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Some Theoretical Aspects of the Use of Inert Gases in Sealed Cabin Environments

For the past several years, sealed cabin environments have held the attention of those interested in the field of space operations. One of the major functional requirements of the cabin is the maintenance of an optimum gaseous environment. A sealed cabin presents to the   or rocket designer, an opportunity to maintain the human passenger in an environment which utilizes gases other than nitrogen as a diluent of oxygen. In this paper, I wish to review the physiological aspects of non-nitrogen environments as they affect climatization of sealed cabins.

The inert gases which are available as oxygen diluents are He, Ne, A, Kr, Xe, Rn, and N_2. Radon is a radioactive gas and can be eliminated as a potential cabin gas. The properties of these gases which will be considered in this paper are tabulated in Table I.

Insert Table I here

The factors to be considered in the use of inert gases other than nitrogen in sealed cabin environments are:

1. Effects on decompression sickness
2. Physiological side effects of the gases
3. Logistic considerations

I. Decompression Sickness

One of the major factors to be considered in space flight is the potential hazard of spontaneous failure of the cabin wall or meteoritic penetration and subsequent decompression of the cabin. Pressure suits may well protect crewmen in the cabin, but at best, a pressure environment of only 40,000 foot equivalent is afforded by these suits.

In most cases, the cabin will be at less than one atmosphere pressure. There is a possibility, however, that the major weight penalty of a cabin wall may be determined not by pressure differences but by stresses of takeoff and landing and a one atmosphere cabin possible from an engineering point of view. Crew members will, therefore, be decompressed from sea level up to 25,000 feet cabin altitude to a 40,000 equivalent and will be exposed to the hazards of decompression sickness. Maximum cabin altitude of 25,000 feet will present to the crewman a potential exposure to decompression sickness only in the early phases of his trips, prior to his attaining full equilibrium with an environment of low nitrogen tension. It would thus appear desireable to choose a diluent gas which will reduce to a minimum, the hazards of decompression to 40,000 feet.

Current physical theory of the origin of pain and other symptoms of decompression sickness has been summarized by L. F. Nims (32). A gaseous bubble growing in tissue must displace and deform adjacent structures to produce pain. The equilibrium forces acting on the bubble within the tissue may be given by the expression:

(1) $P_B = H + (2O/r) + D.$

Where

P_B = sum of the partial pressures of the gas

H = hydrostatic pressure of the fluid surrounding the buble and independent of the size of the bubble

= gas-water interfacial tension

r = radius of bubble

D = deformation pressure of bubble, a function of bubble volume. When the mechanical deformation D, exceeds a given threshold value, nerve endings are stimulated to produce pain sensations and tissues are pathologically deformed to produce the symptom complex in question.

In order to demonstrate the effects of mulitple gases on this deformation pressure, we must expand equation #1 to

$$(2)\quad P_{N_2} + P_{CO_2} + P_{O_2} + P_X + P_{H_2O} = H + \left(\frac{2}{r}\right) + D$$

Where

P_{N_2}, P_{CO_2}, etc. are partial pressures of respective gases within the bubble and P_x = partial pressure of any other inert gas.

The symptoms of decompression sickness, therefore, are independent of the numbers and types of gases present in the bubble, but are dependent only on the sum total of partial pressures. In our analysis, we can assume the P_{O_2}, P_{CO_2}, and P_{H_2O} are rather constant in any one given tissue site and so only P_{N_2} and P_x need be dealt with as far as environmental gases are concerned. W.L. Burkhardt (11) demonstrated that while exercise or elevation of CO_2 production increases the severity of decompression sickness, hyper-ventilation or decrease in CO_2 tension decreases symptoms. Since changes in partial pressure of CO_2 change the total pressure in the bubble, these findings are not inconsistent with the multiple gas hypothesis. The report by L.F. Nims[32] of a patient of W. G. Lennox, who suffered a mild case of decompression sickness after decompressing from a high oxygen environment is also in keeping with the multiple gas hypothesis. However, the relatively small partial pressure contributions of CO_2 and O_2 reduce their significance in this analysis of the problem.

Whenever the free hydrostatic pressure (H) is reduced, we can expect the occurrence of two physical processes in the body. The first is the diffusion of local gases into a cavitation nucleus produced within the tissue by pressure pulses of muscular activity and thence into the resulting bubbles as hypothesized by E.N. Harvey(20). The second is the desaturation of tissue gases via the blood and lungs.

Let us analyze each of these factors. The tendency to enlarge a gas bubble is determined by the pressure head P, the difference between the dissolved gas tension and the local hydrostatic pressure P. Numerically, then, $P = - P$. If, as in an altitude decompression, increase in P results from a decrease in hydrostatic pressure, the factor determining the rate is largely the inertial resistance of the water. Gas molecules therefore, move into the large water vapor cavity of the cavitation nucleus from the surface of the cavity in proportions that depend on the solubility of the gases rather than their partial tension. With the passage of time, one would expect the composition to change to those proportions of gas representing tensions rather than gas solubility.

As seen in Table I, the solubility coefficients of the gases in question (volume of gas when reduced to STP absorbed by one volume of water when the pressure of gas = 760 mm H_2O) increase with molecular weight.

The value of nitrogen lies between neon and   One would expect a bubble formed in water orignally in equilibrium with equal tensions of the above gases to first contain gas in proportion to the solubilities, and then, as diffusion directs, in equal proportions.

The rate of growth of a bubble and most probably the rate at which bubble gas proportions assume those representing gas tensions is determined by the following equation outlined by E.N. Harvey[20].

$$(3) \quad \frac{dr}{dt} = \frac{RT \times D}{r} \quad \frac{P}{P} \quad \frac{(r - 2 \;/\; P)}{(r + 4 \;/3P)}$$

where

$\frac{dr}{dt}$ = rate of increase of radius r in cm; t in seconds

R = gas constant in ergs/degree C./mole (8.3136×10^7).

T = absolute temperature o.k.

= solubility in moles/dyne.cm

D = diffusion coefficient cm^2/sec

r = thickness of diffusion shell (3 x 10 - 3 cm) If r = 3×10^{-3} cm, r = r

P = hydrostatic pressure in dynes/cm

P =   -P = dynes/cm^2, where   = gas tensions in the tissue

+ surface tension in dynes/cm.

It would thus appear that a gas with physical properties such as would offer a minimum product of solubility and diffusion coefficient (x D) would present a minimum rate of bubble growth.

The other major factor in controlling the history of bubble size is the rate of desaturation of tissue gases via the lungs. R. E. Smith (35) and M. F. Morales(31). have made a theoretical analysis of this deday factor by assuming that the exchange of dissolved inert gases between tissue and blood is controlled by five physiological parameters (1) oil-water solubility ratio of the gas, 2) tissue blood volume, 3) tissue volume 4) permeability of tissues and 5) rate of blood flow. They weighed these factors: Tissue penetration - 68 percent blood; blood and tissue volume - 5%; fat partition - 20 percent, and rate of blood flow 7 percent. H. Jones (25), on the other hand, has demonstrated that the time constant of gas exchange as determined by these factors depends mostly on the tissue perfusion factor or rate of blood flow and the partition coefficient between blood and tissues and that these account for 90 percent of the value of the time constant. H. Jones,[26] demonstrated this concept experimentally when they showed that time constants such as those of radioactive nitrogen, krypton and argon uptake by the hand were remarkably similar. Time constants obtained from data on whole body exchange of helium nitrogen, krypton and xenon were also similar. The amounts of noble gases eliminated in each case are in good agreement with the calculated amount on the basis of solubility in body tissue and on the uptake during saturation periods as predicted by known time constants for the subject's gas exchange. Were diffusion or permeability factors limiting gas exchange, H. Jones pointed out, the results would be influenced by predicted diffusion rate of the gas in question which is proportional to the reciprocal of the square root of the molecular weight. In spite of a tenfold range in relative diffusion rates (Table 2) (helium 1.0 to xenon o.13), results in gas exchange rates for the body give similar time constants, and the amounts of gas so exchanging can be predicted from solubility in body tissues. These data imply that diffusion rates of these gases are very rapid over such barriers as may exist at tissue or lung level compared to the relative rate of movement of blood through the capillaries in these areas. Fib. (1) is a graph showing the simultaneous elimination of nitrogen and radioactive xenon from the whole body and the independence on diffusion of the two gases. No report on the time constant is available for neon but one can assume no dependence on diffusion. Thus we see that whereas the rate of entry of gas into the bubble is controlled by gas diffusion and tissue solubility factors, the time constant governing exchange of gas between tissues and alveolar air is, for all practical purposes, independent of diffusion and dependent only on the tissue/blood solubility ration and rate of flow of blood through the tissues.

The complexity of the present analysis of factors affecting bubble history is augmented by a key difference in the formulas which have been derived to describe bubble growth. Formula (3) of Harvey utilizes solubility of gases as a factor as does the formula discussed by Bateman (4) which is:

$$(4) \quad \frac{dV}{dt} = 4 \quad a(\quad) \; \frac{T\,(P_t - P_1)}{273}$$

where

V = volume

t = time

a = radius

= absorption coefficient

= diffusion coefficient

p = gas pressurewhich would be in equilibrium with dissolved gas

P_1 = partial pressureof gas in bubble

P = Total pressure in bubble and equals hydrostatic pressure around a bubble large enough to satisfy the condition

where = interfacial tension.

Deviation of this formula is after H. Mache(30), but this paper was not available to this writer. The formulas of J. B. Bateman and E. H. Harvey are essentially similar with respect to diffusion and solubility factors.

The formulas proposed by L. F. Nims(32), however, do not include gas solubility as a factor in rate of bubble formation. This author proposed that the differential equation describing the rate at which nitrogen enters a bubble is

$$(5) \quad dP_{N2}/dt = k_2^1 \, SB \, (P_t - P_{N2})$$

where

P_{N_2} = partial pressure of nitrogen in the bubble of time t

k' = apparent diffusion constant for transfer of nitrogen from tissue to bubble

S_B = surface area of bubble

Pt = partial pressure of nitrogen in tissues at time t

Solubility of gas does not enter into this equation or in subsequent analysis of the history of a bubble. Validity of the equations proposed by Nims is strengthened by the author's attempt to correlate the history of a bubble with the history of decompression sichness in a large population exposed to altitude in a pressure chamber. It is common experience that immediately after ascent the rate of production of symptoms is very low. The rate then increases, reaching a peak from 20 to 60 minutes and then declines to practically zero. It has been shown that an individual can sit out the symptoms and will be free of symptoms after a given period at altitude. The data of R.A. Antony et al (1) and F.M. Henry(22) (23) tend to illustrate this rate of onset of symptoms. The data of R.A. Anthony et al[1] is plotted in Figure 2, and shows the peak at 20 minutes to be rather well marked. J. H. Lawrence and J.G. Hamilton[27] have demonstrated that the rate data of symptoms in a larger population follows the formula

$$\frac{d\left(\frac{N_s}{N}\right)}{dt} = A_1 e^{-k_1 t} - A_2 e^{-k_2 t}$$

Where

N_s = number of symptoms

N = population exposed to altitude

t = time

A_1 and A_2 are constants relating to maximum potential intensity of symptoms

k_1 = velocity constant of "growth factor"

k_2 = velocity constant of "decay factor"

L.F. Nims[31] has pointed out that this equation is very similar in form to his equation which describes the history of a single bubble of constant size and increasing pressure.

$$d\,\frac{N_s/N}{dt} = C(D-D^*) = C(P_{N_2} - P_{N_2}{}^*)$$

$$= C\frac{\quad}{\quad}$$

Where

C = constant of proportionality

D = deformation pressure in tissue produced by bubble

D^* = deformation pressure in tissue at threshold of pain

$(D-D^*)$ = measure of stress to which the population is exposed

P_{N_2} = partial pressure of nitrogen in bubble causing deformation.

$P_{N_2}{}^*$ = partial pressure of N_2 in tissues when deformation pressure reaches threshold or when $D = D^*$

t = time

k_2 = "apparent" diffusion constants between tissues and alveolar air

k_1 = "apparent" diffusion constants between tissues and alveolar air

${}_oP_t$ = partial pressure of nitrogen in tissue fluids prior to decompression

Nims points out that this theoretical equation, which relates group symptoms to bubble history, can be reduced to the empirically derived equation of Lawrence and Hamilton by the addition of small constant term $CP_{N_2}{}^*$ and the inclusion of $Ck_{2\,o}P_t/(k_2 - k_1)$ in the constant A_1 and the inclusion of $(A_1 - CP_{N_2})$ and in the constant A_2.

Thus we see that the equation of Nims has experimental validity and yet no solubility factor is employed. However, closer inspection of the constants k_1 and k_2 indicates that they are "apparent" diffusion constants of gas into the bubble and "apparent" diffusion constant governing exchange of tissue nitrogen between tissues and alveolar air. It appears most probable that the k_2 of Nims represents the (   ) product of Harvey or the (   ) product of Bateman. Nims also states on page 205 of reference(32) that k_1 represents the "time constant of Jones" (25), which in turn depends on both tissue blood flow and tissue blood solubility ration of the gas in question.

From the above review it appears that the analysis of enert gases within a tissue bubble during decompression episodes is a valid method of interpreting the tendency of a gas to caase symptoms in a given population. It also indicates that the bubble growth factor (XD) of a gas is the important consideration in determining growth of a bubble while the tissue/blood solubility ratio is the only gas factor to be considered in the decay phase of the bubble. The tissue/blood solubility ratio will vary for each tissue as will the X D factor, depending on percent fat or water in the tissue in question. If we assume that the areas of the body most critical as far as serious decompression symptoms are concerned are fatty, we should consider the oil D oil as the most important growth factor and the oil/water solubility ratio ( ) as the most important decay factor. As reported by A.R. Behnke and O.D. Yarborough(6), the solubility of helium in blood is only one percent higher than the solubility in water and that of nitrogen only 1-2 percent higher. The solubility of inert gases in oil is also within several percent of their respective solubilities in body fat. Substitution of solubility in water for solubility in blood and solubility in oil for that in fat does not seem unreasonable. It is rather difficult to determine the relative importance of and in analyzing the growth of critical bubbles. Weighting this product to cover the fact that the body is 14 percent fat is far from adequate. The importanve of fat is far greater than its percentage of body weight since the fatty tissues appear to be involved in severe decompression episodes and fat is the only tissue seen to have many microscopic bubbles during animal studies[18]. The

will therefore be used in analysis of the optimum gas. Since that gas with the lowest will be that which is most readily lost from the tissue to the blood and lungs, the overall factor determining minimum bubble size would be

That inert gas with the lowest bubble factor should produce the mildest of symptoms on decompression.

Table I demonstrates the average of measurements of solubility in water and oil presented in the literature and reviewed recently by J.H. Lawrence et al[28]. Both the water and oil solubilities increase with molecular weight. No figures are available for the of neon at 38° and so interpolation was made between the values for Helium and Nitrogen using molecular weight as a baseline. Extrepolation of oil solubility data from water solubility is not valid as shown by D.D. Van Slyke et al[38]. The oil/water solubility ratio of neon was calculated from the experimental value of water and the interpolated

$_{oil}$. The relative diffusion of these gases through oil was not available in the literature. The relative diffusion through gelatin (D_g) at 23° C was the only experimental value approaching D_{oil} and was therefore used in the calculations. These gases appear to follow Graham's law of diffusion which states that the rate of diffusion of a gas is inversely proportional to the square root of the density or molecular weight. The relative diffusion of Neon through gelatin was therefore determined by comparing it with helium which was given a value of 1. The relationship used was

The product of are recorded in Table II. Neon and Nitrogen have the lowest values at .0044 and .0047, respectively. The product of are also recorded in Table II. Helium has the lowest value at 0.18 with helium next at .021 and nitrogen and close by at .024. The bubble factor which is had to be converted to becuase no data on D_{oil} was available. The bubble factor as determined with D gelatin is recorded in Table II. The relative bubble factors with nitrogen = 1 is also recorded in Table II. These values indicate that the lowest bubble factor is that of He and the gas factors increase with molecular weight. It would therefore appear that from the standpoint of minimum bubble size, helium is better than nitrogen by a factor of 4.2, and neon is better than nitrogen by a factor of 1.3.

It is now of interest to review the medical literature on the use of inert gases in decompression phenomena and see how the gas factor predictions are substantiated in practice. Helium and the other inert gases have been studied in diving operations, but little work has been done at altitude. R. R. Sayers, et al[34] found that when animals inhaled helium-oxygen mixtures under increased pressures they could be decompressed safely in 1/4th to 1/3rd of the time required for safe decompression when nitrogen-oxygen mixtures were used. Hildebrand explained this advantage on the fact that helium was less soluble in water than introgen, more diffusible, and much less soluble in fat than is nitrogen.

It is of interest that the factor of one-fourth is almost that predicted by the ratio for He vs. N_2 which is recorded in Table II is 1/4.2.

In 1937, E. End(17) reported on the use of helium in human diving. Some divers were decompressed in as little as 1/23 that predicted by the air tables being used at that time. These air tables, however, were known to be very conservative.

In 1938, A.R. Behnke and O.D. Yarborough(6) reported on their experiences with helium in diving operations. Helium had been used to decrease the narcotic effects of high pressure nitrogen at depths greater than 300 feet. This gas allowed divers to descend to 500 feet (16 atmospheres) without intoxication. The difference between helium and nitrogen were attributed to the lesser fat solubility of helium. Table I demonstrates this difference as well as the difference in fat/water solubility ratio. An analogy was drawn comparing nitrogen with the alphatic hydrocarbons, the anesthetic activity of which, according to the Meyer-Overton Law appeared to be related to their ratio of solubility in fat compared with water.

Behnke noted in these studies, that there was an absence of grave symptoms of decompression sickness in a large number of divers who experienced bends. No cases of unconsciousness or paralysis were reported. Itching and skin rashes occurred without sequeleae and pains occurring in 1/3 of the cases were promptly relieved by decompression, unlike those in nitrogen diving which tended to persist. Behnke attributed the absence of grave symptoms to the low fat/water solubility ratio of helium as compared to nitrogen and to the fact that grave symptoms usually occurred in the fat rich nervous tissue. He further postulated that in diving operations employing helium, the important or controlling tissues during decompression were those which are relatively rapid with regard to saturation and desaturation, whereas with nitrogen the slow or fatty tissues are important.

Later work by A.R. Behnke and T.C. Willmon(9) added to our understanding of the relationship between the rate of body saturation with He and decompression. A helium desaturation curve was determined and the helium capacity of the body found to be 8.0 ± 1.3 cc/kg body weight when the tissues are in equilibrium with a helium alveolar pressure connected to 760 mm Hg. This figure is about 40 percent of the total nitrogen absorbed. They also found the time required to eliminate absorbed helium is 50 percent of the time required for nitrogen elimination. Relative rates of elimination are best seen in the following curve drawn by A.R. Behnke (Fig. 3)(8).

In diving operations, the duration of time at depth is an important value in predicting decompression sickness since the amount of gas dissolved in the body at depth is determined by these time saturation curves. When one compares the relative dangers of helium and nitrogen in decompression sickness, duration at depth need by considered. A.R. Behnke[10] reviewed these factors in the following manner. About 75 percent of total body nitrogen is eliminated from the bodies of lean men in about two hours, After exposure at the usual diving depths, this nitrogen is eliminated without causing symptoms. It is the small amount of gas dissolved in fatty tissue that requires many hours for elimination. Table III[10] demonstrates that air breathing depth of 90 feet, a 100 minutes of exposures requires a period of 57 minutes for decompression to avoid bends and other symptoms. At the same depth, a nine hour exposure requires about 12 hours decompression. If helium-oxygen mixtures are used instead of air, there is required no more than 79 minutes decompression time after all exposures at 90 feet. Behnke attributes this to the rapid rate at which the body saturates with helium.

If the lipid substances are responsible for the prolongation of nitrogen absorption or elimination, helium posessing a lower solubility coefficient in slowly perfusing fatty tissue should be eliminated in a shorter period of time. As previously mentioned helium leaves the body in about half the time required for nitrogen. R.E. Smith and M.F. Morales[35] have found that helium removal from the body can be predicted by only two exponential expressions as compared to the three required for nitrogen. Since the number of exponential expressions equal one more than the number of gas solvents in the body, it would appear that helium is released as if from one body solvent while nitrogen is released from two - fat and aqueous fluids. The low oil/water solubility ratio of 1.7:1 for He as compared to 5.24:1 for nitrogen and the slow blood perfusion of fatty tissue obscure the role of fat as a helium solvent. The rapid rate of diffusion of helium which Behnke calls on to explain the single solvent phenomenon has been shown by Jones[26] to be an insignificant factor in total body exchange of a gas. Table III also demonstrates that the decompression times required following short high pressure exposures in a helium oxygen atmosphere are actually longer than those required for air. Since danger of decompression symptoms are dependent on the content of gas in slowly perfusing fatty tissues, short exposures would limit the amount present, and would therefore present both nitrogen and helium with an apparent aqueous solvent. As was demonstrated in the theoretical analysis of bubble factors the gelatin growth factor is smaller for nitrogen (.0047) than it is for helium (.0086). If water were the only solvent, the would equal gelatin. This would explain why nitrogen is safer than helium on dives of short duration. This behavior of nitrogen and helium, therefore appears to be not inconsistent with the predictions in the theoretical analysis of the problem as presented in the first part of this paper.

Another test of this concept of inert gas exchange is available in a recent paper presented by A.P. Webster[39]. Theoretical aspects of multiple gas mixtures in diving are discussed and an analysis of the Navy Diving Tables for air and oxygen-helium mixtures is presented which indicates that there appears to be an optimum mixture of helium and nitrogen which minimizes the tendency towards decompression sickness. Curves were drawn by entering the U.S. Navy Standard and Helium Tables[38] and determining the time required for safe decompression from various depths of mixtures containing percentages of helium and nitrogen from 12 to 84 percent. The times are plotted against percent of each gas in such a way that in the abscissas, helium percentages are plotted with 12 percent at one end of the scale and nitrogen is plotted with 12 percent at the other end of the scale. Figures (4) and (5) demonstrate these curves. It can be seen that for the shorter dive (30 minutes) the summed curve (dotted) shows a more distinct minimum at a lower helium percentage. As the duration at depth increases, helium becomes the better gas and appears at a higher percentage in the optimum mixture at 60 minutes at which time the body is only 50 percent saturated[8] for that depth. Durations of air diving long enough for complete Nitrogen saturation, are not permitted by the Navy Talbes so that curves of very long duration are not available. It would appear that a summation of such curves would present a dotted line which had no distinct minimum and tended to be negatively sloping down through the entire mixture range with 80 percent He, 20 percent O_2 being the mixture offering minimum decompression time. There would probably be no optimum mixture under conditions of complete saturation.

I.H. Gersh, et al[18] have compared mixtures containing 20 percent oxygen and 80 percent nitrogen, helium and argon with that of 100 percent O_2 on their effects on microscopic changes in guinea pigs. After compression in small chambers for 60 minutes at 30 to 105 psi ,the animals were decompressed within 4 seconds. In fat tissue, extra vascular bubbles occur in the order of decreasing frequency, after $A-O_2$, N_2-O_2. O_2 and $He - O_2$ mixtures. Intracellular bubbles occurred after $A-O_2$,N_2-O_2, $He-O_2$ but not after oxygen breathing. Intravascular bubbles are present with all gas mixtures. In the adrenal cortex, bubbles occur at the same frequency as in fat except that only rare bubbles are seen after oxygen. The same is true in myelin sheathes and in the lever where oxygen gives no bubbles. Gas bubbles are not found in muscle fibers or in the tissue space of skeletal muscle after decompression in any of the gas mixtures. Bubbles are present intravascularly after all except oxygen. Survival limit of guinea pigs was 75 psi in O_2 (with O_2 toxicity a great lethal factor); 75 psi in $He-O_2$, 45 psi in N_2-O_2, and 30 psi in $A-O_2$. Gersh felt that fat/water solubility ratios appear to account for these findings as does the metabolic utilization of oxygen in the tissues.

These survival limits indicate that nitrogen is less than twice as dangerous as helium in decompression. This is ½ the ratio expected from bubble factor which would predict a ratio of 4.2. It must be remembered, however, that these animals were exposed to high pressure for a period of only 1 hour at which time their bodies were only 50% saturated with nitrogen. From the previous discussion, one would expect the dangers of nitrogen to be minimized when compared to those of helium under these conditions. It is of interest that argon, which has the same fat water solubility ration as nitrogen and most probably the same total body saturation curve, is 1½ times as dangerous as nitrogen, a ratio which is predicted from the bubble factor data of Table II.

In 1939, A.R. Behnke[7] reported on the use of argon in deep sea diving. As expected by virtue of a fat solubility, twice that of nitrogen, argon had a more narcotic effect than did nitrogen. At one atmosphere, no difference was noted between these gases. No report of bends incidence is reported, though one would expect a greater incidence than with nitrogen because of the simularity in fat/water solubility ratios and diffusibilities but the

The dynamics of argon exchange in the human body have been studies by Jones[25] who demonstrated tissue perfusion and solubility to be the major factors, and not diffusion. Krypton and Xenon followed the same pattern. Radio Krypton and radio Xenon have been used by Jones[25] in the study of cerebral blood flow and gave values similar to nitrous oxides in these studies.

It is of interest that no studies are available of neon exchange or relative hazard of this gas during decompression. The only mention of this gas in the physiological literature available to the author was the classification of this gas by H. Haggard and Y. Henderson as a simple asphyxiant, as a gas which is non toxic except for a capacity for displacing oxygen in a breathing mixture.

2. Physiological Side Effects.

Helium was first extensively used by A. L. Barach in the treatment of asthma.[2][3]. He pointed out that the marked relief of labored breathing was due to the fact that it was 66 percent lighter than nitrogen and almost three times as diffusive. Barach reported that mice were maintained for 2½ months on an 80 percent He- 20 percent

O_2 mixture with no ill effects.

The low molecular weight of helium does present a problem in commumications. As Behnke pointed out[6], the laryngical muscles, controlling as they do, the tension on the vocal cords, are trained from childhood to produce different tones. The muscular training is performed in an air medium. Because the rate of flow is, according to Graham's Law, inversely proportional to the square root of the density of a gas under constant pressure head, the resulting sound as the gas passes the vocal cords is higher in pitch and of more nasal quality than when air is breathed. Divers have learned to overcome this difficulty and can always detect a novice at helium diving by his inability to modify his tone.

Another factor arising from the low molecular weight and density of the gas is the high thermal conductivity[19]. Chilling is much more marked in helium diving than it is on air diving. The U.S. Navy has had to increase the heating capabilities of diving suits to make up for this difference.

Argon, on the other hand, has been shown to require 11 percent more pulmonary airway pressure than air for an equal flow rate[7]. This is just as one would expect from density factors involved. The thermal conductivity of Argon is much lower than that for helium. Hirschfelder, et al[14] compared the thermal conductivity of the noble gases at 0°C and found them to be (in units of

Nitorgen at 8°C has a value of 524 and oxygen, 563. The practical significance presented by these thermal conductivity considerations will be discussed later in the paper.

Another interesting side effect to be encountered is the abberation in metabolism produced by enert gases. The narcosis produced by the enert gases have been attributed to the solubility in fat. Just how the gases dissolved in fats exert their effect is still unknown. It appears that the total concentration of the gas in fat and no the fat/water solubility ratio is important. Argon has a fat/water solubility ratio almost equal to that of nitrogen but twice the fat solubility and also has twice the narcotic effect(7). One might expect that, even though nitrogen and argon are narcotic at great pressures, xenon and Krypton should be narcotic at one atmosphere. Reasoning from the fat solubilities, (Table I) one might expect 80 percent Kr at sea level to be equal to 6 atmosphere of air and 80 percent xenon equal to 25 atmospheres of air. This was tested by J. H. Lawrence et al(28). A human breathing 56 percent Krypton gas in O_2 at sea level reported only dizziness. Mice exposed to 58-60 percent xenon for 30 minutes to an hour developed convulsive head movements, partial paralysis of limbs and ataxia with complete recovery upon return to air. S. C. Cullen and E. G. Gross(15) studied the anesthetic qualities of Xenon and Krypton in animals and man. Rats, mice and rabbits "exhibited no unequivocal evidence of narcosis" with either an 80 percent mixture of Krypton (95 percent) and Xenon (5 percent) or 80 percent nitrous oxide. Three humans inhaling mixtures of 80 percent krypton and 20 percent O_2 reported changes in voice quality, desire to breath more deeply and ill defined dizziness or discomfort but no significant narcosis. Mixtures with 80 percent xenon, on the other hand, produced minimal narcotic effects in rabbits with some loss of lid reflex, apparent dimunition in response to painful stimuli and tendency to remain in unnatural positions. Recovery was complete.

Six humans inhaling 50 percent Xe - 50 percent O_2 mixtures were shown to have a 15 percent increase in pain threshold. Each subject reported more pronounced subjective sensations of dizziness and incipient loss of consciousness. Seventy percent xenon, 30 percent O_2 produced narcotic effects and incipient loss of consciousness in two other men. One of two patients, and 81 year old male was then anesthetized with 80 percent Xe and 20 percent O_2 mixtures and orchidectomized. There was no evidence of pain and 1st plane 3rd stage anesthesia was reported. Vital signs were normal and fair and phanygical muscle relaxation was noted. Recovery was normal. The patient began to recover two minutes after xenon gas was stopped and was oriented after 5 minutes. The other patient underwent a Fallopian tube ligation with similar good results. Cullen and Gross compared xenon to ethylene in anesthetic capacity and noted the similarity in solubility coeffecients in oil 1.3 for ethylene and 1.7 for xenon. Ether has a solubility coefficient of 50 in oil, while nitrous oxide has one of 1.4. It appears that the fat/water solubility ratio is of no consequence as far as anesthesia is concerned and only fat solubility is important. Since the fat solubility and molecular weight of the noble gases increase simultaneously, it is difficult to determine whether fat solubility or some other factor based on molecular weight is the key to the anesthetic effect.

It is of interest to note that hydrogen with a molecular weight of 2 has an oil solubility coefficient of .045 while He with a molecular weight of 4 has an oil solubility of about .015[33]. No report of H_2 narcosis has been noted. It appears that this study of hydrogen as an anesthetic agent may shed some light on this problem.

S.F. Cook[12] has studied the metabolic effects of He and argon at sea level. Helium, when substituted for air had no effect on Drosophila, Melanogaster, Zootermopsis nevadeusis or Coleonyx variegatus. It accelerates O_2 consumption by Tenebrio molitor. Helium increases CO_2 production by normal larvae but depresses it in adults and starved larvae. Helium increases CO_2 production by mice but decreases it in the case of lizards. Argon appeared to be less active than He, though it resembles He in its effect on Tenebrio and two species of lizards. Agron did not alter CO_2 production in mice. Helium definitely and argon, less clearly, decreased the total development time of Drospphila and Tenebrio. S. F. Cook et al[13] then reported that statistically significant increases in O_2 consumption of 140 percent $\pm$ 6.4 and CO_2 production of 124.7 $\pm$ 4.68 were evident in mice breathing 80 percent He, 20 percent O_2 mixtures. Oxygen consumption, in vitro, of straited muscle, liver, ventricle, and sarcoma increased to the same degree in an 80 percent He environment. In an attempt to pin down the exact site of He action in the metabolic cycle, F. E. South and S. F. Cook[36] performed metabolic studies on mouse liver slices. They found He produced no change in RQ and a decrease in magnitude of cyanide inhibition. No effect of He was noted, even when lactate or pyruvafe were added as substrates on fluoride inhibition of the cycle. A change in the rate and the shape of the curve of O_2 consumption in liver homogenates which are utilizing pyruvates as substrates were noted.

The use of He in an anearobic chamber as a substitue for nitrogen produced a depression of glycolytic rates in both mouse liver slices and diaphragms. An increase in the carbon dioxide evaluation and lactic acid production of mouse liver homogenates oxidizing either glucose or hexose diphosphate were noted. Smith hypothesized from the above that 1) helium does not alter the subsuate utilized by the tissue; 2) the gas interferes in some way with the cyanide-cytochrome bond but may not effect cytochrome oxidase in the absence of cyanide; 3) the citric acid cycle is not subject to influence of helium in the tissue slices, but is altered in an unexplained fashion in homogenates. A possible rearrangement of particulate surfaces may be a significant factor. 4) The glycolytic cycle is the site of both an inhibitory and acceleratory effect of helium. The location of the inhibition lies above aldolase reaction and that of the acceleration between the aldolase and enolase reactions.

In further studies, Cook and South[14] demonstrated that helium increases rate of oxygen consumption of brain and sarcoma slices in vitro. This increase is greater for sarcoma than brain, but differences between these tissues and liver and diaphragm are less pronounced. Under anaerobic conditions helium decreases glycolysis of brain slices, liver, and diaphragm but evolves no response from sarcoma tissue.

Helium is therefore thought to only indirectly alter the rate of phosphorolation of glucose by action on some unknown factor which is present at quantitatively different levels in different tissues.

In an attempt to define the site of action of helium in increasing metabolism of mice, D. R. Young and S. F. Cook[40] noted that heavier mice with a lower standard metabolic rate showed a greater acceleration by 80 percent He environments than did the lighter mice. In experiments with three groups of mice: radio-thyroidectomized (I^{131}) normal controls, and a group fed heavy doses of dessicated thyroid, acceleration of O_2 was greatest in the thyroidectomized group. It was concluded that He worked inversely proportional to the level of standard metabolism regardless of the nature of the origin of this metabolic state.

3. Logistics -

Present day methods of producing the noble gases by the fractional distillation of liquid air have reduced the prices of these gases considerably. The Matheson Company, Inc. of East Rutherford, New Jersey, lists the 1956 prices of 100 liters of the inert reagent grade gas at 500 psi as: He - $150.00, Ne - $150., H - $150., Ki - $1300. and Xe - $3,000. Cost is therefore no factor in the choice of the 3 best gases, He, Ne, and Xe.

Since there is a possibility of having to maintain a constant cabin air environment in face of a small calculated cabin leak rate, it will be necessary to have an inert gas source on board a rocket cabin. Liquid forms of the gas would be possible for short trips where expansion losses are not prohibitive. The boiling point of these gases therefore come into play. As seen in Table #1, helium is at a disadvantage with a B. P. of -268.8° and neon next at -245.9°C, Nitrogen boils at -195.8 while argon and oxygen boils at -185.8C and -183°C respectively. Krypton and xenon present their only gross advantage in this study in having rather high boiling points at -151.8 and 106.9°C.

The Herrick L. Johnson Company of Columbus is attempting to improve liquid helium insulation designs to better the more than 15 percent per day minimum daily standby loss which is mandatory for this gas. This figure can be compared to the 4-6 percent daily standby loss for nitrogen and oxygen liquid systems. No data is available for neon, though a figure of about 13 percent is the comparative loss expected on interpolation of boiling point figures. It thus appears that compressed gases will be more favorable than liquid forms for the lower molecular weight inert gases in trips of long duration. Storage of different inert gases in the compressed form does not present a large penalty range. The 1.02 cu ft steel spheres of the Walter Kiddie Company can supply helium 3000 psi with a penalty of .05 pounds per pound of equipment, while the fiber glass spheres of the same size offer .086 pounts of He per pound of equipment. Equal volumes of the other gases will weigh progressively more as the density increases from .178 g/l of He to 5.85 g/l for Krypton.

The total weight of a 1.02 cu ft fiber glass cylinder filled at 3,000 psi plus the contained gas is 24.8 pounds with helium; 30.8 pounds with Ne; 44.8 pounds, with argon; 67.6 pounds, with Xenon; 88.4 pounds, with krypton and 36.8 pounds with nitrogen.

It thus appears that the total weight penalty in the range of gases which are of physiological significance would be from 24.8 pounds for He to 36.8 pounds for nitrogen. Such a small difference in total weight penalty for 200 cu ft of gas at one atmosphere should not influence the choice of gas were the fiberglass sphere the appropriate vessel of choice. The duration of the mission would, of course, determine optimum form of gas storage.

Another factor in the choice of gas is leakage rates in sealed cabins as a function of the diffusivity of the gas. C.E. Dryden et al (16) have made an engineering survey of this problem. The basic consideration is the fact that the leak rate in volume of gas per unit time is inversely proportional to the square root of the molecualr weight. The relative diffusion through gelatin as recorded on Table I is a good maesure of the relative volumes of unit gas leaving the cabin through any effective hole size and pressure head. The leakage rate on a pound-mass basis will be much lower with the use of helium in place of nitrogen for the same cabin total pressure and oxygen partial pressure. It is of interest to note that the pound rate of leakage varies very little with different oxygen percentages when nitrogen is used since the two gases are of almost equal molecular weight. The leakage parameter of heliu, however, decreases appreciably as the oxygen concentration is reduced. Thus, higher cabin pressures can be maintained without increasing the leakage rate as the percent of He is increased. Leakage rates at low cabin altitudes are appreciably lower with helium than with nitrogen as the inert component. Thus the leakage rate with helium-oxygen having .15 atmospheres of oxygen at 18,000 feet cabin altitude is equal to that for nitrogen-oxygen at the same oxygen partial pressure at 25,000 ft. This would amount to 40 pounds of gas per hour through a 0.1 square inch opening. If one were planning a perfectly sealed cabin, these leak rates would be a problem only during accidental decompressions. Once again, the type and duration of mission will determine the advantage of helium over nitrogen in terms of leak rate problems.

Metering of inert gas into a sealed system to maintain a constant environment under a variable leak rate to the vacuum of space can be accomplished rather simply. By metering oxygen into the cabin so as to maintain a constant partial pressure of oxygen as detected by a paramagnetic analyzer, one can adjust the enert gas flow through an anaeroid so as to maintain a constant total pressure in the system. Thus, both gases may be controlled to stabilize the milieu of the cabin.

From the above review of the literature, it appears that the physical analysis of decompresion bubble history within the body provides an adequate working model for selection of several potential inert gases in sealed cabins. Decompression sickness data in those areas where inert gases are currently being used can be logically interpreted in light of the bubble theory.

It appears that in terms of decreasing the tendency toward decompression symptoms in sealed cabins, helium, neon, and nitrogen are the only gases to be considered. Helium appears to be the best single gas. Mixtures of helium-neon, neon-nitrogen, helium nitrogen and helium-neon-nitrogen may well offer a more effective mixture in terms of minimizing side effects, though helium itself appears to be the best medium for avoidance of decompression symptoms.

Voice changes and increased thermal conductivity of helium and neon appear to be minor factors which can be compensated for by speech practice and air conditioning adjustments. The narcotic effects are sub-threshold with these low molecular weight gases at subatmospheric pressures. The minor changes in metabolic rate produced by helium are interesting but do not appear to be of gross practical import. Continuation of metabolic experiments in mammals and man appears necessary to define the problem more clearly.

There arises the question of the practical aspects of substituting the inert gases for nitrogen in sealed cabin environments. Were a cabin to be maintained at ground level pressures, high percent inert gases would be present to maintain relatively high gas tensions in the tissue prior to decompression. Elevation of oxygen percentage in sea level cabins would decrease the percent of inert gases but at the same time increase the rate of propagation of flame and thereby increase fire hazards. It would therefore seem that most effective use of helium or neon would be in the sea level cabin with normal oxygen environment.

Elevation of cabin altitude would require proportional elevation in O_2 percentage and reduction in inert gas components to maintain normal partial pressure of O_2. The natural denitrogenation of crew members occurring in cabins of this type would tend to protect them from subsequent decompressions to 40,000 feet. From the analysis of Bateman[5] it would appear that prolonged denitrogenation above the 10,000 foot skin level would protect almost all subjects against subsequent decompression to 40,000 foot pressures suit altitudes. It would appear that substitution of helium and neon for nitrogen would be of no practical phsyiological advantage in cabins maintained at these altitudes and their use should probably be determined only by leakage considerations.

Summary

1. Some pertinent phsical properties of inert gases, He, Ne, A, Kr, Xe, and N_2 were outlined.
2. The relationship between the size history of a tissue bubble and the onset of symptoms in men during decompression were reviewed.
3. Analysis of gas factors controlling rate of growth and decay of tissue bubbles during decompression in an idealized model showed that the factor (solubility in oil)^2 x diffusion coefficient in oil/solubility in water determined maximum size of bubble and symptoms. By this helium appeared to be four times better than nitrogen and neon 1.4 times better than nitrogen in minimizing symptoms after decompression to altitude.
4. Review of diving literature and experimental studies using inert gases corroborated the advantages of helium and neon over the other inert gases and apparent reliability bubble factor concept.
5. The side effects and logistic consideration of these gases were discussed and the factors governing the use of inert gases in operational sealed cabins were outlined.

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TABLE I INERT GASES AND PROPERTIES

PROPERTY	GAS.. He	Ne	A	Kr	Xe	N2	Reference
1. Atomic Number	2	10	18	36	54	7	(17)
2. Molecular Weight	4.00	20.18	39.93	82.92	130.2	28.02	(17)
3. Density (G/L)	.178	.889	1.78	3.71	5.85	1.25	(17)
4. Boiling Pt (°C)	-268.8	-245.9	-185.8	-151.8	-106.9	-195.8	(17)
5. Solubility Coefficient in water @ 38°C	.0086	.0097	.026	.045	.085	.013	(28)
6. Solubility Coefficient in Oil @ 38°C	.018	(.046)a	.14	.43	1.7	.067	(28)
7. Oil/Water Solubility Ratio	1.7	(4.7)b	5.3	9.6	20.0	5.2	(28)
8. Relative Diffusion Through Gelatin @ 23°C	1.0	(.45)c	.30	.21	.13	.36	(22)

a. = interpolated from molecular weights
b. = calculated from this table
c. = calculated from Graham's Law factors

TABLE II DECOMPRESSION BUBBLE FACTORS

FACTOR / GAS	He	Ne	A	Kr	Xe	N2
Solubility in H_2O @ 38°C X Relative Diffusion in Gelatin @ 23°C	.0080	.0044	.0078	.0095	.011	.0047
Solubility In Oil @ 38°C X Relative Diffusion in Gelatin @ 23°C	.018	.021	.042	.090	.22	.024
Bubble Factor	.031	.099	.22	.86	4.4	.13
Relative Bubble Factor Nitrogen = 1	.24	.76	1.7	6.6	34	1

Table III - Comparison of total decompression time following exposure in compressed air and exposure in a helium-oxygen atmosphere - After Behnke(10)

Depth (feet)	Exposure (Minutes)	Decompression (minutes)	
		Air	Helium - oxygen
90	100	57	75
90	180	-	77
90	360	-	79
90	540	683	79
150	80	141	121
150	180	-	126
150	360	-	128
200	65	217	154
200	90	-	164