to respond to Dr. Vann's question regarding the coagulation mechanisms and the absence of thrombotic phenomena in decompression sickness. How can we reconcile this with the theory that we've presented? The fact that there is no thrombosis does not necessarily mean that other components of this chain reaction don't play a role such as, for instance, bradykinin activated through the Hageman factor. The formation of thrombi is a dynamic phenomenon. That involves a balance between thrombogenic and a fibrinolytic mechanism. Thrombi may be produced but the simultaneous activation of the fibrinolytic system may strike a balance resulting in clinically undetectable thrombotic phenomena. This happens in many other clinical conditions. It is the disturbance of that balance that results in the formation of thrombi. Thus, the Hageman factor can be activated and produce bradykinin without disturbing the balance and creating a clinically observable thrombosis.

DR. LOEWENHERZ: What do you think about the application of tissue thromboplastin activator in established decompression sickness?

DR. CHRYSSANTHOU: Decompression sickness is a complex phenomenon which is not only due to the effects of vasoactive substances. Mechanical obstruction of blood vessels by gas bubbles can occur, causing anoxia which, in turn, may lead to increased vascular permeability, and edema. What Dr. Ward and I are saying is that one important component of the pathogenesis of decompression sickness is the activation of chemical mediators that enter a vicious circle, which facilitates further production and growth of gas bubbles. These substances promote their own release by the effects they have on the circulatory system. Fluid extravasation, increased blood viscosity, slowdown of circulation, and stasis resulting from the effects of bubble-activated mediators or bubble-induced vascular obstruction, all facilitate the further production and growth of gas bubbles. We are saying that one component of decompression sickness is mechanical while another component is chemical. Vasoactive substances can explain pain, edema, hemoconcentration, and, to some degree, respiratory distress. Perhaps a better description than a chain reaction would be a network reaction that is triggered by bubbles. As for TPA in decompression sickness, I doubt its effectiveness since thrombosis does not sem to be implicated in the pathogenesis of the disease.

CAPTAIN THALMANN: Dr. Ward, were all your rabbits sensitive to complement? Does that mean that none were insensitive or that none of the insensitive rabbits ever got decompression sickness?

DR. WARD: The rabbits all got decompression sickness on the first dive profile.

CAPTAIN THALMANN: Even the insensitive ones?

DR. WARD: At that point, you just don't know whether they're sensitive

or insensitive. You can't establish their sensitivity until you collect the blood.

CAPTAIN THALMANN: You mean, you didn't do it prospectively as in the divers?

DR. WARD: We couldn't. With rabbits, you have to collect the blood to determine whether they're sensitive or not. They all got decompression sickness on the first two profiles. Before the third profile, half were decomplemented and half were not. After a period of time that was sufficient to allow the complement system to recover, we found that they were all sensitive.

CAPTAIN THALMANN: Why couldn't you determine whether they were sensitive or insensitive before you exposed them?

DR. WARD: If you take a blood sample to determine sensitivity you can't run the subsequent experiments.

DR. HOMER: Is that because the volumes of blood required are too large?

DR. WARD: Yes, for rabbits, they're too large.

CAPTAIN THALMANN: How can you argue that your methods haven't influenced your results? You determined sensitivity after the pressure exposures which your theory says will modify the sensitivity. If a rabbit does gets decompression sickness, his complement level will be reduced, and your sensitivity analysis occurred after the pressure exposure. Yet, you were confident that the rabbits had recovered sufficiently after the last exposure so that they were normal?

DR. WARD: Yes, because the rabbits returned to normal sensitivity within 3 days, and we gave them 5 days.

CAPTAIN THALMANN: Did you ever find any insensitive rabbits?

DR. WARD: I found one insensitive rabbit. About one-third to one-quarter of the rabbits are insensitive. I took the insensitive rabbit out of the series because he didn't bend on the second test dive profile, and when I tested him for sensitivity, he turned out to be insensitive.

CAPTAIN THALMANN: In your human data, none of the insensitive individuals got decompression sickness and you believe all profiles to be equally stressful. Did the sensitive individuals have a spectrum of symptoms or were they all pain-only?

MR. NISHI: I think they were all pain only.

CAPTAIN THALMANN: When a diver is recompressed to treat him for decompression sickness, he gets better. If he is decompressed too quickly after treatment, the pain returns, but the pain goes away with another recompression. This demonstrates--and I don't think there can be any doubt--that at least initially bends are a mechanical effect. I think the biochemical effects may produce long-term results. We have seen pressure-sensitive individuals, however, who get relief a week after getting bent if you compress them. When you decompress them, the pain comes back, and if you recompress again, they get better. This pressure-sensitive and almost instantaneously responsive mechanism would seem to be mechanical. It could not be biochemical unless activation and deactivation are almost instantaneous.

DR. WARD: I don't see how you can maintain that it's mechanical. Dr. Chryssanthou pointed out yesterday that production of bradykinin would be extremely fast. When I inject a sample of plasma that has been incubated with bubbles into a suspension of the polymorphonuclear leukocytes, the reaction is instantaneous. The strip chart recorder jumps in immediately if you've already got the activated substance. The only

pertinent question you raise is how long does it take to produce the activated substance? We can't answer that, but I can say that it is a very rapid phenomenon.

CAPTAIN THALMANN: Is activation rapid enough to occur during compression and decompression which take only minutes?

DR. WARD: Yes.

CAPTAIN THALMANN: And pain can appear and disappear as a result of the activation and deactivation of biochemical mediators within the few minutes needed for decompression and recompression?

DR. WARD: We're not talking about minutes, we're talking about seconds.

DR. CHRYSSANTHOU: We cannot and do not exclude a direct mechanical effect in the production of symptoms. On the other hand, bradykinin, histamine, and other substances can, as Dr. Ward said, exert their effects within seconds, not minutes. An insect bite is a good example of this speed. When the acid is injected at the moment of the bite, let's say bradykinin is immediately activated and you feel instantaneous pain. The activation of biochemical mediators by a bubble can be just as rapid. If you put ammonia on the bite, the pain disappears in seconds. Carboxypeptidase-B, which is pH dependent in its action, inactivates bradykinin almost instantaneously. The rate of activation and inactivation of bradykinin depends on the pH of the tissue and whether you have an aerobic or anaerobic metabolism. Bradykinin kinetics will be altered by changes in the local environment.

DR. ZANNINI: Dr. Ward, what is your opinion about the role of oxygen in the activation of complement in decompression sickness?

DR. WARD: I have been trying to measure complement activation by different types of gas bubbles for at least a year and a half. Gases are very different in their activation--oxygen activates complement more readily than nitrogen, for example. Individual sensitivity clouds the picture, however, and makes it difficult to classify specific people.

DR. HOMER: Dr. Ward, can a suitably susceptible complement system help produce bubbles in addition to being activated by bubbles?

DR. WARD: We do not know at the moment. An initial set of experiments indicated that there was a change but subsequent experiments have not supported that conclusion.

DR WARD: Let me return to the mechanical effects of bubbles. We calculated that bubble nucleation within an osteoclast of the hard bone of the semicircular canal would produce a pressure large enough to break the bone. This is a case where a pressure change has a mechanical effect. We have demonstrated this effect experimentally. Because that bone is so hard and rigid, a tremendous pressure develops which culminates in catastrophic fracture. A flexible structure such as a cell, however, will expand, and high pressures will not occur. Dr. Francis will probably ask if bubbles in the spinal cord are confined enough to produce high pressures when they expand, but this can happen only when the bubble is tightly confined. If any tissue expansion occurs, the pressure increase will be small.

DR. FRANCIS: I'm having difficulty going from the biochemical chaos in venous blood, as a result of bubbling to scattered punctate lesions in the spinal cord. If all these nasty substances are entering the kidney, wouldn't you expect glomerular nephritis.

DR. WARD: I don't know what to expect, but the fluid transport and

edema that you described fits very well. Why the kidneys aren't affected, I can't say.

DR. HAHN: Dr. Ward, is the sensitivity of the complement system like blood groups? Is it inherited or acquired? Can it be changed by disease?

DR. WARD: I don't know if complement sensitivity is inherited, but it does vary for a given individual. The diver with the secondary infection I mentioned earlier had a very active complement system.

DR. KINDWALL: In regard to Dr. Francis's question about bubbles and the kidneys, we treated a man who had embolized coming up from 80 feet and was unconscious. He was put in a very steep Trendelenburg position and when he got to us an hour later, he had totally recovered. Nevertheless, we treated him on a table 6 and later admitted him to the hospital because he was complaining of flank pain. For the next few days, he produced plus-four proteinuria, but returned to normal within 3 days. My explanation was that the steep Trendelenburg caused bubbles to rise into his kidney. This is an unusual event.

REFERENCES

1. Thalmann Ed, Zumrick JL, Schwartz HJC, Butler, FK. Accomodation to depression sickness in HeO_2 divers. Undersea Biomed Res 1984; 11(suppl):11-12.
2. Chryssanthou C. Pathogenesis and treatment of decompression sickness. NYS Med 1971; 74:808-812.
3. Chryssanthou C. Dysbaric osteonecrosis in mice. Undersea Biomed Res 1976; 3:67-83.
4. Chryssanthou C, Springer M, Lipschitz, S. Blood-brain and blood-lung barrier alteration by dysbaric exposure. Undersea Biomed Res 1977; 4:117-129.
5. Chryssanthou C. Dysbaric osteonecrosis: etiological and pathogenetic concepts. Clin Orthop Relat Res 1978; 130:94-105.
6. Chryssanthou C, Graber B, Mendelson S, Goldstein G. Increased blood-brain barrier permeability to tetracycline in rabbits under dysbaric conditions. Undersea Biomed Res 1979; 6:319-328.
7. Chryssanthou C, Rubin L, Graber B. Amelioration of decompression sickness in mice by pretreatment with cyproheptadine. Undersea Biomed Res 1989; 7:321-329.

ADAPTATION TO DECOMPRESSION STRESS

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There appears to be universal acceptance that adaptation to decompression stress occurs and can be exploited in manned diving activities. The studies supporting this concept are numerous, although the evidence cannot be referred to as rigorous - largely consisting of retrospective and incidental reports (for review, see ref. 1). Surprisingly, this situation persists to this day, with few good prospective studies in either humans or animals reported or underway. This lack of information and interest exists despite the great promise that knowledge of adaptive mechanisms has for enhancing our understanding of the pathobiology of decompression sickness (DCS), a goal not only of this workshop, but of decompression science in general. Thus, in a sense, this brief comment can be viewed as a plea for further study in this area.

If we accept that an adaptive process to DCS does occur, then the popular responsible mechanism appears to be a reduction in the endogenous gas load elicited on repetitive exposure to a decompression, possibly through depletion of the bubble "seeds," or micronuclei. This seemingly reasonable "physical" hypothesis ignores the vast array of physiologic events that are probably necessary for the DCS syndromes, and which are probably responsible for the marked degree of variability in decompression tolerance (one of the few invariable features of DCS). Furthermore, the experimental evidence for this mechanism operating under physiologic conditions is, unfortunately, totally lacking. In fact, the only relevant human information suggests that no change in the endogenous gas load occurs with repetitive exposures (1). As with any unpopular notion, several criticisms of these human studies, which were performed at the Naval Submarine Medical Research Laboratory in Groton, CT, have been raised. Thus, in an attempt at clarification, I will briefly discuss what I consider to be four broad categories of criticism of this human work:

1. The results are contrary to the conclusions of many well done retrospective studies, and many incidental laboratory results. This is simply untrue. Most of these previous studies have examined changes in the incidence of symptoms with repetitive exposures, and we only examined changes in precordial venous gas emboli (VGE). Thus, our conclusion could only be that if adaptation does occur, it probably does not rely on a change in bubble formation. Another way of saying this is that there may be an uncoupling of stimulus and effect. Our only symptom results (pruritus scores) are actually consistent with an adaptive process.

2. Exposure insufficiently stressful. The 150 for 30 min. USN decompression schedule was used for these exposures, and is generally accepted as being provocative. We confirmed this with one subject sustaining spinal cord DCS. Further, over 80% of the subjects had detectable bubbles, with many being of

the highest grade. Not only did we see no adaptive trend in the group, but also, no single individual showed a significant adaptive trend. The substantial day-to-day variability in VGE, which we observed in these subjects, makes a large sampling period and population essential to decrease the probability of type I error. Thus, studies that report VGE results from only 2 or 3 exposures, or in only a few subjects, should be viewed with caution. In any case, if this protocol was insufficiently provocative to produce adaptation and a decrease in bubbles, then adaptation is of only academic interest as the necessary work-up exposures are too dangerous for routine use. Alternatively, and more likely, adaptation is not associated with a decrease in bubbles.

3. Wrong gas. Because of different elimination kinetics, the suggestion has been made that helium may deplete micronuclei more completely than nitrogen. Superficially, this appears to be reasonable, as tissue helium elimination is faster than nitrogen, and thus micronuclei may be depleted in a faster 'burst.' However, it seems likely that micronuclei depletion is more related to the volume of evolved gas, not the speed, and because of its greater solubility, more volume might be expected with nitrogen. In any case, the necessary data concerning VGE production, rate and size under similar conditions with both gases, are totally lacking. In addition, the theoretical basis for a differential nitrogen/helium effect implies that the micronuclei kinetics under physiologic conditions are understood - something that could not be further from the truth. Data from isobaric counterdiffusion experiments suggest that micronuclei are either reformed very quickly, or are attached and not depleted, since there is no evidence of a decrease in VGE production rate under steady-state exposure conditions for periods in excess of 8 hours (2).

4. Wrong repetitive interval. In our studies, the interval was chosen for convenience, but is believed to be a representative interval as far as a working or sport diver is concerned. Therefore, if this interval will not invoke adaptation, then once again, adaptation is of only passing interest to the average sport or working diver for the same reasons as cited above. However, it is indeed possible that other compression-decompression schedules may produce different results, and this is an area where more work is required. For example, the "mirror image" to our exposures, that of altitude exposures, may be a interesting start.

SUMMARY

Further studies in this area are sorely required, not just to establish whether or not adaptation exists, but as another way to get at the physiologic basis of decompression sickness. If in fact animals can adapt to DCS, yet the bubbles persist, an invaluable situation exists in which the uncoupling between stimulus and effect can be examined experimentally. It may be possible to correlate changes in certain physiologic indicators, at any level, to the loss of reaction to the foreign gas bubble. This has the potential of allowing a peek at the pathobiology of DCS, and how it might be modified to our advantage.

REFERENCES

1) Eckenhoff RG, Hughes, JS. Acclimatization to decompression stress. In: Bachrach & Matzen, eds., Underwater Physiology VIII: The Eighth Symposium on Underwater Physiology. Bethesda; Undersea Medical Society, Inc., 1983.
2) Lambertsen CJ, Cunnington JPW, Cowley JRM. The dynamic and composition of spontaneous, continuous gas embolism in the pig during isobaric gas counterdiffusion. Fed. Proc. 34:452, 1975.

A DECOMPRESSION SICKNESS EMBOLIZATION GUINEA PIG CARDIOVASCULAR SHOCK MODEL

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In our experiments, male guinea pigs weighing 400 ± 50 grams were anesthetized with Ketamine and an injection of Procaine (4% in the sternohyoid area). A Swan-Ganz thermodilution thermistor was placed in the right carotid artery, advanced to the arch of the aorta for the determination of cardiac output and measuring core temperature. In the left jugular vein, a 3.5F injectate catheter was advanced caudally (to the right atria). Sulfathiazole was applied topically as the incision was closed. On the day of the experiment, two pre-samples of cardiac output, core temperature, heart rate and normal EKG (lead two) were obtained while at surface. The animals were compressed to 6 ATA (165 fsw) air in a multilock, multiplace recompression chamber (5 feet X 12 feet). The animals were kept at pressure for: 60, 30, 22, and 15 minutes. Upon surfacing, the following parameters were monitored: cardiac output, core temperature and EKG. By one-half hour post-surfacing animals exposed for 60, and 30 minutes had died. Cardiac output fell precipitously in the pre-death period. In animals compressed to 6 ATA for 22 minutes, cardiac output fell 50% and the animals survived. Their heart rates seemed to accelerate and the EKG tended to indicate ischemia while the core temperature did not fall. At compression time periods of 20 minutes or less, cardiac output fell less than 25% with no mortality and EKG changes were not remarkable. It was found that even with a marked reduction in cardiac output in animals with decompression sickness, there was no significant decrease in body core temperature or in EKG rate.

Introduction

Decompression sickness, unlike almost all other forms of trauma has not had extensive research into the shock mechanism.(1) We know today that each type of trauma produces different cardiovascular and metabolic consequences, however, some consider decompression shock to be similar to other shock forms.(2, 3) In other trauma models in this species it is well known that a 50% body surface area 3^{o} burn reduces the cardiac output 50% and that in untreated burned animals this constitutes a lethal toxic dose of fifty percent (LD50).(4, 5, 6) Therefore it can be considered that decompression sickness that causes a fifty percent reduction in cardiac output could be an LD50. A fifty percent reduction in cardiac output then provides a sensitive measure to study the effectiveness of any treatment. We initiated a series of investigations into the cardiovascular consequences of a defined decompression shock schedule in a controlled laboratory animal model. We feel that with increasing available technological sophistication an understanding of the

perturbations of decompression sickness should be defined in terms of cardiovascular and cardiopulmonary function.(7) The focus being on the host's or the patient's response to the injury at a whole body level rather than the effect of the particular bubble on the host.(8, 9, 10, 11)

The guinea pig was selected as the experimental animal because of its small size (which allows quantitative measurement of full body metabolic responses) and its metabolic and physiologic similarities with man.(12) Extensive previous experimentation has delineated the guinea pig's cardiovascular and metabolic responses to different forms of injury. The metabolism of glucose, free fatty acid and glycerol as well have been clearly demonstrated in this model. The salient axis of advance of this research was to determine the role of cardiovascular shock as it is related to decompression sickness.

Materials and methods

We developed a conscious animal model for studying decompression sickness using guinea pigs with indwelling arterial and venous catheters. Guinea pigs, Hartley strain (Cavia cobaya) of either sex, weighing 400±50 grams were anesthetized the day before the experiment with injections in the sternohyoid area. The appropriate anesthetics were Ketamine®, 2- (o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride, (150 mg/kg) and Procaine®, 4-amino,2-(diethylamino)ethyl ester, monohydrochloride, (10 mg subcutaneous).(13) An Edwards Laboratories thermal dilution probe 2.5F (1 mm outside diameter, 45 cm long) was implanted in the right carotid artery and was advanced down into the arch of the aorta. This catheter was used for determination of cardiac output by thermal dilution and for the measurement of body temperature. Also a 3.5F (1.75 mm outside diameter, 30 cm long) injectate catheter was advanced by way of the left jugular vein approximately to the vena cava. An appropriate antibiotic, Sulfathiazole, was applied topically before the incision was closed. The catheters were externalized through the skin, wrapped around the neck, and held in place with adhesive tape so that they were accessible at the back of the animal's neck. Recovery from anesthesia post-surgery was enhanced with a warming light. Food was withheld, but water provided ad libitum until the experiment began the next day. Neither food nor water was given to the animal during the experiment, but both were provided after that time.

On the day of the experiment, the arterial and venous catheters were connected to an Edwards Cardiac output computer 9520 A. EKG electrodes and leads were attached to right and left thoracic cavity (Lead 1) of the guinea pig. Mean body core temperature, cardiac output, heart rate, and EKG were measured.

For the cardiac output measurement, a thermal dilution technique was used in which 0.5 ml of 0°C saline was infused through the venous catheter and the Edwards cardiac output computer determined the value. Thermodilution cardiac output techniques use temperature change as an indicator of the cardiac output. A chilled solution is recorded at a downstream site. The widespread clinical application of thermodilution is relatively

recent, dating only to about 1971. Not only does the thermodilution technique have a firm theoretical basis for its use, but clinical studies have shown excellent correlation between dye-determined and thermal determined cardiac outputs. The use of thermal dilution has gained acceptance because of its accuracy and ease of use, particularly in supplementing care of the critically ill patient. Our thermodilution cardiac output method was calibrated using cardiac output by the "Direct Fick Method" as the standard reference voltage.

For cardiac output determination, a syringe was quickly removed from the ice bath and, with minimum handling of the barrel, the contents were rapidly injected as a bolus into the proximal catheter lumen which emptied into the vena cava near the right atrium. The special purpose computer (American Edwards Laboratories Cardiac Output Computer) then calculated the cardiac output from the aortic thermistor.

For the EKG measurements the Lifeguard defibrillator/monitor, marketed by Survival Technology, Inc., was used. This monitors EKG and simultaneously displays the signal on a cathode ray screen and makes a hard copy. In addition to monitoring, this equipment could also be used as a defibrillator in the event of ventricular fibrillation.

The animal was then disconnected from the equipment, placed in a hyperbaric chamber (Bethlehem Corporation Model 615), and brought to a simulated sea water depth of 165 feet (6.0 ATA). The animal was kept at this depth (pressure) for 60 minutes (Animal #1), for 30 minutes (Animals #2 and #3), for 22 minutes (Animals #4 and #5), and for 15 minutes (Animal #6). After this time the animal was brought to surface (atmospheric pressure) at a rate of 16 psig/min to cause decompression sickness to develop. After decompression, measurements of body temperature, cardiac output, heart rate, and EKG were taken at 15 minute intervals for two hours.

Results

As the experimental animal died from decompression sickness, an autopsy was performed to examine the location and extent of bubble formation. The heart and vessels were examined along with the hepatic portal system.

The animals were each compressed for different times because it was necessary to determine the exposure which would induce acute decompression sickness in a guinea pig. The criteria used for acute decompression sickness was that the animal had to survive long enough for measurements to be made, and it also had to be sick enough to have a fifty per cent reduction in cardiac output.

All animals were autopsied immediately after death or four hours after return to surface. It was found in the animals who died that there was extensive bubble formation in the cardiovascular system including the ventricles and inferior vena cava. It was also observed that there was an engorgement of the venous system with blood. Further, bubble formation was found within the omental adipose beds in the abdomen. However, none of these animals showed cranial nerve or neurological

deficits. The reduction in cardiac output could be observed to be directly related to the bubble formation within the heart and lungs. The maintenance of a constant temperature is a significant finding since in all other forms of shock, whether it is the guinea pig or human, body core temperatures drop significantly concomitantly with a decrease in cardiac output. The underlying metabolic changes are not clearly understood as of this time. Frankly, further studies in lactic acid, glucose and free fatty acid metabolism clearly need to be undertaken to investigate these metabolic perturbations.

Discussion

Even though there has been over six decades of investigation in the area of decompression sickness in both patients and experimental animals, minimal information exists concerning the cardiovascular/metabolic shock consequences of this enigma.(14, 15) Not wishing to enter the controversy over recompression, we wished to focus on the untreated cardiovascular and metabolic impact of this problem. In other forms of critical care management today, cardiac output is a common important assessment of progressive circulatory shock and the cardiovascular system. Cardiac output could be the single most important assessment of cardiovascular malfunction in decompression shock sickness.(16, 17)

References

(1) Altura BM, Lefer AM, Schumer W, eds. Handbood of shock and trauma. New York; Raven Press Books, Ltd., 1983.

(2) Bredenberg CE, Nonoto S, Webb WR. Pulmonary and systemic hemodynamics during hemorrhagic shock in baboons. Annals of Surgery July, 1980. 192 1:86-94.

(3) Cassuto Y, Farhi LE. Circulatory Response to Arterial Hyperoxia. Journal of Applied Physiology 1979. 46, 5:973-977.

(4) Wolfe RR, Miller HI. Ineffectiveness of heparin treatment in burn shock in the guinea pig. Aviation, Space and Environmental Medicine, June 1976, 652-656.

(5) Guyton AC. Circulatory physiology: cardiac output and its regulation. Philadelphia:W.B. Saunders Company, 1981.

(6) Guyton AC. Textbook of medical physiology. 6th ed. Philadelphia§ W.B. Saunders Company, 1981.

(7) Lundgren CEG, ed. Monitoring vital signs in the diver. Bethesda: Undersea Medical Society, Inc., 1978.

(8) Hallenbeck JM, Bove AA, Elliot DS. Mechanisms underlying spinal cord damage in decompression sickness. Neurology April 1975. 25:308-316.

(9) Hills BA. Decompression sickness: the biophysical basis of prevention and treatment. Chichester:John Wiley and Sons, Ltd. 1977.

(10) Bachrach AJ, Matzen MM, eds. Underwater physiology VII. Bethesda: Undersea Medical Society, Inc., 1981.

(11) Shilling CW, Werts MF, Schandelmeier NR, eds. The underwater handbook (a guide to physiology and performance). New York:Plenum Press, 1976. 500-501.

(12) Lynch PR, Wilson JS, Shaffer TH, Cohen N. Decompression incidence in air and liquid breathing hamsters. Undersea Biomedical Research, March 1983. 10, 1:1-10.

(13) Hughes HC. Anesthesia of Laboratory Animals. Lab Animal September 1981. 10:40-56.

(14) Davis JC, Hunt TK, eds. Hyperbaric Oxygen Therapy. Bethesda: Undersea Medical Society, Inc., 1977, 25-43.

(15) Davis JC, ed. Treatment of serious decompression sickness and arterial gas embolism. Bethesda:Undersea Medical Society, Inc., 1978.

(16) Hahnloser PB, Domanig E, Lamphier E, Schenk WG. Hyperbaric oxygenation: alterations in cardiac output and regional blood flow. Journal of Thoracic and Cardiovascular Surgery. August, 1966. 52, 2:223-231.

(17) Smith EB. The biological effects of high pressures: underlying principles. Phil. Trans. R. Soc. Lond, 1984. 304:5-16.

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INDIVIDUAL FACTORS AFFECTING DECOMPRESSION SICKNESS

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Several individual risk factors felt to increase susceptibility to decompression sickness have been investigated. These factors concern age, level of obesity or body type, sex, prior training and performance criteria, and type of diving done concomitant with level of exertion. Obesity appears to give the strongest relationship. Other factors which should be considered include serum chemistries (especially lipids) and hematology indices, smoking, alcohol and coffee intake, and chronic occupational exposures such as gases, particles, and fumes. All of these have been implicated as risk factors for acute or chronic diseases in the epidemiology and occupational medicine literature. Studies which examine any individual risk factors for decompression sickness must include: 1) a large well-defined population base of numbers of dives done and types of decompression sickness experienced by each member of that population, over a defined time of study; 2) sufficient demographic, behavioral, historical, and physical examination data for each individual diver at initial entry into the study and periodically thereafter; and 3) appropriate staff, equipment and financial resources, and epidemiological/statistical expertise to plan for and carry out these types of studies. Such studies may be retrospective (using data acquired in the past which covers a sufficient period of time) or prospective (using data acquired now or in the future and subsequently accumulated over time). Occupational diver populations present optimal sources for study; information on select aerospace and tunnel workers is important. Recreational diver data bases should also be considered, although obtaining periodic health data on large numbers of divers is difficult.

Introduction

I approach this subject from the vantage point of my several years work in diving medicine combined with further medical training in preventive medicine and epidemiology. Much of my recent research and practice has been concerned with looking at information and data on large populations of Navy divers and trying to figure out why they experience medical accidents and how they can prevent them.

There are several reasons to examine individual human susceptibility to the processes of decompression and, hence, decompression sickness (DCS). These include: 1) the requirement to set up, maintain, and analyze population studies of divers; 2) to spur further laboratory, clinical, and epidemiological investigations to help us better understand the process of decompression; 3) to establish guidelines for fitness for diving for recreational and occupational diving; and 4) to prevent DCS from occurring in as many situations as possible. The latter is important whether the diver is working hundreds of feet below the North Sea surface or exploring

Caribbean waters miles and hours away from proper medical and hyperbaric treatment.

To accomplish these tasks, especially numbers 2) and 3), requires in many instances the often-difficult extrapolation of animal laboratory data to human populations. It also requires leaps of faith or empirical assumptions when results of investigations are based on small numbers of human subjects, different methodologies for testing the same hypothesis, and findings from statistical testing that do not give airtight or statistically significant results despite "clinical significance."

An open mind is required in looking at this problem. Susceptibility can be affected by a wide spectrum of individual factors: anatomic/biochemical/physiological makeup; health behaviors; occupation and worksite exposures above and below the surface; and the environment in which one dives. Susceptibility is in all likelihood determined by a combination of factors in one individual; however, population studies on decompression sickness must be sufficiently large so that statistical techniques of multivariate analysis can describe the contribution of one factor alone or several factors in combination. High DCS-risk versus low risk profiles can then be developed and applied in the determination of individual suitability for diving.

Is DCS a rare phenomenon or is it common? Among U.S. Navy divers, it generally occurs less than 5 times per 10,000 dives (1,2). The risk for sport divers is roughly estimated to be less than 1 incident per 10,000 dives (3). DCS could thus be considered relatively uncommon, but exactly for whom and why (that person) it occurs can only be determined by refined retrospective or prospective epidemiological studies (4). Unfortunately, the data bases to examine uncommon events in recreational diver populations are not yet in place or sufficient, for these have to include all information on each dive done, accident and non-accident, as well as individual demographics, physical status, and behaviors. The work of the Divers Alert Network in developing a comprehensive questionnaire for the investigation of each diving medical consultation is very promising. Concurrently, more epidemiological work should come out of military and civilian industrial diver populations which monitor the health of their divers at initial entry and at periodic intervals during the course of a diving career.

I will now discuss several of these factors to which I alluded above. Some of my discussion will be based on the existing literature; the excellent summary of Hills (5) on many of these issues provides a solid basis on which to address very recent studies. Some will be anecdotal, and some will be speculation and/or questions which I hope will be food for thought and future research.

Age

Very young ages, teens and below, and divers over, say, 45-50 are the two areas of hypothesis. Those in between these extremes should be grown and healthy and are not in age populations that can be considered at high risk

for chronic diseases or significant changes in performance effectiveness.

Young divers

Young divers--and here I arbitrarily categorize them as below the age of 18--dive, and I am certain do so in increasing numbers. They dive primarily as the result of courses which let them dive formally as young as twelve years (and perhaps younger, as instructor discretion allows for individual age minimums) and much younger overseas, e.g., reported as low as four years of age (6). Does their age put them at risk for DCS?

Only one study of young divers--in this case, Tahitian children--has been reported (6). It found that physical development was not adversely affected, and no diving-related emergencies occurred. On the other hand, many young divers from mid-teens and below theoretically would not have the requisite emotional and intellectual maturity to handle course work or the unpredictable stresses or panic situations which can arise during a dive (7,8). This might make them susceptible to DCS on an indirect behavioral basis, such as not following prescribed decompression tables.

Aside from obesity and smoking, which I discuss later, I can think of no other individual factors of a general nature which would make a teen-age or younger person specifically susceptible to DCS.

Old divers

This risk is of more concern, because : 1) commercial divers with years of experience want to continue diving as a livelihood; and 2) the increasing popularity of recreational scuba diving among persons desiring new outlets for physical fitness but who suffer from chronic diseases associated with aging may put themselves at exacerbation of that disease or a diving accident such as DCS.

Much of the literature suggests that aging divers are more susceptible to DCS (9-11); divers over 40 are reported in (11). On the other hand, Wise (12) found that age was not related to DCS risk. Gray reported an age-DCS relationship with aviators (13).

It is not clear when this age risk begins: over 30? over 40? over 50? Military studies dealt with populations primarily in their 30's, so it is difficult to say that ages over 45 are at greater risk. Walder, cited in (5), was especially concerned with ages over 50. Also, how do the types of DCS vary with increasing age? Also, is Type II DCS--which is more problematic for continuance in diving--more common among one of these groups? Finally, how is age interrelated with years of diving and type of diving done? These have been examined somewhat.

Aging manifests itself in degenerative joint disease, changes in pulmonary function or reaction time or visual acuity, cardiovascular disease which impairs circulation or exercise tolerance, and the effects of personal habits acquired over time which have direct consequences on health and fitness, e.g., alcohol intake and cigarette smoking. Determining the risk

of DCS would have to be individualized for each older diver on the basis of medical evaluation and the type of diving involved.

Body Fat (Obesity)

Since the end of the nineteenth century, numerous investigators in laboratory and operational settings have reported a relationship between obesity (increased subcutaneous body fat) and subsequent DCS. As reported by Hills (5) and Bradley (14), this phenomenon has been observed in animal experiments (15-17). Pol and Watelle (18), Smith (19), and Hill (20) observed a DCS-obesity relationship among caisson workers, since supported by the Medical Research Council (21). Gray (13) described work with groups of USAF aviation trainees that found a relationship between weight-to-height ratio (one measure of body type used by some investigators) and group susceptibility to DCS. Obesity and aviation DCS was later addressed by Allen, Maio, and Bancroft (22) and Bason, Pheeny, and Dully (23), among others. In studies of U.S. Navy divers, Wise (9) found no relationship between obesity and DCS; this is in contrast to the findings of Doll and Berghage (9) and, recently, my colleagues and I at the Naval Submarine Medical Research Laboratory/Yale University (24). Carlioz et al. (11) found a similar association among French divers, as did Hayashi for Japanese divers (25).

Despite the strong indication of a DCS-obesity relationship from these studies, it is difficult to translate this into practical guidelines. If obesity is to be used in physical standards, what is the most reliable and practicable measure of determining obesity in the individual who comes to the office for a medical examination? Body fat has been measured through the use of body composition formulas after underwater (volume displacement) weighing of individual divers. While this is a highly regarded experimental tool, other means of body fat determination have to be used in observational studies of large populations of divers, who may be re-evaluated longitudinally through their diving careers. Weight/height indices, specifically, the ratio weight/(height squared), has been found to be a very appropriate measure of obesity in population studies of divers (26) and non-divers (27). However, skinfold thickness determinations, using one or usually more sites on the body, have been employed in numerous studies of divers, e.g., the Medical Research Council (21), Dembert et al. (28), Nakayama, Murai, and Hong (29), as well as various other athlete and military populations. Skinfold thicknesses are felt to be a representative measurement of body fat when values are inserted into established formulas for body composition such as developed by Womersley and Durnin (30).

Based on all that has been observed, I would recommend skinfold thicknesses for further diver studies, including the often-used triceps, suprailiac, and subscapular sites. At present, however, there is still not enough data available to confidently set absolute standards or levels of body fat as determinants of fitness to diving (31).

Biochemical/Hematological Factors

To establish a relationship between one or more biochemical indices and the subsequent development of DCS, whether in experimental animals or humans, it is important to first identify those individuals with high, low, and normal levels of the factor in question and then follow them through hyperbaric exposure(s). The rate of DCS among those with pre-established abnormal levels can be compared to the rate of those with normal levels. Measuring changes in blood indices during hyperbaric exposure only helps to describe the body's response to the hyperbaric environment, but it does not shed light on risk factors for DCS unless these changes are related to observed rates of DCS in the test populations.

The one class of biochemical compounds that has consistently appeared to be related to DCS susceptibility are the serum lipids. This has been observed in studies of animals (32,33) and humans (24,34). In some way, high concentrations of blood lipids may predispose to bubble growth, for example, reduction of surface tension in the blood (discussed with citations of older references in (34)). These high lipids may also enhance the microthrombosis seen with DCS, as obesity is associated with both high serum lipids and potentiated hemostasis (35,36).

Other chemistries (e.g., calcium, magnesium, electrolytes) and hematological/hemostatic indices (e.g., platelets, fibrinogen, clotting factors) can be measured in observational and experimental studies of divers. These may have an important role in the pathophysiology of and individual susceptibility to DCS.

In summary, until large populations of divers have reliable and repeated body fat measurements made in the office setting, and are followed in their diving careers to see the types of morbidity they experience, we can only offer common sense advice. The clinically obese diver--especially the one who will be using decompression tables routinely--appears to be at some increased risk for experiencing DCS on this basis alone and should therefore be counseled on reducing obvious excess body fat, high blood lipids, and paying strict attention to his or her safe and appropriate diving practices.

Smoking

Anecdotally and epidemiologically (28), many occupational divers are smokers. Could smoking contribute to susceptibility to DCS? Pons (37) suggests this in interesting speculations about the interaction of ions in the blood, tobacco and nicotine, and platelet aggregation. However, only one study of (Navy) divers to date has closely looked at a smoking-DCS relationship but found non-significant results (24). This hypothesis merits further investigation.

Smoking is a very significant risk factor for atherosclerotic peripheral arterial disease (38). Chronic smokers experience the longlasting effects of nicotine "intoxication" and related effects even during periods of

nonsmoking. Blood vessel damage due to chronic nicotine effects and lipid deposits, and the enhanced thrombosis associated with smoking (36), present an environment conducive to bubble formation, changes in blood rheology, microthrombosis, and the pathogenesis of DCS in general. Finally, would the known damage to lung tissue and function caused by chronic smoking also increase individual susceptibility to DCS (impairment of ventilation/perfusion? impairment of the removal of the dissolved nitrogen from the bloodstream to the lungs during decompression?)? Smoking as a contributory (individual or synergistic) risk factor is rarely identified or accounted for in experimental or epidemiological studies of divers. It should be.

Sex

This has engendered much discussion, research, and a comprehensive and detailed workshop (Women in Diving) recently sponsored and published by the Undersea and Hyperbaric Medical Society. The latter provides a comprehensive and detailed assessment of this subject. It is difficult to say whether all the evidence is in, but I tend to side with those who feel there is likely no real sex difference in DCS susceptibility.

There have been some animal studies, but I would rather look at human studies. And there are few. Bangasser (39) provides a good overview of the subject and studies done. She cites Bruce Bassett's two studies which found a significant female susceptibility to DCS among hypobaric trainees in the Air Force in San Antonio. In contrast, Waligora's research on hypobaric DCS, while on a smaller group of persons, found no sex difference in susceptibility to DCS as well as the formation of venous gas emboli (40). For divers, Bangasser's analysis of questionnaire responses from male and female recreational divers found a statistically significant increase in risk among females. However, the design of the study may have been inherently biased towards such a finding due to the nature of studies which use voluntary participation, e.g., women who experienced DCS may have been more likely to respond than women who never suffered DCS. Desola Ala and Masurel (41) found that women divers had less susceptibility to form venous gas emboli then men. Now Zwingelberg et al. have published their study of Navy divers, using cases and controls and feasible dive profiles (42). He and his co-workers found no real difference in susceptibility for the particular group of women he studied.

Aside from the pregnancy and diving issue, I don't believe that any recommendations regarding safety, performance, and medical advice can be specifically given to female divers on the basis of some increased susceptibility to DCS. A large, well-controlled population study of sport divers would be helpful. However, before that is done, I ask the members of this workshop the following: Are there enough cases of DCS occurring among recreational or occupational women divers--with no evident omitted decompression, obesity,, etc.--to really justify further looking for a sex difference in susceptibility to DCS? Is there enough evidence now, or will there be in the future, to cause us to modify diving medical standards for female divers?

Alcohol Intake and Coffee Intake

I mention these two dietary factors, because they are standardly examined and analyzed in epidemiology studies of chronic disease such as heart disease and cancers. They are important not only as risk factors which contribute to disease or injury on an individual basis, but also because people who ("to excess") smoke cigarettes or drink coffee or drink alcohol or eat fatty diets or develop some degee of obesity, etc. tend to do several of these all the time.

Again, occupational divers appear to drink a lot of coffee and alcohol (28). It is purely speculative to say what effect caffeine would have at the cellular level as regards bubble formation or hemostatic activity, but heavy coffee drinkers should carry the effects of the caffeine body burden into their actual dives.

Admonitions against mixing alcohol and hyperbaric exposure were made decades ago (20). Excessive alcohol ingestion could impair performance and safe diving behavior (43,44); this includes the proper use of decompression tables and monitoring of depth and bottom-time profiles. One recent study of Japanese divers found a positive association between habitual alcohol drinkers and risk of DCS (25). The occasional or social drinker should not have any direct longlasting cellular or biochemical effect from the alcohol when he dives later. However, the chronic alcoholic diver, who is knowingly or unknowingly permitted to dive, would likely have some degree of liver dysfunction and performance impairment on a longstanding basis.

Alcohol's indirect contribution to DCS susceptibility is obvious. However, it is speculative on alcohol's direct contribution to DCS by its effect on blood surface tension, inert gas uptake/release in tissues, etc. As with smoking, blood lipids, and obesity, the effects of coffee and alcohol consumption would have to be teased out of the observations on large populations of divers.

Occupational/Worksite Exposures

Military divers often have primary ratings which additionally expose them to hazardous fumes, vapors, solvents, or other materials on a frequent if not almost daily basis during their diving careers. The same could be said for civilian occupational divers, whether in wet or dry (tunnel) conditions during or before/after hyperbaric exposure. Could some of these exposures affect susceptibility to decompression sickness, through effects on the lungs or blood vessels?

The lungs are prone to injury and disease by a wide variety of substances and disorders related to the worksite. These include, for example, respiratory irritants such as nitrogen oxides and halogen compounds, industrial bronchitis (complicated by cigarette smoking), siderosis or arc welder's lung and other mineral dust respiratory diseases, asbestosis, organic fumes, fumes and vapors containing metals, and hypersensitivity reactions of the lung (see Rom (45) for a complete review of occupational

exposures in general). These can cause chronic bronchitis, obstructive lung disease, interstitial fibrosis, pneumonia (alveolar or interstitial), and other inflammatory reactions from particle deposition. Affected divers may have interstitial/alveolar damage and perfusion-ventilation abnormalities. Smokers who have one or more of these above exposures may be at far greater risk of lung damage because of a synergistic or potentiating effect. I would think that many of these could seriously impair normal inert gas exchange during diving?

The byproducts of welding and thermal cutting should be especially considered. von Nieding and co-workers provide the only study in the literature on the effect of welding in a hyperbaric condition on lung function (46). The effects were neglible, found to be similar to those experienced at sea level. However, theirs was a one-time study and did not follow these men over long periods of exposure and time.

We should also consider chronic exposure to volatile organic solvents as a potential hazard to some divers. These compounds would pass from the lungs after inhalation--or be absorbed directly through the skin--and exert profound behavioral, intellectual, and psychological effects through action on the central and peripheral nervous systems. These could adversely affect performance, diving safety, and adherence to decompression schedules.

Any relationship between occupational chemical/particle/fume exposure and DCS is unknown at present, but it should be investigated further, especially in light of the current climate in occupational safety and health.

Training and Experience

I know of no large studies which examined psychological or behavioral criteria, stress endurance, job performance, or training and a later association with DCS. However, some of these variables are obtainable from diving logs, while others can be obtained from preplanned educational/vocational/psychological tests or questionnaires (47). Morgan (48) and Jensen, Vaernes, and Stokke (49) provide brief but excellent discussions of the approach to and research in the psychobiology of scuba diving. It is conceivable that characteristics of one's performance, behaviors, and reaction to stressors (planned and unplanned) can indirectly influence individual susceptibility to DCS.

One would assume that the more experienced and trained diver is less likely to get into trouble, to ignore decompression tables, to allow air to run out on a sport or working dive, to panic, to not dive with a buddy, to cavort underwater at the expense of safety. I think that many of us can testify to anecdotal experiences of treating such divers for DCS; usually, the diver was foolhardy or ignorant. These incidents are preventable.

INDIVIDUAL DCS FACTORS

Drugs

I am not aware of any prescription/over-the-counter drugs which are commonly taken and would predispose to DCS by activating clotting/thrombosis mechanisms or by action on blood rheology. Illicit drugs taken before diving would obviously impair performance and safe diving behavior. Some have raised the question of aspirin-loading before diving, in hopes that aspirin's antithrombotic effect would lessen one's susceptibility to DCS. Again, I think that this would take a large clinical trial to show this. However, any results suggesting a protective effect would open a Pandora's Box to encourage people to dive with less regard for decompression tables.

Miscellaneous

Under this final category, I will mention areas that have been scantily discussed in the literature but may merit further consideration.

Can we gain important physiological data from the experiences of fishermen-divers from Asia and Hawaii? I think so. These men and women use diving practices that appear more risky for DCS, because they dive hard, long, and repetitively, may flaunt decompression tables, and may use compressed air of unknown quality (50,51,52). However, we don't know the true incidence of DCS among these groups, so we can't say if their practices make them more, or even less, susceptible. Economic realities make them dive all the time, even after they have been bent previously and recovered to some degree.

There is mixed opinion about whether divers who suffer DCS should continue diving and what risk do they have of experiencing DCS in the same anatomic location. This would be of more concern for initial cases of serious or Type II DCS. This latter phenomenon has been reported by Kizer (50); undoubtedly, it occurs among Asian diving populations as well. I have not found references to this among Western diving populations. Likewise, does previous injury increase susceptibility to DCS, especially in the area of injury? Reports on aviation DCS by Thompson et al. in 1944 and Fryer in 1969 that are cited in (5) indicate this; however, I have not found recent studies, on divers. I would empirically suspect this association to be real, but it would have to depend upon the type of injury, residual damage to circulation and mobility, etc.

Could an end-of-dive or post-dive valsalva maneuver associated with equalizing middle ear spaces, coughing, urinating, or defecating make one immediately susceptible to DCS occurrence? An increase in intra-abdominal pressure, experimentally induced by external abdominal compression, was theorized to lead to obstruction of the extra-vertebral venous system and spinal DCS in dogs subjected to DCS-producing dive profiles (53). This same large increase could occur with a sudden valsalva maneuver performed topside after a dive that was near no-decompression limits.

Circadian rhythm influence on DCS susceptibility has already been investigated, with inconclusive results (54). Although interesting,

research in this area could be biased or confounded in numerous ways.

I know of no established differences in susceptibility to DCS by the race of the diver.

Could diving equipment which fits improperly and perhaps constricts major joints or movement, or restricts posture, make one susceptible to DCS? It would be difficult to prove in human experiments, but I raise this thought after reading about tight neck seals in diving suits leading to carotid sinus syndromes while in the water (55).

Summary

Numerous so-called risk factors for DCS have been discussed. The feasibility of some enjoy the support of research among divers, caisson workers, and aviators. Others are purely speculative but possible.

This brings me to several final questions, which I pose to the members of this workshop. To what extent should we worry about susceptibility for DCS? Is it for academic reasons? purely scientific reasons? for medical and economic reasons, e.g., a case of DCS is an injury and could affect that person's livelihood or overall health? To what extent can we--or should we—predict who will get DCS, based on individual factors? Are studies such as these for everyone, or should they just be applied to certain groups, e.g., military divers, commercial divers--and to what type of diving? Can individual or endogenous factors which put a diver at increased risk for DCS be given the same emphasis and amount of importance for aviators?; in other words, how comparable is the research in this area? Finally, once such factors are identified, how willing are we as hyperbaric and hypobaric medicine practitioners and advisors to force our working personnel to modify these factors, many of them age-old traditions or habits?

References

1. Berghage TE, Rohrbaugh PA, Bachrach AJ, Armstrong FW. Navy diving. Who's doing it and under what conditions. Bethesda, MD: Naval Medical Research Institute, 1975.
2. Commander, U.S. Naval Safety Center. Diving statistics and diving accident injury analysis for the period 1 January through 31 December 1981. Norfolk, VA: Naval Safety Center, June 1982.
3. Wachholz C. Diving equipment and the Diving Accident Network. In: Fife W, ed. Women in diving. Thirty-fifth Undersea and Hyperbaric Medical Society Workshop. Bethesda, MD: Undersea and Hyperbaric Medical Society, 1987:125-133.
4. Mausner JS, Bahn AK. Epidemiology. An introductory text. Philadelphia, PA: W. B. Saunders, 1974.
5. Hills BA. Decompression sickness. Volume 1. The biophysical basis of prevention and treatment. New York, NY: John Wiley, 1976:41-47.
6. Pouliquen H. L'Enfant et la plongee. South Pacific Underwater Med Soc J (October-December) 1982:3.

7. Betts J. The bones of the matter. Diver (England) 1984; 29:10.
8. Dembert ML, Keith JF. Evaluating the potential pediatric scuba diver. Am J Dis Children 1986; 140:1135-1141.
9. Doll RE, Berghage TE. Interrelationships of several parameters of decompression sickness. Report 7-65. Washington, DC: U.S. Navy Experimental Diving Unit, 1967.
10. Biersner RJ. Factors in 171 Navy diving decompression accidents occurring between 1960-1969. Aviat Space Environ Med 1975; 46:1069-1073.
11. Carlioz M, Comet M, Gardette B. About individual factors influence in man on the bubble formation in air diving decompression. In: Ornhagen H, ed. Proceedings of the XIth annual meeting of the European Undersea Biomedical Society on diving and hyperbaric medicine, August 21-23, 1985. Goteborg, Sweden: National Defence Research Institute, 1986:229-237.
12. Wise DA. Constitutional factors in decompression sickness. Report 2-63. Washington, DC: U.S. Navy Experimental Diving Unit, 1963
13. Gray JS. Constitutional factors affecting susceptibility to decompression sickness. In: Fulton J, ed. Decompression sickness. Philadelphia, PA: W. B. Saunders, 1951:182-191.
14. Bradley ME. Metabolic considerations. In: Vorosmarti J, ed. Fitness to dive. Thirty-fourth Undersea and Hyperbaric Medical Society Workshop. Bethesda, MD: Undersea and Hyperbaric Medical Society, 1986:98-104.
15. Boycott AE, Damant GCC. Experiments on the influence of fatness on susceptibility to caisson disease. J Hyg 1908; 8:445-456.
16. Gersh J, Hawkinson GE. The formation and appearance of tissue and gas bubbles after rapid decompression of guinea pigs from high pressure atmospheres. Naval Medical Research Institute Project x-284 Report 1, 1944.
17. Philp RB, Gowdey CW. Experimental analysis of the relation between body fat and susceptibility to decompression sickness. Aerosp Med 1964; 35:351-356.
18. Pol B, Watelle T. Memorie sur les effets de la compression de l'air appliquee an crecsment des peuts a houille. Ann Hyg Lang Fr Med Twtr 1854; I:241-279.
19. Smith RH. The effects of high atmospheric pressure including caisson disease. Brooklyn, NY: New York and Brooklyn Bridge Co., 1873.
20. Hill L. Caisson sickness and the physiology of work in compressed air. New York, NY: Edward Arnold, 1912:164-177.
21. Medical Research Council. Decompression sickness and aseptic necrosis of bone: Investigations carried out during and after the construction of the Tyne Road Tunnel (1962-66). Brit J Ind Med 1971; 28:1-21.
22. Allen TH, Maio DA, Bancroft RW. Body fat, denitrogenation and decompression sickness in men exercising after abrupt exposures to altitude. Aerosp Med 1971; 42;518-524.
23. Bason R, Pheeny H, Dully FE. Incidence of decompression sickness in Navy low-pressure chambers. Aviat Space Environ Med 1976; 47:995-997.
24. Dembert ML, Jekel JF, Mooney LW. Health risk factors for the development of decompression sickness among U.S. Navy divers. Undersea Biomed Res 1984; 11:395-406.
25. Hayashi K. Medical survey on 299 helmet divers. In: Third joint meeting of the Panel on Diving Physiology and Technology, Tokyo, Japan, July 18-19, 1975. United States-Japan Conference on Development

and Utilization of Natural Resources (UJNR): 38-39.
26. Dembert ML, Jekel JF, Mooney LW. Weight-height indices and percent body fat among U.S. Navy divers. Aviat Space Environ Med 1984; 55:391-395.
27. Criqui MH, Klauber MR, Barrett-Connor E, Holdbrook M, Suarez L, Wingard DL. Adjustment for obesity in studies of cardiovascular disease. Am J Epidemiol 1982; 116:685-691.
28. Dembert ML, Mooney LW, Ostfeld AM, Lacroix PG. Multiphasic health profiles of Navy divers. Undersea Biomed Res 1983; 10:45-61.
29. Nakayama H, Murai T, Hong SK. Seadragon VI: A 7-day dry saturation dive at 31 ATA. I. Objectives, design, and scope. Undersea Biomed Res 1987; 14:377-386.
30. Womersley J, Durnin JVG. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974; 32:77-97.
31. McCallum RI, Petrie A. Optimum weights for commercial divers. Br J Ind Med 1984; 41: 275-278.
32. Philp RB. The ameliorative effects of heparin and depolymerized hyaluronate on decompression sickness in rats. Can J Physiol Pharmacol 1964; 42:819-829.
33. Philp RB, Gowdey CW, Prasad M. Changes in blood lipid concentration and cell counts following decompression sickness in rats and the influence of dietary lipid. Can J Physiol Pharmacol 1967; 45:1047-1059.
34. Jauchem JR, Waligora JM, Conkin J, Horrigan DJ, Johnson PC. Blood biochemical factors in humans resistant and susceptible to formation of venous gas emboli during decompression. Eur J Appl Physiol 1986; 55:68-73.
35. Haines AP, Imeson JD, Meade TW. Skinfold thickness and cardiovascular risk factors. Am J Epidemiol 1987; 126:86-94.
36. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham study. JAMA 1987; 258:1183-1186.
37. Pons RB. Ionization and decompression sickness. In: Desola Ala J, ed. Proceedings of the IX Congress of the European Undersea Biomedical Society, September 23-25, 1983. Barcelona, Spain: Centre de Recuperacio I D'Investigacions Submarines, 1984:141-143.
38. Fielding JE. Smoking: Health effects and control. New Engl J Med 1985; 313:491-498.
39. Bangasser S. Decompression sickness in women. In: Fife W, ed. Women in diving. Thirty-fifth Undersea and Hyperbaric Medical Society Workshop. Bethesda, MD: Undersea and Hyperbaric Medical Society, 1987:65-79.
40. Waligora JM, Horrigan DJ, Conkin J, Gilbert JH. Incidence of symptoms and venous gas bubbles in male and female subjects after decompression. Presented at the 57th annual scientific meeting of the Aerospace Medical Association, April 23, 1986.
41. Desola Ala J, Masurel G. Less bubble formation in women divers? In: Ornhagen H, ed. Proceedings of the XIth annual meeting of the European Undersea Biomedical Society on diving and hyperbaric medicine, August 21-23, 1985. Goteborg, Sweden: National Defence Research Institute, 1986:247-256.
42. Zwingelberg KM, Knight MA, Biles JB. Decompression sickness in women divers. Undersea Biomed Res 1987; 14:311-318.

43. Jennings RD, Jones W, Adolfson J, Goldberg L, Hesser CM. Changes in man's standing steadiness in the presence of alcohol and hyperbaric air. Undersea Biomed Res 1977; 4:A16.
44. Somers LH. Drinking and diving. Diver education series. Report No. MICHU-SG-86-511. Ann Arbor, MI: Michigan Sea Grant College Program, 1986.
45. Rom WN, ed. Environmental and occupational medicine. Boston, MA: Little, Brown, 1983.
46. von Nieding G, Press H, John S, Wagnitz K. Studies on formation of toxic substances during welding under hyperbaric conditions and of associated health hazards. In: Desola Ala J, ed. Proceedings of the IX congress of the European Undersea Biomedical Society. September 23-25, 1983. Barcelona, Spain: Centre de Recuperacio I D'Investigacions Submarines, 1984:281-291.
47. Biersner RJ, Dembert ML, Browning MD. Comparisons of performance effectiveness among divers. Aviat Space Environ Med 1980; 51:1193-1196.
48. Morgan WP. Psychological characteristics of the female diver. In: Fife W, ed. Women in diving. Thirty-fifth Undersea and Hyperbaric Medical Society workshop. Bethesda, MD: Undersea and Hyperbaric Medical Society, 1987:45-64.
49. Jensen A, Vaernes R, Stokke K-T. Psychological and physiological stress reactions among sportsdiver-students. In: Ornhagen H, ed. Proceedings of the XIth congress of the annual meeting of the European Undersea Biomedical Society on diving and hyperbaric medicine. August 21-23,1985. Goteborg, Sweden: National Defence Research Institute, 1986:179-189. .
50. Kizer KW. Dysbarism in paradise. Hawaii Med J 1980; 39:109-116.
51. Sasaki A, Ohtsuka R, Suzuki T. Work styles of Okinawan diving-fishers in relation to decompression sickness and physical complaints. J Human Ergol 1983; 12:219-222.
52. Dembert ML. Decompression sickness among Filipino divers. Pressure (in press).
53. Hallenbeck JM, Bove AA, Elliott DH. Mechanisms underlying spinal cord decompression sickness. Neurology 1975; 25:308-316.
54. Vroege D. Decompression sickness and circadian rhythm. In: Proceedings of the eight annual congress of the European Undersea Biomedical Society, October 5-8, 1982. Lubeck, West Germany: Dragerwerk AG, 1983:119-130.
55. Shennan C. Safety. A new danger identified. Diver (England) 1985; 30:19.

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DISCUSSION

DR. LUNDGREN: There is a very distinct correlation between obesity and altitude decompression sickness. Almost all cases of so-called decompression shock occur during altitude exposure and always in overweight individuals. The reason that we perhaps don't see that in diving, usually, is that the altitude exposure resembles decompression from saturation. Most of our systemic studies of decompression sickness are in bounce diving where fat is probably not saturated.

On a different note, Astrup in Copenhagen found that rabbits subjected to a higher cholesterol diet were more likely to develop arteriosclerosis when exposed to carbon monoxide. Thus, the carbon monoxide levels in the blood of heavy smokers, which can reach up to 10%, may make things worse in decompression sickness once the coagulation cascade has started.

DR. ZWINGELBERG: Dr. Dembert, based on our current knowledge, we cannot conclude that there is a difference between men and women in susceptibility to decompression sickness in diving. Perhaps this difference does exist in aviation as Basset's study suggests. Only further study can resolve these questions.

DR. LAMBERTSEN: Dr. Weathersby, that was a very simple and neat exposition on the need for statistical handling of decompression sickness. Do you think it's really going to be possible, in light of the many different kinds of diving and altitude exposure, to do proper statistical comparisons to determine the answer about individual susceptibility?

DR. WEATHERSBY: I don't think we're going to be able to come up with the complete answer to the full list of things that you stated and implied. But, I sure think we've got to start. I think it's possible to come up with a satisfactory statistical design and answer questions with individual experiments, as I think we have recently done with oxygen and bounce diving.

DR. LAMBERTSEN: Isn't it necessary to create an experimental design in which you're going to get a large number of cases of decompression sickness instead of none? You're going to have to generate the conditions in order to develop decompression sickness, rather than to prevent its occurrence.

DR. WEATHERSBY: That's certainly true. You can't claim you're studying decompression sickness if you never cause it.

DR. WARD: Dr. Weathersby, you say that people were not consistent within Gray's study and you also say that the results are not random within the study. That should be very encouraging to someone like myself who's trying to identify a factor that suggests individual variation within the population?

DR. WEATHERSBY: I think these results would probably help one be more optimistic with the approach you're taking of coming up with a biochemical measurement that you already know has some short-term variability. Then with some extraordinary luck, which I certainly wish you, you may find that there is a strong correlation between the temporal change in complement sensitivity and the temporal change in decompression susceptibility. I think it's much worse news for people who would like to get things like risk factors from an annual health questionnaire, because this kind of rapid individual change is certainly going to occur at higher frequency than you could pick up from those kinds of vehicles (e.g., an annual questionnaire).

DR. KINDWALL: Dr. Dembert, Dr. Lambertsen raised the question of how you study a disease that is quite rare. When you're talking about one case in 10,000 dives, it's very hard to put any kind of statistical meaning behind a variable that you may find and you'll have to sift through tons of data to even find one case that would make a point. My suggestion is that we not study divers, but that we study caisson workers. Right now in the U.K., to give you an idea of the numbers involved, there are some 500,000 records of man decompressions. Caisson workers, however, never report the true incidence of decompression sickness. I would suggest that anyone wishing to study diving disease and decompression sickness get to know where a caisson contract is going on and then become friendly with the caisson workers and initiate an anonymous system of reporting symptoms in a way that there is no possibility of job loss for the man. This factor is quite real. Using this method you will find a true incidence of bends. We've found bends on 40% of the working days--that's a lot of bends. For purposes of statistical analysis, all the caisson tables presently in use, everywhere in the world, are universally bad, so we're going to have plenty of bends. And you'll find these tables are never padded. With regard to Navy diving schedules, if you go to the U.S. Navy Experimental Diving Unit and ask, "Have you ever had any problems with the 150 feet for a 30-minute dive schedule?" they'll look up the 150/30, which we all know bends people like pretzels, and they'll say, "No, we've got no problems with it," and it's because it's never been used as the 150/30 schedule. This is because experienced Navy master divers never use the tables as written. They always pad them. An exception occurred using that table in 1968, when we filled up every chamber in New London with 6 divers who compressed "on the money" with that table, having spent exactly 30 minutes at an actual depth of 150 feet. The caisson tables are always "on the money" because contractors cannot afford to allow people to take extra time. If you approach caisson workers right, they will be very cooperative with you. I was trying to do hematologic studies in Milwaukee and found not a single person who refused to have blood drawn. This was a very gratifying thing when you're trying to get the cooperation of a large group. If you approach them right, these people will be willing to help you, but you have to understand their problems, too.

DR. DEMBERT: I was trying to present both sides of the coin. As an epidemiologist tries to find the answers from a large defined population, one side of me has to present the challenge of assessing the risk of DCS and that is exciting for me. But on the other hand, DCS seems uncommon enough in military and other populations that maybe it doesn't warrant large, sophisticated studies. However, studies of patterns of DCS presentation and direct experience are important because they can point to policy or procedural changes to short-term remedies, such as changes in medical treatment/and use of adjunctive drugs, effectiveness and need for air ambulance service, other ways of transport, and changes in decompression or work schedules. Good risk assessment studies have to use large numbers of cases as well nonaffected divers.

DR. VANN: What about existing data bases such as the Navy's 9940 report system which is maintained by the Naval Safety Center? Is this of use for your work? I know some people don't think it's as effective as it might be.

DR. DEMBERT: I used some of the Naval Safety Center data several years ago as a baseline for my Master's thesis work on the health risk factors of diving. A lot of the data is technical, related to dive conditions. They really don't have any medical data.

DR. WEATHERSBY: I attempted to use dive records from the Naval Safety Center as a database to model decompression outcomes, and failed.

DR. ZWINGELBERG: I also tried to look through that database for information on women in diving but found nothing useful. The Safety Center database has holes in it.

DR. QUIGG: Can anyone comment on the DCS incidence in commercial divers as compared with Navy divers?

MR. GALERNE: We treat civilian divers in New York City in our hyperbaric center and most of those people don't know to what depth they've been or how long they've been on the bottom, so we have no statistics whatsoever. In professional diving we have better statistics, but it is sometimes difficult to talk about because a statistic means a lawsuit and lawyer problems. Moreover, the figures have to be correct. In my organization, 20 years ago, I reviewed my dive records and I discovered very quickly that the dives did not correspond to the proper decompression schedules because the divers have a tendency to change them. If they want to use the 200-foot table, or they go 200-feet deep, they will use a 220-foot table. Why, I don't know; perhaps because they feel more comfortable by increasing the depth of the time. Also I discovered very quickly that often "their knees stopped." When you go very deep, up to 650 feet in bounce dives, decompression is very long and "often their knees stop." I don't know why and they don't know why. So, it's very difficult to obtain any statistics in which you can have confidence. We are now legally obliged to keep all our records of every dive for 30 years. Our successors who buy our company will have to do the same thing. Those data will be available to anyone with adequate reason who demands them. If we can furnish reliable data as a diving contractor, maybe we will have a good answer in a few years. We are under heavy pressure to do it now.

MR. MINICLIER: Let me defend the lawyers a little bit. I think one of the biggest problems you have in separating the commercial environment from the Navy environment is the profit motive. I think a lot of type I bends are not reported in commercial diving simply because the individual will lose his depth pay or chance to make another dive. Diving companies also don't want to release their databases. As an ex-Navy diver now working in the commercial environment, I know that the Navy uses far more topside support personnel which can include a corpsman, diving medical officer, and up to 10 people for deep dives. Also the decompression tables on the commercial side are too modified on the bounce dives to compare them to Navy tables. In my perspective in the last 3 years, the incidences of decompression sickness that I've seen, which is ultimately when they come to the litigation stage, have decreased dramatically.

DR. QUIGG: To what extent should we in the Navy in occupational medicine be getting involved, and in the civilian community, to what extent do people think the Occupational Safety & Health Administration should be getting involved? Is this a dangerous enough area? We regulate so much industry. We go into the automobile industry. We go into chemical industries. What regulation is occurring and if none, what should be occurring?

DR. KINDWALL: I've been trying for 15 years to get OSHA to change the decompression tables for caisson workers. We have known since 1982, when

it was published in the open literature, that 33% of the people who used the federally enforced OSHA tables over 36 psig developed bone necrosis. I've been informed that it will be 9 years from the time that it first appeared in the open literature until it will be possible, with priority, to get a change or rescinding of those orders in the Federal Register. I have tried through congressmen. I have tried through my friends in the diving community who have some compassion for these poor human beings who work in compressed air, but I can't seem to find anybody, except perhaps the union, who wants to make a change because no one seems to understand the depth and magnitude of the problem.

DR. DEMBERT: Dr. Quigg, it's hard for me, from the Navy, to comment on the civilian community. But, from my experience in the Navy and from the work that Dr. Zwingelberg and others have done, I believe that diving has become more noticed as a problem in occupational medicine. I would like to see the Navy's 9940 dive log be revised in the future. That might be a herculean task, but if information on medical status, medications, etc., can be incorporated and tied to past and present physical examination data, the benefits would be immense from an epidemiological perspective. The military, particularly the Navy, is the one organization that has physical standards for diving and can follow people in their career for 5, 10, 15 years. If we're going to get anywhere in the future, looking at diving, dive profiles, and risk factors, I think the Navy will do it, but it's going to take a lot of pushing, proving, and funding.

DR. WHIDDEN: The physical conditioning of your population is very important. We observe within shock populations that a difference in physical condition can mean a large shift in LD_{50} when you're looking at a particular trauma modality. I think it's very important when you compare a commercial diving population to a sport diving population to look at physical condition and exercise patterns.

MR. IMBERT: I would like to respond to comments about decompression safety in commercial diving. COMEX started a data bank about 12 years ago and has accumulated information on diving because we wanted to improve safety. Unfortunately, it is difficult for us to publish this information because the tables are the official French tables and do not belong to COMEX. We've recently produced new improved tables and have presented them to the French Government, which has accepted them. Thus, in less than 14 years, the official French tables have been received and revised as a result of carefully maintained diving records. The situation is not desperate, it just takes a long time to collect sufficient information.

INDIVIDUAL SUSCEPTIBILITY TO DCS

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In talking about differences in DCS susceptibility among people, we must also consider differences within each individual. I, as have many of you, observed individuals repeat an identical or more severe dive that previously produced DCS but on the new occasion was uneventful. The parallel history of an individual suffering DCS following a dive previously safe for that person is also known to many of you. To my knowledge, the extent of this "people are not consistent" phenomenon has not been studied systematically in hyperbaric exposures.

During World War II a large study of altitude decompression included several serious examinations of intra-individual variability. One particularly extensive study reported by Gray and colleagues (J Aviat Med 34: 88-95, 1947) is reproduced below:

INTRA INDIVIDUAL VARIABILITY
IN DCS
43 SUBJECTS, 5 REPEAT ALTITUDE EXPOSURES

CASES DCS	0	1	2	3	4	5
ACTUAL	19	12	7	2	2	1
HYPOTHESES:						
PEOPLE CONSISTENT	34	0	0	0	0	9
RANDOM OCCURRENCE	13	18	9	3		

In the Table are given the number of subjects (out of 43 total) who suffered symptoms of DCS. For example, 19 never had symptoms, while 12 subjects had symptoms in only 1 of their 5 exposures. Note that less than half of the subjects were totally consistent (19 never with symptoms plus 1 always with symptoms).

With such data we can ask specific questions, such as: are people totally consistent in their susceptibility to DCS in a controlled, repeated exposure? or as an extreme alternative: is the occurrence of DCS totally random within a population with no tendency of individuals to behave consistently? If all were consistent, the total number of DCS cases (45) would be concentrated in 9 subjects who were always stricken and all exposures of the other 34 subjects would be uneventful. Obviously this did not happen - people did not react consistently.

On the other hand is susceptibility totally random? Applying the binomial distribution to 5 trials with the same overall outcome (45 cases in 215 total exposures or 20.9% DCS) leads to the "Random Occurrence" entry in the table. By this view we predict 13 subjects would have no cases, 18 with 1 case, 9 with 2 cases and 3 subjects total would have 3-5 cases of DCS. It is not so obvious, but this model fails to fit the actual outcome as well ($p < .02$ by Chi-square). A few more subjects are consistent than the random occurrence model precits (20 vs. the predicted 13).

In this trial, people were found to react neither with total consistency nor totally at random, but rather in between. Gray's paper presented similar outcomes in other studies with fewer repeat exposures. Since these studies have demonstrated such a large random component in individual response to DCS, we should be exceedingly wary of labels on divers like "especially susceptible" and wary of decompression tests that incorporate such ideas. We should also recognize the additional challenge to those who search for selection tests and measures of susceptibility.

CAISSON DECOMPRESSION

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ABSTRACT

Kindwall, EP, Caisson Decompression, Proceedings of UHMS Symposium, The Physiologic Basis of Decompression, Duke University, November 16-18, 1987.

Cummulative evidence indicates that all the current caisson decompression schedules in use are inadequate. The reported incidence of decompression sickness is considerably lower than the actual. Most decompression schemes for tunnel workers are extrapolated from naval schedules albeit navies have had very little experience with long duration dives at shallow depths. The new Milwaukee tables based on commercial data are several times longer than existing schedules. Oxygen decompression appears to be the only viable method of decompressing tunnel workers on a daily basis. Oxygen tables have been devised which appear safer than existing tables but regulating bodies in Great Britain, the United States and Japan have failed to keep pace with recent developments in physiology. Traditionally, aseptic necrosis was the most feared complication of tunnel decompression, but now there is increasing awareness of the possibility of central nervous system damage secondary to improper decompression. Saturation exposures for tunnel workers are now planned in Germany and Denmark with helium-oxygen breathing at the higher pressures. Tables from Japan, the United States, Great Britian, Germany and France are compared.

Caisson and compressed air tunnel exposures are different from those seen in diving in several important ways. Caisson work is invariably carried out at very modest pressures never exceeding the equivalent of 34 meters (112 feet) of sea water or 50 pounds per square inch. Bottom times or shift lengths, however, almost always range between 4 and 8 hours on a daily basis with 6 to 8 hour exposures being the most common. Furthermore every caisson exposure completely fills the envelope covered by the decompression schedule in use. A new schedule is provided for every additional 1 to 1.5 meters equivalent seawater depth. This is done for economic reasons as a pound or two difference would mean a new schedule and contractors with large gangs of men need to minimize decompression time. Thus, approximately 4 out of 5 caisson exposures will test the table to its limit whereas only about 3 in 10 water dives pushes the table to a similar extent. Diving tables are invariably set up in 3 meter increments.

Caisson workers also work in a dry environment and thus must support the weight of their own bodies throughout the exposure as well as the tools and the burdens which they carry. The atmosphere in the tunnel

frequently has more contaminants than are present in the divers air supply. Tunnelers are rarely chilled during the exposure but may be exposed to excessive heat during concrete pours. Chilling takes place during decompression when they are seated in a dry chamber. Balldin has demonstrated that there is 30% less nitrogen elimination in those decompressing in the dry as opposed to those decompressing while immersed.[1] Finally, caisson exposures are much more numerous than diving exposures. At the present time some 236,000 man-decompressions are being analyzed which were carried out using the Blackpool caisson schedules.[2] Despite the great amount of material available for analysis, there has been relatively little study or scholarly work invested in caisson tables as opposed to those for deep sea divers. Physiologists used to dealing with the diving community often assume that caisson decompression sickness data can be treated in the same manner as diving statistics. This is not true as the decompression sickness figures from caisson work are never correct as reported. Official rates deal only with <u>treated</u> cases of decompression sickness. This is because the men fear for their jobs if they complain of symptoms. Because caisson tables have been notoriously bad for so many years, those engaged in this kind of work accept symptoms of decompression sickness as a fact of life[3]. They rarely report for treatment unless symptoms are unbearable or incapacitating. Too frequent recompression treatment would mean loss of job. Using an anonymous system of reporting on a tunnel project in Milwaukee in 1971-72, we found that up to 26%[4] of a shift might be bent on any given day and that we had decompression sickness present on the job on 42.5% of the working days. This was despite the fact that our "official" decompression sickness incidence was 1.44%.

The French were the first to have used compressed air to exclude water in mines starting in the early 1840's and the first case of decompression sickness was reported in a compressed air mine worker in 1841 by Triger.[5] The Eads Bridge in St. Louis and the Brooklyn Bridge in New York were built on foundations constructed with pneumatic caissons before the cause of decompression sickness was known. The word "bends" was coined on the Brooklyn Bridge job.[6] Decompressions were accomplished by simply opening the valve to the manlock at the end of each shift and pressures were bled off uniformly in a continuous manner. Stage decompression was unknown. There was a 25% mortality among the workers building the Hudson tubes which dropped to 4% with the introduction of a recompression treatment chamber. Knowing that shorter exposures seemed to decrease the incidence of decompression sickness, the concept of the split shift arose. This meant that instead of one continuous long working period during the day, the workmen would work a relatively short shift in the morning, followed by a rest period on the surface which in turn would be followed by a second shift in the afternoon. It was thought that by working two shorter shifts, the decompression sickness rate would be lower. What was not understood however by the contractors and the workers alike, was that the time period on the surface between the two shifts was pitifully inadequate to allow release of meaningful amounts of nitrogen present in the body. The second failing of the split shift was that it exposed the worker to the trauma of two decompressions per day instead of just one.

In addition to devising the first set of decompression tables in 1908, Haldane also tested different decompression schemes. He found that continuous decompression, such as caisson workers used, is inferior to stage decompression causing serious symptoms or death 25 times more often than stage decompression[7]. Nevertheless, in 1922 the State of New York produced a decompression code embodying not only the split shift but continuous or uniform decompression.

Unfortunately, the split-shift is still in use in Japan. Figure 1 shows how the Japanese caisson schedule compares to a U.S. Navy repetitive dive for the same exposures.

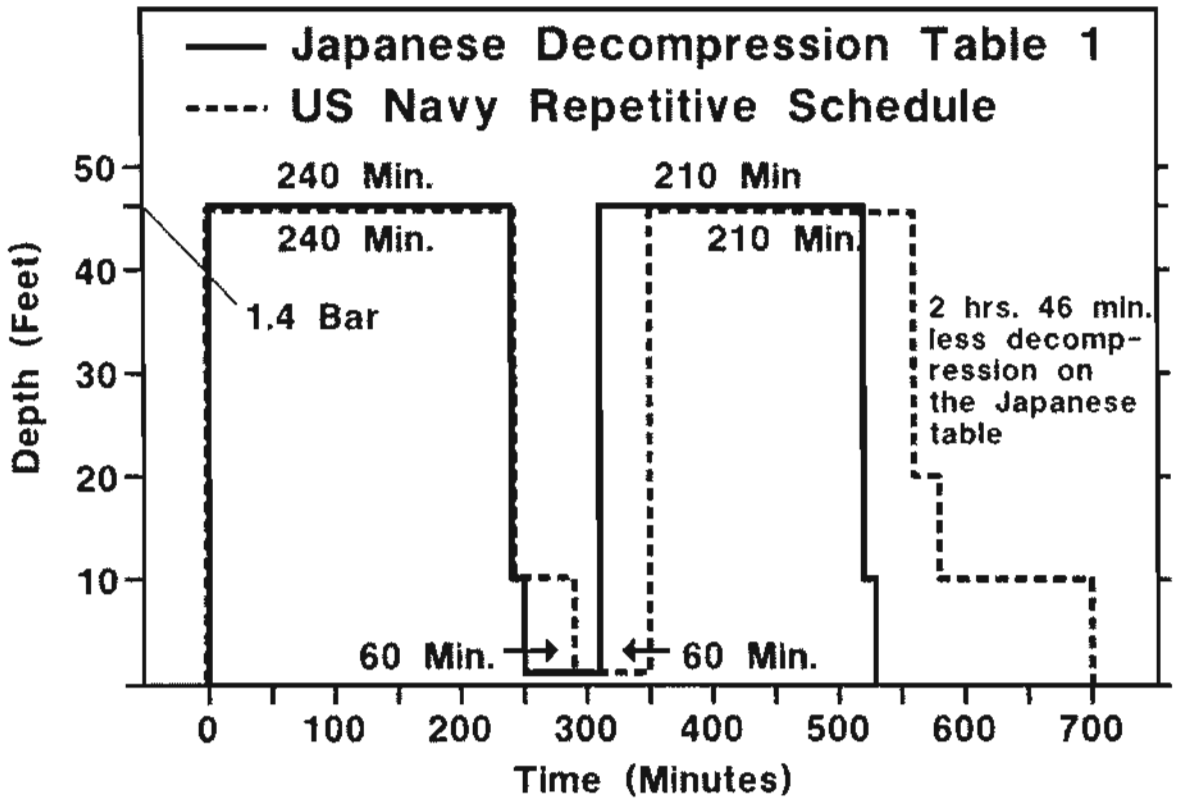

Figure 1

Aseptic necrosis was first recognized in tunnel workers in 1912[8] but was not recognized in divers until 1942. Nevertheless, the regulatory bodies paid no attention to these data and no experiments were done to devise tables to avoid it.

I consider dysbaric osteonecrosis as another form of decompression sickness as bone is simply another target organ, along with spinal cord and brain. Despite theories to the contrary, bone disease appears to be caused by improper decompression. Very costly human experimentation has shown that in the production of bone necrosis, decompression time is the only independent variable. Short tables produce necrosis - long tables produce less or none.

The 1922 New York table remained the gold standard of decompression in the United States until the 1960's. Beginning in 1958, the British Medical Research Council Panel on Decompression Sickness began to investigate the incidence of aseptic necrosis in tunnel workers and found a 19% incidence of bone disease in the workers building the Clyde tunnels.[9] The British 1958 tables were then in use. Because of the bone disease problem, these tables were discarded. For the first time, a regulatory change was based on scientific findings. The Blackpool tables were adopted in 1966 in an effort to avoid aseptic necrosis. Nevertheless, 5 of 59 workers on the Dungeness SB power station contract developed bone disease on the Blackpool tables.[10] Yau has reported that 83% of the men working on the Hong Kong Subway project reported decompression symptoms in association with the Blackpool schedules[11]. The "official" bends rate however was low.

In 1963, Duffner devised the Washington State tables which later were adopted as the OSHA tables in 1971. These tables abolished the split-shift, but retained continuous or uniform decompression in stages after an initial pressure drop. This was in deference to the contractors and workers who did not wish to break with tradition. When asked why he did this, Duffner said, "There are certain battles that you just can't win"[12]. The Washington State tables used only 3 tissue half times, (the 30, 60 and 120 minute) but were basically Haldanian[13]. Duffner's new tables produced no incidence of aseptic necrosis when used in Seattle and in the construction of the San Francisco subway, but on this latter job only 135 feet of tunnel was dug at greater than 17 pounds. Ten years later, Sealy [14] surveyed 83 workers who had worked on the Seattle project and found only 4 men with tibial shaft lesions, one bilateral. There was no juxta-articular involvement, which requires a greater decompression insult. These tables were adopted in Milwaukee in 1970 by emergency order because of a 35% incidence of aseptic necrosis which had been experienced using a modification of the 1922 New York code which had been part of Wisconsin law.[15,16] Nevertheless, at pressures greater than 36 pounds, the Washington State tables (which by then had become the federally enforced OSHA tables) produced a 33% incidence of aseptic necrosis[15]. Figure 2 compares the OSHA and Blackpool tables for the 2, 4, 6 and 8 hour exposures. Note that on the Blackpool tables, the decompression time at any given pressure is the same for any time period over 4 hours up to 8 hours. The OSHA schedule is more conservative for most long exposures between 14 and 44 psig. The lines (dashed or solid) become thicker with increasing exposure.

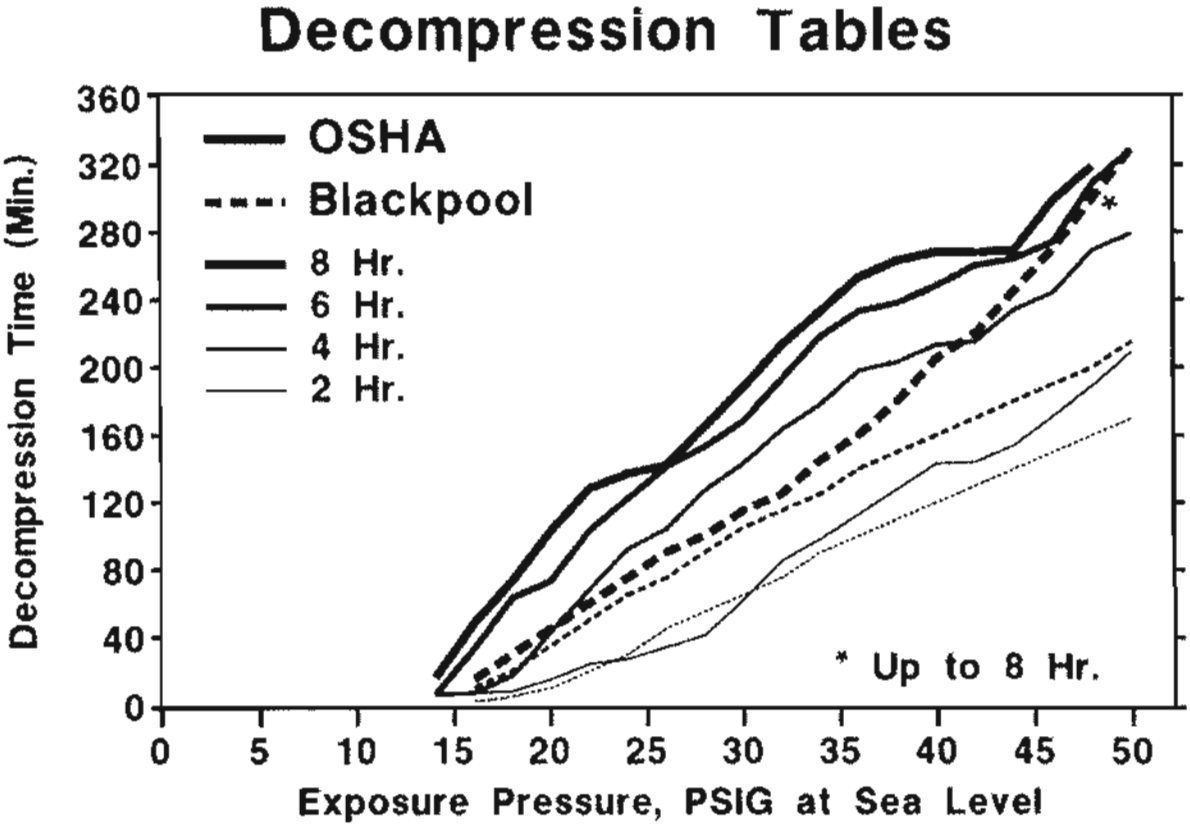

Figure 2

In retrospect, there was a high bends rate using the OSHA table both in Seattle and California which was confirmed by the Milwaukee experience. Because of this problem, we obtained a grant from the National Institute of Occupational Safety and Health to devise new decompression tables for tunnel workers. Using Peter Edel's computer memory bank which contained data on 15 years of successful and unsuccessful dives in the Gulf of Mexico and elsewhere, the computer was directed to construct a line between safe and unsafe decompressions. The final result was the Milwaukee tables which were prohibitively long when air was breathed for decompression.[17] Thus, truly "safe" tables seemed incompatible with the use of compressed air in underground construction or caisson work. However, when an oxygen variant of the table was developed and tested, the decompression times compared favorably with the present OSHA schedules.

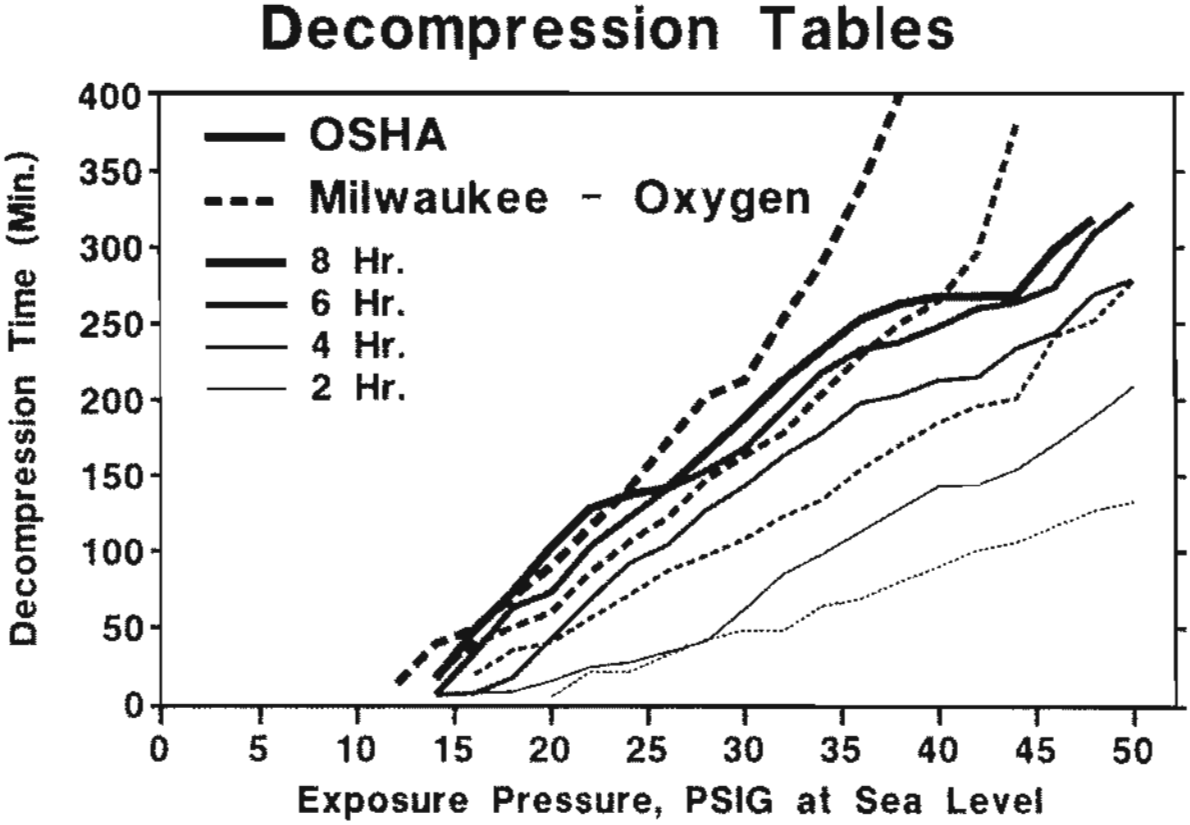

Figure 3

The reason Edel's decompressions were so long was that he included commercial diving data, altitude work and data from his own experiments. Previously, most investigators had relied almost exclusively on naval data for extrapolating to tunnel exposures. However, navies have little or no experience in the extremely long exposures used by tunnel workers, the stressfulness of which is compounded by an unbroken string of daily decompressions which may go on for months or years. Decompressions from 7 and 8 hours exposures are getting close to limits we would consider for saturation.

The new oxygen tables were tested in increments of 0.14 kg/cm^2 (2 psig) from 14 to 46 psig. Spot checking of these tables using the longest shifts which could be fitted into an 8 hour working day failed to produce any decompression sickness or aseptic necrosis in our test subjects. These tests, of course, could not predict an incidence of decompression sickness but could only rule out a catastrophic error.

Tunnelling has taught us that daily decompression from extreme exposures even at modest depth require inordinate lengths of time if air is breathed during decompression. However, I am beginning to doubt that even long air decompression can accomplish this reliably. In Milwaukee we have had bends symptoms following 7 hours exposure to 15 1/2 psig followed by 54 minutes decompression. Behnke has remarked that the same incidence of decompression sickness may be seen after the same exposure with widely divergent air decompression times[16]. For all the above reasons I believe that air decompression has now shown its limits.

Figure 4 shows the OSHA table compared to the U. S. Navy decompression table. Note that at pressures from 15 to 25 psig, the OSHA table is equal to or slightly more conservative than the Navy table but at higher pressures for longer times, the Navy table is much more conservative. These 6 and 8 hour exposures on the Navy table, however, were taken from the exceptional exposure air tables which have shown a bends incidence between 17-33% on test. Therefore, one would predict that the OSHA tables would be inadequate for the longer time periods. The irregularities seen in the OSHA table curves are due to the fact that these tables were put in final form by placing a ruler across a nomogram. A very slight movement of the ruler can produce the aberrancies noted.

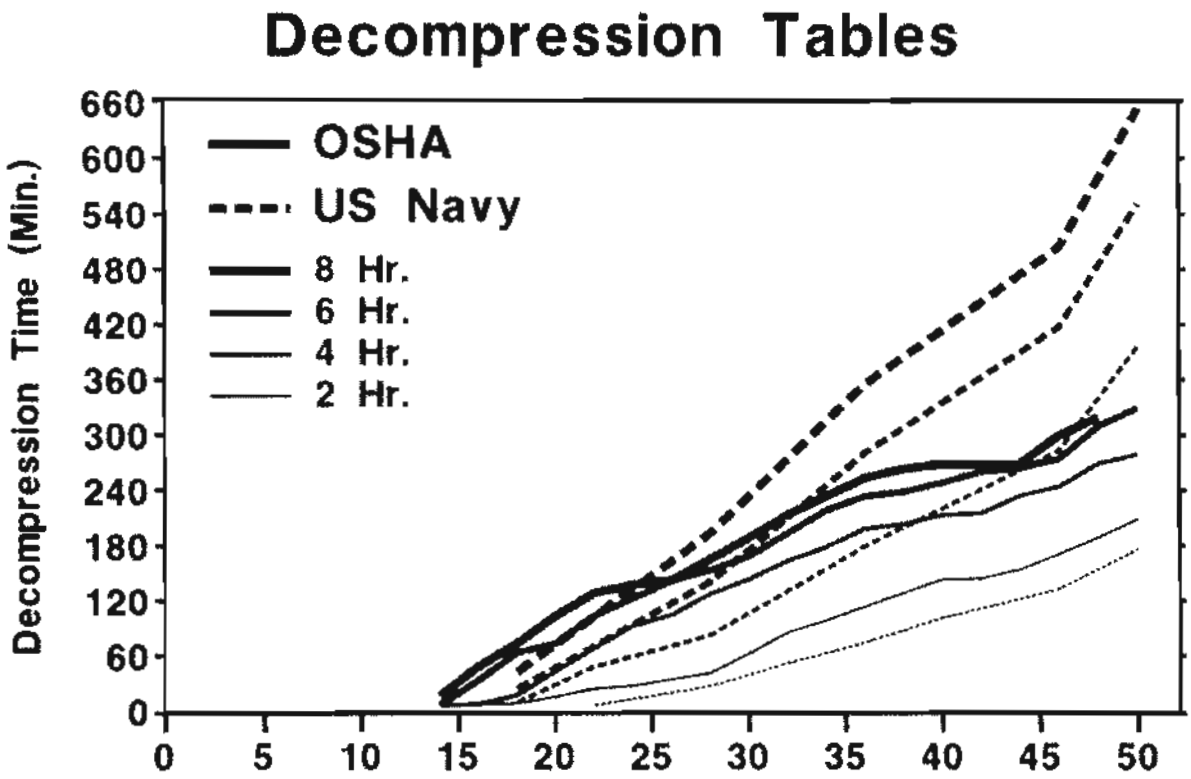

Figure 4

Figure 5 compares the French air table to the OSHA table. Note that it is much more limited and that work at above approximately one bar is not permitted for more than a duration of 4 hours. The French tables appear to be inadequate by OSHA or Navy standards but obviate many problems by not permitting long duration work at high pressure.

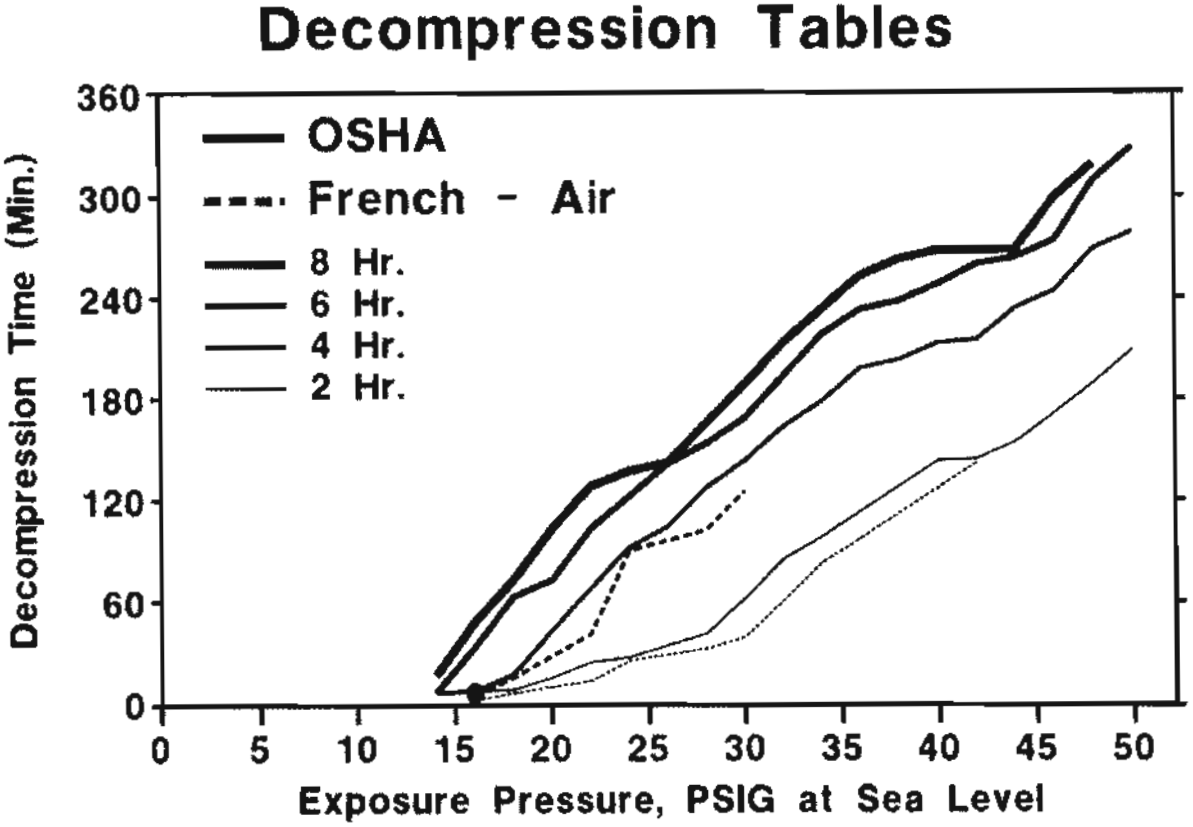

Figure 5

Figure 6 compares the German air tables to OSHA schedules. Again, the OSHA schedules appear to be more conservative despite their known prediliction to produce aseptic necrosis at high pressure.

Figure 7 compares the exposure limits of the various tables. The French are most conservative, cutting back their time sharply after 1 bar is reached. The Germans are next in line. The Blackpool tables limit all exposures to a maximum of 8 hours at 3.4 bar but note that the diagonal lines depict the area where the decompression is the same at a given pressure for any work period between 4 and 8 hours. The U. S. Navy exceptional exposure air tables go to 12 hours but have been arbitrarily cut off for exposures deeper than would be of interest in tunnel work. They, like the Blackpool Tables, increase decompression in 4 hour increments of exposure. The OSHA tables are shown to extend infinitely as a schedule is given for "greater than 8 hours" for all of the working pressures up to 46 psig.

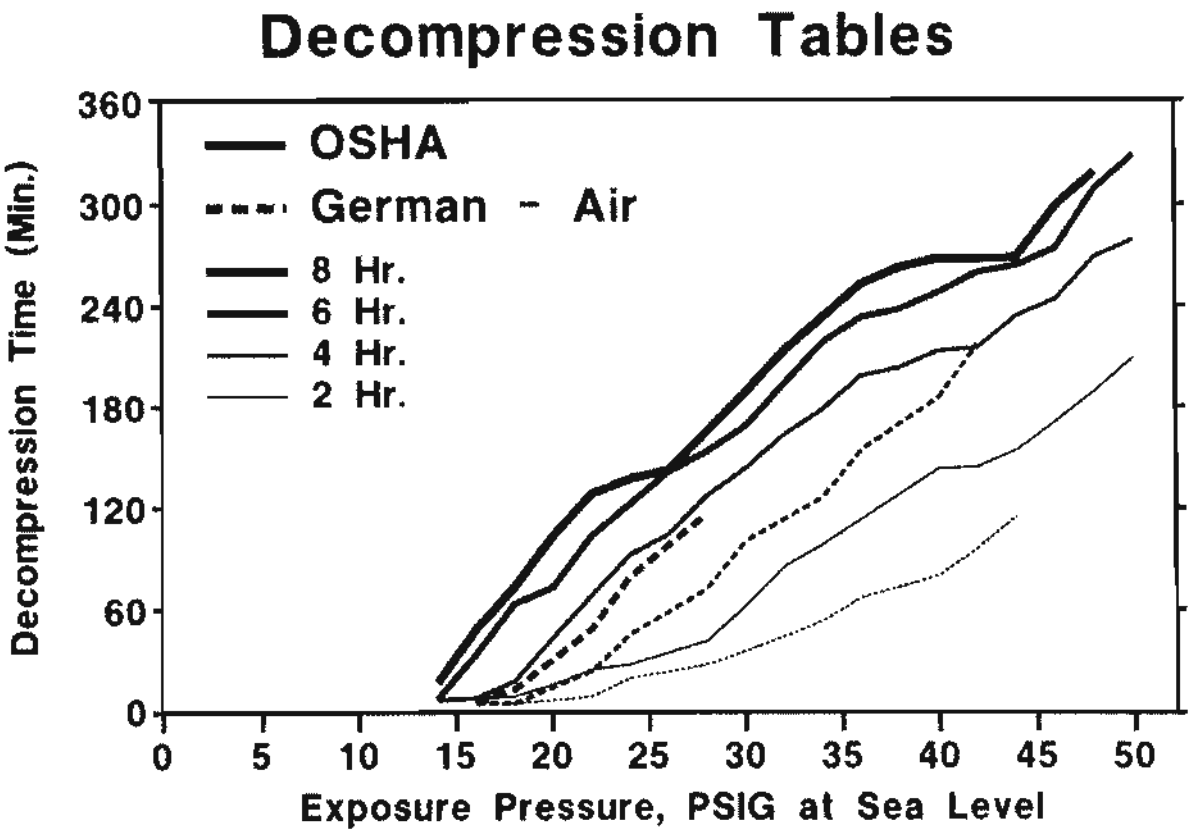

Figure 6

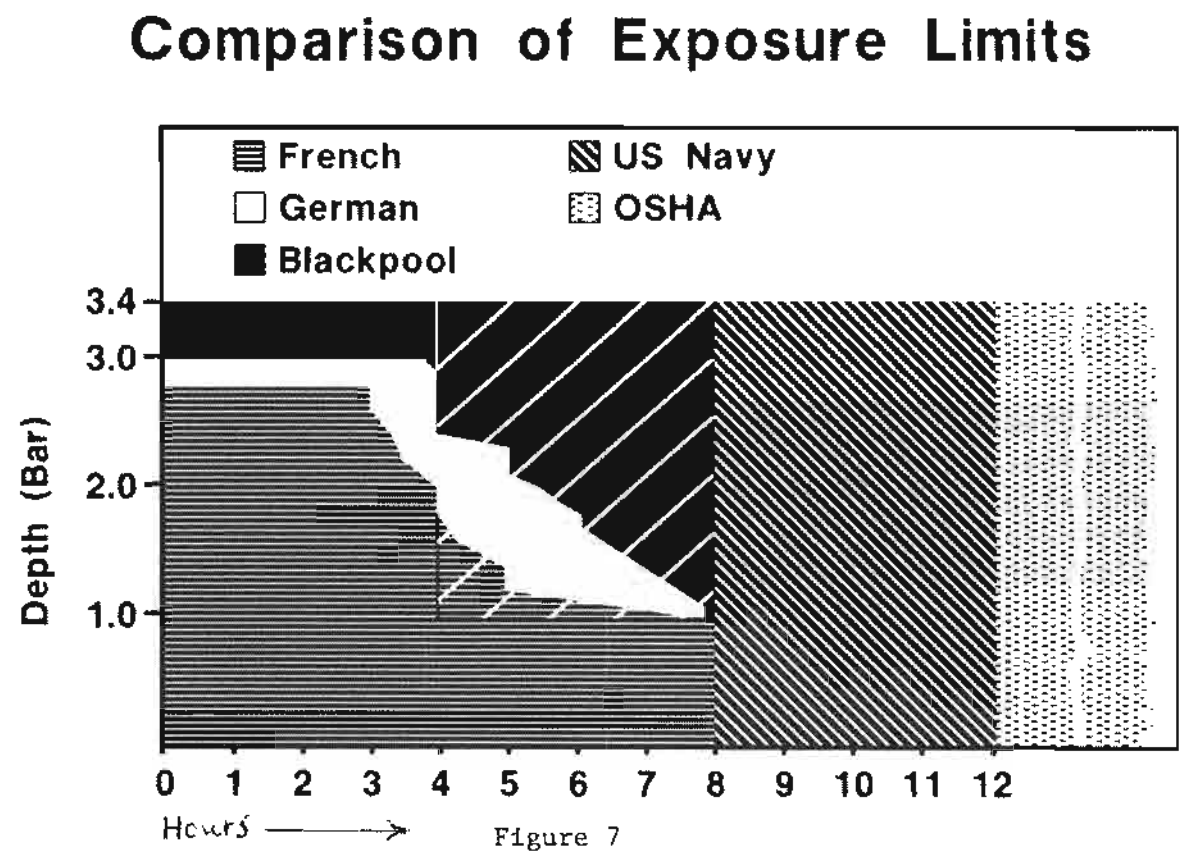

Figure 7

The decompression profiles have also been of interest to physiologists. Figures 8 - 11 show the time spent at the intermediate decompression stops when decompressing from exposure pressures of 1.5 and 1.8 bar for 4 and 6 hour exposures. For some years now, it has been recommended by Behnke, Hills and others that the preliminary decompression stops be taken somewhat deeper. Behnke feels that the U. S. Navy decompression stops are "too shallow".[19] Behnke and Kindwall[20,21] have demonstrated more gas can be eliminated at 50 feet than at 10 feet in a given amount of time, and Hills[22] has shown that goats can be decompressed in a shorter period of time without bends symptoms if the 20 and 30 foot stops are prolonged instead of coming to 10 feet for the final stop.

Figure 8 shows that only the British and the French make a stop at 0.6 bar decompressing from 1.5 bar, with everyone else commencing decompression at 0.3 bar after the initial ascent. Note that the OSHA table averages 0.2 bar and that it is a constant bleedoff from 0.4 bar to the surface. Half the time in this stage is wasted as it is spent at less than 0.2 bar where there is little bubble suppression.

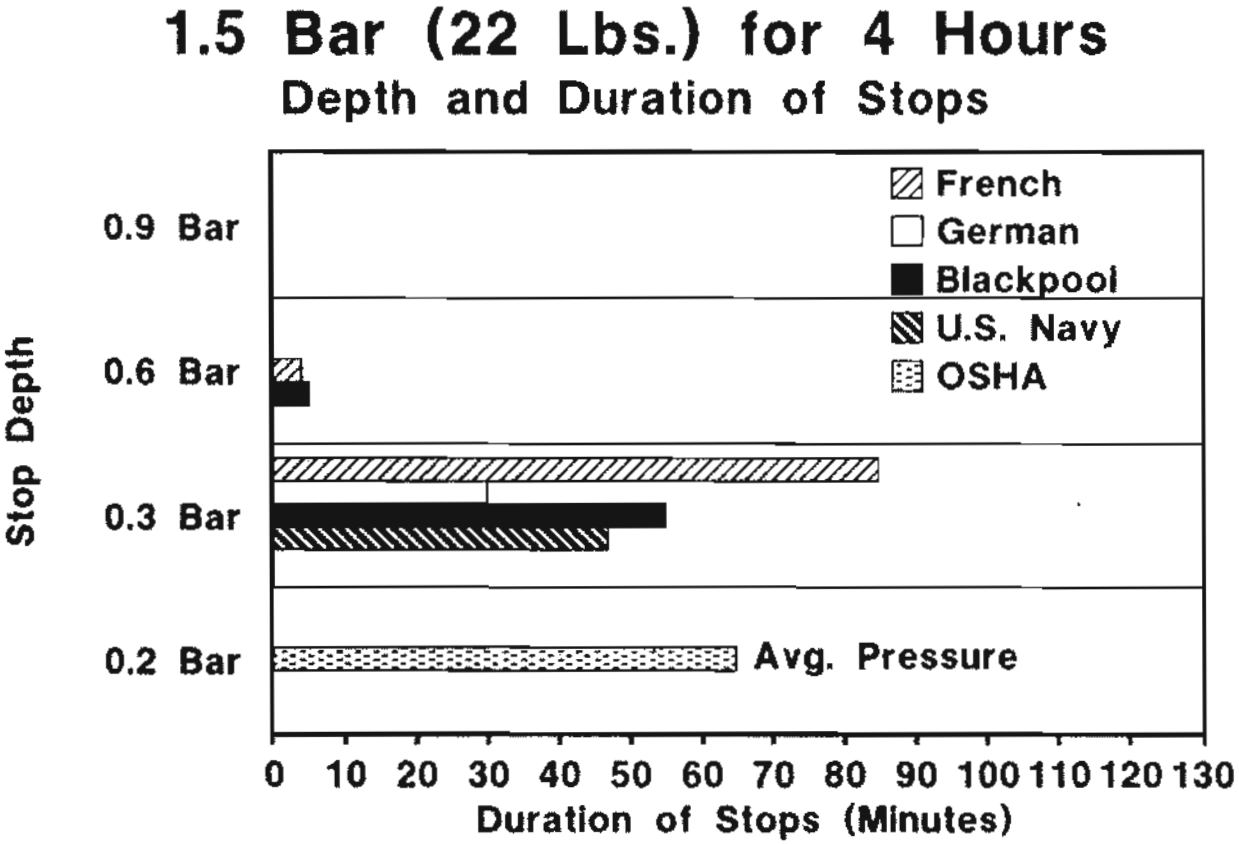

Figure 8

Figure 9 showing the decompression stops from 6 hours exposure at 1.5 bar shows the British and U. S. Navy adopting a 0.6 bar stop. French exposure limits do not permit 6 hours exposure at 1.5 bar so they are absent from the diagram. Figures 10 and 11 show decompression stops from 1.8 bar. Note that the Blackpool table is again apparently superior as it calls for a stop at 0.9 bar. However, these nuances related to the depth of the decompression stops may be of little importance because of the overall brevity of these air decompression tables.

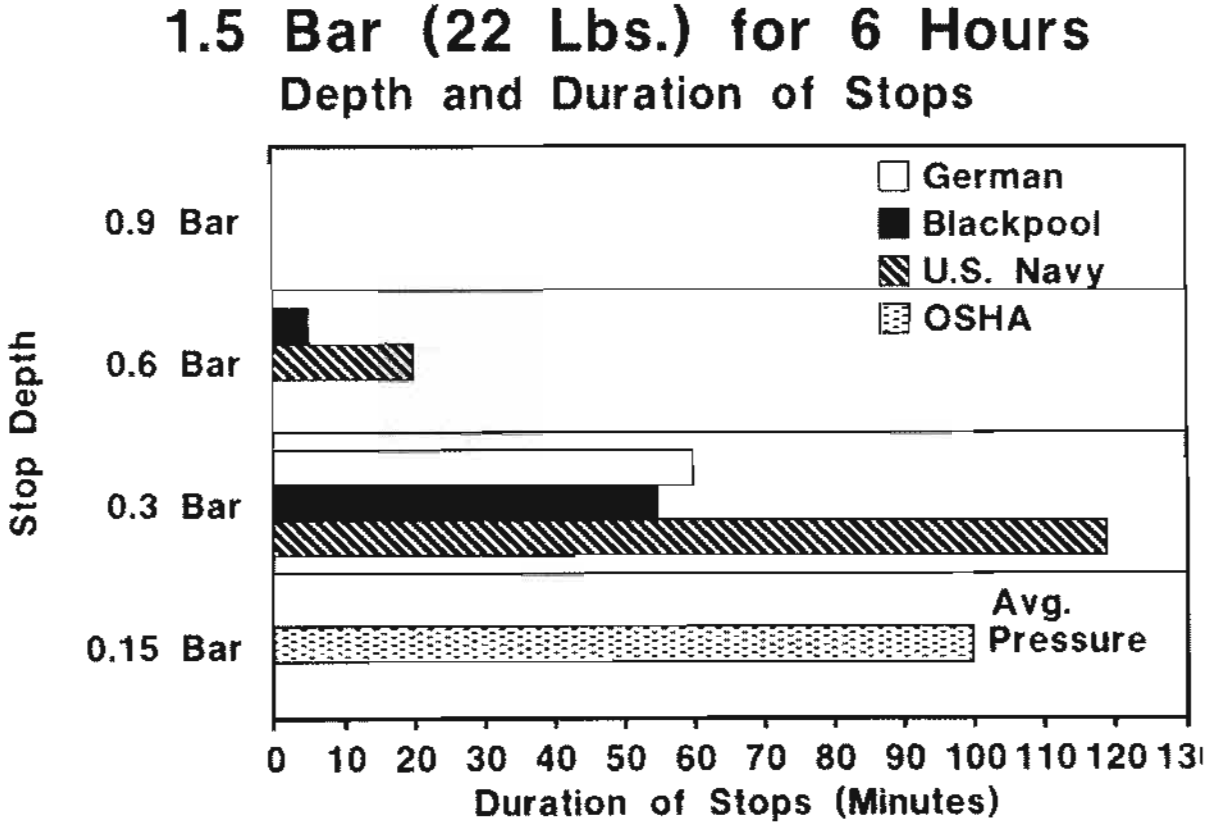

Figure 9

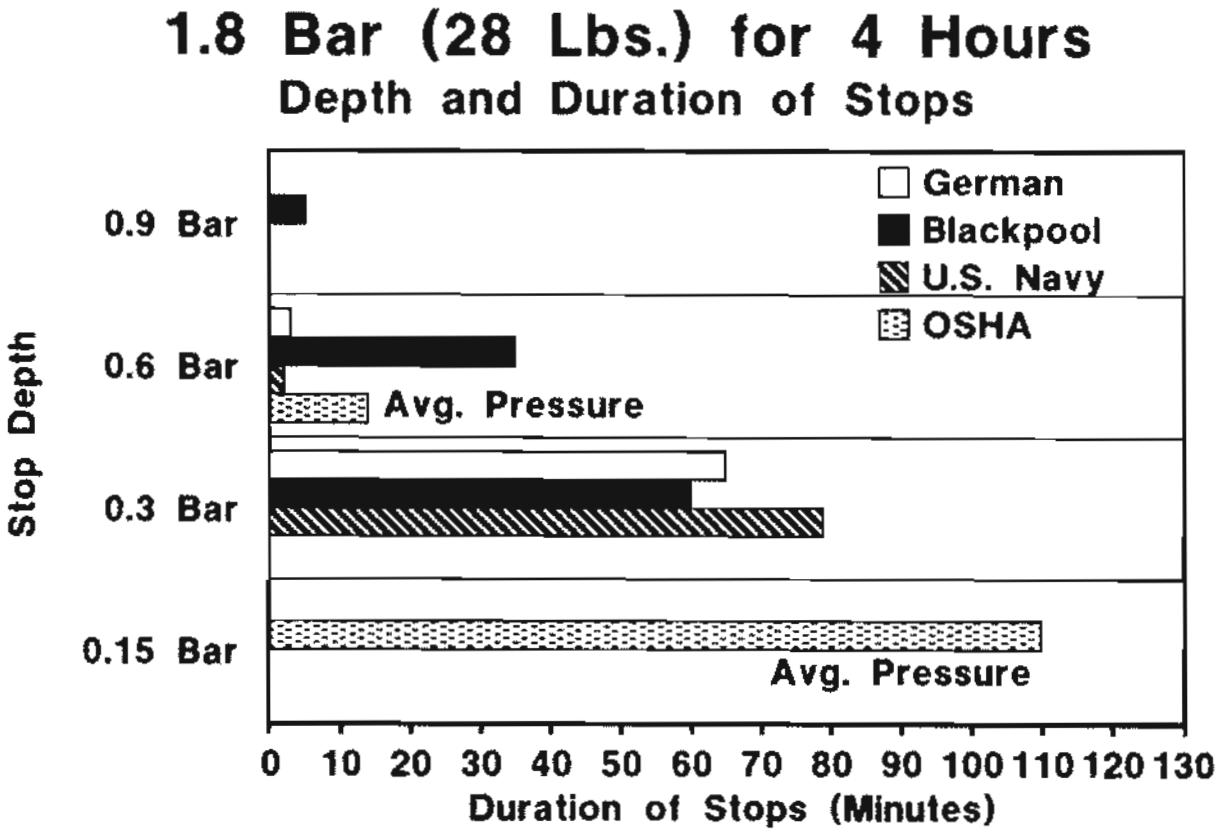

Figure 10

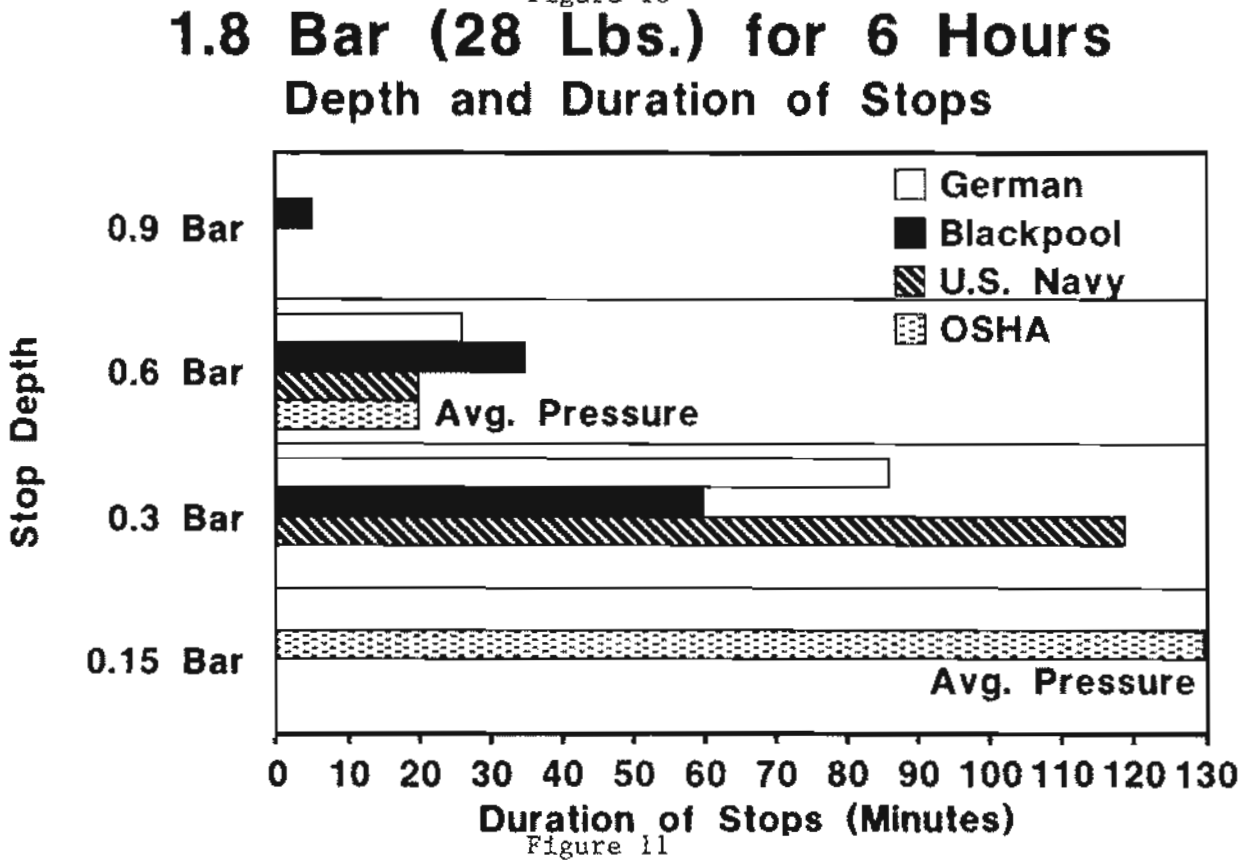

Figure 11

Figures 12, 13 and 14 show a comparison of the decompression times for 4, 6 and 8 hours work at 1.5, 2.0 and 3.0 bar. The "X" above the vertical bar indicates an oxygen variant of the table. At the pressures noted, the German air tables are the least conservative with the Blackpool and OSHA tables not far behind. The OSHA schedule is slightly better or equal to the Blackpool table at most exposure pressures. Note, however, the length of the new Milwaukee air table which is orders of magnitude greater than any of the existing air tables. This is what renders it unusable commercially. However, the oxygen variant of the new Milwaukee table brings it into the range of commercial utility which compares favorably with any of the existing schedules for the usual working times. The Canadian DCIEM tunnel tables are better than any of the tables on the graphs which are currently in use, but they are still less conservative than the new Milwaukee tables and they sharply limit exposure.

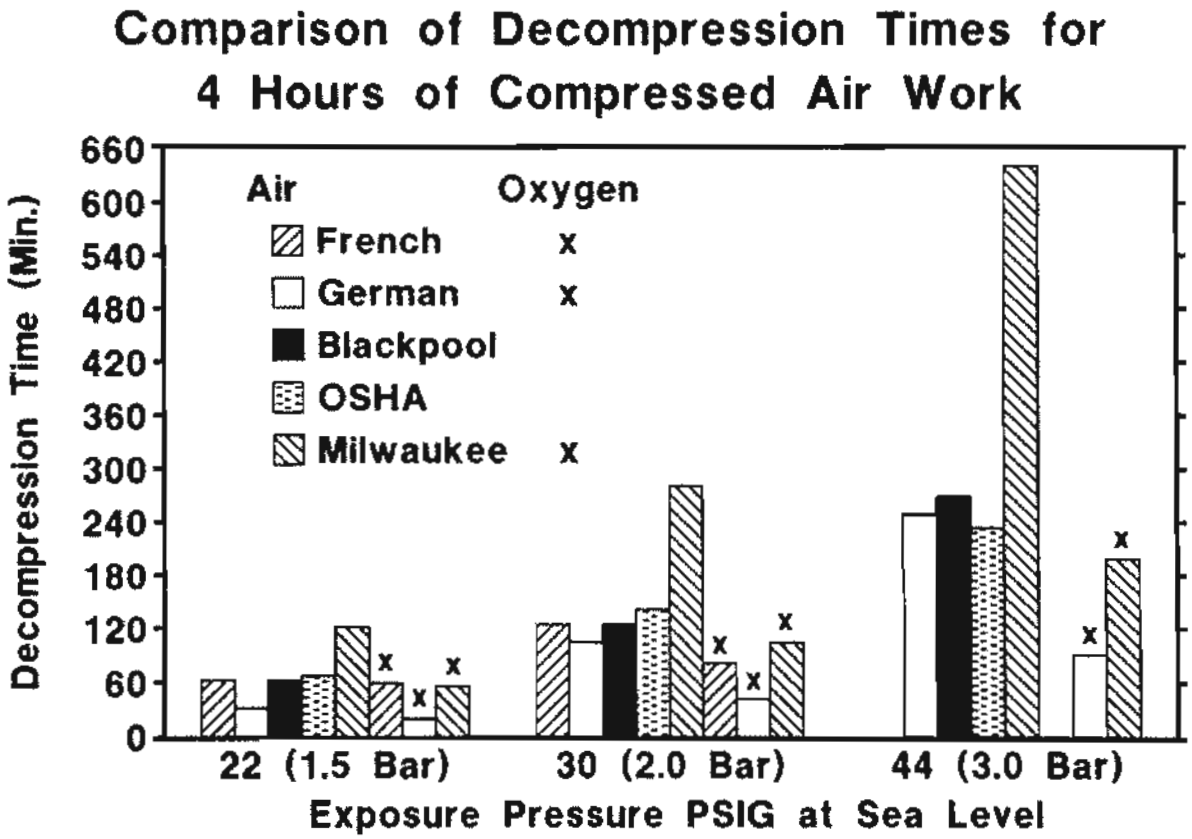

Figure 12

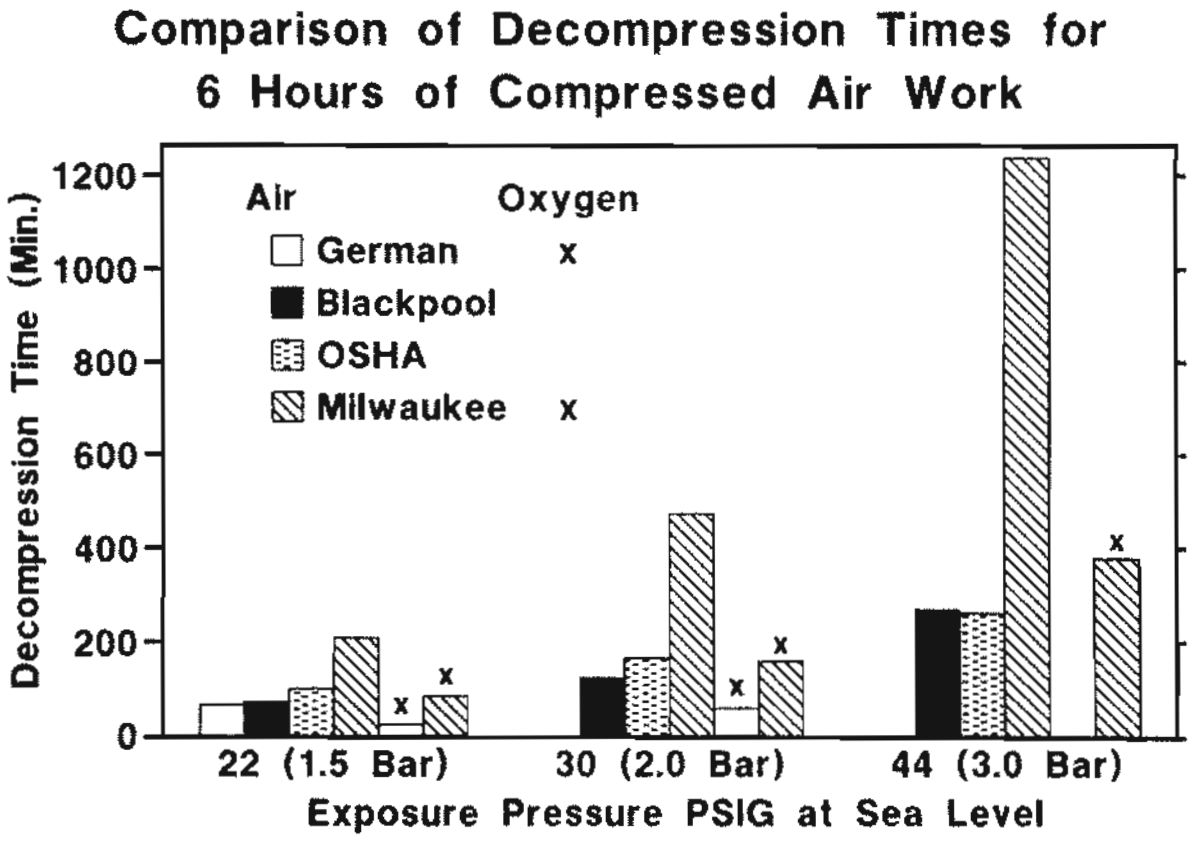

Figure 13

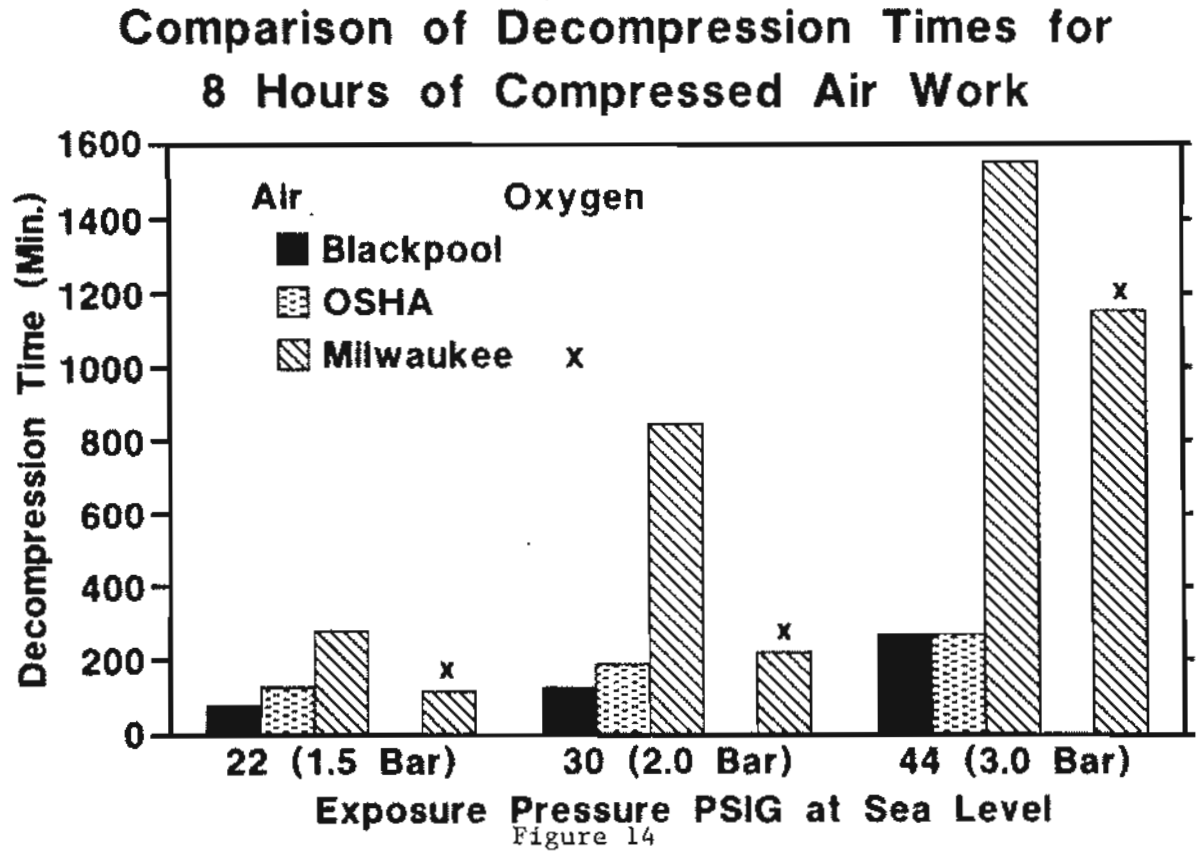

Figure 14

Traditionally, there has a been a cavalier attitude in the tunnel industry and also among physiologists that mild musculo-skeletal bends are an annoyance, but really nothing more, and that we shall just have to put up with them. This attitude is no longer tenable. In 1965, Rozsahegyi reported that 42% of Hungarian tunnel workers who had never experienced neurologic decompression sickness had abnormal electroencephalograms[23]. Gorman, et al. have demonstrated abnormal EEG's, abnormal psychometric testing and abnormal CAT scans showing brain atrophy in divers who have been treated for pain-only bends[24]. There must be no letup in our effort to improve caisson schedules until the bends incidence is truly minimized.

I would like to give a word of advice to people who will compute new caisson tables. Tunnel tables should look different than dive tables. Ideal tables should be computed for all pressures above 0.90 Kg/cm^2 in 0.1 Kg/cm^2 or 1 pound increments. Exposure times should not only be listed in regular half-hourly increments, but should also be listed as the maximum working time at any given pressure which, when combined with the decompression time, produces an eight hour working day. This will make them "user friendly". The Germans are the only ones who have attempted this thus far. I favor this approach, even for countries where a greater than 8 hour workday is acceptable, as I feel that at least a 16 hour surface interval should be afforded the workers before the next shift. Additionally, exposures of exactly 4 hours and 6 hours should be listed, as these divide evenly into a 24 hour day and make either 4 or 6 work shifts possible per day. On some jobs, the working face cannot be left unguarded between shifts, so one shift must immediately relieve the other. On this type of job, the only other alternative is to erect breasting boards between shifts, a costly and time consuming procedure. A listing of "no-decompression" exposures for each pressure should also be supplied for brief visits of one-time visitors such as company officials and the physician. Finally, repetitive exposure schedules must be provided to accommodate non-shift workers such as inspectors, electricians, engineers and others who need to be in the tunnel for short periods more than once a day. Failure to do this forces the people involved to "add up their times" and take all their decompression at the end of the day. This is non-physiologic and dangerous, and may have produced some of the aseptic necrosis seen in Hong Kong[11,25]. These multiple schedules should not be too difficult to produce with the aid of the computer.

It is clear from past experience that physiologists must no longer permit themselves to compromise on the length of decompression times, the decompression profile or the gas breathed during decompression out of deference to tradition or contractors' and unions' wishes. These compromises have always produced tables ranging from bad to catastrophic. Economics do play the principal role in the construction business, but those who derive tables must supply useable schedules which will not cause injury. Our job is not to compromise based on tradition, but to protect the worker through new technology.

Of utmost importance is that any new table enacted into an officially enforced regulation be labeled as an interim schedule. A method for quick modification of the new table as experience dictates must also be included in the regulation. This will avoid the present dismal situation where a given table is known to be bad but it must be grudgingly enforced because there is no mechanism to abolish it. In Russia all tables are brought up for automatic change every five years should any need have arisen.

Oxygen decompression which was first used in tunnelling on a regular basis by the Germans in 1972 and then adopted by the French in 1974 seems to be the only viable daily decompression technique which is acceptable for tunnelling. Based on comparisons in our computer data bank, the French and German tables seem to be too short. Indeed the Germans report that they plan on revising them although they have reported a "remarkable drop in decompression sickness despite longer shifts."[26] The French have reported no aseptic necrosis since the adoption of their tables in 1974, but as yet these new oxygen tables remain to be tested on a large project[27]. Brazil used oxygen decompression successfully in 1975 in the construction of the Sao Paulo subway with a nearly 80% drop in decompression sickness[28].

Because of a tunnel fire which occurred during early experimentation with oxygen decompression in Japan in the early 1960's, there has been much resistance on the part of British and American regulating bodies to adopt oxygen decompression. This is despite the fact that some 14,000 experimental oxygen decompressions were carried out without mishap in 1938 and 1939 in the City of New York during the construction of the Queens Midtown tunnel[29]. The oxygen delivery system was poor on that project, providing the workers with too much breathing resistance. Nevertheless, there were no serious cases of decompression sickness in those workers who breathed oxygen. The main advantages of oxygen are vast savings in time, which of course makes economic sense for the contractors.

There are other advantages of oxygen decompression which are frequently not considered. End, in 1939, described a marked reduction in blood sludging in bent animals concommitant with simply raising the arterial pO_2 [30]. Recently Mathieu, et al have reported that red blood cell filterability is doubled after 15 hyperbaric oxygen treatments[31]. The need to improve the filterability of the blood during and after decompression is underscored by the work of Pimlott, Ormsby and Cross who found that white cells show an 81% decrease in deformability and filterability after exposure to air at 1.5 bar for 4 hours[32]. The toxicity of oxygen is well understood and its early signs, should they appear in tunnel workers, are easily reversible. This is not true for brain damage and bone disease.

The regulatory bodies in Great Britian are nevertheless adamant in refusing to accept any change in the present tunnelling decompression schedules until it can be assured that "no new risk is added". The United States is slightly more advanced in that the Office of Variance

Determination of the Occupational Safety and Health Administration has now indicated that "oxygen decompression may be feasible" and they will permit contractors to apply to use this method under an "interim order"[33]. Based on the known record of the present OSHA tables to produce bends and bone necrosis, we petitioned the Secretary of Labor to rescind these tables immediately as an imminent hazard, but we were told that it may be up to nine years from the time the first report of aseptic necrosis appeared in the open literature until these tables are rescinded. Meanwhile, U. S. contractors may be permitted to work under an interim order when the Office of Variance Determination is able to supply its "standard" for the workplace.

On large jobs at high pressure, saturation exposures may be indicated. Here the workers would remain at pressure for a week or two at a time in a pressurized habitat which has some of the amenities of a small submarine. They then would go to work via personnel transfer capsule (PTC) or connecting lock to the heading. The advantage here is that daily 8 hour shifts are possible with no decompression required, and workers are exposed to decompression trauma only once every week or two weeks. Saturation for compressed air workers was originally suggested by Behnke in 1969[18]. It is only now that an economic demand for tunnel saturation is materializing.

Compressed air for tunnelling work is much less used now than in the past because of improved dewatering techniques, pressure balanced shields and the use of remotely controlled automated excavating equipment in caissons. Nevertheless, there are certain situations which cannot easily be resolved without the use of this time tested method. The recently completed Hong Kong subways were constructed with compressed air techniques and it is in wide use in Japan despite Japanese leadership in the design and manufacture of automated tunnelling equipment. Taipei is planning a very large underground transit system in which pressures up to 2 kg/cm^2 (30 psig) are envisioned. The English Channel tunnel (Transmanche) will be bored largely through chalkstone but according to J. M. Anderson, Inspector of Health and Safety for the British Government, pressures up to 65 psig are possible where fractures exist in the chalk. On the French side, J. C. LePechon reports that it is possible 10 kg/cm^2 (147 psig) may be required[27]. Obviously, under such circumstances, conventional tunnel work will be impossible using large gangs of men. However, automated machinery which will have to be used always requires maintenance. For these purposes, diving techniques may be necessary for maintenance personnel even though they may be operating in a dry atmosphere. Certainly, at pressures greater than 5 kg/cm^2 (74 psig), helium-oxygen breathing apparatus will be necessary.

H. J. Weynans of the Draegerwerk in Germany reports that saturation techniques with helium-oxygen breathing will be used on the 3rd tube of the Elbe tunnel starting in the summer of 1988 and also on a three tube auto tunnel under the Big Belt to augment the ferry service between Korsor and Nyborg in Denmark[34]. The latter will commence in 1989. A pressure of 5 bar is anticipated on both projects and the workers will saturate for 7 days at a time. The tunnel will be at atmospheric

pressure, but the area between the cutters and the shield will be pressurized. When needed for boulder clearance or cutter maintenance, the men will transfer through the shield via pressurized PTC from their regular habitat in the tunnel.

In summary, modern caisson and tunnel construction is a high technology industry. Rapid advances have been made in automated tunnelling machinery, but where personnel must be exposed to these pressures, government regulations have failed to keep pace with requirements. Modern advances in decompression physiology have made possible oxygen decompression which is not only more economical but vastly safer than traditional air decompression. The diving industry has led the way in this respect. However, even though these techniques are now available to the tunnelling industry, bureaucratic inertia must first be dealt with so that both the contractor and the worker may reap its benefits.

REFERENCES

1. Balldin UI & Lundgren CE, The Effect of Immersion on Inert Gas Elimination; Acta Physiologica Scandinavika (Suppl.) 1969:330:63

2. Evans A, Plan Announced at Meeting of the Compressed Air Working Group; British Medical Research Council, Sept. 22, 1987

3. Nashimoto, Ichiro, Personal Communication, 1987

4. Kindwall EP, Medical Aspects of Commercial Diving and Compressed Air Work, In: (C. Zenz, Ed.) Occupational Medicine, Principles & Practical Applications, Year Book Medical Publishers, Chicago, 1975:pp 361-421

5. Triger, Memoire sur un Appareil a Air Comprime, pour le Percement des Puits de Mine et Autres Travaux, sous les Eaux et dans les Sables Submerges: Compt. Rendus Acad. des Sciences, 1841:Vol. 13, pp.884-896

6. McCallum RI (Ed) Decompression of Compressed Air Workers in Civil Engineering, Oriel Press Limited, Newcastle-Upon Tyne: 1967

7. Boycott AE, Damant GCC & Haldane JS, The Prevention of Compressed Air Illness, Journal of Hygiene (Cambridge), 1908:Vol. 8, pp 342-423

8. Bornstein A and Plate E, Uber Chronische Gelenkveranderungen, Entstanden Durch Presslufterkrankung, Fortschr. Geb. Rontgenstrahlen, 1911-12:18:197

9. Jones, JP and Behnke AR, Jr., Prevention of Dysbaric Osteonecrosis in Compressed Air Workers, Clin. Orthopaed. and Related Research. 1978:130:118-128

10. Trowbridge WP, Bone Necrosis in British Compressed Air Workers. In: Aseptic Bone Necrosis, Proceedings of the Symposium of the European Undersea Biomedical Society, Newcastle-Upon Tyne, 1977

11. Yau KP, Personal Communication, 1987

12. Duffner GJ, Personal Communication 1987

13. Sealey JL, Safe Exit from the Hyperbaric Environment, JOM, 1969;11(5):273-275

14. Sealey JL, Aseptic Bone Necrosis Survey in Compressed Air Workers, JOM 1975;17(10):666-667

15. Kindwall EP, Nellen JR and Spiegelhoff DR, Aseptic Necrosis in Compressed Air Tunnel Workers Using Current OSHA Decompression Schedules, JOM 1982;Vol.24,(10):741-745

16. Nellen, JR and Kindwall EP, Aseptic Necrosis of Bone Secondary to Occupational Exposure to Compressed Air: Roentgenologic Findings in 59 Cases, The Amer. J. of Roentgenology Radium Therapy and Nuclear Med,1972;Vol.65,No.3:512-523

17. Kindwall EP, Edel PO and Helton HE, Safe Decompression Schedules for Caisson Workers, Final Report, National Institute of Occupational Safety and Health Research Grant No. 5R 01 OH 00947-03, Washington 1983

18. Behnke AR, Jr, New Approaches to Medical Aspects of Work in Compressed Air, JOM 1969;Vol.11,No. 5:266

19. Behnke AR, Jr, Personal Communication, 1971

20. Kindwall EP, Baz A, Lanphier E, Lightfoot E and Seireg A,Nitrogen Elimination in Man During Decompression, Undersea Biomedical Research; December 1975,Vol. 2,No.4,

21. Willmon RL and Behnke AR, Jr, Nitrogen elimination and oxygen absorption at high barometric pressures. Am J Physiol,1941; 131(3):633-638

22. Hills BA, Limited Supersaturation versus Phase Equilibration in Predicting the Occurence of Decompression Sickness. Clin. Sci;Feb 1970;38:251-267

23. Rozsahegyi I, Neurological Damage following Decompression: In: (Ed) R. I. McCallum, Decompression of Compressed Air Workers in Civil Engineering, Oriel Press Ltd, 1967, p.131

24. Gorman DF, Edmonds CW and Beran RG, The Neurological Sequelae of Decompression Sickness: A Preliminary Report, Proceedings of the Ninth International Symposium of Underwater Physiology, Kobe, Japan, Undersea and Hyperbaric Medical Society, Bethesda, MD; 1986

25. Walder DN, Personal Communication, 1987

26. Altner, Dipl.Ing. Fachausschuss, Tiefbau, Munich, Personal Communication, 1986

27. LePechon JC, Personal Communication, October 1987

28. Ribeiro IJ, Personal Communication, 1985

29. Jones RR, Crosson JW, Griffith FE, Sayers, RR, Schrenk HH & Levy E: Administration of Pure Oxygen to Compressed Air Workers during Decompression: Prevention of the Occurence of Severe Compressed Air Illness. J Ind. Hyg.& Tox., 1940;22(10):427-444

30. End, Edgar, The Physiologic Effects of Increased Pressure. In: Proceedings of the Sixth Pacific Science Congress, 1939; Vol.6:91-97

31. Mathieu D, Coget J, Vinkier L, Saulnier F, Durocher A, Wattel F. Erythrocyte Filterability and Hyperbaric Oxygen Therapy (French) Medsubhyp, 1984;Vol.3,No. 3:100-104

32. Pimlott J, Ormsby PL and Cross MR, The Effect of White Cells on Blood Filterability at Pressure, Proc. of the European Undersea Biomedical Society Ann. Sci. Mtg., 1987, Palermo

33. Concannon, James, Chief, Office of Variance, Occupational Safety and Health Administration, Personal Communication 1987

34. Weynans HJ, Personal Communication, November 1987

DISCUSSION

DR. NASHIMOTO: Dr. Kindwall mentioned that the split shift is still used in Japan although it is inadequate to prevent DCS. Let me comment on this matter. The Ministry of Labor established a special regulation for compressed air work in 1950. In 1974, the regulation was revised, but the split-shift table was not changed. In Britain, the Blackpool schedules adopted in 1966 have significantly reduced DCS and bone necrosis. I have advised the Ministry of Labor to change from the current split shift to a single shift using the Blackpool or other good tables. We have not yet had a positive response from them, perhaps because they think the current Japanese tables are not bad.

Contractors or subcontractors have not reported the occurrence of DCS because the inspector of the Ministry of Labor will think that they didn't obey the regulations. Indeed, some of them say that they have violated the limit of the working periods and sometimes extended the working time arbitrarily. They said the shifts were not long enough according to the regulations, but they officially reported they had obeyed regulations. I regret that the Ministry of Labor received incorrect information that there were few DCS cases with the current tables. As a result, the Ministry of Labor has disregarded the problem.

We investigated the effectiveness of a single shift and oxygen breathing after surfacing in preventing DCS at a pneumatic caisson used to build a big shaft for horizontal sewage tunnels. When the working pressure became greater than 3.3 bar (kg/cm^2) and many caisson workers suffered from DCS, the chief of the construction site requested our advice. We proposed to change from a split shift to a single shift according to the modified Blackpool schedule, to shorten the working period, and to use oxygen after surfacing.

Figure 1 shows the caisson workers breathing oxygen in their resting room after surfacing. Table 1 shows the modified Blackpool schedules. Figure 2 shows the changes in working pressure and DCS rate over a 40 day period.

The DCS rate was 3.49% in the split shift period, 1.59% in the single shift period without oxygen breathing, and 0.9% at 4 to 4.2 bar, and 3.08% at 4.3 bar with oxygen breathing. We feel these results show that a single shift with oxygen breathing after surfacing and a shorter working period is effective in reducing DCS.

Table Modified Blackpool schedule for exposure time of three hours.

Working Pressure (kg/cm^2G)	Decompression Stops (min)							Total Decompression Time (min)
	2.1	1.8	1.5	1.2	0.9	0.6	0.3	
3.0 — 4.0	—	10	20	35	40	50	85	240
4.2 — 4.4	5	10	20	40	45	60	90	270

Fig 1. Caisson workers, breathing oxygen after surfacing.

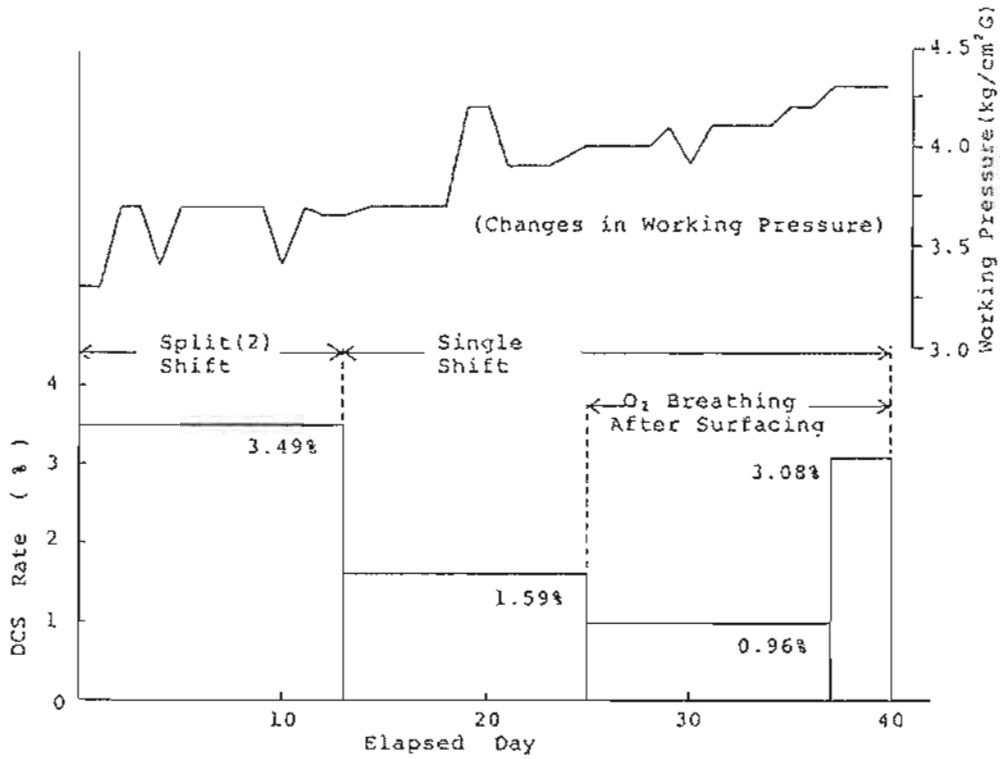

FIG 2. Compressed air work and DCS rate

DISCUSSION ON PRESENTATION BY DR. SHIELDS

MR. IMBERT: Years ago, COMEX realized that thousands of dives were carried out each year at our work sites and it would be extremely useful if we could analyze this information. We started a system of diving reports that would enter the information into a computer and make it immediately available. We were aware of the limitations of such a system but felt that we had enough control over our own data to achieve some degree of accuracy. We used this data bank to assess the safety and violations of our diving procedures.

COMEX uses the official 1974 French diving table, which only uses in-water decompression. Surface decompression was forbidden in 1970 for reasons I don't know. Because our experience was with in-water decompression, it complements Dr. Shield's data in which 90% of the operations were carried out with surface decompression.

In 1983, the French Government supported COMEX to do a survey of the safety of the French decompression tables. Figure 1 shows the incidence of decompression versus time and depth. The incidence is shown in three categories: less than 0.5%; 0.5 to 2%; and 2 to 3%. Figure 1 shows what we already knew, that long dives have a higher rate of decompression sickness.

Let us focus on two types of tables, the air standard which only uses air during decompression, and air-oxygen which uses oxygen during decompression.

We use oxygen tables for deep and long dives because it shortens decompression time. We achieve higher safety with the oxygen decompression tables. When in-water decompression and surface decompression are compared, surface decompression seems to be more dangerous than air decompression.

Following the initial survey, the French Government funded us to review and modify the French tables. This was done 2 years ago, and the new table was sent to selected work sites for a 2 year evaluation. Our aim was to achieve less than a 0.5% decompression sickness incidence and avoid any type II decompression accidents. We found the new French table is improved to a degree where the risk is evenly distributed. We also included surface decompression tables with recompression and oxygen breathing to 12 msw in a chamber. After 2 years of evaluation and 1300 exposures with this table, we still had type II decompression sickness. In order to get rid of the type II symptoms, we had to limit the depth and bottom line combinations. So even with a conservative table there seems to be a natural limit to the use of surface decompression. I have no idea why this limit exists, but surface decompression was invented by divers, not scientists, and might be considered a successful treatment for decompression sickness. Perhaps, however, the depth of recompression is insufficient. Nevertheless, surface decompression can be safely carried out as long as the exposures remain reasonable.

DR. NASHIMOTO: I'd like to comment on the importance of obtaining precise dive profiles in actual diving. Dive procedures must be carried out according to specified decompression schedules in order to prevent DCS. These are calculated from tables according to depth-time increments. The bottom depth in an actual dive is, however, not always constant. Almost all Japanese diving fishermen make excursions from the bottom.

Figure 1, for example, shows the profiles of helmet divers who gathered

abalone. All divers made many excursions from the bottom, as well as from the decompression stops.

Figure 2 shows the profiles of a Tairagi shellfish diver who used surface decompression. (Tairagi shellfish is a kind of a scallop. Its ligament is big and nice but expensive. It is used for raw fish or sushi.) After the final dive of the day, he rapidly took off his helmet and diving suit and entered a small, high pressure chamber on his boat. Note his excursions once again. Figure 3 is a profile of an Italian pink coral diver who breathed trimix at 86 to 90 meters using scuba. Professor Zannini of Genoa University will comment on this dive.

Figure 4 shows a comparison of dive profiles recalled from the dive recorder and diver's own memory. The dive profiles he remembered were incorrect, although he thought his memory was exact.

Two years ago, my friend Dr. Sawada, Professor of Emergency Medicine at Osaka University, and Dr. Gotoh of our laboratory, went sport diving off Izu Island south of Tokyo. He wore the dive recorder shown in Fig. 5 but dropped it during his third dive. He wished to recover the recorder but was advised not to do so to avoid the bends.

About one month later, Dr. Gotoh's friend recovered the dive recorder. Fortunately sea water had not entered it. Figure 6 shows the dive profiles from the recovered recorder. The third profile shows the recorder had been at about 25 meters. The manufacturer says it can record data for 15 hours and store for 2 months. Thus, a dive recorder could be useful in a diving accident, much like a flight recorder.

In conclusion, the recording of precise dive profiles is very important to assess both the risk of DCS and the effectiveness of decompression schedules in preventing DCS.

DR. ZANNINI: We are studying diving from 70 to 100 meters with a trimix consisting of 30% helium and 70% air. We shift to air during decompression stops in the water and then surface for recompression in a chamber on 100% oxygen. We have had no bends or nitrogen narcosis and fewer problems than with heliox diving. As yet, there's no bone necrosis. We use a dive recorder and Doppler bubble detector during surface oxygen stops and for 1 hour or more after surfacing.

DR. JAMES: It is of interest to consider the occupational risk of Dr. Shields 2-year Department of Energy study in the United Kingdom. In the years 1982 and 1983, 25,712 dives were logged and 35 cases of type II decompression sickness occurred. If an average dive is about two hours long, this represents a total of 51,000 hours of time in the water. For a man working a 40-hour week, 48 weeks per year, the 35 type II cases would be sustained by 27 men working for a year. This gives you some indication of the risk in relation to the number of hours worked. I think it's really quite prodigious.

DR. SHIELDS: I agree that the risk is very low.

MR. WACHHOLZ: There has been a recent influx of decompression computers and new decompression schedules for sport divers which we haven't heard much about here. Would anyone care to comment on the effects this may have on the incidence of decompression sickness among sport divers.

My suspicion is that some risk-taking divers may be a little safer because they can't cheat the computers as easily as the tables. On the other hand, timid divers may, in fact, be at greater risk because they dive longer and deeper.

DR. SHIELDS: The Decompression Sickness Panel of the Medical Research Council has studied this question. Computers are being used more

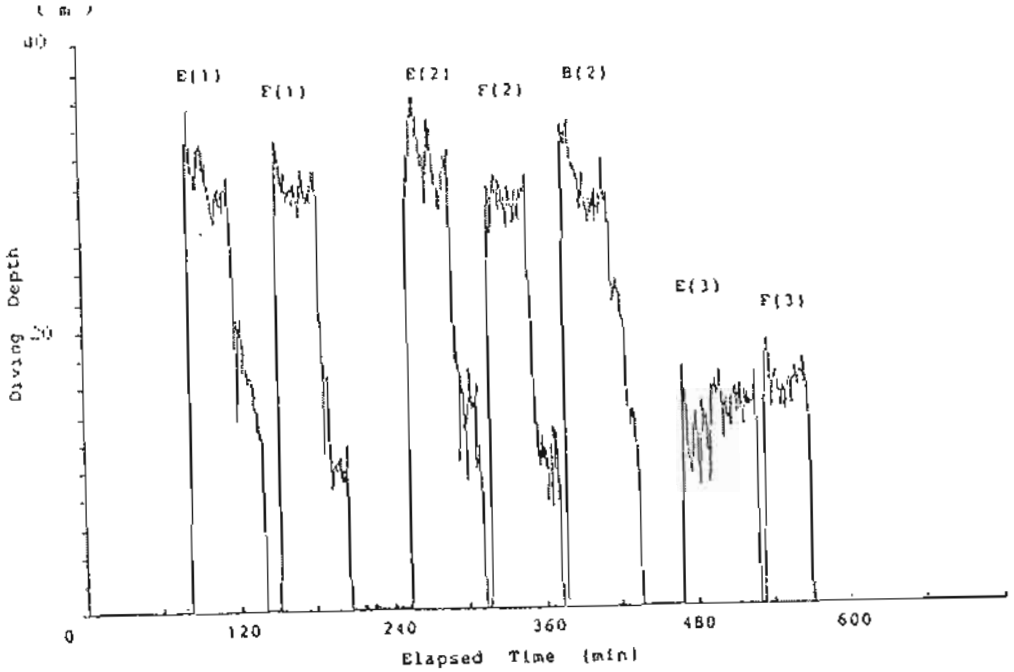

Fig 1. Daily profiles of shell fish divers
Alphabet is used instead of diver's name. In the graph (1),(2) and (3) represent the first, the second and the third dive respectively.

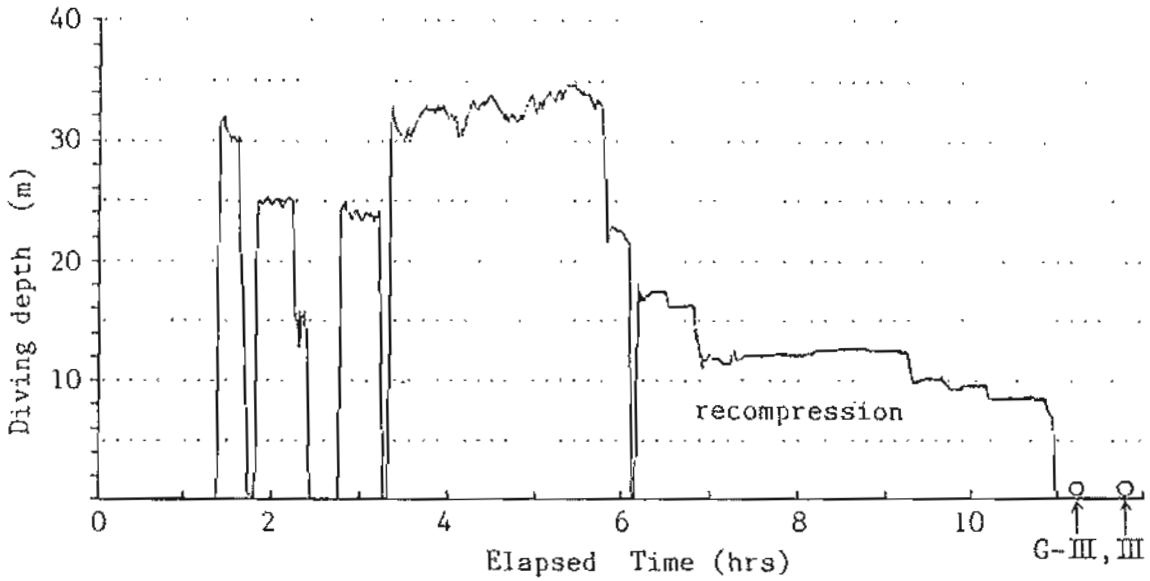

Fig 2. Dive profiles of a Tairagi shellfish diver using a surface decompression (1st Day). G represents VGE grade.

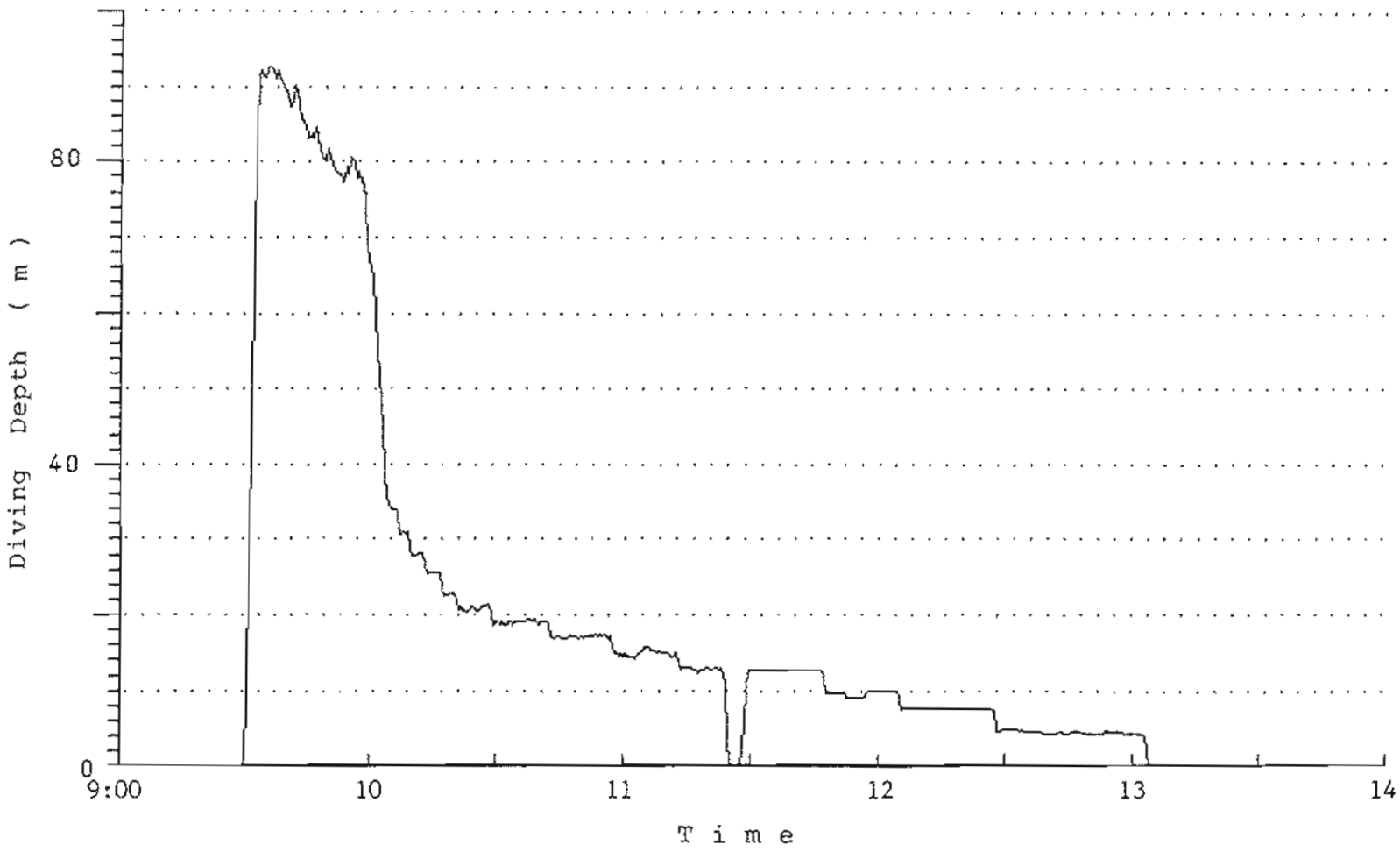

Fig 3. Dive profile of a coral diver.

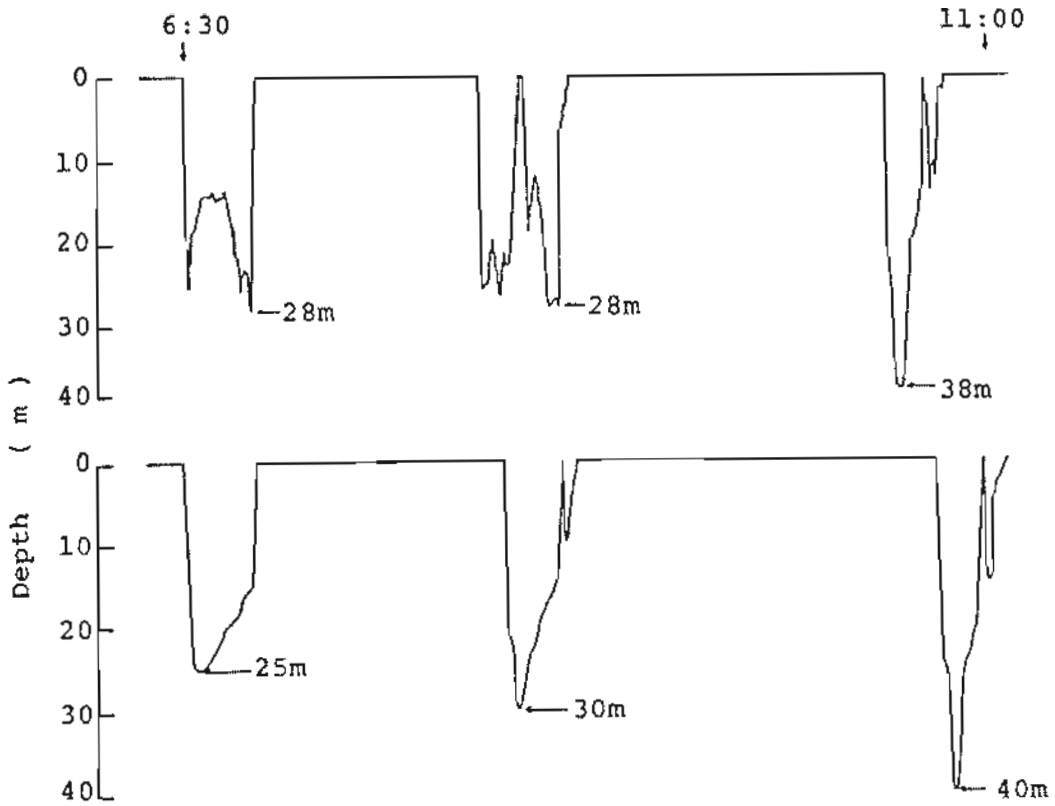

Fig 4. Comparison between dive profiles with dive memory recorder (upper) and those from divers own memory (lower).

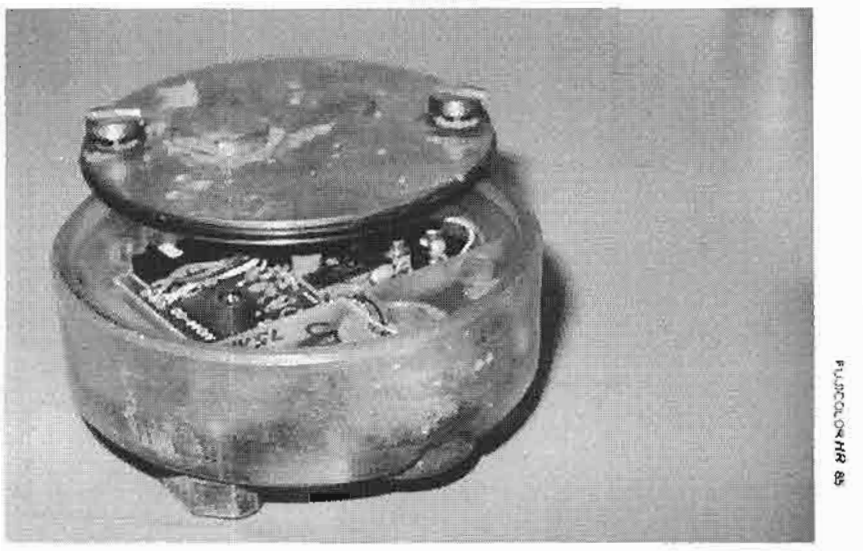

Fig 5. Recovered dive memory recorder.

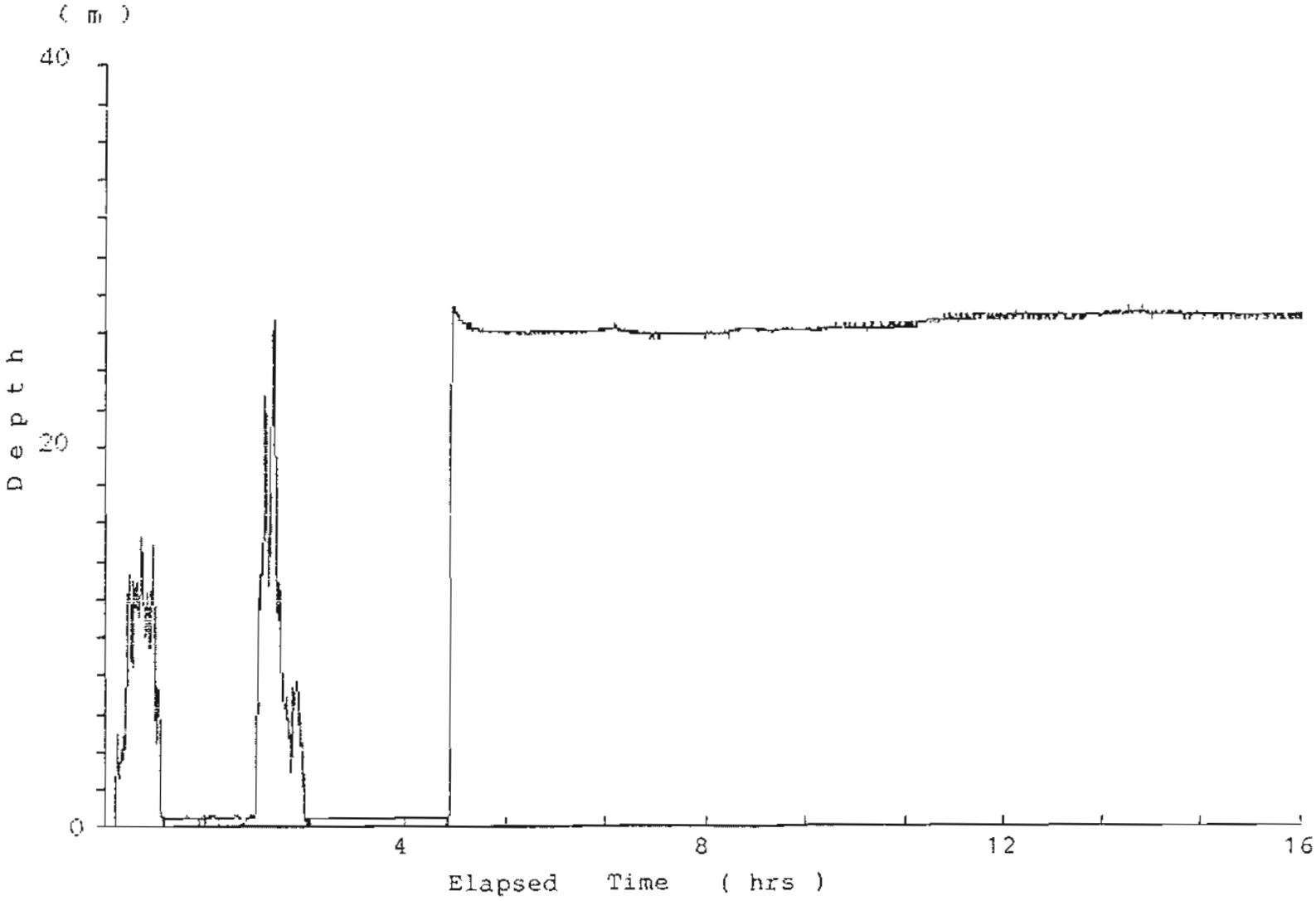

Fig 6. Dive profiles of a sport diver.
He lost a dive recorder at the beginning of his third dive.

frequently and are highly accurate, reflecting the algorithms with which they're programmed. The problem is they are used to get longer bottom times than tables would allow. Tables have built-in safety factors as dive profiles are seldom rectangular, but they are calculated as though they were. Dive computers get around these safety factors by specifically calculating for multilevel dives. I suspect that is the reason we're getting more cases of decompression sickness with dive computers. We saw this difficulty with the Scottish Sub-Aqua, in which a diver using a computer would stay down longer than a diver using a table.

DR. KINDWALL: The DCS risks of dive computers will improve when their decompression algorithms are made more conservative.

DR. VANN: The cases of decompression sickness with dive computers collected by DAN indicate that most problems occur on dive profiles which are deep, repetitive, and often involve decompression. The shallower dives are less trouble. As Dr. Kindwall indicated, the decompression algorithms must be made more conservative for the more hazardous dive profiles. I am sure the computer manufacturers will do this as it is in their best interest to make diving safer.

DR. MOON: Dr. Shields, when you compared your survey of surface oxygen decompression with the French survey of in-water decompression, the suggestion was that in-water decompression was safer, but as you pointed out, there may be an under-reporting of type II decompression symptoms because of financial penalties. Is it possible that the French financial penalties are somewhat greater than those of the British?

DR. SHIELDS: That might be so to some degree, but the difference in type II incidence is so large, 45% for surface decompression versus 1.5% for in-water decompression, that the conclusion would probably not be affected.

MR. IMBERT: We have reasonably good control of our divers in COMEX. We may miss a few type I cases but not many type II cases. There is definitely a difference in DCS incidence between type II surface and in-water decompression.

DR. KINDWALL: If a French diver develops type II decompression sickness and is treated successfully, how long must he wait before returning to diving?

MR. IMBERT: It's up to the medical doctor to decide.

DR. KINDWALL: What do they usually say?

MR. IMBERT: I don't know. We only had six type II cases in over 60,000 dives, so there is no general rule.

DR. MOON: Dr. Kindwall, you pointed out very nicely the value of oxygen in decompression of caisson workers, but there are other possibilities. Dr. Balldin has shown us that immersion and the use of terbutaline as a pharmacologic agent may hasten gas elimination, and Dr. Vann has found exercise to be effective. Are any of these methods practical for augmenting gas elimination? Maybe the ultimate technique would be to sit in the whirlpool during decompression after the end of a long shift.

DR. KINDWALL: I think the Food and Drug Administration would have a problem with terbutaline because of the daily exposure. They probably would insist on a long-term study of daily exposures that could last for months or years. A pharmacological agent might be useful for a very short job, but for the continuous daily exposures used by tunnelers, I think the use of drugs is out. The use of hot tubs would depend on the size of the tunnel. Immersion to the neck in a hot tub, however, only increases nitrogen elimination by 30% while the *theoretical* increase in elimination

of nitrogen with oxygen is 80%. In addition, the cost of oxygen and the space it would take up are less than that of a hot tub. It probably would be better to have them lying down rather than sitting up during oxygen breathing as this also accelerates nitrogen elimination. Of course, there would be overboard dumps on the masks which would require two hoses, one to the mask and one away. Oxygen must never be permitted to appear in the tunnel.

CAPTAIN THALMANN: Dr. Shields, there were eight type II bends in the commercial divers and six type IIs in sport divers. How many dives were conducted?

DR. SHIELDS: For the commercial diver, I think it was about 8000 in the first 2 years and probably about 50,000 overall. The group of sport divers at Orkney had done 15,000 to 18,000 dives. The bends incidence was vanishingly small.

CAPTAIN THALMANN: These dives were on the BSAC tables which have slightly shorter no-"D" limits than the USN tables. Perhaps the divers who were bent were unusually susceptible due to unknown anatomical variations. If this were so, it might be impossible to totally eliminate decompression sickness. The only answer would be to identify these individuals and tell them to stop diving, but sport divers might not listen.

DR. SHIELDS: I agree with your last comment, but I don't know if there are individuals' who are predisposed to bends. I still think this is, at the risk of raising some hackles, a random event. If you do enough dives, someone will get hurt. It is interesting that the eight type II commercial bends, out of about 60,000 dives, were mostly after long, shallow dives whereas the six sports divers were carrying out deep repetitive short dives. I believe you're looking at two opposite ends of a spectrum.

CAPTAIN THALMANN: Let me comment about dive computers. It is very difficult to find a decompression algorithm which will work for repetitive diving. In testing a decompression algorithm on air dives, we have been doing three and four repetitive dives and have very weird cases of bends. This sort of multiple repetitive diving is exactly how dive computers are being used in the Caribbean. We do not know what are the long term effects of such diving.

DR. BENNETT: Dr. Shields, can you comment on whether there might be any long-term neurological problems as a result of the 0.5% DCS incidence in surface oxygen decompression?

DR. SHIELDS: Yes, of course, that's the $64,000 question isn't it? Most of these individuals respond to rapid therapy and have no residua. They carry on diving. Some have permanent residua and are employed as divers in areas other than the North Sea, which are not so well regulated. We've persuaded the Department of Energy to fund a long-term health study on these divers which means following them when they finish their diving careers. We don't yet know what tests we're going to use. Should we do serial MRI scans? So far, we have collected 250 cases of decompression sickness of which about 100 are neurological. Their dive profiles are stored in a computer.

DR. BENNETT: Do you know how many of those 100 cases made an immediate recovery on therapy?

DR. SHIELDS: About 90% made an immediate recovery because they're compressed immediately offshore.

DR. BENNETT: You don't know if any of those who did recover had subsequent neurological effects?

DR. SHIELDS: No, but we are currently studying whether a second case of neurological decompression sickness is worse or harder to treat than a first case that was successfully treated.

DR. YOUNGBLOOD: I believe COMEX uses oxygen in the water during decompression. I wonder why the Anglo-Saxon community hasn't adopted this method since we have hot-water suits, and breathing oxygen in the water should be relatively safe? Mr. Imbert, have you had any fires or explosions in your divers face masks? From what we've heard today, being immersed in the water, wearing a hot water suit, and breathing oxygen without surface interval should be an affective and physiological way to decompress. From commercial experience, surface decompression with oxygen is very efficient and effective and seems quite safe if done well, but you're hanging by an operational thread. If anything goes wrong between the time you get out of the water and the time you get into the chamber, you are in effect treating decompression sickness which can be quite severe.

MR. IMBERT: We've been using quite a lot of in-water decompression with oxygen breathing. We have two types of tables. One uses a 6-meter oxygen stop and is designed for a surface demand regulator. A second type of table uses a 12 meter oxygen stop in a wet bell or submersible chamber. The British Department of Energy questioned the validity of oxygen breathing in the water. I checked the COMEX data bank and found some 5600 dives using the 12-meter oxygen stop with more than 30 minutes oxygen breathing. We had a few cases of oxygen toxicity which were related to error in procedure, such as sending the wrong gas to the diver, but no other problems. So our experience with in-water oxygen decompression with oxygen breathing hasn't been bad.

DR. BALLDIN: Dr. Shields, you show that there was an increased incidence of decompression sickness with the use of the hot-water suit. That might have been due to an increased uptake of inert gas during the bottom phase of the dive. Do you think that the use of the hot-water suit should be restricted during the bottom phase and encouraged during decompression?

DR. SHIELDS: Yes. There appeared to be an increase in decompression sickness with hot-water suits during severe dives, but no difference on shorter, shallower dives. The hot-water suit is discarded during decompression when the diver climbs into a chamber. In the North Sea, I strongly suspect that those chambers are cold, more often than not. A diver who is hot for a long time at pressure and cool during decompression is likely to be at a higher risk of DCS.

DR. PETERSON: Is anything known about the recent diving history of the sport divers who suffered the serious decompression sickness in the DAN experience or in Scapa Flow? In some such cases, the people that had the problems were making their first dive in a very long period of time to a depth of 130 fsw in relatively cold water.

DR. SHIELDS: We found that all bends treated recently occurred on a Thursday or Friday after 5 or 6 days of diving, so there's an accumulated effect. An earlier case, however, occurred on the first dive of the season. He hadn't dived since the previous summer. The next case, a youngster who was the worst case of the lot, had dived every weekend throughout the preceding winter.

DR. KINDWALL: Were the Scapa Flow dives no-stop or decompression dives?

DR. SHIELDS: They were decompression dives. The BSAC table simplifies the decompression. You do one stop at 10 meters, and one stop at 5 meters. They all had an obligatory stop at 5 meters and several of them inserted a 10-meters stop on their own, as a Jesus factor.

DR. ZWINGELBERG: Dr. Shields, in your analysis of surface decompression versus in-water decompression, were the dives equally stressful?

DR. SHIELDS: They were of comparable severity.

DR. ZWINGELBERG: Recent U.S. Navy and Canadian tests are showing that safe decompressions for long dives must be 2 to 3 times as long as the USN Standard Air schedules. Perhaps the 20 to 30 min Jesus factors which are being added in the North Sea are just not long enough.

MR. GERNHARDT: What were the onset times for type I and type II symptoms in the sport and commercial divers and for surface decompression?

DR. SHIELDS: The commercial cases are not as well documented as the sport diving cases. The cases that come out of the water have a rapid onset while the onset time of the commercial surface decompression cases can arise many hours after leaving the chamber. I don't recall if the onset time of types I and II symptoms were different.

DR. LUNDGREN: With nearly 20% of the general population having an open foramen ovale, the six sport divers with type II symptoms may have shunted venous bubbles from the right to the left side of the heart and into the arterial circulation.

DR. SHIELDS: I cannot think of any other explanation.

DR. LANPHIER: At the Tokyo workshop on surface-based decompression last year, Dr. Sterk reported some unusual chronic oxygen exposure symptoms. Has anyone seen similar symptoms and might they be a problem for tunnel decompression using oxygen?

DR. KINDWALL: Sterk reported not only pulmonary signs, but numbness of fingers. We see these in hyperbaric patients treated daily for up to a month or so over 20 treatments. For this reason, the Milwaukee oxygen tables use oxygen at decreasingly shallower stops, whereas in commercial diving, oxygen would be used only at 9 meters. We use increasingly shallow stops to reduce the oxygen toxicity risk.

DR. VAN LIEW: The use of oxygen after a dive seems more in the nature of a cure than a prevention. Oxygen will increase the elimination rate of bubbles by a factor of about 10, while the elimination rate of dissolved nitrogen increases only by a factor of about 2. Oxygen breathing should have dramatic effects on arterial bubbles as well as stationary bubbles.

DR. KINDWALL: This is the very reason why we see better results than predicted when oxygen is added to a decompression table.

DR. VAN LIEW: It may be that oxygen after surfacing is as good as oxygen before surfacing for bubbles.

DR. KINDWALL: Dr. Nashimoto had good results using postdecompression oxygen.

DR. NASHIMOTO: It's very difficult to maintain discipline in the chamber when using oxygen. Therefore, we used it for about 30 minutes after decompression with care to eliminate the exhaled oxygen by a tube to outside of the resting room.

DR. KINDWALL: Let me address the discipline question. Discipline is no more of a problem sitting in a room on a mat than it is in a tunnel. Anyone who pulls a cigarette out on the job can be fired immediately. This was done in Cairo where there was no smoking even though oxygen was not used. Normally, people smoke in tunnels unless there's a rule against it.

DR. YOUNGBLOOD: I'd like to say a word in defense of hot-water suits as I sense a trend here to alter our hot-water suit practices to suit our diving profiles. From a commercial standpoint, hot-water suits have made it possible for a man's hands and brain to function for an extended time in cold water. If you compromise that, you will have stupid, inept, stumbling divers who will make fatal mistakes, not just get decompression sickness. What the hot-water suits have done is to show the inadequacies of the present tables at prolonged depths and times. We need to change the tables, not the suits. Pertaining to the numb fingers as a result of oxygen breathing, I think Dr. Strauss reported this at the recent Long Beach meeting, and I've seen it in three cases, one of these at Duke. In extreme cases, there are no pulses in the hands and feet due to vasoconstriction. It seems to occur in highly fit individuals. My cases were a Seal and two ex-SAS people right out of the service. All were running 10 miles a day and extremely fit. They had what, for want of a better description, was severe idiosyncratic vasoconstriction.

DR. WHIDDEN: I heard recently that in the United Kingdom the brains and spinal cords of all divers who died from whatever cause were to be preserved. How do you tag the divers later on after they've left the profession and would you consider looking at the hearts as well?

DR. SHIELDS: We have a resident ghoul who goes after the spinal cords and brains of divers who die from acute trauma. He has amassed about 15.

DR. JAMES: 26 brains and 17 spinal cords.

DR. SHIELDS: You can rely on Philip. Thank you, Philip. This is extremely valuable material. We would like to tag our 250 divers so that sometime in the next century, their brains and spinal cords will appear under the microscope. We don't know how to do it now because when a diver leaves his profession, he is very difficult to follow. We might have used the Newcastle Bone Necrosis Registry until it was closed in 1981. Perhaps it or a similar registry will be reinstated.

DR. JAMES: I've seen eight individuals who have had type II decompression sickness and been treated successfully perhaps over several weeks. Some years later, they developed a return of symptoms with a progression of neurological dysfunction. Has anyone in this audience seen this phenomenon?

DR. KINDWALL: There are a number of cases in which a diver makes a complete recovery, and a month or two later, having contacted a lawyer, begins to develop very convincing symptoms. My initial reaction is that financial profit is the motive. On the other hand, is a complete recovery really complete or is there a worsening of symptoms secondary to DCS? I've been doubtful of that because I haven't seen a case where litigation wasn't involved.

DR. JAMES: There was no litigation involved in the eight cases I referred to. All were diagnosed with classical neurological disease. The interval between the DCS and the subsequent deterioration was years rather than months.

DR. KINDWALL: Has anyone else seen a case of deterioration?

DR. YOUNGBLOOD: Cross studied decompression sickness after multiple breath-hold dives (taravana) in French Polynesia. This sort of diving is no longer done, but ex-divers are sometimes pointed out on the waterfront in Hawaii for their punch-drunk appearance. This population could use some study with imaging techniques, except it's so far away. They're deteriorating more rapidly than Polynesians at other islands who were not divers.

DR. MILLER: I have maintained contact with the first of the saturation nitrox therapy people treated at Duke in about 1978. About 3 years ago, one man began to show some further neurological impairment. He was having residual bladder problems and now has developed foot drop. Another fellow sustained a severe type II decompression accident, was treated with USN table 4 off the coast of Athens, and ended up with bilateral foot drop. When I met him again several years later he had begun to show further decrement in neurological status. I haven't, however, made a systemic neurological examination of either of these people.

DIVING AT ALTITUDE AND FLYING AFTER DIVING

A.A. Bühlmann

Abstract

The relation between the tolerated nitrogen oversaturation and the ambient pressure is practically linear. Tissues with short half-value times have a higher tolerance than tissues with long half-value times. The human body can be regarded to consist of 16 compartments with half-value times for nitrogen from 4 up to 635 minutes, and 1.5 up to 240 minutes for helium, respectively. The coefficients to calculate the minimal tolerated ambient pressure for a given PN_2 in the tissue can be derived mathematicaly from the half-value times for nitrogen.

The results of 573 simulated air dives and 544 real dives in mountain lakes show a good correlation between the experimental values of the PN_2 in the tissues with N_2-half-value times from 8 up to 635 minutes and the "theoretical" calculated limits of tolerance. The accordance has been tested for ambient pressures from 0.460 bar up to 2.2 bar.

The system ZH-L16 is applicable for all exposures with air or oxygen-nitrogen mixtures. The adaptation for breathing oxy-helium or trimix is simple.

The electronic decompression-computers developed in Switzerland are based on the same concept.

Diving at altitude. The concept ZH-L16 to calculate the decompression

The linear relationsship between the maximal tolerated PN_2 in the tissue (PN_2 t.) and the ambient pressure (P amb.) can be formulated.

$$(PN_2 \text{ t.} - a) \times b = P \text{ amb. tolerated.}$$

The tolerated N_2-overpressure decreases with diminishing ambient pressure. Diving at altitude is therefore a sensitive test to prove a concept of decompression and to determine the limits of tolerance.

The coefficients a and b have to be verified by experiments and real diving. Based on empirical data, the coefficients a and b can be derived directly from the N_2-half-value time (N_2-1/2 t):

$$a = 2 \text{ bar} \times \left[\frac{N_2\text{-1/2 t}}{\text{min}}\right]^{-1/3}$$

$$b = 1.005 - 1 \times \left[\frac{N_2\text{-1/2 t}}{\text{min}}\right]^{-1/2}$$

example: N_2-1/2 t 27.0 min

a = 0.6667 bar

b = 0.8126

These "theoretical" limits of tolerance have been compared with simulated dives in the chamber and real dives at altitude (Table 1).

Table 1

The experimental basis of the system ZH-L16

I. 2 cases of paraplegia after diving at altitude (Swiss Army 1969)

II. **Retrospective:** 573 simulated dives in the chamber
   a. 493 dives included 131 repeated dives. Decompression according the limits of ZH-L16. 2.8% symptoms of DCS (skin, muscles, joints)
   b. 146 decompressions to subnormal ambient pressure after a dive. 10.3% symptoms of DCS (skin, joints)
   c. 80 dives with unsufficient decompression-time during the last step. 42.5% symptoms of DCS (skin, muscles, joints)

III. **Prospective:** 544 real and protocolled dives at altitude. No case of DCS of GE
   a. 254 dives in Switzerland, 1000 - 2600 m above sea level (1985-1986)
   b. 290 dives in the lake Titicaca, 3800 m above sea level (1987)

Figure 1 shows the tolerated PN_2 t. at an ambient pressure of 1.0 bar for the tissues with N_2-half-value times of 8 minutes up to 635 minutes. The curve represents the "theoretical" limit according the coefficients a and b derived from the N_2-half-value time. 234 subjects of 14 different trials decompressed after a first dive conform to this limit have in 1.7% slight symptoms of DCS. If the limits of the N_2-half-value times of 54.3 minutes up to 635 minutes are exceeded by 4%, in 42.5% symptoms of DCS occur. The 80 subjects have been exposed in 8 different simulated dives. These results demonstrate that the "theoretical" limit is the upper limit of tolerance.

The short N_2-half-value times up to 18.5 minutes represent the spinal cord. The Swiss Army performed in 1969 more than 1000 No-decompression dives at normal ambient pressure without symptoms of DCS of GE. At an altitude of 1800 m above sea level in 2 of 8 divers paraplegia occured after a dive of 20 minutes at 30 m. After that event, diving at altitude was stopped in Switzerland for 3 years.

The recalculation of this well documented dive shows that the limits according the "theoretical" coefficients a and b for the N_2-half-value times of 8.0 and 12.5 minutes are exceeded at the end of bottom time and at surface in the range of at least 5% (Table 2).

Both diver were successfully recompressed. The incident gave the motivation for experimental work with reduced ambient pressure.

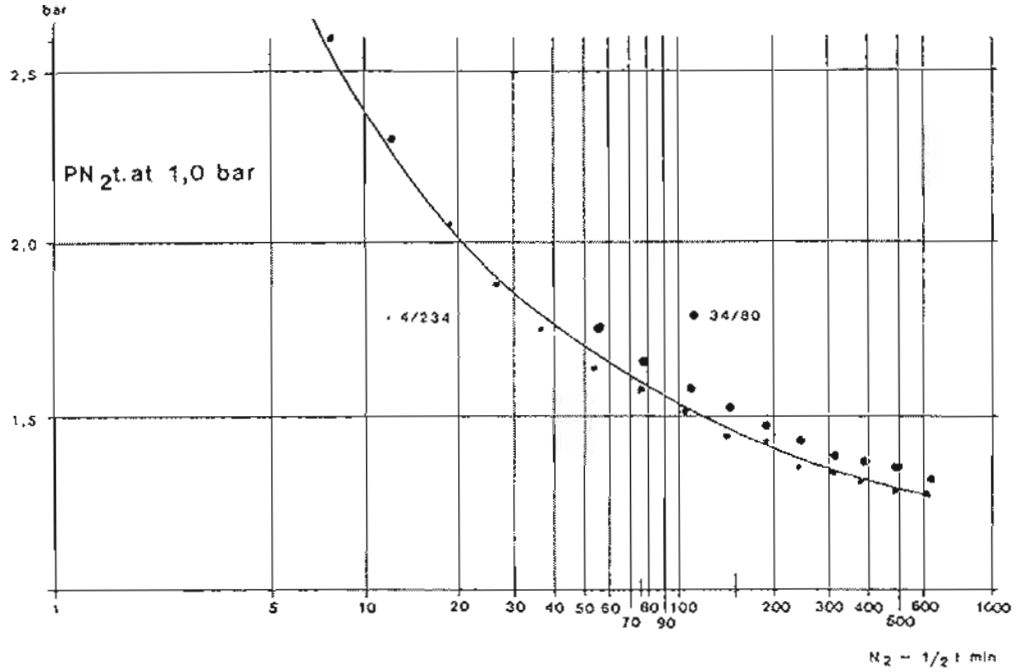

Fig. 1 The tolerated PN_2 in the tissue (PN_2 t.) at an ambient pressure of 1.0 bar for tissues with N_2-half-value times from 8.0 minutes up to 635.0 minutes according the "theoretical" coefficients a and b.
·Experimental values of 234 subjects with 1.7 % slight symptomes of DCS, skin or joints. (No repeated dives).
●Experimental volues of 80 subjects with unsufficient decompression. 42.5 % symptoms of DCS, skin, muscles, joints. (No repeated dives, Table 1.I.c).

Table 2

2 cases of paraplegia after diving at altitude

1800 m above sea level, P amb. 0.815 bar
8 dives: 20 minutes at 30 m fresh water, 3.7571 bar

N_2-1/2 t min.	8.0	12.5	18.5
PN_2 t. at the end of BT, bar	2.4707	2.1111	1.7822
PN_2 t. after 2 min ascent, bar	2.3568	2.0736	1.7802
Limits ZH-L16 at 0.815 bar	2.2512	1.9902	1.7976

The figures 2, 3 and 4 show the experimental PN_2 t.-values for tissues with N_2-half-value times of 12.5, 27.0 and 54.3 minutes in relation to the line according the "theoretical" coefficients a and b. The points represent mean values of different subjects. The points at ambient pressure 1.0 bar and elevated ambient pressure during decompression are determined by simulated dives in the chamber. The values at reduced ambient presure are derived from dives in different mountain lakes in Switzerland and from the lake Titicaca (expedition conducted by Capt. M. Moody, UK, 1987).

The coefficient b presents the angle of the relation between PN_2 t. and the ambient pressure. The results prove the utility of the "theoretical" coefficient b, derived from the N_2-half-value time.

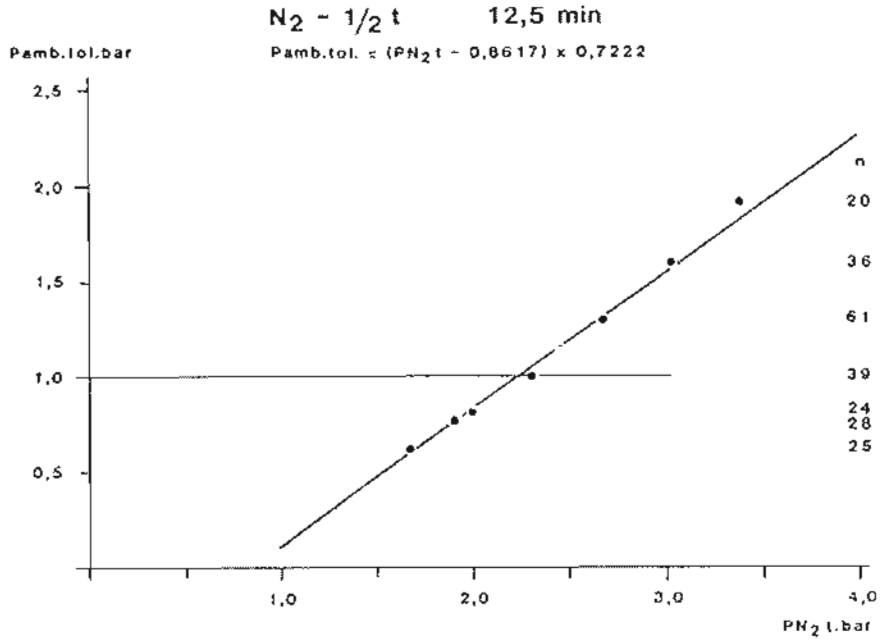

Fig. 2 N_2-half-value time 12.5 minutes. The experimental values correspond with the "theoretical" line according the coefficients a and b derives from the half-value time. n = number of subjects. The values at subnormal ambient pressure proceed from real diving at altitude (Table 1 III.).

The real dives at altitude with PN_2 t.-values less than 95% of the "theoretical" limit are not considered in the figures 2, 3 and 4. The water temperature in the mountain lakes in Switzerland was 4-8°C, in the lake Titicaca 12-16°C.

Most of the dives have been no-decompression dives, using an ascent rate of 10 m/min.

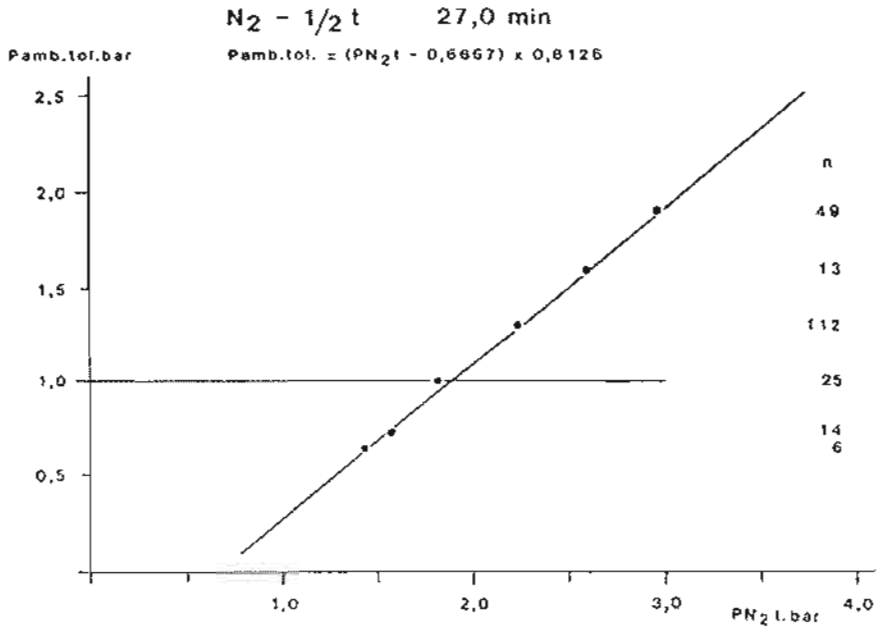

Fig. 3 N_2-half-value time 27.0 minutes. Good correlation between the experimental PN_2 t.-values and the "theoretical" line. Values at subnormal ambient pressure from real diving at altitude.

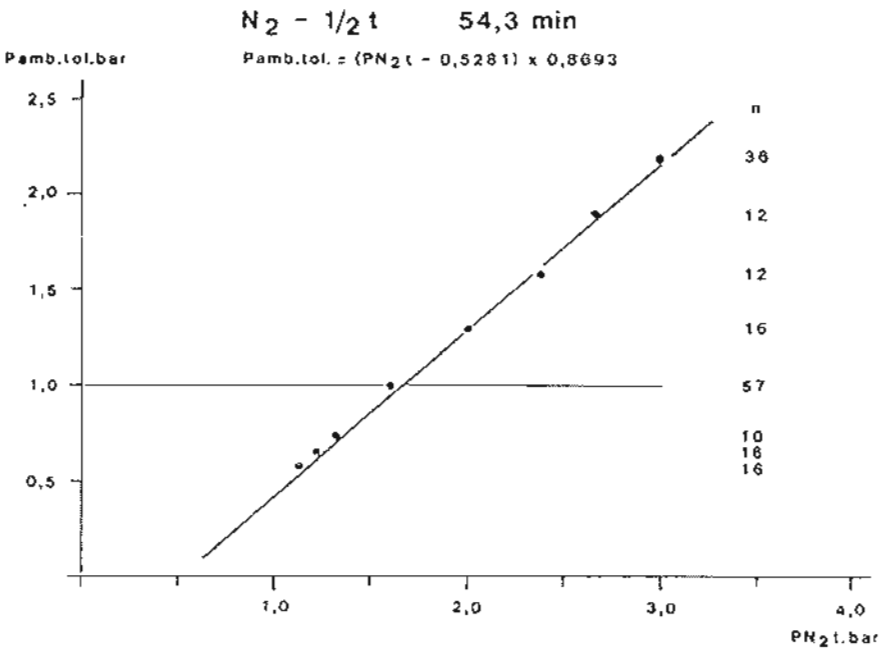

Fig. 4 N_2-half-value time 54.3 minutes. Good correlation between the experimental values and the "theoretical" line. Values at subnormal ambient pressure from real diving at altitude and decompression to subnormal pressure in the chamber.

Flying after Diving

The situation can be simulated in the chamber for short and long lasting dives. Figure 5 shows the decompression to an ambient pressure of 0.60 bar, 4200 m above sea level. After the decompression-time of 11 minutes, the tissues with N_2-half-value times of 18.5 and 27.0 minutes have PN_2 t.-values according to the "theoretical" limits. After 40 minutes breathing air at 1.0 bar, the tissues with N_2-half-value times of 77 upt to 146 minutes give the limitation for the additional decompression. 5 of th 16 subjects noticed itching of the skin for some minutes.

Figure 6 shows the decompression to an ambient pressure of 0.70 bar, 3000 m above sea level, after a 120-minute dive at 4.2 bar. This experiment is representative for tissues with longer N_2-half-value times. After a decompression time of 176 minutes, the ambient pressure can be reduced to 0.90 bar. The tissues with N_2-half-value times of 146 upt to 305 minutes are "leading". After an interval, lasting 200 minutes at 0.90 bar, the ambient pressure is reduced to 0.70 bar. This reduction is determined by the tolerance-limits of the tissues with N_2-half-value times of 305 upt to 635 minutes. These long half-value times are important for the joints and bones. In the case of insufficient decompression typical bends can occur.

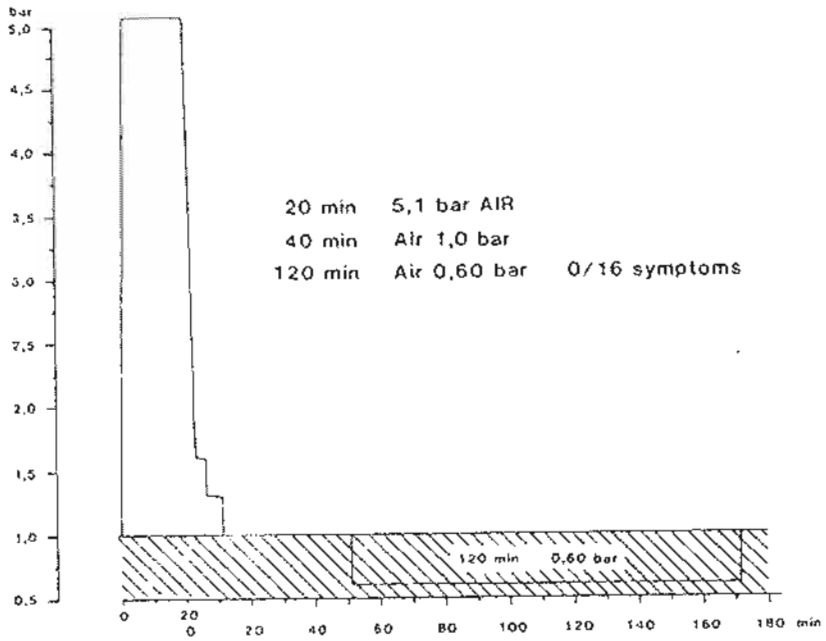

Fig. 5 Exposure to air at 5.1 bar for 20 minutes including 2 minutes descent time. 11 minutes decompression time up to 1.0 bar breathing air. After breathing air at 1.0 bar 40 minutes, the ambient pressure is reduced to 0.60 bar for 120 minutes. 5 of 16 subjects have mild skin-symptoms disappearing at altitude.

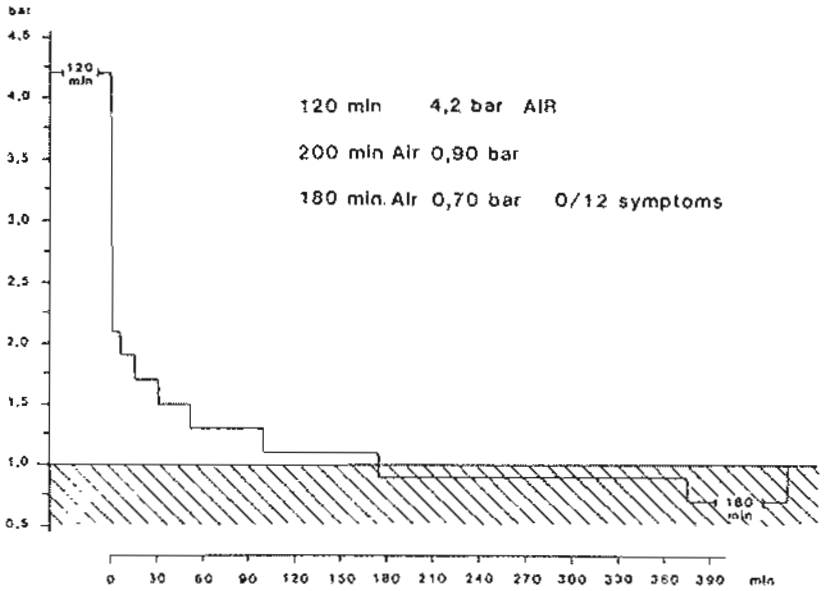

Fig. 6 Exposure to air at 4.2 bar for 120 minutes. Decompression with breathing air up to 0.90 bar. After breathing air at 0.90 bar 200 minutes, the ambient pressure is reduced to 0.70 bar for 180 minutes.

The reduction of the ambient pressure after breathing air at surface was also studied with oxy-helium dives. Figure 7 shows an example. The decompression time of 80 minutes, breathing 100% oxygen, is barely sufficient for a tissue with a He-half-value time of 147 minutes, corresponding to a N_2-halfvalue time of 390 minutes. After 60 minutes at surface, breathing air, the compartments with He-half-value times of 147 up to 240 minutes, corresponding to the N_2-half-value times of 390 up to 635 minutes, are "leading". The FN_2 in these compartments is 0,48-0,51

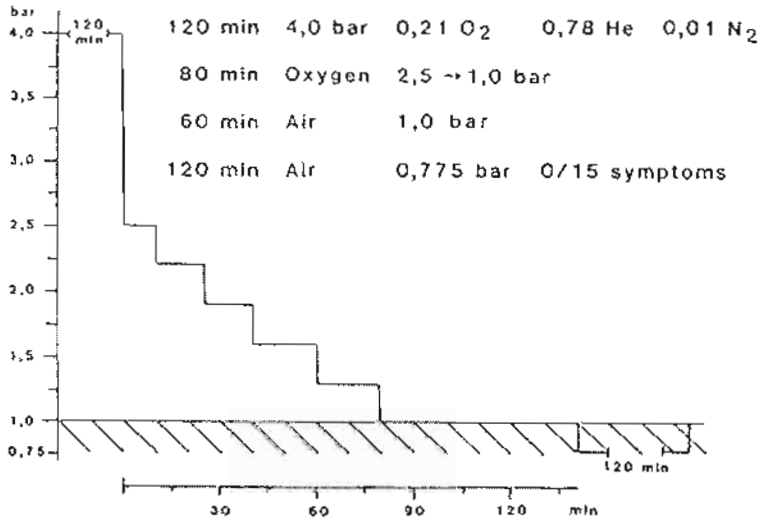

Fig. 7 Exposure to heliox at 4.0 bar for 120 minutes. 80 minutes decompression breathing 100 % oxygen. After breathing air for 60 minutes at 1.0 bar, the ambient pressure is reduced to 0.775 bar for 120 minutes.

The experimental PN_2 t.-values for the N_2-half-value times of 109, 305 and 635 minutes demonstrate also a good correlation with the "theoretical" lines (Figures 8, 9 and 10).

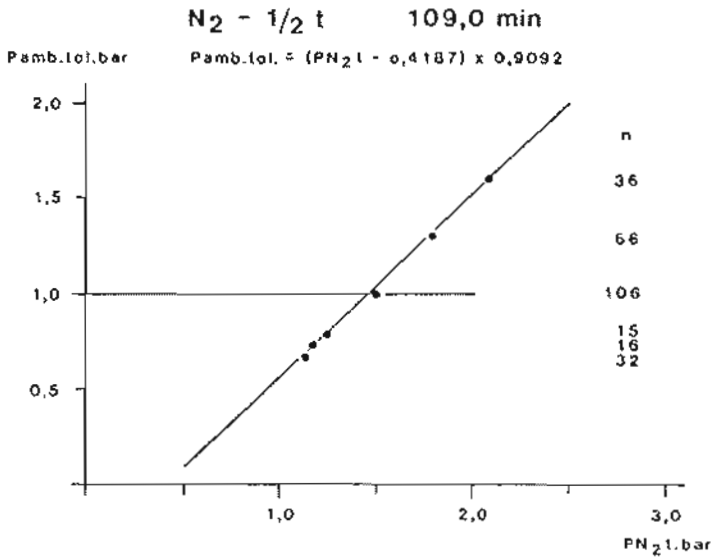

Fig. 8 N_2-half-value time 109.0 minutes. Good correlation between the experimental PN_2 t.-values and the "theoretical" line.

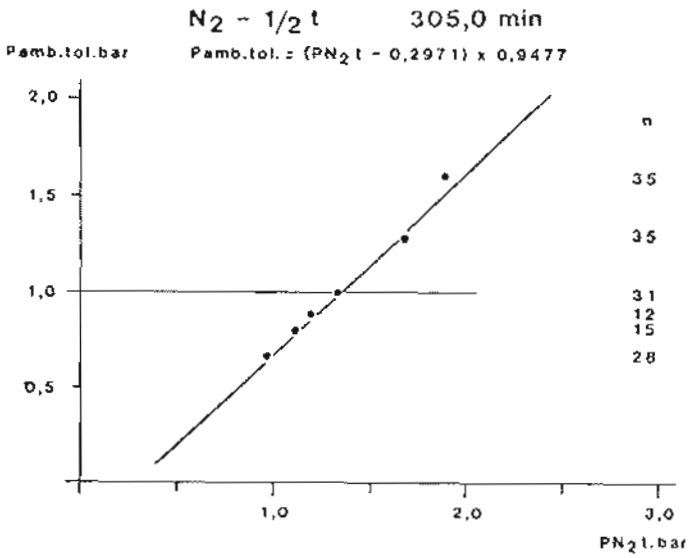

Fig. 9 N_2-half-value time 305.0 minutes. Good correlation between the experimental values and the "theoretical" line, excepting at 1.6 bar.

The N_2-half-value time of 635 minutes is the longest half-value time of the system ZH-L16. This N_2-half-value time corresponds to the longest half-value time of 240 minutes for helium. The PN_2 t.-values of 8 subjects at an ambient pressure of 1.9 bar in figure 10 date from the decompression after long-lasting dives at 30 m. The point at an ambient pressure of 0.700 bar belongs to the trial shown by figure 6.

The point at an ambient pressure of 0.460 bar, is the result of a special experiment. 16 subjects, 15 men, 1 woman, saturated with air at the region of Zurich (PN_2 t. = 0.720 bar) were decompressed in 15 minutes to an ambient pressure of 0.460 bar, 6200 m above sea level. The 16 subjects remained in this altitude for 180 minutes, breathing air and working every hour for 10 minutes 150-180 Watt on a bicycle-ergometer. Mild symptoms of hypoxia but no bends occured.

The decompression limit of 6000 m above sea level after saturation with air at sea level is will known in the aviation medicine. Breathing oxygen for 6 hours at 1.0 bar, the ambient pressure can be reduced to 0.260 bar, 10'000 m above sea level, without risk of serious bends. These experiences agree with the "theoretical" coefficients a and b, derived from the N_2-half-value time of 635 minutes. If the longes N_2-half-value time is not 635 minutes but 720 minutes, the difference in the tolerated altitude is only 150 m.

This experiment without preceding dive leads to the problem of the N_2-elimination during the surface-interval after a dive. If the elimination in the lung is temporaryly reduced, the real PN_2 t. is higher than the conventionally calculated value. In this case the tolerance-limit is exceeded, and symptoms of DCS can be expected.

Table 3 shows an increased incidence of mild skin symptoms after decompresion to altitude. Symptoms of DCS of the central nervous system or severe pain have never been observed in these trials. The situation is comparable

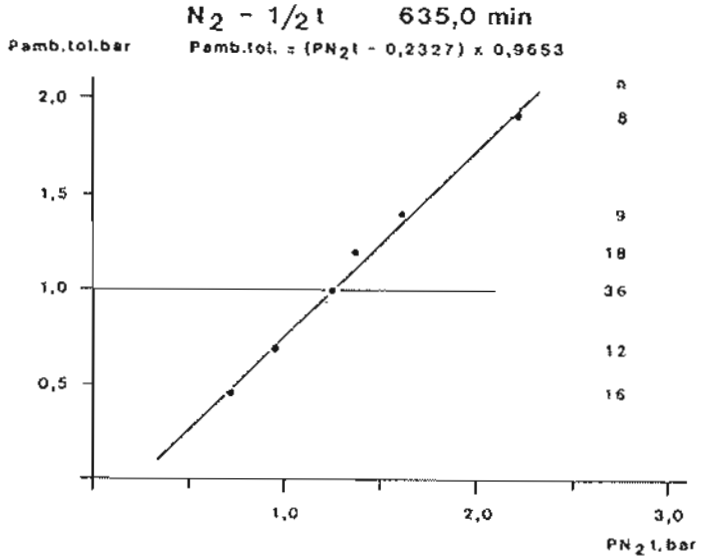

Fig. 10 N_2-half-value time 635.0 minutes. The experimental PN_2 t.-values correspond with the "theoretical" linebetween an ambient pressure of 0.460 bar up to 1.9 bar.

to repeated diving. The incidence of mild skin symptoms after repeated dives is twice of three times as frequent as after the first dive using the same limits of tolerance.

Table 3

Incidence of symptoms of DCS after decompression in few minutes to altitude.

146 simulated dives with PN_2 t.-values of 96-100% of the "theoretical" limits.

Dive m	BT min	Interval min	Controlling N_2-1/2 t min	Altitude bar	Symptoms*
38-42	20-60	40, 45	77.0-239.0	0.587-0.726	7/60 skin
30-35	60,120	60, 74	109.0-305.0	0.686-0.853	8/59 skin, m.b.
30-32	120	60,200	305.0-635.0	0.686-0.775	0/27
*disappearing at altitude					15/146 = 10.3%

The higher incidence of mild symptoms of DCS (type I) after repeated dives and after decompression to altitude after a surface interval can be diminished by a reduction of the coefficient a for the N_2-half-value times of 30 up to 300 minutes and/or a correction of the N_2-elimination during the surface-interval. Both possibilities are realized in the advanced electronic decompression-computers developed in Switzerland. According to our present knowledge, it is necessary to find a good compromise.

The new decompression tables used in Switzerland (0-700 m, 701-2500 m above sea level) are calculated with reduced coefficients a, supplements for depth and for the surface-interval before repeated dives or before flying after diving.

Bühlmann AA, Schibli RA, Gehring H. Experimentelle Untersuchungen über die Dekompression nach Tauchgängen in Bergseen bei vermindertem Luftdruck. Schweiz Med Wochenschr 1973;103:378-383

Bühlmann AA. Untersuchungen zur Dekompression bei erniedrigtem Luftdruck. Schweiz Med Wochenschr 1984;114:942-947

Bühlmann AA. Decompression after repeated dives. Undersea Biomed Res 1987;14:59-66

Bühlmann AA. Decompression-decompression sickness. Berlin, Heidelberg, New York, Tokyo: Springer, 1984

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DISCUSSION

DR. BALLDIN: Dr. Buhlmann, in some of your altitude exposures, you have subjects at 6000 meters where the pressure is less than 0.5 ATA, and they are working on a bicycle ergometer at 200 watts. They must be pretty hypoxic during that exposure. Do you think that that could have reduced the risk of decompression sickness a little?

DR. BUHLMANN: The subjects were a little hypoxic, but not severely so. There was a physician with experience on the Himalayas and 6 other men who were experienced glider pilots. I don't believe that mild hypoxia reduces the risk of DCS.

CAPTAIN THALMANN: You said that in Switzerland last year there were 100,000 dives and only one or two cases of decompression sickness. This is certainly a much better incidence than I think we would find in this country. Is that because Swiss tables are better or Swiss divers are just better at following procedures?

DR. BUHLMANN: Both! Both!

CAPTAIN THALMANN: Do the divers mainly use your tables, or do they use a variety of tables in Switzerland?

DR. BUHLMANN: The majority of the Swiss divers used at sea level the old French tables (GERS) or the tables of the U.S. Navy up to 1976. In 1976 we published tables for different altitudes (1). Since then our tables have been used by the majority. In 1986 we made new tables using reduced tolerance limits. We are now more conservative than in 1976. I find that altitude divers are better trained and have more discipline.

CAPTAIN THALMANN: Were most of those dives made on the altitude tables developed for diving at 0.7 atmospheres?

DR. BUHLMANN: Most of the dives in mountain lakes are performed at 1500 to 2000 meters above sea level, 0.80 to 0.85 ATA. The new altitude table is valid up to 2500 meters above sea level (0.76 ATA).

DR. VANN: Professor Buhlmann, can you tell us how long a sport diver should wait at sea level before flying at altitude in a commercial aircraft?

DR. BUHLMANN: We have a waiting time of 2-12 hours depending on the Repetitive Group of the dive.

DR. VANN: Our experience with the 5-day DAN courses in the Caribbean leads us to believe that a 12-hour surface interval before flying is inadequate. A number of bends have occurred in the aircraft at 15 or 16 hours. We are now advising a 24-hour surface interval. I wonder if that is long enough.

DR. BUHLMANN: The minimal surface interval before flying after an air-saturation dive is 23 hours according to our limits. If there are symptoms of DCS, 48 hours. For multiday diving, a 24-hour surface interval before flying should be long enough.

DR. BALLDIN: But if you go higher, of course, then you have to wait for longer times?

DR. BUHLMANN: Nitrogen elimination during the surface interval is better at altitude than at sea level. The water vapor pressure in the alveoli is always the same (47 Torr).

DR. BALLDIN: My own experience is somewhat different. We exposed subjects to scuba dives, waited for 12, 18, or 24 hours, and exposed them to flying at 9000-meter altitude, about 0.33 ATA. If the flights lasted more than 50 minutes, bubbles and decompression sickness became more frequent than without the dive. A 24-hour surface interval after a 15-

meter, 100-minute dive or a 39 meter, 10-minute dive was not sufficient to protect against bends for a flight lasting more than 50 minutes. If the flight was longer than 1 hour, much more decompression sickness occurred.

DR. BUHLMANN: I agree. We calculated the surface interval after a dive before flying at an altitude of 4000 meters. If the dive has been performed at sea level, the diver is permitted to ascend to 4000 meters above sea level after the surface interval. If the dive has been performed at 2000 meters above sea level, the same Repetitive Group and the same surface interval permit to ascend to 6000 meters above sea level.

DR. HAHN: I believe there's misunderstanding. Dr. Balldin, you assumed the plane was at a higher altitude while Professor Buhlmann assumed the diver lived at a higher altitude.

DR. BALLDIN: So when a diver is at higher aircraft altitude, he has to wait 24, 36, or more hours.

DR. BUHLMANN: Yes. When diving at sea level, the longest time to wait before flying at 4000 meters above sea level is according to our limits, 24 hours. If you are flying higher than 4000 meters, the waiting time is longer.

DR. BALLDIN: According to my experience, 24 hours was not sufficient for more than 15 minutes at 9000 meters without causing symptoms of decompression sickness and intracardiac gas bubbles.

DR. WEAVER: Dr. Buhlmann, did you look at venous gas embolism during any of your studies?

DR. BUHLMANN: No.

DR. WEAVER: You mentioned that you had two dive computers. Which ones were those?

DR. BUHLMANN: Decobrain and Aladin.

DR. WEAVER: How did they perform at Lake Titicaca?

DR. BUHLMANN: The Decobrain with the program P2-4 calculates the nitrogen elimination during the adaption to altitude. The Aladin calculates the decompression with the nitrogen partial pressure in all tissues according to the conditions at sea level. On this basis, the Aladin indicated at Lake Titicaca longer decompression times than the Decobrain for the same dive. The British and the Swiss divers followed the Decobrain and a decompression table given for 2501 to 4500 meters above sea level.

DR. WEAVER: Did it give a schedule you felt was appropriate?

DR. BUHLMANN: Yes. I think, our schedules 0 to 700 and 701 to 2500 meters, and 2501 to 4500 meters above sea level are appropriate.

DR. WEAVER: Dr. Bennett, Divers Alert Network makes a very conservative recommendation about diving at altitudes above about 2000 meters. Why was that recommendation made and might it be changed as a result of Dr. Buhlmann's presentation?

DR. BENNETT: That recommendation is based on the earlier literature, but we recognize that Professor Buhlmann's has the best tables, and we'll go by his in future.

DR. VANN: What is the effect of adaptation to altitude? I'm speaking of the equilibration with the inert gas at altitude. If you dive immediately upon ascending, you're presumably at a higher risk than if you dive after you've been at altitude for a day or two.

DR. BUHLMANN: Yes, that's an important matter. The table 701 to 2500 meters is calculated on the basis of an ascent time of 60 minutes. The diver is only partly adapted. The table 2501 to 4500 meters is calculated for a full adaptation to altitude. Some of the divers at the Lake

Titicaca suffered at the beginning under altitude sickness and stopped the diving.

REFERENCE

1. Boni M, Schibli R, Nussberger P, Buhlmann AA. Diving at diminished atmospheric pressure: air decompression tables for different altitudes. Undersea Biomed Res 1976; 3:189-204.

DECOMPRESSION IN SPACE

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ABSTRACT

The prevention of decompression sickness (DS) during space flight has been successful in that no reports of symptoms have been made or debilitating signs of this syndrome observed during flight. In this paper we will review some of the relevant work done in the past leading up to the procedures to prevent DS in space and summarize our current data on the subject. In discussing our recent data, the relationship of precordial doppler bubble grade and DS will be discussed as well as a comparison made of susceptibility between the sexes. Finally, a discussion will be made of possible changes in susceptibility of space crewmembers to DS based on the physiological effects of exposure to microgravity.

Introduction

Although the possibility of bends at altitude had been suggested previously and others had described joint pain at altitude (1), Harry Armstrong is credited with proposing that such symptoms are due to bubbles of nitrogen in blood vessels or tissues (1,2). In the half century that has passed since then, many studies have been done on the susceptibility of humans to altitude decompression sickness, especially in the relationship of oxygen breathing before decompression to the onset of DS at altitude (3,4,5,6,7). However, to consider only altitude data in an analysis of space decompression would overlook the very relevant physiology of the diver who in his buoyant state is operating in a similar fashion to the astronaut during extravehicular activities (EVA). It is for this reason that the EVA crewmembers spend many hours in water tanks practicing their required tasks in the simulated weightlessness of the underwater facilities. One of the major differences between diving and space decompression, however, is the fact that the astronaut does up to 6 hours of work after his decompression whereas the diver completes his work before the decompression.

Elimination of Nitrogen and Protection Against Altitude DS

One of the earliest studies which attempted to quantify the relationship of "prebreathing" and protection against DS at altitude was that of Behnke in 1942 (4). His data is summarized in Table 1.

TABLE 1
EARLY BENDS STUDIES
(BEHNKE, 1942)

EXPOSURE AT 38,500 FEET FOR A PERIOD OF 4 HOURS

	NUMBER OF MEN	NUMBER OF EXPOSURES	BENDS	CHOKES	NO SYMPTOMS
CONTROL TESTS	28	32	28	3	1
PREOXYGENATION FOR PERIODS OF 80 TO 240 MINUTES	27	29	3*	0	26
PREOXYGENATION 30 MINUTES, MODERATE EXERCISE	25	25	19	0	6

*All three men subsequently were resistant to decompression sickness when the preoxygenation period was adequate, i.e., 4 hours for 2 men, 12 hours for 1 man.

Behnke's subjects were exposed to a significantly lower pressure (2.8 psi) than that of the current NASA space suit (4.3 psi). However, the duration of oxygen breathing used for protection in our exercising subjects falls within the range of his study (6). Robinson, in 1944, reported that exercising subjects at 30,000 feet of altitude (approximately equivalent to the Shuttle space suit pressure) had a higher incidence of DS than non-exercising subjects at 38,000 feet after prebreathing with oxygen before decompression (8). Later studies emphasized the importance of body fat content (5) and addressed specific altitude profiles (5,6,10,11).

Prebreathing for space flight

Based on the early data, the decompression to the space cabin in the Mercury, Gemini, and Apollo missions required 3 hours of oxygen breathing prior to launch. The cabin pressure was 5 psi and the decompression from sea level pressure during launch provided a greater possibility of DS than did the later decompression to space suit pressure which was 3.7 psi. The cabin atmosphere was 100% oxygen during these programs once the spacecraft was in orbit. During the Skylab Program, the cabin atmosphere was 70% O_2 and 30% N_2 with a total pressure of 5 psi. However, the

crewmembers breathed 100% oxygen in the Apollo module on the way to dock with the Skylab. The low PN_2 in the Skylab did not cause a DS problem during the decompression to the 3.8 psi suit. Although no reports of DS were made during flight, one crewmember described having a significant knee pain on Gemini and Apollo flights (9).

Prebreathing for Shuttle involved a different problem. Since a normal earth atmosphere at sea level is used, the EVA crewmembers must denitrogenate in the cabin prior to EVA. This situation prompted NASA to study various aspects of the prebreathing scenario. Studies by both the U.S. Air Force and NASA caused concern about air breaks in the prebreathing process (10,11,12). If the EVA crewmember was to denitrogenate by breathing from a mask, it would be possible for him to break the prebreathing during the transition from mask to suit. The alternative was to either prebreathe in the space suit or to investigate a staged decompression wherein the entire spacecraft cabin would be reduced to a pressure between sea level equivalent and that of the suit. Although the "straight prebreathing" in the suit is still an option, the latter course of action was chosen and several investigations of candidate procedures were made both by our laboratory at the Johnson Space Center (JSC) and that of the USAF School of Aerospace Medicine (SAM) at Brooks AFB. The staged decompression procedure involved a decompression of the cabin from sea level to 10.2 psi and is illustrated in Figure 1. This was one of the protocols tested and is the one chosen for use in the Shuttle Program.

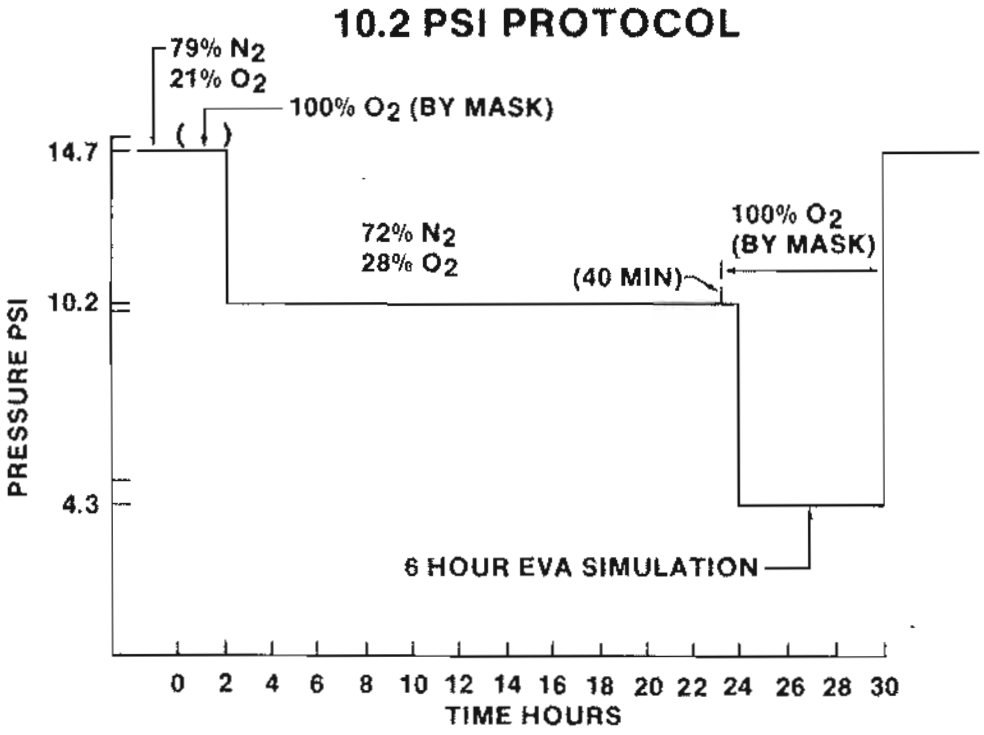

FIGURE 1. DECOMPRESSION PROTOCOL TESTED FOR SHUTTLE

As previously reported (6), we used a precordial doppler to detect intravenous gas bubbles. The subjects were instructed to report any symptoms immediately; in addition, they were periodically questioned as to whether they had any DS symptoms. The subjects were selected to match the astronaut population as closely as possible in age and body fat content. Figure 2 combines the data from NASA JSC and USAF, SAM; and it illustrates the percentage of venous gas emboli (VGE) and DS as a function of tissue ratio (estimated 360 minute tissue PN_2 to simulated suit pressure). The ratio used in Space Shuttle and planned for Space Station are depicted on the graph by vertical lines drawn at the appropriate ratios. The lowest line on the graph estimates types of symptoms which would potentially cause an abort of an EVA. The middle line shows symptoms of mild pain or joint awareness. The Space Shuttle Decompression Procedure, as tested, is approximately equivalent in terms of estimated denitrogenation to 4.0 hours of breathing 100% oxygen.

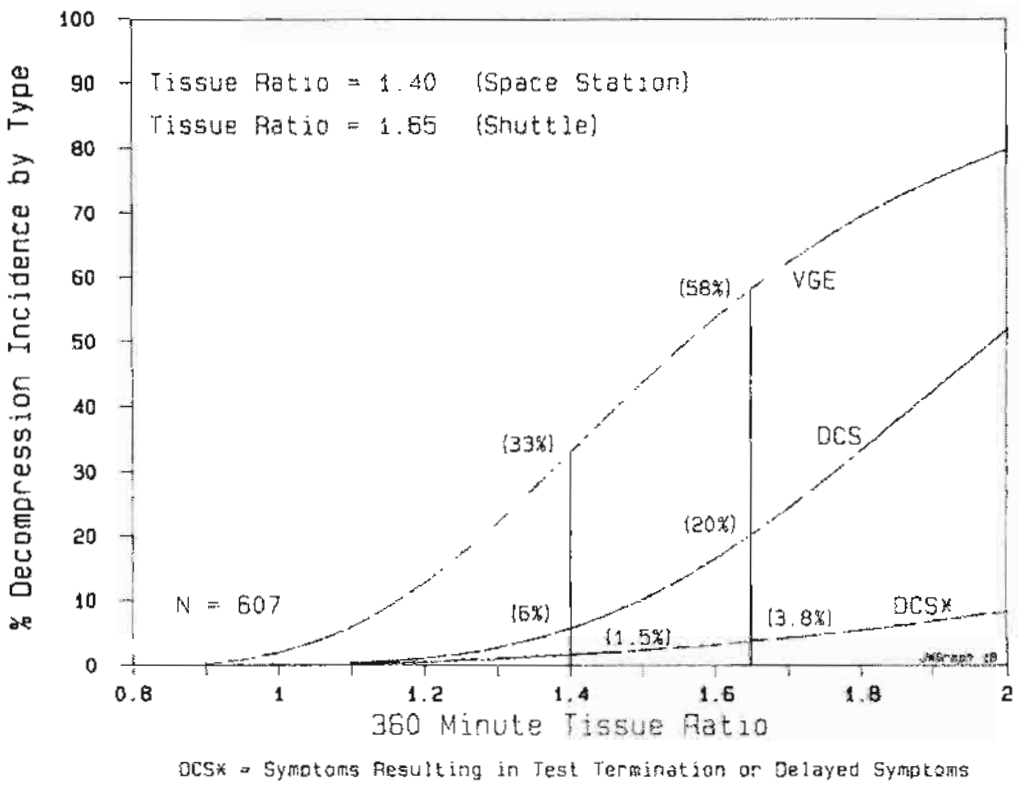

FIGURE 2. COMBINED DECOMPRESSION DATA vs TISSUE RATIO

Extended oxygen prebreathing and decompression studies without prebreathing have been done recently at NASA JSC and USAF SAM respectively (7,13). In Table 2 we compare the data on bubbles and symptoms of extended oxygen prebreathe studies (6 and 8 hours of oxygen before decompression) with our previously reported data on 3.5 and 4.0 hours of prebreathing. This study was done to complete the data on oxygen breathing prior to hypobaric decompression and to define the decompression ratio at which no

bubbles or symptoms occur. The USAF study used no prebreathing in an attempt to define the pressure at which no bubbles and no symptoms occur. In Table 3 we compare the data from the two laboratories using a common decompression ratio of 1.2. These data now give us a cogent basis for predicting the risk of DS, at EVA work rates, for selected decompression ratios based on either oxygen breathing or staged decompression. The values are also considered reliable only for the population tested.

TABLE 2

ONSET AND SEVERITY OF BUBBLES AND SYMPTOMS AS A FUNCTION OF TIME OF O_2 PREBREATHE

	HOURS OF O_2 PREBREATHING			
	3.5	4.0	6.0	8.0
$\bar{X}$ TIME OF 1ST SYMPTOM REPORT (MIN)	138	141	211	0
$\bar{X}$ TIME OF 1ST BUBBLE DETECTION (MIN)	119	73	159	0
$\bar{X}$ BUBBLE GRADE AT 1ST DETECTION	2.3	2.5	2.4	0
$\bar{X}$ MAXIMUM BUBBLE GRADE	3.3	3.8	3.0	0
N =	23	28	38	8

TABLE 3

COMPARISON OF STUDIES USING DECOMPRESSION RATIO OF 1.2

USAF S.A.M.			NASA J.S.C.	
DECOMPRESSION (PSI)	14.7 TO 9.5		10.2 TO 6.0	
	NUMBER	%	NUMBER	%
N	31		29	
MILD BUBBLING (GRADES 1 & 2)	4	13	2	7
SEVERE BUBBLING (GRADES 3 & 4)	0	0	1	3
SYMPTOMS OF DCS	0	0	1	3

Precordial Doppler Grade and Decompression Sickness

During our altitude decompression studies, we used precordial doppler and graded the results according to Spencer (14). As previously reported (6), each subject is monitored every 15 minutes by laying on a cot and flexing his four limbs sequentially while a technician holds the sensor in place. This procedure is the same as that used by Adams in acquiring the USAF data. Except for the doppler monitoring period, the subjects are engaged in continuous low level upper body exercise for the rest of the period at altitude.

During the oxygen prebreathe studies of 3.5, 4.0, 6.0, and 8.0 hours of oxygen breathing, both bubble and symptom incidence were determined and are shown in Figure 3. As we decrease the duration of oxygen breathing, there is an increase in both symptom and bubble incidence, but also an increase in the difference between the two percentages. At our operational values of 4.0 hours of prebreathing, all of those with DS had bubbles detected but only about half of those with bubbles showed symptoms. Those who have grade 1 or 2 bubbles are less likely to have symptoms than those who had grades 3 or 4 (15).

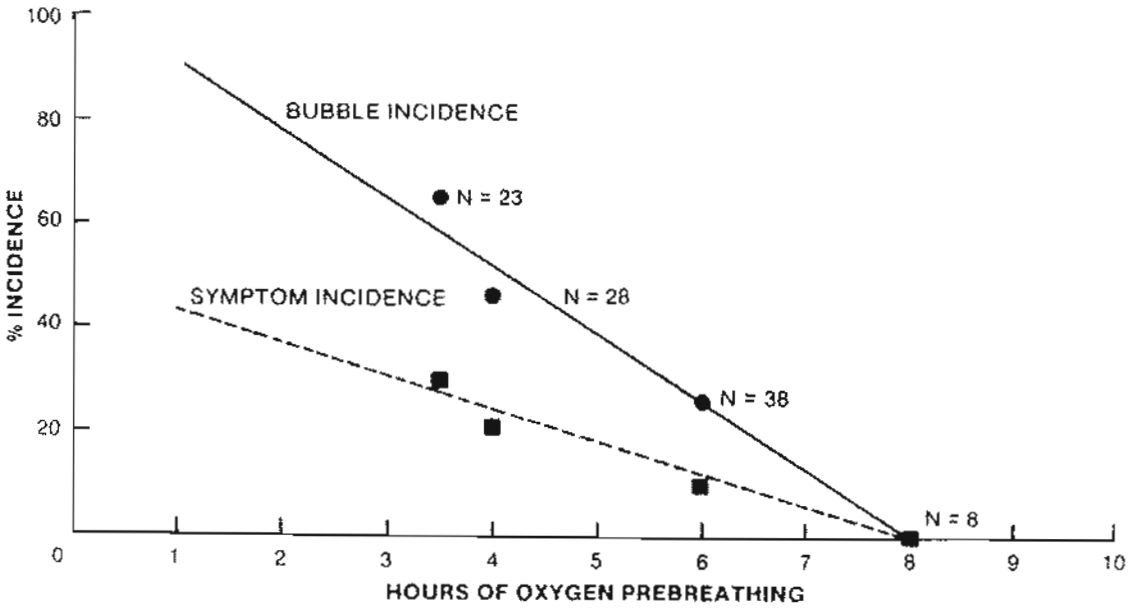

FIGURE 3. THE INCIDENCE OF VENOUS GAS BUBBLES AND SYMPTOMS OF DECOMPRESSION SICKNESS DURING SIMULATED EVA AT 4.3 PSI

anything that would modify gas exchange or the formation of a gas phase in blood and other tissues. Pulmonary studies yet to be conducted in space will investigate the effect of microgravity on ventilation, perfusion ratio, and other pulmonary function parameters. Nitrogen elimination studies are planned to investigate the effects of null gravity and time in space on this important parameter. Space Station plans, however, include a suit for EVA at a pressure of 8.3 psi which is expected to eliminate the need for prebreathing and reduce the hazard of decompression sickness. A hyperbaric chamber is included in the Space Station planning in the event of decompression sickness or air embolism. The "back up" pressure in the space suit is planned at about 6.5 psi in the event of loss of the primary system. Chamber tests are now planned to investigate this decompression from the sea level cabin with exercise representative of EVA.

Summary

Although we have not had any reported cases of decompression during EVA, ground studies have shown the potential for a significant amount of intravascular bubbles and mild bends cases. This has prompted a conservative approach to DS protection in future Shuttle missions and the Space Station. Precordial doppler has been useful in validating reported chamber results. Differences in susceptibility as a function of gender is not clear. However, conservatism in decompression procedures is expected to yield a low possibility of DS during EVA for both sexes. No in-flight research has been done to investigate the effects of the space environment on DS. However, the changes in physiological functions would suggest several areas where gas exchange and pressure effects should be studied.

Nitrogen Elimination, Venous Gas Bubbles, and Decompression Sickness Symptoms in Males and Females

Bassett, in a retrospective study, had reported an increase in incidence of reports from females undergoing altitude chamber runs (16). Dixon reported females to have more delayed DS symptoms requiring hyperbaric treatment than male subjects under the same experimental conditions (17). Some differences in nitrogen washout data between the sexes were noted in our laboratory and reported in 1987. These differences were not statistically significant (18). Further data and normalization of body size is needed to determine whether there is a gender related difference in nitrogen elemination (19,20).

Operationally the Space Shuttle decompression procedures have recently been modified to provide greater protection by requiring 24 hours of equilibration to the reduced pressure of 10.2 psi prior to EVA. The Procedure is being used for both male and female crewmembers. If a gender related difference is found to exist in susceptibility, our goal is to have an operational procedure that will provide an acceptable level of protection for both genders.

Microgravity Effects and Decompression Sickness

Adaptation to a new environment with its accompanying physiological changes prompts us to consider whether any of these changes affect the etiology of DS or the effectiveness of our preventive measures. Table 4 lists some of the issues being investigated with the goals of further understanding and the development of appropriate countermeasures (21).

TABLE 4
ISSUES CONSIDERED IMPORTANT FOR
HUMAN ADAPTATION TO THE SPACE ENVIRONMENT

BONE LOSS
MUSCLE REMODELING
MOTION SICKNESS
CARDIOVASCULAR AND PULMONARY CHANGES
RADIATION EFFECTS
CHANGES IN RED BLOOD CELL MASS
FLUIDS AND ELECTROLYTES
ABILITY TO CARRY OUT EXTRAVEHICULAR ACTIVITIES

Large losses of water including plasma volume and an accompanying redistribution of fluid to the head, neck, and trunk occur. Although there is a decrease in leg volume, leg blood flow is increased. Areas that would concern us in assessing decompression hazards would be, of course,

References

1. Fulton JF. Historical introduction. In: Fulton JF, ed. Decompression sickness. Philadelphia & London. WB Sanders Co, 1951:437.

2. Armstrong HG. Principles and practice of aviation medicine, first ed. Baltimore, MD: Williams and Wilkins, 1939:496.

3. Boothby WM, Lovelace WR, Benson OO. High altitude and its effect on the human body. J. Aero Soc Amer 1940; 7:1.

4. Behnke AR, Welham W, Yarbrough OD. The value of preliminary oxygen inhalation for the prevention of decompression sickness during high altitude flight. US National Research Council (NRC, CAM) Committee on Aviation Medicine, Dec 1942, Report No. 114.

5. Allen TH, Maio DA, Bancroft RW. Body fat, denitrogenation and decompression sickness in men exercising after abrupt exposure to altitude. Aerospace Med 1971; 42(5):518-524.

6. Waligora JM, Horrigan, DJ Jr, Conkin J, Hadley AT III. Verification of an altitude decompression sickness prevention protocol for Shuttle operations utilizing a 10.2 psi pressure stage. NASA Johnson Space Center 1984; Technical Memorandum 58259

7. Waligora JM. The effect of extended O_2 prebreathing on altitude decompression sickness and venous gas bubbles. Aviat Space Environ Med 1987; 58(9, Suppl): A110-112.

8. Robinson TW, Donnelly DP. High altitude tolerance tests. US NRC, Committee on Aviation Medicine, May 1944 Report No. 316.

9. Collins M. Carrying the flame. New York: Farrar 1974:368.

10. Cooke JP. Denitrogenation interruptions with air. Aviat Space Environ Med 1976; 47(11):1205-1209.

11. Adams JD, Theis CF, Stevens KW. Denitrogenation/renitrogenation Profiles: interruption of oxygen prebreathing. Aerospace Medical Association Proceedings 1977.

12. Horrigan DJ, Wells CH, Guest MM, Hart GB, Goodpasture JE. Tissue gas and blood analyses of human subjects breathing 80% argon and 20% oxygen. Aviat Space Environ Med 1979; 50(4):357-362.

13. Dixon GA, Adams JD, Harvey WT. Decompression sickness and intravenous bubble formation using a 7.8 psi simulated pressure suit environment. Aviat Space Environ Med 1986; 57:223-228.

14. Spencer MP, Clarke HF. Precordial monitoring of pulmonary gas embolism and decompression bubbles. Aerospace Med 1972; 43:762-767.

15. Horrigan DJ, Waligora JM, Hadley AT III. Doppler measurements of intravenous gas bubbles during 6 hours of exercise at space suit pressures. Aerospace Med Assn Scientific Program, 1984.

16. Bassett BE. Twelve year survey of the susceptibility of women to altitude decompression sickness. Aerospace Med Preprints 1980; 12-13.

17. Dixon GA, Krutz RW. Female susceptibility to decompression sickness and bubble formation using a simulated 7.8 psi suit environment. Abstract of paper presented; Aviat Space Environ Med 1986; 57(5):511.

18. Waligora JM, Horrigan DJ, Conkin J, Gilbert JH. Incidence of symptoms and venous gas bubbles in male and female subjects after decompression. Abstract of paper presented; Aviat Space Environ Med 1986; 57(5):511.

19. Edwards BF, Gilbert JH, Horrigan DJ, Waligora JM. Dynamics of whole body nitrogen washout while breathing 100% oxygen. Abstract of paper presented; Aviat Space Environ Med 1987; 58(5):516.

20. Edwards BF, Waligora JM, Horrigan DJ Jr. Statistical comparison of pooled nitrogen washout data of various altitude decompression response groups. NASA Johnson Space Center 1985, Technical Memorandum 58265.

21. Nicogossian AE, Parker JF. Overall physiological response to space flight. In: Nicogossian AE, Parker JF, eds. Space physiology and medicine. National Aeronautics and Space Administration, 1982; NASA SP-447.

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DISCUSSION

DR. HAMILTON: Mr. Waligora, have you seen any difference in the decompression pattern of people in weightlessness versus those tested at sea level gravity?

MR. WALIGORA: We have had no report of symptoms in our 26 EVA flight exposures, and we have not measured for bubbles.

DR. HAMILTON: Do you believe that no decompression sickness has occurred in EVA?

MR. WALIGORA: That's a hard question. Many of the symptoms that we see in our chamber tests are very mild and, in fact, there seems to be a continuum down to almost nothing. Many symptoms we have reported would probably be difficult to notice in a pressure suit where you have all kinds of discomfort. Some of the more significant symptoms, I suspect would be noticed, but these symptoms in most cases are very mild pain such as people have experienced before in normal life. Thus, if you had something that wasn't too serious, you wouldn't know if it was decompression sickness or not. There may also be some real differences in the activity in the suit versus our unsuited simulations. That might influence the incidence of decompression sickness.

CAPTAIN THALMANN: You quoted a study of decompression from 1 ATA to 9.5 psia in which bubbles were detected. Did you have symptoms?

MR. WALIGORA: There was one incident of symptoms at going to 9.5 psia and one incident out of 30 going to 8.3 psia.

CAPTAIN THALMANN: How many people were in the 9.5 psia series?

MR. WALIGORA: Well, the 9.5 psia exposure was part of a pilot study where the Air Force was using people who were particularly susceptible. I don't remember how many people were in it because it wasn't my study, but the symptoms were mild.

CAPTAIN THALMANN: You also showed that the incidence of bends decreased linearly with the time of oxygen prebreathing.

MR. WALIGORA: We plotted it that way, and it seemed to be fairly reasonable.

DR. FRANCIS: Have you had any incidence of central nervous system decompression sickness in all these trials with so much bubbling?

MR. WALIGORA: We had one serious symptom, I believe it was a systemic hit, in one of our early exposures to the 10.2 psi protocol. The subject started bubbling and had early limb bends symptoms in one knee very soon after we did the second decompression from 10.2 to 4.3 psi. Later in the test he had a rapid onset of extreme fatigue, a cold clammy feeling, and mottling of the chest. The symptoms disappeared during recompression to sea level, except for the mottling, which disappeared in about 5 minutes. Our test surgeon and I were not certain that it was a CNS hit. We consulted by phone with the hyperbaric personnel at the School of Aerospace Medicine and, based on the recommendations at the time, we did not treat him immediately in the hyperbaric chamber. We maintained him on O_2 and transported him to the hyperbaric chamber where he breathed O_2 for 4 hours. He had no recurrence of symptoms. He was given a neurological exam, which was negative, observed for 12 hours and then released. We had some other individuals, undergoing the same early staged decompression protocol, who also had heavy bubbling very early after the second decompression. Based on that, we incorporated a 1-hour prebreathe in later protocols before the decompression from 14.7 to 10.2 psi to make sure that

we did not form silent bubbles at 10.2 that would sit there and be ready to expand on going to 4.3 psi.

DR. FRANCIS: So, you've had no cases of paralysis or anything like that?

MR. WALIGORA: No.

DR. MASUREL: I would like to comment about the possibility of increasing DCS susceptibility and bubble formation as a result of using Doppler bubble detectors. I'd like to say definitively that we have tried to produce bubbles with Doppler and found it's not possible. The French Doppler normally uses an electric power of about 140 milliwatt. This represents an acoustic power of 40 milliwatts, but with refraction and the absorption in tissue, the acoustic power at the heart is just 4 milliwatts. We tried to cause bubbles to form by using 4 watts of ultrasonic energy at the same frequency. This is a thousand times more energy than the bubble detector uses, but no bubbles formed.

MR. WALIGORA: That's good, but I didn't mean to imply that Doppler causes bubbles to form. I was talking about predicting the DCS incidence from the incidence of bubbles, but it's good to know that Doppler won't form bubbles.

DR. BALLDIN: Are you also interested in reducing the preoxygenation time and in increasing the nitrogen elimination rate?

MR. WALIGORA: Yes.

DR. BALLDIN: You told us that there are cardiovascular and hemodynamic effects in microgravity which may increase the circulation but might be transient. Have you considered using other methods to augment nitrogen elimination, such as increased body temperature, drugs, or, as we discussed yesterday, reduced pressure. Perhaps a shift to another gas mixture such as helium/oxygen instead of a 100% oxygen to reduce oxygen-induced vasoconstriction. On the other hand, that might increase the risk of counterdiffusion.

MR. WALIGORA: We've considered some of these ideas and we're sponsoring some research such as that of Dr. Vann and Dr. Gerth. I'm interested in your comments. If, in fact, we identified promising procedures, we would verify them in chamber tests.

DR. BALLDIN: Can you speculate about whether microgravity causes increased cavitation that could lead to a greater risk of decompression sickness in space.

MR. WALIGORA: You probably don't get as much tribonucleation, at least in joints, but I don't know if that is of any significance.

DR. YOUNGBLOOD: I noted with interest the difference in the incidence of symptoms versus bubbles in females. These were not lady astronauts but local volunteers at Johnson Space Center?

MR. WALIGORA: It's true they're local volunteers and not astronauts, but we did try to match the level of physical activity and percent of body fat.

DR. YOUNGBLOOD: I wonder if asymptomatic mitral valve prolapse in a group of females of that age might induce cavitation that would become more prevalent in microgravity. A greater concern, however, is repetitive EVA decompressions such as in surface oxygen decompression day after day where the DCS incidence increases rather than decreases. Perhaps this reflects a loss of surfactant in the lung and a decrease in the lung's ability to filter the bubbles. You've shown on your protocol that you have bubbles. If surfactant is lost, you might expect more problems

later. Have you had the opportunity to expose the same subjects to a multi-week EVA operation?

MR. WALIGORA: No, but we have done a 3-day exposure at 10.2 psia where we did 6 EVA's, two each day. We observed the bubble level to decrease from the first day to the second and third days. There were no bubbles or symptoms on the second EVA of each of the days. Thus, for that relatively short period of time, there doesn't seem to be an increased incidence on repeated exposure for the protocol that we'll be using with Shuttle operations. When we go to Station we'll have a more protective protocol, but I don't plan on doing a 6-month repeated exposure chamber test at this time.

DR. YOUNGBLOOD: It's usually between the third and fourth week that we see an increase in bends.

DR. VAN LIEW: I was impressed by the good fit of your dose-response curves, but I want to be sure I know what you plotted. Was that the over-pressure in a particular tissue at the time of the decompression?

MR. WALIGORA: That's right. It was based on a calculation for a 360-minute half-time tissue.

DR. GERTH: Dr. Balldin, our studies that Mr. Waligora is sponsoring are directed at answering some of the questions you raised. During EVA, however, the prebreathes are done in zero-G adapted man. We are attempting to assemble baseline data as best we can using head down tilt to simulate microgravity. We need to find if factors that augment nitrogen elimination in a one-G adapted man are as effective after the zero-G adaptations occur. We haven't used drugs or gas exchanges yet, but exercise during prebreath has proved effective at accelerating nitrogen elimination and protecting against DCS. Zero-G adaptation is a central issue here, and it will be very interesting to get nitrogen elimination profiles from people in microgravity who have undergone various stages of adaptation.

DR. KINDWALL: Mr. Waligora, what would happen after the initial decompression to EVA in the catastrophic situation of a total loss of suit pressure and emergency rescue is necessary? During EVA on the moon, the astronauts were totally denitrogenated and should catastrophic decompression have occurred, they would have had no nitrogen in their bodies at the time of decompression to absolute vacuum. The space station will be run at 14.7 pounds, however, and even with some preoxygenation, nitrogen will be present in the body during EVA. It would be very interesting to do an animal study to determine the difference in survival between total and partial denitrogenation. The survivals from ebulism have been remarkable. Ebulism is the elaboration of all gases dissolved in tissue including oxygen, nitrogen, carbon dioxide, and water vapor. Would survival be even more remarkable if all nitrogen had been removed? This might reflect on both design and operational considerations and might save money in the long run.

MR. WALIGORA: I don't know of any exposures that have been conducted on animals with nitrogen elimination prior to embolism. That would be very interesting.

DR. LEHNER: Mr. Waligora, have you observed signs and symptoms that would be indicative of mild chokes such as fatigue or dyspnea.

MR. WALIGORA: No.